

Chapter 2

The Variety of Deep Eutectic Solvents



The following definition is generally used in this book: deep eutectic solvents (DESs) are binary mixtures of the definite composition of two components, one of which being ionic, that yield a liquid phase at ambient conditions, ≤ 25 °C. Some cases that do not conform to this restrictive definition are, however, also included, since they have properties and uses similar to those that do. The general mode of preparation of deep eutectic solvents, if their ingredients are solids at ambient conditions, is to mix the components at the prescribed molar ratio and heat the mixture to a moderately elevated temperature (generally 60–100 °C) for a few hours until the entire mass is converted to a homogeneous clear liquid. If one of the ingredients is itself liquid at ambient conditions the other component is dissolved in it, if necessary by moderate heating for some time. A variant is to dissolve both components in water, which is then vacuum evaporated or removed by freeze-drying, and to dry the resulting deep eutectic solvent in a desiccator [1, 2].

One general mode for the formulation of a deep eutectic solvent is to have one component of the binary mixture a hydrogen bond acceptor (HBA), e.g., an ionic component with an anion such as chloride, and the other a hydrogen bond donor (HBD), such as an amide, an alcohol, or a carboxylic acid. The deep eutectic solvent keeps the identities of the components which interact via hydrogen bonding, and no covalent compound between them is formed. The optimal ratio of the hydrogen bond acceptor and hydrogen bond donor that forms the eutectic depends on the mutual hydrogen bonding abilities of the components.

The concept of natural deep eutectic solvents (NADES) involves as the hydrogen bond donor components of the binary mixtures any of the many substances from natural origins that form deep eutectic solvents with choline chloride (itself a natural product) or other hydrogen bond acceptor ingredients of natural origin. The advantage of natural deep eutectic solvents over other deep eutectic

solvents is that the natural ones are expected to be nontoxic, biodegradable, hence more environmentally friendly, and to be prepared easily from readily available low-cost materials.

Figure 2.1 shows the structures of commonly used hydrogen bond acceptor ingredients of deep eutectic solvents and Fig. 2.2 shows the corresponding structures of the hydrogen bond donor components [3].

Some publications consider eutectic mixtures that have melting/freezing points above 25 °C as deep eutectic solvents, but here mainly those that melt/freeze below this temperature are dealt with. However, some mixtures do not crystallize on cooling but have a glass transition point rather than having a freezing/melting point. Such mixtures are termed ‘low transition temperature mixtures’ (LTTMs) and act like deep eutectic solvents in most respects and are dealt with here. The scope of deep eutectic solvents is extended by the addition of a third component, another hydrogen bond donor agent, as, for example, water. However, here mostly binary mixtures of one hydrogen bond acceptor agent and one hydrogen bond donor agent are dealt with.

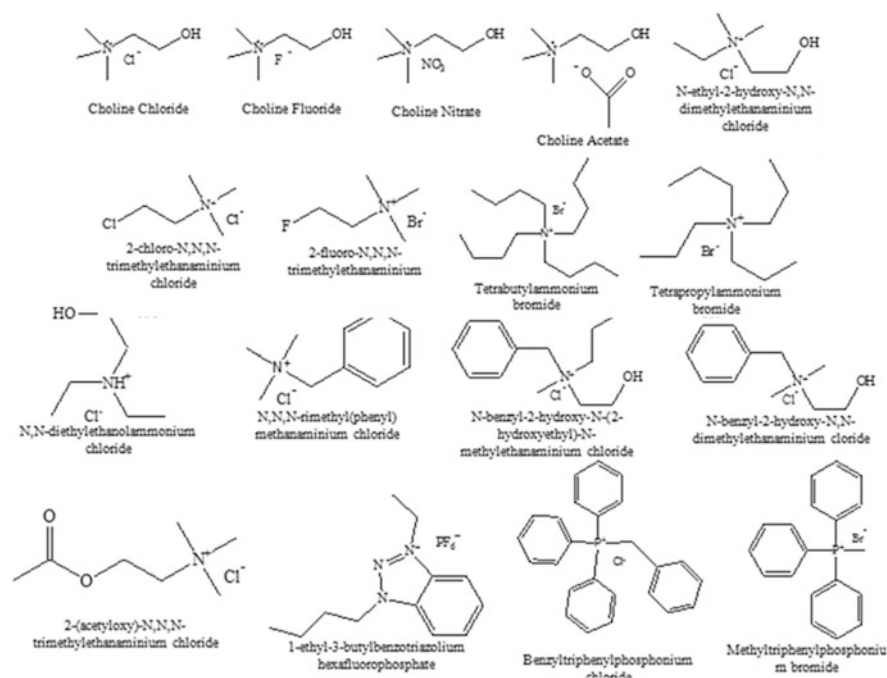


Fig. 2.1 Structures of hydrogen bond accepting components of deep eutectic solvents (from [3], by permission of the publisher, Elsevier)

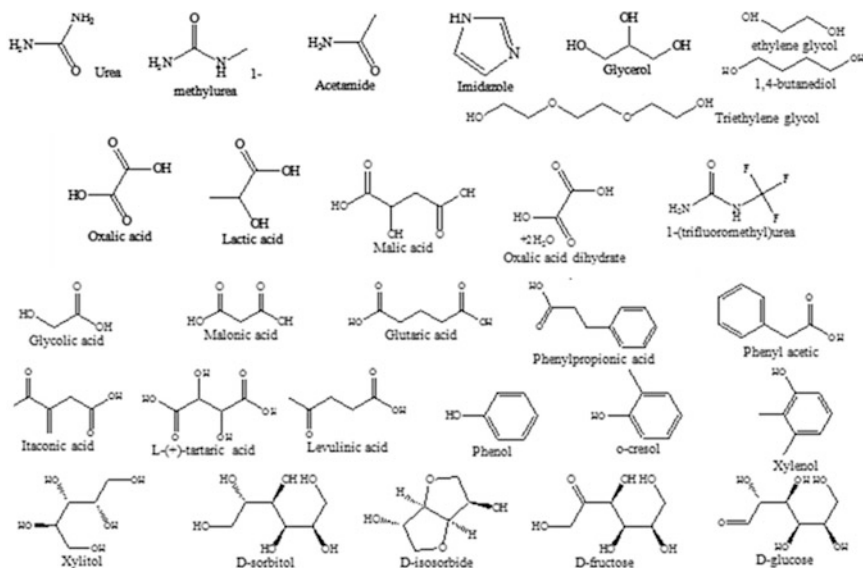


Fig. 2.2 Structures of commonly used hydrogen bond donor components of deep eutectic solvents (from [3] with permission of the publisher, Elsevier)

2.1 Deep Eutectic Solvents Based on Choline Chloride and Analogs

The first deep eutectic solvent (DES) was suggested by Abbott et al. [4]: the eutectic combination of choline chloride and urea. This deep eutectic solvent is nowadays known under the trade name “Reline” and is commercially available. However, it is simply prepared by mixing the solid components at the appropriate molar ratio, 1 choline chloride: 2 urea, heating while stirring to 80 °C, and the homogeneous transparent liquid deep eutectic solvent is thereby formed. For the 1:2 eutectic, the melting point is $t_{me}/^{\circ}\text{C} = 12$ [4] (but see Sect. 3.1 for disagreeing values), making the liquid mixture an attractive solvent so that Reline is widely used as a solvent for a host of applications.

The raw materials for this particular deep eutectic solvent, Reline, are widely available natural products and are biodegradable, hence environmentally friendly, i.e., ‘green’, making this combination a NADES. Choline chloride (2-hydroxyethyl-*N,N,N*-trimethylammonium chloride ($\text{HOC}_2\text{H}_4\text{N}(\text{CH}_3)_3^+\text{Cl}^-$, CAS No. 67-48-1) is mass produced as a growth-promoting chicken feed additive at a price of ~850 USD/ton. It is a white deliquescent crystalline solid, has a molar mass of $M/\text{g mol}^{-1} = 139.62$ and has a melting point of $t_m/^{\circ}\text{C} = 302$ (but it decomposes on melting). It is very hydrophilic: its octanol/water distribution constant is $\log K_W^O = -5.16$, and it is highly soluble in water: $s/\text{g dm}^{-3} > 650$ at room temperature. Choline chloride is a skin irritant and hazardous in case of ingestion, but

potential chronic health effects are not known. The material is combustible but not readily flammable.

Urea ($\text{O}=\text{C}(\text{NH}_2)_2$, CAS No. 57-13-6) is mass produced as a nitrogen fertilizer at a price of ~ 200 USD/ton. It is a white crystalline solid, has a molar mass of $M/\text{g mol}^{-1} = 60.06$, and has a melting point of $t_m/^\circ\text{C} = 132.7$. It is moderately hydrophilic: its octanol/water distribution constant is $\log K_W^{\text{O}} = -1.52$, and it is highly soluble in water: $s/\text{g dm}^{-3} = 1080$ at 20°C . Urea is a skin irritant and hazardous in case of ingestion and inhalation, but potential chronic health effects are not known. Urea is nonflammable, but may be combustible at high temperatures.

The eutectic distance for the 1:2 choline chloride: urea eutectic combination is $\Delta t_m/^\circ\text{C} = 178$, in view of the melting points of the ingredients: 302 and 133°C . The hydrogen bond acceptor chloride anion of the choline salt may be exchanged for other anions that also have good hydrogen bond accepting abilities, such as nitrate ($t_m/^\circ\text{C} = 4$) or fluoride ($t_m/^\circ\text{C} = 1$) for the resulting deep eutectic solvent [4]. However, for a choline salt with an anion less prone to accept hydrogen bonds the melting point of the 1:1 combination is considerably above ambient: $t_m/^\circ\text{C} = 67$ for the tetrafluoroborate salt.

Choline chloride may be substituted by other similar quaternary ammonium salts that form deep eutectic solvents with urea [3, 4]. A change of one of the methyl groups of the choline cation to an ethyl or benzyl group lowers the melting point of the quaternary ammonium salt/urea deep eutectic solvent. The chloride of 2-hydroxyethyl-ethyl-*N,N*-dimethylammonium has $t_m/^\circ\text{C} = -38$ and that of 2-hydroxyethyl-benzyl-*N,N*-dimethylammonium has $t_m/^\circ\text{C} = -33$. Other substitutions of choline, such as 2-acetyethyl-*N,N,N*-trimethylammonium, $t_m/^\circ\text{C} = -14$, *N,N*-bis(2-hydroxyethyl)-benzyl-methylammonium, $t_m/^\circ\text{C} = -6$, and 2-chloroethyl-*N,N,N*-trimethylammonium, $t_m/^\circ\text{C} = 15$, are further examples [4].

