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New generation extraction solvents: from ionic liquids and aqueous biphasic systems to deep eutectic solvents

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The review is devoted to extraction solvents of new generation, so called combined solvents, which include ionic liquids, aqueous biphasic systems and eutectic solvents. Most of modern combined solvents are based on organic ionic components. These solvents are associated with high expectations as they are able to provide the environmental safety and green character of extraction, which are priority tasks for the development of chemistry and chemical engineering. For all classes, an overview and a brief history of research are presented; details of structure and properties are discussed; various extraction systems are compared; and typical examples of extraction of metal ions and organic compounds are given. The lack of uniform terminology and difficulties in interpreting the behaviour of some systems, especially eutectic solvents, are outlined. The advantages and drawbacks of new generation extraction solvents and relevant research tasks are summarized.
The bibliography includes 408 references.

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1. Introduction

Methods for separation and isolation of substances is an essential part of modern chemistry. These methods are critically important for both analysis and synthesis and also for studying the properties of compounds, materials and natural products. Their importance is remarkably illustrated by the fact, mentioned by Arne Tiselius in his Nobel Lecture [1] (The Nobel Prize in Chemistry of 1948 for his research on electrophoresis and adsorption analysis), that the Dutch word Scheikunde (art of separation) is a synonym of the word Chemie.[2]

Extraction occupies a prominent place among the large inventory of separation methods.[3]

1.1. Terminology

In Russian literature, the word *ekstraksiya* corresponding to *extraction* is typically used in a narrow sense to mean liquid – liquid extraction (and we follow this practice in the Russian version of the review).

However, in English chemical literature, the meaning of the term *extraction* is much broader: it refers to the recovery of substances into liquids (more precisely, into fluids; apart from usual liquids, this notion includes supercritical fluids important for practical purposes) from both liquids and solids, in particular multicomponent solids such as plant raw materials or complex minerals.

In Russian, extraction from a solid matrix is commonly labelled by another term (*ekstragirovanie* or *vyshchelachivanie*, which correspond to English *extracting* or *leaching* and are typically applicable to organic and inorganic matrices, respectively). Again, we follow this practice in the Russian version of this review. In this English version we deliberately use *extraction* in a broader native meaning, providing a clarification 'extraction from solid matrix' or 'liquid – liquid extraction' if necessary. Extraction from solid matrices is quite abundant and has been known for ages; examples can be found in many fields ranging from metallurgy to pharmaceutics and cookery. Indeed, every morning cup of coffee is a result of extraction from a solid, and if coffee is decaffeinated, two extraction processes are involved (by the way, it is likely that caffeine has been removed using environmentally unsafe dichloromethane [4]). For chemical science and chemical industry, liquid – liquid extraction is equally or, perhaps, more important. This review deals mainly with solvents for liquid – liquid extraction (most often, extraction from aqueous solutions). However, since many solvents are employed in extraction from solid matrices as

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well, examples of the latter usage are sometimes mentioned.

The new extraction solvents addressed in this review are associated with some terminological uncertainty. Sometimes this refers even to fundamental definitions, for example, what is meant by 'aqueous biphasic systems' or which eutectics are actually deep. Some of the English terms have no established Russian analogues, and the appearing Russian terms are not always a good choice. We tried to fix this situation or, at least, state our point of view (see discussion in Sections 1.3, 2.1, 3.2, and 4.3).

1.2. Extraction solvents: challenges and prospects

The main benefits of extraction are simplicity and versatility. Usually, readily available solvents are used to carry out extraction in laboratory; this does not require special equipment. However, a flow diagram optimized for a particular process can provide the basis for an industrial process that requires tailored equipment (the engineering aspects of extraction have been thoroughly elaborated long ago) and even specially produced solvents.

It is not surprising that extraction is widely used everywhere from analytical procedures, which require millilitres or even microlitres of liquid phases, to hydrometallurgy and radiochemistry, which operate on the scale of many tons and cubic metres.

Extraction is impossible without solvents, but exactly solvents are its major problem.

In the last quarter of the 20th century, there appeared strong people's demand for safe and environmentally friendly (green) chemistry. Currently, advancement towards green chemistry is a dominant trend, which seems to have affected all branches of chemical industry and chemical science as a whole.

Unfortunately, organic solvents, including extraction solvents, are a textbook example of non-compliance with the ideology of safety and green chemistry. Owing to the volatility of solvents, they can be readily removed after extraction; however, this brings about the hazard of ignition, air pollution and adverse effect on living organisms; furthermore, solvents give rise to not always pleasant smell. The most important molecular organic solvents are either combustible or toxic, or carcinogenic, or they interfere with fertility (or possess all these features). Often, solvents are poorly biodegradable. As a result, organic solvents are gradually falling under restrictive measures and are even being withdrawn from use.[5] Thus, avoiding the use of molecular organic solvents is a challenge critical for the development of extraction and for preserving the position of extraction among the most important separation methods.

This challenge could be partly addressed by sharp decrease of the consumption of solvents, which is possible by passing from extraction to microextraction. Indeed, microextraction is used more and more often to replace conventional extraction in analytical chemistry;[6,7] however, this is not an option for those cases where large volumes of phases are unavoidable (chemical engineering, hydrometallurgy, radiochemistry and so on).