Table 2.1 summarizes the compositions regarding deep eutectic solvents based on choline and its analogs, their molar masses M and their melting/freezing points t_m . Some amides besides urea also produce deep eutectic solvent with choline chloride, the most effective being trifluoroacetamide ($\text{CF}_3\text{C}(\text{O})\text{NH}_2$, CAS No. 354-38-1) at a molar ratio of choline chloride: amide of 2:5, with $t_m/^\circ\text{C} = -43.6$. The eutectic distance, in this case, is $\Delta t_m = 184^\circ\text{C}$ [5, 6], slightly larger than for urea as a component. Some other amides than urea and trifluoroacetamide have also been tried with choline chloride, but do not produce deep eutectic solvents: they have melting points above ambient. Methyl-substituted ureas are examples: 1-methyl-, 1,2-dimethyl-, 1,1-dimethyl-urea eutectics with choline chloride have $t_m/^\circ\text{C} = 29, 70, 149$, respectively. The eutectic of choline chloride with acetamide has $t_m/^\circ\text{C} = 80$, with benzamide has $t_m/^\circ\text{C} = 129$, and with thiourea has $t_m/^\circ\text{C} = 175$ [4].

Choline chloride is an ingredient of a wide range of other deep eutectic solvents, for instance, those formed with a carboxylic acid as the hydrogen bond donating ingredient. When a monobasic acid is employed, the ratio 1:2 choline chloride: acid produces the low-melting eutectic: $t_m/^\circ\text{C} = 20$ for phenylpropanoic acid

Table 2.1 Deep eutectic solvents based on choline chloride and its analogs formed at the indicated ratios of HBA:HBD, their molar masses M , and the melting point of the eutectics, t_{me}

HBA	HBD	$M/\text{kg mol}^{-1}$	$t_{me}/^{\circ}\text{C}$	Ref.	
Choline chloride	urea (1:2), Reline	0.25974	12	[4]	
	Thiourea (1:3)	0.36790	<10	[5]	
	trifluoroacetamide (1:2)	0.36570	-44	[6, 7]	
	propanoic acid (1:2)	0.28778	<-80 ^b	[8]	
	chloroacetic acid (1:2)	0.32862	<-80 ^c	[8]	
	trichloroacetic acid (1:2)	0.46640	<-80 ^d	[8]	
	phenylacetic acid (1:2)	0.42595	25	9	
	phenylpropanoic acid (1:2)	0.43998	20	[9]	
	malonic acid (1:1), Maline	0.24368	10	[9]	
	glutaric acid (1:1)	0.27174	-16 (t_{ge})	[3]	
	glycolic acid (1:1)	0.21507	-16 (t_{ge})	[9]	
	lactic acid (1:2)	0.31978	-78	[9]	
	levulinic acid (1:3)	0.48795	-11	[10]	
	oxalic acid dehydrate (1:1)	0.26569	-40	[3]	
	malic acid (1:1)	0.27371	-56	[9]	
	Trifluoromethanesulfonic acid			< 25	[11]
	p-toluenesulfonic acid (1:2)	0.52007	<-80 ^e	[8]	
	ethylene glycol (1:2), Ethaline	0.26376	-66	[12]	
	diethylene glycol (1:3)	0.45738	< -20	[13]	
	triethylene glycol (1:3)	0.58953	-19.8	[14]	
	glycerol (1:2), Glyceline	0.32380	-40	[15]	
	1,2-propanediol (1:3)	0.36732	< -20	[16]	
	1,4-butanediol (1:2)	0.31986	-32	[2, 9, 10]	
	2,3-butanediol (1:3)	0.40938	< -20	[16]	
	PEG 200 (1:2)	0.53902	< 25	[17]	
	furfuryl alcohol (1:3)	0.43392	-36	[10]	
	xylitol (1:1)	0.29177	LRT ^a	[19, 20]	
	d-sorbitol (1:1)	0.32179	9	[7]	
	d-isosorbide (1:2)	0.43190	LRT ^a	[19, 20]	
	xylose (1:1)	0.28915	LRT ^a	[21]	
	fructose (2:1)	0.43237	10	[3]	
	glucose (2:1)	0.43237	15	[3]	
	Sucrose (1:1)	0.48132	LRT ^a	[21]	
	phenol (1:3)	0.42195	-20	[3, 22]	
	o-cresol (1:3)	0.43597	-24	[3, 22]	
	p-cresol (1:2)	0.33699	<20	[23]	
2,3-xyleneol (1:3)	0.50613	18	[3, 22]		
4-chlorophenol (4:5)	0.29972	< 20	[3, 22]		
2-methoxyphenol ^f (1:3)	0.51144	<20	[24]		

(continued)

Table 2.1 (continued)

HBA	HBD	$M/kg\ mol^{-1}$	$t_{me}/^{\circ}C$	Ref.
	ethanolamine (1:2)	0.27168	< -20	[25]
	triethanolamine (1:2)	0.43800	LRT	[31]
Choline acetate	urea (1:2)	0.28334	18	[4]
	glycerol (1:1.5)	0.30175	13	[32]
Choline bromide	levulinic acid (1:4)	0.53240	10.7	[4]
Choline fluoride	urea (1:2)	0.24329	1	[4]
Choline nitrate	urea (1:2)	0.28630	4	[4]
$Me_3-(2-ClEt)N^+Cl^-$	urea (1:2)	0.27619	15	[4]
$Me_2Et-(2-HOEt)N^+Cl^-$	urea (1:2)	0.27377	-38	[4]
$Me_2Bz-(2-HOEt)N^+Cl^-$	urea (1:2)	0.33574	-33	[4]
	levulinic acid (1:2)	0.44794	< 20	[33]
	xylose (1:1)	0.36585	-30 ^b	[34]
	ribose (1:1)	0.36585	-28 ^b	[34]
	glucose (1:1)	0.39588	-7 ^b	[34]
	mannose (1:1)	0.39588	-16 ^b	[34]
	fructose (1:1)	0.39588	-47 ^b	[34]
Acetylcholine ⁺ Cl ⁻	urea (1:2)	0.26627	-14	[4]
	imidazole (1:3)	0.38590	-66	[35]
	Triazole (1:1)	0.25073	-65	[35]
	xylose (1:1)	0.33179	-11 ^b	[34]
	ribose (1:1)	0.33179	-49 ^b	[34]
	glucose (1:1)	0.36382	-7 ^b	[34]
	mannose (1:1)	0.36382	-45 ^b	[34]
	fructose (1:1)	0.36382	-49 ^b	[34]
	2-methoxyphenol ^f (1:3)	0.55408	<20	[24]

^a LRT = liquid at room temperature. ^b Glass transition temperatures $t_{ge}/^{\circ}C = -64$. ^c $t_{ge}/^{\circ}C = -40$.

^d $t_{ge}/^{\circ}C = -53$. ^e $t_{ge}/^{\circ}C = -55$. ^f Guaiacol

($C_6H_5C_2H_4CO_2H$, CAS No. 501-52-0), but when a dibasic acid is used, the ratio is 1:1, e.g., with malonic acid ($CH_2(CO_2H)_2$, CAS No. 141-82-2) $t_{me}/^{\circ}C = 10$ [7]. The deep eutectic solvent with malonic acid is commercially called “Maline”. However, some other carboxylic acids produce with choline chloride eutectics with melting points above ambient: so do phenylacetic acid, $t_{me}/^{\circ}C = 25$, oxalic acid, $t_{me}/^{\circ}C = 34$, and succinic acid, $t_{me}/^{\circ}C = 71$ among others [7]. With glutaric acid (1,3-propanedicarboxylic acid, CAS No. 110-94-1) a low transition temperature mixtures (LTTMs), $t_{ge}/^{\circ}C = -16$, is produced, where t_{ge} is the glass transition temperature, i.e., the deep eutectic solvent is a liquid above this temperature but does not crystallize. Oxalic acid dihydrate (CAS No. 6153-56-6) forms with choline chloride at a 1:1 ratio a low transition temperature mixtures, $t_{ge}/^{\circ}C = -40.2$ [3], contrary to the anhydrous oxalic acid.

Hydroxy- and keto-carboxylic acids may produce with choline chloride low-melting deep eutectic solvents. Levulinic acid (4-ketopentanoic acid $\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$, CAS No. 123-76-2) of natural origin has been promoted as an ingredient of deep eutectic solvents, the 1:3 choline chloride: levulinic acid deep eutectic solvent has a $t_{\text{me}}/^\circ\text{C} = -11.2$ [8]. With other hydroxylic acids considerably lower melting eutectics are produced, thus with the monocarboxylic glycolic acid ($\text{HOCH}_2\text{CO}_2\text{H}$, CAS No. 79-14-1) $t_{\text{ge}}/^\circ\text{C} = -16$ (glass transition), with lactic acid (2-hydroxypropanoic acid, $\text{CH}_3\text{CH}(\text{OH})\text{CO}_2\text{H}$, CAS No. 50-21-5) at a 1:2 ratio $t_{\text{me}}/^\circ\text{C} = -78$ and with the dicarboxylic malic acid (2-hydroxybutanedioic acid, $\text{HCO}_2\text{CH}(\text{OH})\text{CH}_2\text{CO}_2\text{H}$, CAS No. 617-48-1) at a 1:1 ratio $t_{\text{me}}/^\circ\text{C} = -56$ [7]. Two carboxylate groups are seen to be needed to hydrogen bond with the chloride anion. On the other hand, citric acid (2-hydroxypropane-1,2,3-tricarboxylic acid, $\text{HO}_2\text{CCH}_2\text{C}(\text{OH})(\text{CO}_2\text{H})\text{CH}_2\text{CO}_2\text{H}$, CAS No. 77-92-9) produces with choline chloride a eutectic melting above ambient: $t_{\text{me}}/^\circ\text{C} = 69$ [7]. The deep eutectic solvent formed by choline chloride with glycolic, oxalic, malonic, and glutaric acids at 1:1 molar ratios and with levulinic acid at a 1:2 ratio have also been described in [9], but without their melting points, only glass transition temperatures $< -12^\circ\text{C}$ having been reported.

Some of these carboxylic acids are natural products, hence they form with choline chloride natural deep eutectic solvents (NADES). Malonic acid, the hydrogen bond donating agent in Maline, was listed as one of the top 30 chemicals to be produced from biomass by the US Department of Energy. Its reference price is USD 7400/ton, i.e., it is rather expensive. In food and drug applications, malonic acid can be used to control acidity, either as an excipient in pharmaceutical formulation or natural preservative additive for foods. Glutaric acid is naturally produced in the body during the metabolism of some amino acids. It is used in the production of polymers such as polyesters and polyamides, the odd number of carbon atoms being useful in decreasing polymer elasticity. Its reference price is USD 4300/ton, less expensive than malonic acid. The glutaric acid may cause irritation to the skin and eyes and it may be harmful by ingestion, inhalation, or skin absorption. Levulinic acid occurs naturally in papaya and rice bran, among other natural products. Its largest application is its use in the manufacturing of DALA a biodegradable herbicide used in South Asia. Another key application is its use as ethyl levulinate in cosmetics, fragrances, and perfumes. The reference price for levulinic acid is USD 3500/ton and this substance is relatively nontoxic. Lactic acid occurs naturally in sour milk and is produced by bacterial fermentation of sugar and starch. Its reference price is USD 1300/ton, its annual production is 300,000 tons globally, and it is used in cosmetics to adjust acidity and for its disinfectant and keratolytic properties.

Polyols have been used to produce deep eutectic solvents with choline chloride, foremost among which is ethylene glycol (1,2-ethanediol, $\text{HOC}_2\text{H}_4\text{OH}$, CAS No. 107-21-1), forming at the 1:2 molar ratio the deep eutectic solvent, commercially available and called "Ethaline", $t_{\text{me}}/^\circ\text{C} = -66$. Very useful is also glycerol (1,2,3-propanetriol, $\text{HOCH}_2\text{CH}(\text{OH})\text{-CH}_2\text{OH}$, CAS No. 56-81-5), forming at the 1:2 ratio the so-called "Glyceline", $t_{\text{me}}/^\circ\text{C} = -40$. Also useful is 1,4-butanediol

(OHC₄H₈OH, CAS No. 110-63-4) at a ratio of 1:3 forming deep eutectic solvents with $t_{me}/^{\circ}\text{C} = -32$ [2, 7, 8]. Other polyols, derived from sugars, are also effective with choline chloride: furfuryl alcohol (2-furyl-methanol, CAS No. 98-00-0) at a 1:3 ratio has $t_{me}/^{\circ}\text{C} = -36$ [10] or -35.8 [8] and d-sorbitol (hexahydroxyhexane, CAS No. 50-70-4) at the 1:1 ratio has $t_{me}/^{\circ}\text{C} = 8.6$ [6]. Two further polyols are mentioned in [11] that form deep eutectic solvents with choline chloride, i.e., mixtures that are liquid at room temperature: xylitol (pentahydroxypentane, CAS No. 87-99-0) at a 1:1 ratio and d-isosorbide (CAS No. 652-67-5) at a 1:2 ratio, but the melting points were not reported [12]. Sugars, such as d-fructose and d-glucose, also form deep eutectic solvents with choline chloride at 1:2 molar ratios, with $t_{me}/^{\circ}\text{C} = 10$ and 15 , respectively [3].

As for the carboxylic acids, some of the polyol hydrogen bond donors are natural products that form with choline chloride natural deep eutectic solvents. Glycerol, the hydrogen bond donor component of Glyceline, is obtained from the hydrolysis of fats and oils in the manufacture of soap at a reference price of USD 500/ton on a >1 million tons scale annually. Glycerol serves as a humectant, solvent, and sweetener in food and beverages, and is also used as filler in commercially prepared low-fat foods. Xylitol is naturally found in low concentrations in the fibers of many fruits and vegetables as well as fibrous material such as corn husks and sugar cane bagasse. Industrial production of xylitol, at a reference price of USD 3000/ton, starts from a hemicellulose extracted from hardwoods or corncobs, which is hydrolyzed and catalytically hydrogenated. Xylitol has no known toxicity in humans and is used as a sweetener. Sorbitol is obtained by reduction of glucose at a reference price of USD 500/ton. It is used as a sweetener and has no toxicity to humans. Furfuryl alcohol is manufactured industrially at a reference price of USD 1500/ton by the catalytic reduction of furfural, which is obtained from corncob and sugar cane bagasse. It is used as a solvent and as a chemical intermediate for furan resins in thermoset polymer matrix composites, cements, adhesives, and coatings. It is irritating to eyes, skin, and respiratory tract and harmful if inhaled or swallowed. The two sugars mentioned above, are, of course, nontoxic ingredients of natural deep eutectic solvents.

Another kind of hydrogen bond donors for deep eutectic solvents with choline chloride are phenols at a 1:3 mol ratio. With phenol itself (CAS No. 108-95-2) the deep eutectic solvents based on choline chloride has $t_{me}/^{\circ}\text{C} = -20.1$, with *o*-cresol (2-methylphenol, CAS No. 95-48-7) it has $t_{me}/^{\circ}\text{C} = -23.8$, and with 2,3-xyleneol (2,3-dimethylphenol, CAS No. 526-75-0) it has $t_{me}/^{\circ}\text{C} = 17.7$ [3, 13]. The phenols are toxic and this should be considered if they are to be employed.

The hydrogen bond donor agent producing with choline chloride a deep eutectic solvent needs not be an organic substance: calcium chloride hexahydrate provides water as the hydrogen bond donor agent, and various molar ratios of it with the choline chloride have freezing temperatures below ambient, ranging from the 1:4 mixture, $t_{me}/^{\circ}\text{C} = 16.8$ to the 1:10 mixture, $t_{me}/^{\circ}\text{C} = 24.1$ [14].

It should be noted in Table 2.1 that some of the hydrogen bond donor components of the deep eutectic solvents are themselves liquid at ambient temperatures and that some of the eutectic temperatures are very low indeed, down to more than

90 °C below ambient (25 °C), i.e. $t_{me}/^{\circ}\text{C} < -65$, for example, those with ethylene glycol and lactic acid. In cases where no melting or glass transition points have been reported but physical properties or applications have been reported down to a certain temperature $t/^{\circ}\text{C}$, this is denoted as $<t$ in the appropriate column.

2.2 Deep Eutectic Solvents Based on Other -Onium Salts

Quaternary ammonium salts other than those of choline or its analogs have been used as hydrogen bond accepting ingredients (HBA) of deep eutectic solvents. However, non-quaternary alkylammonium salts have also been used for this purpose. Symmetrical tetraalkylammonium salts are not useful as room temperature ionic liquids (RTILs), of which deep eutectic solvents are a subcategory, because they have melting points much above ambient. However, when suitable hydrogen bond donating substances (HBD) are added, they do form low-melting eutectics. In many cases, the hydrogen bond donating ingredient employed was a liquid at ambient conditions, so that the solid salt hydrogen bond acceptor and the liquid hydrogen bond donor could be shaken together in an incubator shaker at 80 °C for 2 h, and the colorless homogeneous transparent liquid deep eutectic solvents was formed.

Ethylammonium chloride ($\text{C}_2\text{H}_5\text{NH}_3^+\text{Cl}^-$, CAS No. 557-66-4) forms a deep eutectic solvent at a 1:4 ratio with glycerol having a melting point (read from a figure) of $t_{me}/^{\circ}\text{C} = -58$ [15]. With urea and trifluoroacetamide, it forms deep eutectic solvents at 2:3 ratios having melting points (read from a figure) of $t_{me}/^{\circ}\text{C} = 30$ and 20, respectively [16]. Alkylammonium bromides form deep eutectic solvents at a 1:2 molar ratio with glycerol: ethylammonium bromide ($\text{C}_2\text{H}_5\text{NH}_3^+\text{Br}^-$, CAS No. 593-55-5) $t_{me}/^{\circ}\text{C} = -6$, propylammonium bromide ($\text{C}_3\text{H}_7\text{NH}_3^+\text{Br}^-$, CAS No. 4905-83-3) $t_{me}/^{\circ}\text{C} = -4$, and butylammonium bromide ($\text{C}_4\text{H}_9\text{NH}_3^+\text{Br}^-$, CAS No. 15567-09-6) $t_{me}/^{\circ}\text{C} = -10$ [17]. Another example of a non-quaternary ammonium salt is *N,N*-diethylethanolammonium chloride ($((\text{C}_2\text{H}_5)_2(\text{HOC}_2\text{H}_4)\text{NH}^+\text{Cl}^-$, CAS No. 14426-20-1) that at 1:2 mol ratios with ethylene glycol forms a deep eutectic solvent with $t_{me}/^{\circ}\text{C} = -31.0$ and with glycerol it forms one with $t_{me}/^{\circ}\text{C} = -1.3$ [18]. This tertiary salt also forms deep eutectic solvents at a 1:1 ratio with malonic acid and with zinc nitrate hexahydrate as the hydrogen bond donating agents, but their freezing points were not specified [19].

Tetraethylammonium chloride ($(\text{C}_2\text{H}_5)_4\text{NCl}$, CAS No. 56-34-8) forms a deep eutectic solvent at a 1:4 molar ratio with levulinic acid, with $t_{me}/^{\circ}\text{C} < -60$, i.e., a freezing point not detectable in the range $-60 \leq t_{me}/^{\circ}\text{C} \leq 80$ [20]. Tetraethylammonium bromide ($(\text{C}_2\text{H}_5)_4\text{NBr}$, CAS No. 71-91-0) forms deep eutectic solvent at 1:4 molar ratios with ethylene glycol, $t_{me}/^{\circ}\text{C} = -24.4$, and with triethylene glycol (3,6-dioxo-1,8-octanediol, $\text{HOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$, CAS No. 112-27-6) and levulinic acid, all with $t_{me}/^{\circ}\text{C} < -60$ [20]. With 1,2-dimethyl-urea ($\text{O}=\text{C}(\text{NHCH}_3)_2$, CAS No. 98-31-1) it forms a deep eutectic solvent at an unspecified molar ratio with $t_{me}/^{\circ}\text{C}$ in the range 20–25.

Tetrapropylammonium bromide ((C₃H₇)₄NBr, CAS No. 1941-30-6, TPAB) forms deep eutectic solvents with some polyols [20, 21]: ethylene glycol, glycerol, and triethylene glycol. Several ratios of the components were tested, and the lowest melting eutectics were obtained with 1:4 TPAB:ethylene glycol, $t_{me}/^{\circ}\text{C} = -23$, 1:3 TPAB:triethylene glycol, $t_{me}/^{\circ}\text{C} = -19$, 1:3 TPAB:glycerol, $t_{me}/^{\circ}\text{C} = -16$ [21]. With levulinic acid TPAB and tetrapropylammonium chloride, ((C₃H₇)₄NCl, CAS No. 5810-42-4) form low transition temperature mixtures at 1:4 molar ratios $t_m/^{\circ}\text{C} < -60$ [20].

Tetrabutylammonium chloride ((C₄H₉)₄NCl, CAS No. 75-57-0, TBAC) also forms deep eutectic solvents with ethylene glycol, glycerol, and triethylene glycol: 1:3 TBAC:ethylene glycol, $t_m/^{\circ}\text{C} = -31$, 1:3 TBAC:triethylene glycol, $t_m/^{\circ}\text{C} = -13$, and 1:4 TBAC:glycerol, $t_m/^{\circ}\text{C} = -43$ [22]. With levulinic acid, TBAC forms a low transition temperature mixture at 1:4 molar ratios $t_m/^{\circ}\text{C} < -60$ [20]. With urea at a 1:4 molar ratio, the melting point of the eutectic is just above ambient, 27 °C [23]. With levulinic acid, TBAC forms a low transition temperature mixture at 1:4 molar ratios $t_m/^{\circ}\text{C} < -60$ [24], and with propanoic acid (CH₃CH₂CO₂H, CAS No. 79-09-4), phenylacetic acid (C₆H₅CH₂CO₂H, CAS No. 103-82-2), ethylene glycol, and polyethylene glycol (PEG400, CAS No. 25322-68-3) it forms deep eutectic solvents with $t_m/^{\circ}\text{C} < 15$ [25].

Tetrabutylammonium bromide ((C₄H₉)₄NBr, CAS No. 1643-19-2, TBAB) forms deep eutectic solvents with carboxylic acids at a 1:1 molar ratio, whether mono- or dicarboxylic. The deep eutectic solvents with acetic acid have $t_{me}/^{\circ}\text{C} = -18.5$, with propanoic acid $t_{me}/^{\circ}\text{C} = -19.1$, with oxalic acid $t_{me}/^{\circ}\text{C} = -22.2$, and with malonic acid $t_{me}/^{\circ}\text{C} = -18.0$. With formic acid, a deep eutectic solvent is formed too, but its eutectic melting point was not determined [26]. TBAB forms deep eutectic solvents also with ethanolamine (2-aminoethanol, H₂NC₂H₄OH, CAS No. 141-43-5), $t_{me}/^{\circ}\text{C} = 0.4$ [14], but with diethanolamine (HN(C₂H₄OH)₂, CAS No. 111-42-2) and triethanolamine (N(C₂H₄OH)₃, CAS No. 102-71-6) the melting points are much lower: -67.8 and -76.6 °C, respectively [27].

Tetrahexylammonium bromide ((C₆H₁₁)₄NBr, CAS No. 4328-13-6) forms at molar ratios of 1:2 deep eutectic solvents with ethylene glycol and with glycerol, but their freezing points were not determined [28]. Benzyltrimethylammonium chloride (C₆H₅CH₂N(CH₃)₃⁺Cl⁻, CAS No. 53-93-9) forms with levulinic acid a low transition temperature mixture at 1:4 molar ratios $t_m/^{\circ}\text{C} < -60$ [15]. It forms with *p*-toluene sulfonic acid (CH₃C₆H₄SO₃H, CAS No. 104-15-4) a deep eutectic solvent at 1:2 molar ratio, $t_{me}/^{\circ}\text{C} = -1$, and with oxalic acid a deep eutectic solvent at 1:1 molar ratio, $t_{me}/^{\circ}\text{C} = 2$, but with citric acid at a 1:1 molar ratio the freezing point is above ambient, 31 °C [29]. Benzyltrimethylammonium methanesulfonate (C₆H₅CH₂N(CH₃)₃⁺CH₃SO₃⁻) mixed at a 1:1 ratio with *p*-toluene sulfonic acid monohydrate (CH₃C₆H₄SO₃H·H₂O, CAS No. 6192-52-5) forms a clear colorless deep eutectic solvent after mixing at 60 °C for 10 min, having a melting point (read from a figure) of $t_{me}/^{\circ}\text{C} = -5$ [30]. Benzyltriprophylammonium chloride (C₆H₅CH₂(C₃H₇)₃N⁺Cl⁻, CAS No. 5197-87-5) forms low transition temperature mixtures with several hydrogen bond donating agents: ethylene glycol, glycerol,

phenol, and lactic acid at 1:3 mol ratios. They have $t_m/^\circ\text{C} < -90$, except that with lactic acid that has $t_{me}/^\circ\text{C} = -56.3$ [31].

Tetramethyl-, tetraethyl-, and tetrabutylammonium chlorides form low transition temperature mixtures with lactic acid at a 1:2 ratio that do not crystallize on cooling but form glasses, with glass transition temperatures of -69 , -71 , and -66 $^\circ\text{C}$, respectively [32]. Guanidine carbonate mixed with malic acid at a 2:1 ratio probably forms guanidinium malate when heated for prolonged periods at 70 $^\circ\text{C}$, and then forms a deep eutectic solvent with ethylene glycol, useful for the capture of carbon dioxide [33].

Of the quaternary phosphonium salts, mainly methyltriphenylphosphonium bromide ($\text{CH}_3\text{P}(\text{C}_6\text{H}_5)_3\text{Br}$, CAS No. 1779-49-3) has been used to obtain deep eutectic solvents. With the polyols ethylene glycol $t_{me}/^\circ\text{C} = -46$, with triethylene glycol $t_{me}/^\circ\text{C} = -8$, and with glycerol $t_{me}/^\circ\text{C} = -5$, all at the 1:3 ratio [3]. With trifluoroacetamide, it forms a deep eutectic solvent at an unspecified molar ratio with $t_{me}/^\circ\text{C} = -69.3$, and with levulinic acid, it forms a deep eutectic solvent at a 1:4 molar ratio with $t_m/^\circ\text{C} < -60$ [20]. Benzyltriphenylphosphonium chloride ($\text{C}_6\text{H}_5\text{CH}_2(\text{C}_6\text{H}_5)_3\text{PCl}$, CAS No. 1100-88-5) forms eutectics with glycerol (1:5) with $t_{me}/^\circ\text{C} = 50.4$ and with ethylene glycol (1:3) with $t_{me}/^\circ\text{C} = 47.9$, i.e., above ambient, so they are not proper deep eutectic solvents [34]. However, with glycerol a deep eutectic solvent is formed at a 1:16 HBA:HBD ratio, $t_{me}/^\circ\text{C} = -22.0$ and the corresponding allyltriphenylphosphonium bromide ($\text{CH}_2=\text{CHCH}_2(\text{C}_6\text{H}_5)_3\text{PBr}$, CAS No. 1560-54-9) forms with glycerol a deep eutectic solvent at a 1:14 ratio with $t_{me}/^\circ\text{C} = -23.8$ [35]. The symmetrical tetrabutylphosphonium bromide ($(\text{C}_4\text{H}_9)_4\text{PBr}$, CAS No. 3115-68-2) forms with levulinic acid at a 1:4 molar ratio a deep eutectic solvent with $t_m/^\circ\text{C} < -60$ [20]. Such deep eutectic solvents based on the phosphonium salts have definite toxicity toward bacteria and possibly also larvae of aquatic organisms [36].

Deep eutectic solvents based on these -onium hydrogen bond acceptors (HBA) mixed with various hydrogen bond donors (HBD) at appropriate ratios are summarized in Table 2.2. In cases, where no melting or glass transition points have been reported but physical properties or applications have been reported down to a certain temperature $t/^\circ\text{C}$, this is denoted as $<t$ in the appropriate column.

2.3 Unconventional Deep Eutectic Solvents

Prior to the advent of the choline chloride/urea deep eutectic solvent, stoichiometric mixtures of halide salts of organic cations and certain metal halides were found to have melting points below ambient, i.e., to be room temperature ionic liquids. Examples of such moieties are 1-ethyl-3-methylimidazolium chloride mixed at a 1:1 ratio with aluminum chloride forming the tetrachloroaluminate (CAS No. 80432-05-9) $t_m/^\circ\text{C} = 8$ and mixed at a 1:2 ratio forming the heptachlorodialuminate (1-ethyl-3-methylimidazolium⁺ Al_2Cl_7^-), $t_m/^\circ\text{C} = -98$ [37]. However,

Table 2.2 Deep eutectic solvents based on –onium salts as hydrogen bond acceptors, at ratios of HBA:HBD as noted, their molar masses M , and the melting point of the eutectics, t_{me}

HBA	HBD	Ratio HBA:HBD	$M/\text{kg mol}^{-1}$	$t_{me}/^{\circ}\text{C}$	Ref.
$\text{Me}_4\text{N}^+\text{Cl}^-$	acetic acid	1:4	0.34980	< -20	[25]
	decanoic acid	2:9	0.88477	26 ^f	[49]
	lactic acid	1:2	0.28975	-69 ^a	[47]
$\text{EtNH}_3\text{N}^+\text{Cl}^-$	glycerol	1:4	0.44990	-58	[27]
	urea	2:3	0.34326	30	[28]
	trifluoroacetamide	2:3	0.50220	20	[28]
$\text{EtNH}_3\text{N}^+\text{Br}^-$	glycerol	1:2	0.31017	-6	[29]
	2-methoxyphenol ^f	1:3	0.33430	<20	[24]
$\text{Et}_2(\text{HOEt})\text{NH}^+\text{Cl}^-$	ethylene glycol	1:2	0.27779	-31.0	[30]
	glycerol	1:2	0.33765	-1.3	[30]
	Triethylene glycol	1:4	0.60083	-16.6	[14]
$\text{Et}_3\text{MeN}^+\text{Cl}^-$	acetic acid	1:2	0.27178	< -20	[25]
$\text{Et}_4\text{N}^+\text{Cl}^-$	acetic acid	1:2	0.28589		[25]
	butanoic acid	1:2	0.33808	< 25	[50]
	hexanoic acid	1:2	0.45024	< 25	[50]
	octanoic acid	1:2	0.50632	< 25	[50]
	decanoic acid	2:3	0.51031	24 ^f	[49]
	levulinic acid	1:4	0.63014	< -60	[36]
	lactic acid	1:2	0.34586	-71 ^a	[47]
$\text{Et}_4\text{N}^+\text{Br}^-$	ethylene glycol	1:4	0.45844	-24	[36]
	glycerol	1:2	0.31017	-6	[29]
	triethylene glycol	1:4	1.06632	< -60	[36]
	levulinic acid	1:4	0.67460	< -60	[36]
	1,2-dimethylurea			20-25	[36]
$\text{PrNH}_3^+\text{Br}^-$	glycerol	1:2	0.32420	-4	[36]
$\text{Pr}_4\text{N}^+\text{Cl}^-$	acetic acid	1:6	0.58211	< -20	[25]
	butanoic acid	1:2	0.39803	< 25	[50]
	hexanoic acid	1:2	0.45411	< 25	[50]
	octanoic acid	1:2	0.51019	< 25	[50]
	decanoic acid	2:5	0.65216	15 ^f	[49]
	dodecanoic acid	1:2	0.62235	25 ^f	[49]
	levulinic acid	1:4	0.68624	< -60	[36]
	ethanolamine	1:4	0.46613	< -20	[25]
$\text{Pr}_4\text{N}^+\text{Br}^-$ (TPAB)	ethylene glycol	1:4	0.51454	-23	[36]
	glycerol	1:3	0.53653	-16	[36]
	triethylene glycol	1:3	0.90838	-19	[36]
	butanoic acid	1:2	0.28248	< 25	[50]
	hexanoic acid	1:2	0.33856	< 25	[50]
	levulinic acid	1:4	0.73070	< -60	[36]

(continued)

Table 2.2 (continued)

HBA	HBD	Ratio HBA:HBD	$M/\text{kg mol}^{-1}$	$t_{\text{me}}/^{\circ}\text{C}$	Ref.
$\text{BuNH}_3^+\text{Br}^-$	glycerol	1:2	0.33823	-10	[29]
$\text{DcNH}_3^+\text{Br}^-$ ^e	hexafluoroisopropanol	1:2	0.57431	-25	[51]
$\text{DoNH}_3^+\text{Br}^-$ ^e	hexafluoroisopropanol	1:2	0.60235	-29	[51]
$\text{TdNH}_3^+\text{Br}^-$ ^e	hexafluoroisopropanol	1:2	0.63039	-33	[51]
$\text{Bu}_4\text{N}^+\text{Cl}^-$ (TBAC)	urea	4:1	1.17174	27	[39]
	ethylene glycol	1:3	0.46413	-31	[38]
	glycerol	1:4	0.64628	-43	[38]
	triethylene glycol	1:3	0.92004	-13	[38]
	PEG 400	1:2	1.07792	<15	[42]
	acetic acid	1:2	0.39802	< -20	[25]
	propanoic acid	1:2	0.42608	<15	[40]
	butanoic acid	1:2	0.45414	< 25	[50]
	hexanoic, octanoic ac.	1:2		< 25	[52]
	decanoic acid	1:2	0.94144	-12.0	[53]
	dodecanoic acid	?		<25	[54]
	phenylacetic acid	1:2	0.55022	< 15	[40]
	levulinic acid	1:4	0.74236	< -60	[36]
	lactic acid	1:2	0.45808	-66 ^a	[47]
	aspartic acid	1:9	1.47540	25.0	[55]
	glutamic acid	1:10	1.74880	28.8	[55]
	arginine	1:6	1.32270	25.0	[55]
	serine	1:8	1.11822	25.0	[56]
	threonine	9:1	2.62038	20.2	[56]
	methionine	11:1	3.20633	19	[56]
	α -tocopherol	1:4	2.00034	-50	[57]
$\text{Bu}_4\text{N}^+\text{Br}^-$ (TBAB)	formic acid	1:1	0.36839	LRT ^c	[41]
	acetic acid	1:1	0.38242	-19	[41]
	propanoic acid	1:1	0.39645	-19	[41]
	butanoic acid	1:2	0.49859	< 25	[50]
	hexanoic acid	1:2	0.55467	< 25	[50]
	octanoic acid	1:2	0.61075	< 25	[50]
	decanoic acid	1:2	0.66683	< 25	[50]
	oxalic acid	1:1	0.41240	-22	[41]
	malonic acid	1:1	0.42643	-18	[41]
	levulinic acid	1:4	0.78681	0.4	[58]
	ethylene glycol	1:2	0.44651	< 25	[59]
	PEG 200, 600	1:2		< 20	[60]
	sulfolane	1:7	1.16356	< 25	[61]
	ethanolamine	1:6	0.68885	-68	[42]
	diethanolamine	1:6	0.95321	-77	[42]

(continued)

Table 2.2 (continued)

HBA	HBD	Ratio HBA:HBD	$M/\text{kg mol}^{-1}$	$t_{\text{me}}/^{\circ}\text{C}$	Ref.
	triethanolamine	1:3	0.76994	< -60	[42]
$\text{Hx}_4\text{N}^+\text{Br}^-$	ethylene glycol	1:2	0.55872	LRT ^c	[43]
	glycerol	1:2	0.61876	LRT ^c	[43]
$\text{Hp}_4\text{N}^+\text{Cl}^-$	decanoic acid	1:2	0.83623	-16.7	[62]
$\text{MeOc}_3\text{N}^+\text{Cl}^-$	alkanols, alkanediols	1:2		LRT ^c	[63]
	decanoic acid	1:2	0.74870	9.0	[62]
$\text{Oc}_4\text{N}^+\text{Cl}^-$	decanoic acid	1:2	0.84688	2.0	[53]
	perfluorodecanoic acid	1:2	1.53050	LRT ^c	[53]
$\text{Oc}_4\text{N}^+\text{Br}^-$	decanoic acid	1:2	0.89233	9.0	[62]
$\text{BzMe}_3\text{N}^+\text{Cl}^-$	acetic acid	1:2	0.65013	< -20	[25]
	levulinic acid	1:4	0.65013	< -60	[27]
	tosylic acid ^b	1:2	0.53009	-1	[44]
	oxalic acid	1:1	0.27572	2	[44]
	glycerol	1:2	0.36987		[64]
$\text{BzMe}_3\text{N}^+\text{MeSO}_3^-$	tosylic acid ^b	1:1	0.41764	-5	[45]
$\text{BzEt}_3\text{N}^+\text{Cl}^-$	acetic acid	1:2	0.34787	-20	[25]
	oxalic acid	1:1	0.31781	5	[65]
	citric acid	1:1	0.41989	26	[65]
	tosylic acid	1:2	0.57204	2	[65]
$\text{BzPr}_3\text{N}^+\text{Cl}^-$	ethylene glycol	1:3	0.45606	< -90	[66]
	glycerol	1:3	0.54612	< -90	[66]
	phenol	1:3	0.55218	< -90	[66]
	lactic acid	1:3	0.54009	-56	[66]
$\text{Bu}_4\text{P}^+\text{Br}^-$	levulinic acid	1:4	0.80377	< -60	[67]
	ethylene glycol	1:2	0.46347	< 25	[59]
$\text{MePh}_3\text{P}^+\text{Br}^-$	ethylene glycol	1:3	0.54343	-46	[3]
	glycerol	1:3	0.63349	-24	[3]
	1,2-propanediol	1:4	0.66162		[68]
	Triethylene glycol	1:4	0.95790	-18.2	[14]
	triethylene glycol	1:3	0.99934	-8	[3]
	acetic acid	1:4	0.59742	< -20	[25]
	levulinic acid	1:4	0.82166	< -60	[36]
	trifluoroacetamide	1:8	1.26154	-69	[36]
$\text{EtPh}_3\text{P}^+ \text{I}^-$	ethylene glycol	1:6	0.79067	< 30	[69]
	sulfolane	1:4	0.89893	< 30	[69]
$\text{AllylPh}_3\text{P}^+\text{Br}^-$	glycerol	1:14		-24	[70]
	diethylene glycol	1:4	0.80774	<20	[71]
	triethylene glycol	1:10		-19.5	[14]
$\text{BenzylPh}_3\text{P}^+\text{Cl}^-$	glycerol	1:5		50	[74]
		1:16		-22	[70]

(continued)

Table 2.2 (continued)

HBA	HBD	Ratio HBA:HBD	$M/\text{kg mol}^{-1}$	$t_{\text{me}}/^{\circ}\text{C}$	Ref.
	ethylene glycol	1:3		48	[74]
	triethylene glycol	1:8		-19.5	[14]
$\text{Me}_3\text{S}^+\text{TFSI}^-$ ^c	formamide	1:1	0.40307	-20	[72]
	trifluoroacetamide	2:1	0.82910	LRT ^c	[72]
$\text{C}(\text{NH}_2)_3^+\text{Cl}^-$	ethanolamine	1:2	0.21769	< -20	[25]
$\text{C}(\text{NH}_2)_3^+$ malate	ethylene glycol			LRT ^c	[48]
Emim^+Cl^- ^e	ethylene glycol	2:1, 1:1, 1:2		< 20	[72]
LidDec ^d	decanoic acid	1:1		-66 ^c	[73]

^a Glass transition temperature. ^b *p*-toluenesulfonic acid. ^c Liquid at room temperature. ^d LidDec = lidocaine decanoate. ^e Dc = decyl, Do = dodecyl, Td = tetradecyl. ^f 1-ethyl-3-methylimidazolium chloride. ^f Read from a small figure

these mixtures constitute a single molten salt, hence are not proper deep eutectic solvents, for which the two initial components retain their separate identities.

Proper deep eutectic solvents are formed when the metal halide is the hydrogen bond acceptor and a suitable hydrogen bond donor is added: a mixture of zinc chloride and urea at a 2:7 mol ratio has $t_{\text{me}}/^{\circ}\text{C} = 9$, with acetamide ($\text{CH}_3\text{C}(\text{O})\text{NH}_2$, CAS No. 60-35-5) at a 1:4 mol ratio it has $t_{\text{me}}/^{\circ}\text{C} = -16$. In the eutectic mixtures, zinc is present in the cationic species, e.g., $[\text{ZnCl}(\text{urea})]^+$, as shown by mass spectrometry. With ethylene glycol (1,2-ethanediol) at a 1:4 mol ratio, zinc chloride has $t_{\text{me}}/^{\circ}\text{C} = -30$, and with 1,6-hexanediol at a 1:4 mol ratio it forms a deep eutectic solvent $t_{\text{me}}/^{\circ}\text{C} = -23$ [38, 39]. Similarly, 2-chloroethyl trimethylammonium chloride ($\text{ClC}_2\text{H}_4\text{N}(\text{CH}_3)_3^+\text{Cl}^-$, Cas No. 999-81-5) produces with zinc chloride at a 1:2 molar ratio a deep eutectic solvent melting at 23 °C [40], but this may be a chlorozincate room temperature ionic liquid rather than a deep eutectic solvent in which each ingredient retains its identity. Zinc nitrate hexahydrate with urea at a mole ratio of 2:1 forms a deep eutectic solvent with a melting point of 9 °C that remains stable (does not lose water) up to 50 °C [41]. Choline chloride forms a deep eutectic solvent with calcium chloride hexahydrate at several molar ratios, the lowest melting of which is at a 1:2 molar ratio, $t_{\text{m}}/^{\circ}\text{C} = 2.70$ [42]. Other metal halides also form with asymmetrical quaternary ammonium salts low-melting mixtures having melting points below 25 °C [43]. There is no certainty, however, that in all these cases proper deep eutectic solvents are formed, i.e., mixtures in which the components retain their identities, rather than ionic liquids that are single components, made up from a cation and an anion. Potassium carbonate forms low transition temperature mixtures with glycerol at molar ratios 1:4–1:6 that are liquid at 10 °C, but do not crystallize on cooling and have glass transition temperatures (that for the 1:4 ratio of -38 °C) [44]. Potassium and ammonium thiocyanates form with amides low-melting eutectics that can be used as solvents for the absorption of sulfur dioxide [45]. Several deep eutectic solvents have been prepared, based on lithium bis[trifluoromethylsulfonyl]imide as the hydrogen bond acceptor component and amides (urea [46], acetamide [47], *N*-methylacetamide [48]) as the

hydrogen bond donor components. To this category could be added the deep eutectic solvents formed by trimethylsulfonium bis[trifluoromethylsulfonyl]imide as the hydrogen bond acceptor and formamide or trifluoroacetamide as the hydrogen bond donor component, although trimethylsulfonium is not a metal cation [49]. Table 2.3 summarizes the compositions and melting points of the low-melting mixtures formed from metal salts (or their hydrates) and organic substances. In cases, where no melting or glass transition points have been reported but physical properties or applications have been reported down to a certain temperature $t/^\circ\text{C}$, this is denoted as $<t$ in the appropriate column.

Certain amino acids have served as the hydrogen bond acceptor component of deep eutectic solvents with several hydrogen bond donor component, such as urea, 1,2-ethanediol, and carboxylic acids. In many cases, glass formation was observed as the temperature was decreased, but no freezing to a crystalline solid took place [50, 51]. Exceptions to this general trend are the 1:1 mixture of *l*-proline (pyrrolidine-2-carboxylic acid, CAS No. 147-85-3) and oxalic acid ($\text{HCO}_2\text{CO}_2\text{H}$, CAS No. 144-62-7), $t_{\text{me}}/^\circ\text{C} = -14.5$ [52] and trimethylglycine ($(\text{CH}_3)_3\text{NCH}_2\text{CO}_2\text{H}$, CAS No. 107-43-7, betaine) and mandelic acid ($\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{CO}_2\text{H}$, CAS No. 90-64-2) $t_{\text{me}}/^\circ\text{C} = 13$ [53]. Trimethylglycine (betaine) at 1:2 ratios forms with glycolic acid ($\text{HOCH}_2\text{CO}_2\text{H}$, CAS No. 79-14-2) a deep eutectic solvent $t_{\text{me}}/^\circ\text{C} = -36$, with phenylacetic acid a deep eutectic solvent $t_{\text{me}}/^\circ\text{C} = -7$, and with 2-furoic acid (furan-2-carboxylic acid, CAS No. 88-14-2) a deep eutectic solvent with $t_{\text{me}}/^\circ\text{C} = 11$ [53]. When the hydrogen bond donor component is a carboxylic acid, the zwitterionic amino acid is taken to be protonated, so that an ionic deep eutectic solvent is produced.

On the other hand, amino acids have also been suggested as the hydrogen bond donor component of deep eutectic solvents, with tetrabutylammonium chloride as the hydrogen bond acceptor component. In such cases, rather large ratios of the salt to the hydrogen bond donating agent yield the low-melting compositions, but at near ambient temperatures or somewhat above them. The deep eutectic solvent formed with aspartic acid at 9:1 HBA:HBD has $t_{\text{m}}/^\circ\text{C} = 25.1$, that with glutamic acid at 10:1 ratio has $t_{\text{m}}/^\circ\text{C} = 28.9$, that with arginine at 6:1 ratio has $t_{\text{m}}/^\circ\text{C} = 25.1$ [54], that with serine at 8:1 ratio has $t_{\text{m}}/^\circ\text{C} = 24.9$, that with threonine at 9:1 ratio has $t_{\text{m}}/^\circ\text{C} = 20.2$, and that with methionine at 11:1 ratio has $t_{\text{m}}/^\circ\text{C} = 19.1$ [55].

Water could well be a hydrogen bond donor ingredient to form deep eutectic solvents with suitable hydrogen bond acceptor components, such as certain salts and ionic liquids. Alkyl-(2-hydroxyethyl)-dimethylammonium bromide ionic liquids, where alkyl = $\text{C}_n\text{H}_{2n+1}$ with $n = 2, 3, 4$ and 6 , form with water at a 1:2 mol ratio deep eutectic solvents [56]. For $n = 2$ (ethyl) [57] $t_{\text{me}} = -25.1$ $^\circ\text{C}$ and for the other n values t_{me} is somewhat higher, up to -13 $^\circ\text{C}$. It is to be noted that in the case $n = 1$, i.e., of alkyl being methyl, choline bromide, water has not been mentioned as forming a deep eutectic solvent with this salt. Water forms a deep eutectic solvent also with ethyl-(2-hydroxyethyl)-dimethylammonium tetrafluoroborate at a 1:3 mol ratio, $t_{\text{me}} = -27.2$ $^\circ\text{C}$ [57]. Thus, although stronger hydrogen bond acceptor anions such as chloride, acetate, and fluoride are required for the conventional deep eutectic solvent formation with amides, carboxylic acids, and

Table 2.3 Deep eutectic solvents formed between metal salts and organic substances and the melting point of the eutectics, t_{me}

Metal salt	Organic substance	Molar ratio	$t_{me}/^{\circ}\text{C}$	Ref.
LiClO ₄	Acetamide	1:4	n.a.	[89]
	Propionamide	1:4	n.a.	[89]
LiNO ₃	N-methylacetamide	1:2	-75	[90]
LiPF ₆	N-methylacetamide	1:5	-52	[90]
LiTFSI ^a	urea	1:3.6	-37.6	[86]
	acetamide	1:4	-67	[87]
	N-methylacetamide	1:2	-72	[90]
K ₂ CO ₃	ethylene glycol	1:10	-122 ^b	[150]
	glycerol	1:4 – 1:6	< 10	[83]
		1:10	-91 ^b	[150]
KSCN	acetamide	1:3	5	[85]
	caprolactam	1:3	0	[85]
NH ₄ SCN	acetamide	1:3	5	[85]
	caprolactam	1:3	-10	[85]
	urea	2:3	24	[85]
MgCl ₂ ·6H ₂ O	choline chloride	1:1	16	[91]
CaCl ₂ ·6H ₂ O	choline chloride	1:2	2.7	[66]
ZnCl ₂	urea	2:7	9	[78]
	acetamide	1:4	-16	[78]
	1,2-ethanediol	1:4	-30	[78]
	1,6-hexanediol	1:4	-23	[78]
	chloroethyltrimethylammonium ⁺ Cl ⁻	1:2	23	[44]
	choline chloride	2:1	23-25	[82]
	bromopropyltrimethylammonium ⁺ Br ⁻	2:1	22-24	[82]
Zn(NO ₃) ₂ ·6H ₂ O	choline chloride	1:1	<25	[31]
	diethylethanolammonium ⁺ Cl ⁻	1:1	<25	[92]
SnCl ₂	benzyl dimethylethanolammonium ⁺ Cl ⁻	2:1	17	[82]
	2-acetyloxytrimethylammonium chloride	2:1	20	[74]
AlCl ₃	urea	1:1	<25	[78]
	acetamide	1:1	-63 ^c	[78]
FeCl ₃	benzyl dimethylethanolammonium ⁺ Cl ⁻	2:1	21	[82]
	tetrabutylphosphonium bromide	1:2	15.7	[70]
CrCl ₃ ·6H ₂ O	urea	2:1	9	[81]
FeCl ₃	benzyl dimethylethanolammonium ⁺ Cl ⁻	2:1	21	[82]
	tetrabutylphosphonium bromide	1:2	15.7	[70]

^a lithium bis[trifluoromethylsulfonyl]imide. ^b Glass transition temperature

polyols, for water as the hydrogen bond donor even mild hydrogen bond accepting anions, such as bromide and tetrafluoroborate, suffice for deep eutectic solvent formation.

Water features also as the hydrogen bond donor component with more conventional ionic liquids. The deep eutectic solvent formed with 1-butyl-3-methylimidazolium *p*-toluenesulfonate has $t_{me}/^{\circ}\text{C} = -36$ at the water mole fraction $x_W = 0.70$ (read from a figure) [58]. *N*-hexyl-3-methylpyridinium *p*-toluenesulfonate forms with water a deep eutectic solvent that has $t_{me}/^{\circ}\text{C} = -10.0$ at $x_W = 0.879$ [59]. The deep eutectic solvent formed between water and 1-butyl-3-methylpyridinium dicyanamide has $t_{me}/^{\circ}\text{C} = -28$ at $x_W = 0.76$ (read from a figure) [60, 61]. The deep eutectic solvent formed between water with 1-butyl-1-methylpiperidinium thiocyanate has $t_{me}/^{\circ}\text{C} = -56$ at $x_W = 0.66$ [62] and that with 1-butyl-1-methylpyrrolidinium thiocyanate has $t_{me}/^{\circ}\text{C} = -92$ at $x_W = 0.69$ [63]. These values were read from a figure with non-random two-liquid (NRTL)-modeled lines leading to the eutectic point, whereas the experimental points themselves do not necessarily lead to them. Complete solid–liquid phase diagrams (reaching from the pure components to the eutectic) were reported in figures also for the deep eutectic solvents formed between water with 1-butyl-1-methylpyrrolidinium dicyanamide, $t_{me}/^{\circ}\text{C} = -31$ at $x_W = 0.77$, with its trifluoromethylsulfonate, $t_{me}/^{\circ}\text{C} = -30$ at $x_W = 0.60$, and with its tricyanomethanide, $t_{me}/^{\circ}\text{C} = 13$ at $x_W = 0.42$ [64]. Incomplete diagrams were shown there also for mixtures of water with other ionic liquids, but no eutectic points could be deduced from them. Complete phase diagrams, but where NRTL-modeled lines lead to the eutectic point rather than the experimental points themselves, were reported for water with 1-alkyl-1-methylmorpholinium bromide, where alkyl = $\text{C}_n\text{H}_{2n+1}$ with $n = 3, 4,$ and 5 [65]. The eutectic points (read from figures) have $t_{me}/^{\circ}\text{C} = -33$ at $x_W = 0.82$ for $n = 3$, $t_{me}/^{\circ}\text{C} = -42$ at $x_W = 0.82$ for $n = 4$, and $t_{me}/^{\circ}\text{C} = -73$ at $x_W = 0.69$ for $n = 5$. For the corresponding water and 1-pentyl-1-methylpiperidinium bromide system, $t_{me}/^{\circ}\text{C} = -28$ at $x_W = 0.75$ was derived from the NRTL-modeled lines [65].

Table 2.4 summarizes the deep eutectic solvents formed between water and organic salts and ionic liquids.

With monohydric alkanols, on the other hand, no real deep eutectic solvents are formed with room temperature ionic liquids, the observed eutectic temperatures being only 1–6 °C lower than the freezing points of the alkanols themselves. This was reported for 1-butyl-3-methylimidazolium *p*-toluenesulfonate with 1-octanol and with 1-decanol and presumably holds also with ethanol, 1-butanol, and 1-hexanol, although no complete phase diagrams were shown for these three alkanols [58]. The same is the case for 1-hexyl-3-methylpyridinium *p*-toluenesulfonate for these five alkanols [59] and for 1-butyl-1-methylpiperidinium thiocyanate with 1-alkanols $\text{C}_n\text{H}_{2n+1}\text{OH}$, $n = 8, 9, 10,$ and 12 [62].

It is interesting to note that fairly deep eutectic liquids are formed between benzene, devoid of hydrogen bond donating properties, and two ionic liquids: $t_{me}/^{\circ}\text{C} = -27$ at benzene mole fractions $x_B = 0.65$ for 1-hexyl-3-methylpyrrolidinium thiocyanate and $t_{me}/^{\circ}\text{C} = -13$ at $x_B = 0.55$ for 1-butyl-1-methylpiperidinium thiocyanate (where

Table 2.4 Deep eutectic solvents formed between water as the hydrogen bond donor component and organic salts and ionic liquids as hydrogen bond acceptor components and the melting point of the eutectics, t_{me}

HBA Cation	HBA Anion	x_w	$t_{me}/^{\circ}\text{C}$	Ref.
ethyl-(2-hydroxyethyl)-dimethylammonium	bromide	0.642	-25.1	[98]
	BF_4^-	0.737	-27.2	[98]
propyl-(2-hydroxyethyl)-dimethylammonium	bromide	0.65	-31	[97]
butyl-(2-hydroxyethyl)-dimethylammonium	bromide	~ 0.65	-22	[97]
hexyl-(2-hydroxyethyl)-dimethylammonium	bromide	~ 0.65	-13	[97]
1-butyl-3-methylimidazolium	tosylate	0.70	-36	[99]
1-butyl-3-methylpyridinium	$\text{N}(\text{CN})_2^-$	0.76	-28	[101]
1-hexyl-3-methylpyridinium	tosylate	0.879	-10.0	[100]
1-butyl-1-methylpiperidinium	thiocyanate	0.66	-56	[103]
1-butyl-1-methylpyrrolidinium	thiocyanate	0.69	-92	[104]
	$\text{N}(\text{CN})_2^-$	0.71	-37	[105]
	$\text{N}(\text{CN})_2^-$	0.75	-40	[107]
	CF_3SO_3^-	0.60	-30	[105]
	CF_3SO_3^-	0.60	-28.5	[107]
	$\text{C}(\text{CN})_3^-$	0.42	13	[105]
	$\text{C}(\text{CN})_3^-$	0.52	-31	[107]
	$\text{B}(\text{CN})_4^-$	0.43	6	[107]
1-propyl-1-methylmorpholinium	bromide	0.82	-0.33	[106]
1-butyl-1-methylmorpholinium	bromide	0.82	-42	[106]
1-pentyl-1-methylmorpholinium	bromide	0.69	-73	[106]
1-pentyl-1-methylpiperidinium	bromide	0.75	-28	[106]

$t_{me}/^{\circ}\text{C} = 5.5$ for benzene itself and 22.2 and 31.1 for the two ionic liquids, respectively) [66]. Benzene (subscript $_B$) also forms with *N*-butylquinolinium bis(trifluoromethylsulphonyl)imide ($t_m/^{\circ}\text{C} = 56.4$), a deep eutectic having $t_{me}/^{\circ}\text{C} = -8.3$ at $x_B = 0.746$ [67] and with *N*-butylpyridinium bis[(trifluoromethyl)sulphonyl]imide ($t_m/^{\circ}\text{C} = 18.2$), a deep eutectic having $t_{me}/^{\circ}\text{C} = -22.9$ at $x_B = 0.642$ [68].

A further group of binary mixtures that nominally can be termed ‘deep eutectic solvents’, but are not generally recognized as such, are mixtures of ice with certain salt hydrates or mixtures of two salt hydrates. Some salt hydrates that melt congruently, i.e., crystallize unchanged on cooling their melts, yield deep eutectic solvents with water. They feature such properties that commonly used or proposed deep eutectic solvents should have: they are definitely nonflammable, they are nontoxic (heavy metal salts, such as $\text{Cd}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$, are avoided), they are inexpensive (expensive metal salts, such as $\text{CsF} \cdot \text{H}_2\text{O}$, are avoided), and are readily reconstituted after use. Several lithium and magnesium salt hydrates, among a variety of other salts, are prone to yield deep eutectic solvents with ice. As for many other deep eutectic solvents, one of the components (water) is liquid at ambient conditions and the eutectic temperatures may reach very low values. A large body

of information is available in the compilations by Linke and Seidel [69, 70] and by Kirgintsev et al. [71], generally in the form of solid/liquid equilibrium at certain temperatures at compositions given as $w = \text{g anhydrous salt per } 100 \text{ g saturated aqueous solution}$. The mole fraction of the n -hydrate (that with n molecules of water per formula unit of the anhydrous salt) is calculated, using the molar mass of the anhydrous salt, $M/\text{g mol}^{-1}$, and that of water, $18.015 \text{ g mol}^{-1}$, as

$$x(\text{salt} \cdot n\text{H}_2\text{O}) = (1 + n)(w/M) / [(w/M) + (100 - w)/18.015] \quad (2.1)$$

The molar ratios of the components are generally not ratios of integers, unlike most of the deep eutectic solvents with choline chloride, its analogs, and other -onium salts as the hydrogen bond acceptor components. The eutectic distances, $\Delta t_{\text{me}}/^\circ\text{C}$, are not as large as those for, say, choline chloride with urea, 178. Nevertheless, for some salt hydrates, they reach as much as $\Delta t_{\text{m}}/^\circ\text{C} = 137$ for ice/ $\text{Mg}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ and 113 for ice/ $\text{KOH} \cdot \text{H}_2\text{O}$ [72]. If related to the unhydrated salts the eutectic distances, Δt_{m} , are much more appreciable.

Table 2.5 summarizes the formation of deep eutectic solvents between water and salt hydrates.

Mixtures of magnesium chloride hexahydrate ($\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$) with nickel chloride hexahydrate ($\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$) [73] can also be called deep eutectic solvents, see Chap. 1, Fig. 1.3. The melting points of the components are $t_{\text{m}}/^\circ\text{C} = 112$ for $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ and 30 for $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, and the eutectic at the 1:1 composition has a melting point $t_{\text{m}}/^\circ\text{C} = 4$ and the distance $\Delta t_{\text{m}}/^\circ\text{C} = 67$ is quite appreciable. Ammonium nitrate forms with manganese and zinc nitrate hexahydrates deep eutectic solvents with large melting point distances of the eutectics [74]. With Mn (NO_3)₂·6H₂O ($t_{\text{m}}/^\circ\text{C} = 25.8$) at the ammonium nitrate mole fraction of 0.450, the eutectic has $t_{\text{me}}/^\circ\text{C} = 4.6$ and $\Delta t_{\text{me}}/^\circ\text{C} = 100.0$ (given $t_{\text{m}}/^\circ\text{C} = 169$ for NH_4NO_3 [75]) and for Zn(NO_3)₂·6H₂O ($t_{\text{m}}/^\circ\text{C} = 36.4$) at the ammonium nitrate mole fraction of 0.447 the eutectic has $t_{\text{me}}/^\circ\text{C} = 12.7$ and $\Delta t_{\text{me}}/^\circ\text{C} = 109.7$.

Mixtures of the incongruently melting calcium chloride hexahydrate with a few other salt hydrates also form deep eutectic solvents [76]. With 0.35 mol fraction calcium bromide hexahydrate $t_{\text{me}}/^\circ\text{C} = 14$, with 0.25 mol fraction calcium nitrate tetrahydrate $t_{\text{m}}/^\circ\text{C} = 13$ and with 0.17 mol fraction magnesium nitrate hexahydrate $t_{\text{m}}/^\circ\text{C} = 9$ (in the latter two cases these are not necessarily the eutectic points) [73].

The deep eutectic solvents described in this and the previous sections are all more or less hydrophilic, they absorb water from the atmosphere and are soluble in water. For certain uses, hydrophobic (deep eutectic) solvents would be useful and such have been proposed in recent years. Certain tetraalkylammonium halides form hydrophobic deep eutectic solvents with decanoic acid ($\text{C}_9\text{H}_{17}\text{CO}_2\text{H}$, CAS No. 334-48-5) at 1:2 molar ratios: tetrabutylammonium chloride $t_{\text{me}}/^\circ\text{C} = -12.0$, tetraheptylammonium chloride ($(\text{C}_7\text{H}_{13})_4\text{NCl}$, CAS No. 10247-90-2) $t_{\text{me}}/^\circ\text{C} = -16.7$, tetraoctylammonium chloride ($(\text{C}_8\text{H}_{15})_4\text{NCl}$, CAS No. 13125-07-3) $t_{\text{me}}/^\circ\text{C} = 2.0$, and bromide ($(\text{C}_8\text{H}_{15})_4\text{NBr}$, CAS No. 14866-33-2) $t_{\text{me}}/^\circ\text{C} = 9.0$, and methyltricytylammonium

Table 2.5 Deep eutectic solvents formed between congruently melting salt hydrates with ice as the hydrogen bond donor component, the melting points of the salt hydrates, t_{msh} , of the eutectics, t_{me} , the eutectic composition (mole fraction of the salt hydrate, x_{eutectic} , and the eutectic distance, Δt_{me} [114]

Salt hydrate	$t_{\text{msh}}/^\circ\text{C}$ of salt	$t_{\text{me}}/^\circ\text{C}$ of eutectic	x_{eutectic}	$\Delta t_{\text{me}}/^\circ\text{C}$
Al(NO ₃) ₃ ·9H ₂ O	71.0	-27.2	0.36	53
CaBr ₂ ·6H ₂ O	38.2	-22.2	0.59	45
Ca(NO ₃) ₂ ·4H ₂ O	47.7	-28.7	0.38	45
Ca(ClO ₄) ₂ ·6H ₂ O	45.5	-74.6	0.39	90
Co(NO ₃) ₂ ·6H ₂ O	55.8	-26.2	0.42	49
FeCl ₃ ·6H ₂ O	36.8	-55.0	0.36	68
KF·4H ₂ O	18.5	-40.2	0.39	47
KOH·H ₂ O	126.8	-65.2	0.38	113
K ₂ HPO ₄ ·4H ₂ O	13.0	-13.5	0.40	19.4
LiCH ₃ CO ₂ ·2H ₂ O	57.8	-16.1	0.17	26
LiNO ₃ ·3H ₂ O	29.5	-22.9	0.31	32.1
LiClO ₃ ·3H ₂ O	8.1	-40.2	0.32	43
LiClO ₄ ·3H ₂ O	95.1	-18.2	0.21	38
LiI·2H ₂ O	75.0	-69.0	0.45	100
Mg(CH ₃ CO ₂) ₂ ·4H ₂ O	57.2	-29.2	0.31	50
MgBr ₂ ·6H ₂ O	164.4	-42.7	0.38	105
MgCl ₂ ·6H ₂ O	116.2	-33.6	0.34	73
Mg(NO ₃) ₂ ·6H ₂ O	89.5	-4.1	0.40	40
Mg(ClO ₄) ₂ ·6H ₂ O	154.8	-68.6	0.44	137
MnCl ₂ ·4H ₂ O	57.8	-25.6	0.44	51
Mn(NO ₃) ₂ ·6H ₂ O	25.8	-36.2	0.45	48
NaCH ₃ CO ₂ ·3H ₂ O	57.8	-18.2	0.35	38
NaOH·H ₂ O	65.1	-28.2	0.19	41
NiCl ₂ ·6H ₂ O	30.2	-45.3	0.39	57
Ni(NO ₃) ₂ ·6H ₂ O	56.7	-34.1	0.41	57
Zn(NO ₃) ₂ ·6H ₂ O	36.4	-32.0	0.41	46

chloride (CH₃(C₈H₁₅)₃NCl, CAS No. 10247-90-2) $t_{\text{me}}/^\circ\text{C} = -0.1$, and bromide (CH₃(C₈H₁₅)₃NBr, CAS No. 35675-80-0) $t_{\text{me}}/^\circ\text{C} = 9.0$ [77]. These deep eutectic solvents being hydrophobic, i.e., immiscible with water, can be used for solvent extraction purposes.

Lidocaine (2,6-dimethylcyclohexyl-2-diethylaminoglycylamide, CAS No. 137-58-6) forms with decanoic acid lidocaine decanoate and with further 1, 2, or 3 molecules of decanoic acid this salt forms hydrophobic deep eutectic solvents with unspecified freezing temperatures [78]. These hydrophobic deep eutectic solvents can be used to form a biphasic system with water and to extract various

solutes from aqueous media. On the other hand, deep eutectic solvents prepared from tetrabutylammonium chloride and hexanoic, octanoic, decanoic, and dodecanoic acids, although hydrophobic, are not sufficiently stable in water to serve for extraction in biphasic systems [79].

2.4 Nonionic Deep Eutectic Solvents

The definition of the deep eutectic solvents presented at the beginning of this chapter, namely “Deep eutectic solvents (DESs) are binary mixtures of definite composition of two components, one of which being ionic, that yield a liquid phase at ambient conditions” precludes the inclusion of nonionic deep eutectic solvents in this exposition. However, many such moieties have been described in the literature and deserve consideration here, perhaps under the changed subtitle: low transition temperature mixtures (LTTMs). They are characterized by low ionicity, hence by low electrical conductivity, but such solvents appear to be compatible with enzymatic reactions. Most of them consist of naturally originating components and may be classified as NADES. They are of several types: polyalcohols (including sugars) with carboxylic acids, zwitterionic amino acids with non-protonating hydrogen bond donating components, and mixtures of amides. For only very few of the nonionic mixtures described in the literature as deep eutectic solvents have the actual freezing points of the eutectics been reported, although in some cases the glass transition temperatures have been, but in any case, these mixtures are liquid near ambient temperatures. In addition to binary mixtures, some ternary mixtures have also been dealt with in this context and are mentioned here.

The sugars glucose, fructose, and sucrose in 1:1 combination with malic, maleic, and citric acids feature in [1, 80, 81] and in [1] also other sugars and sugar alcohols: xylitol, adonitol (ribitol), and sorbitol are considered. The 1:1 mixtures of citric acid with glucose and adonitol are dealt with in [82]. The 1:1 mixture of fructose with malic acid is used in [83] for extraction purpose and with citric and tartaric acids in [84] as tools for bioavailability. The latter two acids in 1:1 combination with glucose are considered and the glass transition points, 9.8 and -18.3 °C are reported in [85] whereas the polarities of the mixtures are reported in [86]. Menthol (racemic 5-methyl-2-(propan-2-yl)cyclohexan-1-ol, CAS No. 89-78-1) produces eutectic solvents with carboxylic acids at various molar ratios: 1:1 with acetic acid, 1:2 with pyruvic and lactic acids, and 2:1 with lauric (dodecanoic) acid. Their glass transition points are -7.8 , -58.8 and -6.8 , -61.1 , and 7.1 and 13.8 °C, respectively, with two such points detected by thermal analysis for two of the mixtures. Other physical properties, the density and viscosity, and their temperature dependences are also reported in [87]. Menthol forms deep eutectic solvents with several other carboxylic acids (benzoic acid, phenylacetic acid, and ibuprofen CAS No. 15687-27-1) at 3:1 molar ratios [88].

Two zwitterionic amino acids: proline and betaine (trimethylglycine) have received considerable attention as components of deep eutectic solvent mixtures. When mixed with stoichiometric amounts of carboxylic acids, they form ionic liquids that are outside the scope of this section, but with excess acid or with nonacidic hydrogen bond donors they may produce nonionic deep eutectic solvents. Binary mixtures of proline and of betaine with sugars (glucose, mannose, maltose, sucrose) and with sugar alcohols (sorbitol, xylitol) produce nonionic natural deep eutectic solvents [1, 85, 89], as they do with glycerol, and betaine does so with ethylene glycol [47]. Mixtures of betaine and/or carnitine (3-hydroxy-4-trimethyl-aminobutyric acid, CAS No. 541-15-1) with ethylene glycol [89] and with phenol [90] form deep eutectic mixtures that do not freeze down to -60 and -80 °C, respectively. The 2:5 proline mixture with glycerol forms a deep eutectic solvent [91] as does betaine with 1:1, 1:2, and 1:3 glycerol [92]. Non-hydroxylic hydrogen bond donors, namely amides, have also been used with the zwitterionic amino acids to produce nonionic deep eutectic solvents. Thus, 1:1 mixtures of betaine with 1-methylurea and of proline with acetamide yield such solvents [91]. The glass transition temperatures of mixtures of betaine with urea at molar ratios of 1:1–2:5 are below -40 °C [93]. The 1:2 mixture of betaine with urea has been used as a deep eutectic solvent in combination with an aqueous salt solution for the biphasic extraction of proteins [94]. Twelve sulfobetaines (e.g., $(\text{CH}_3)_2\text{C}_4\text{H}_9\text{NC}_3\text{H}_6\text{SO}_3$) form with camphorsulfonic acid (CAS No. 35963-20-3) deep eutectic solvents with low ionicity [95].

Nonionic deep eutectic solvents are also produced by mixtures of two amides. Caprolactam forms such solvents at a 3:1 ratio with urea and at a 1:1 ratio with acetamide, whereas 1:2 urea/acetamide mixtures also form such eutectics, with melting points of 30, 18, and 48 °C and very small electric conductivities [96]. These three mixtures are also mentioned in [97]. The latter mixture has a glass transition point of -67 °C, but its dynamic properties were studied only at >55 °C [98].

Ternary nonionic deep eutectic solvents have also received attention, mainly based on zwitterionic amino acids. The mixture proline/glycerol/sucrose at a 4:9:1 molar ratio is a sustainable efficient extraction medium [99]. The mixtures comprised of betaine/glycerol/glucose at a 4:20:1 molar ratio [100] and betaine/ethylene glycol/water at a molar ratio of 1:2:1 [101] have also been found useful for the extraction of natural products. Solvents consisting of betaine with urea, methylurea, glucose, sorbitol, glycerol, or ethylene glycol and with water as the third component form with an aqueous salt solution a biphasic system useful for the extraction of proteins [102]. Mixtures of 2:3 acetamide and urea melt too high for being useful, but 1 mass of this mixture with 2 masses of PEG 300 (polyethylene glycol with a mean molar mass of 300 g mol^{-1}) is a eutectic melting at 32 °C, i.e., forming a nonionic eutectic solvent [103].

The nonionic deep eutectic solvents dealt with in this book are summarized in Table 2.6. In cases, where no melting or glass transition points have been reported but physical properties or applications have been reported down to a certain temperature t /°C, this is denoted as $<t$ in the appropriate column.

Table 2.6 Some non-ionic low transition temperature solvents for which glass transition temperatures, t_g , have been reported

HBA	HBD	Ratio HBA:HBD	$t_g/^\circ\text{C}$	Ref.	
0.6 acetamide + 0.4 urea	PEG400	13:1	32 ^a	[143]	
proline	oxalic acid	1:1	-14.5	[144]	
	glycolic acid	1:1	-30.7	[145]	
	lactic acid	2:1	-36.7	[144]	
	malic acid	1:3	-44.4	[144]	
	malic acid		-8.2	[145]	
betaine	urea	1:2	-42.5	[134]	
	ethylene glycol	1:4	< -60	[132]	
	phenol	1:3	< -80	[131]	
	2-furoic acid	1:2	11 ^a	[96]	
	phenylacetic acid	1:2	-7 ^a	[96]	
	oxalic acid	1:1	-17.2	[144]	
	glycolic acid	1:2	-36 ^a	[96]	
	lactic acid	2:1	-46.9	[144]	
	mandelic acid	1:1	13 ^a	[96]	
	malic acid	1:3	-20.0	[144]	
	levulinic acid	1:2	< 30	[146]	
dimethyldodecyl-N-oxide	phenylacetic acid	1:1	-34	[68]	
dimethyloctadecyl-N-oxide	phenylacetic acid	1:1	20	[68]	
N-methylmorpholine-N-oxide	phenylacetic acid	1:1	-21	[68]	
N-dodecylmorpholine-N-oxide	phenylacetic acid	1:1	-27	[68]	
carnitine	ethylene glycol	1:4	< -60	[132]	
	phenol	1:3	< -80	[131]	
menthol	acetic acid	1:1	-7.8	[131]	
	$\text{C}_n\text{H}_{2n+1}\text{COOH}$ ($n=3,5,7,9$)	1:1	< 25	[52]	
	octanoic acid	?	<25	[54]	
	dodecanoic acid	2:1	7.1	[128]	
	lactic acid	1:2	-61.1	[128]	
	levulinic acid	1:1	< 25	[52]	
glucose	pyruvic acid	1:1	-58.8	[128]	
	citric acid	1:1	9.8	[147]	
	tartaric acid	1:1	-18.3	[147]	
	sucrose	citric acid	1:1	-14.0	[147]
$\text{BuMe}_2\text{N}(\text{C}_2\text{H}_5)\text{SO}_3$	camphorsulfonic acid	1:2	13 ^a	[136]	
$\text{Bu}_3\text{N}(\text{C}_2\text{H}_5)\text{SO}_3$	camphorsulfonic acid	1:2	9 ^a	[136]	
$\text{DoMe}_2\text{N}(\text{C}_2\text{H}_5)\text{SO}_3$	camphorsulfonic acid	2:3	-1 ^a	[136]	
Octanoic acid	Dodecanoic acid	3:1	9.0 ^a	[148]	
Nonanoic acid	Dodecanoic acid	3:1	9.0 ^a	[148]	
Decanoic acid	Dodecanoic acid	2:1	18.0 ^a	[148]	

^a Melting temperature, $t_m/^\circ\text{C}$

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