One more promising approach is to use supercritical fluids,[8] in particular to extract various organic compounds and metal ions.[9–12] However, the narrow range of available fluids and poor solubility of many extraction reagents in these fluids restrict the use of this method; another impediment is the need for special process equipment.

The most promising outlook is associated with new solvents. The problem could be radically solved by replacing the customary extraction solvents by new solvents of a different nature that would be devoid, at least partially, of the drawbacks of existing solvents. Such solvents appeared and, in the last decades, they have been actively investigated. These new generation solvents include ionic liquids (ILs), low-melting combined solvents called deep eutectic solvents (DES) and aqueous biphasic systems (ABS).

Ionic liquids were first discovered by P.I.Walden in 1914[13] and long remained relatively unnoticed exotic species. However, at the turn of the 21st century, hydrolytically stable ILs appeared, some of which were found to be hydrophobic. In this connection, there was a surge of studies of extraction into ILs. This was promoted by the fact that even an early publication[14] reported record-high distribution ratios of strontium extracted with crown ether from an aqueous solution into ILs (1,3-dialkylimidazolium with fluorine-containing anions). Numerous new ILs suitable for extraction were synthesized and studied; obvious advances were made in the synthesis and investigation of ionic liquids.

However, the prices and the range of available solvents have become critical issues for the widespread use of ILs. Their scope was significantly extended when it was found than not only hydrophobic, but also hydrophilic ILs are applicable for extraction (aqueous biphasic systems with a salting-out agent).[15] Currently, studies of ABS based on ILs (or generally based on organic salts) are in progress.

One more trend that appeared during studying ILs and formed as a separate rapidly growing area is the use of eutectic solvents.[16] It was found that liquids can be obtained using solid salts mixed with appropriate partner compounds. Remarkably, these solvents are prepared using rather simple chemical means. For example, the classical Abbot liquid, reline, is a mixture of an organic salt (choline chloride) with urea. Both initial compounds melt at a temperature markedly higher than 100 °C; it is important that both components of the mixture are very cheap and readily available. The annual output of choline chloride is hundreds of thousand tons and that of urea is tens of million tons. Currently, DES are actively used, in particular, for extraction, especially for extraction from solid matrices.

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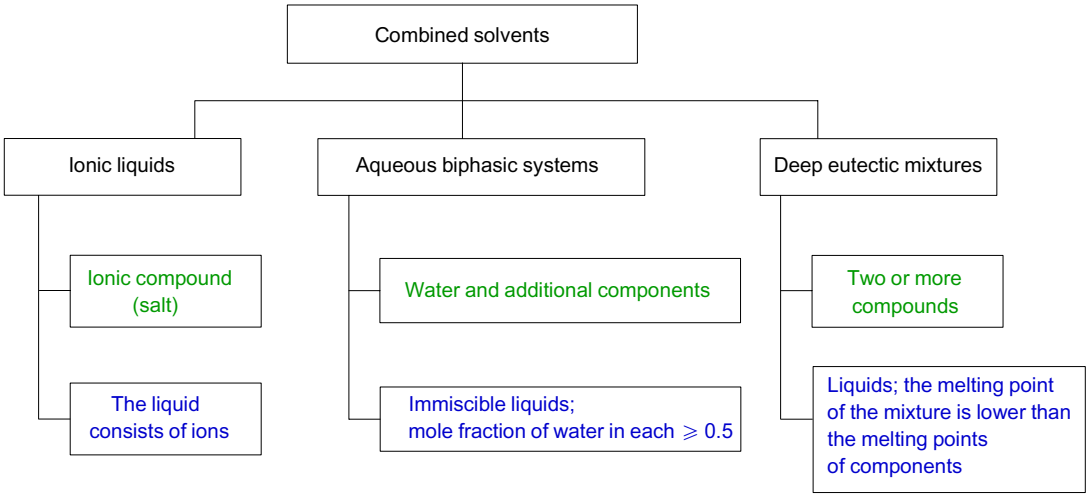


Figure 1. Important classes of combined solvents. The composition is written in green, and the distinctive features of the systems are marked in blue.

1.3. Combined solvents

A common feature of all of the mentioned solvent classes is that they represent combinations of components (Fig. 1).

By a combined solvent (CS), we mean a liquid the existence of which requires the presence of two or more types of species, molecules or ions (if there are only two types of species, this may be referred to as binary liquids, or binary solvents). We are interested in liquids immiscible with water and applicable for extraction.

Ionic liquids consist of ions that do not form liquids without a partner ion. Eutectic solvents are combinations of solids that form a liquid only when mixed with a partner component. Aqueous biphasic systems contain two combined liquids immiscible with each other, each consisting of water and at least one more component (the combined nature of phases is responsible for the phase separation).

It is noteworthy that combined solvents are not merely solvent mixtures. In a certain sense, they are related to supramolecular systems.

The combined nature of a liquid offers additional options for varying their properties in comparison with molecular solvents. Indeed, the range of molecular solvents is quite limited, while the number of component combinations is enormous. We will illustrate this in relation to ILs. By July 14, 2020, the physicochemical NIST database IL Thermo [17] alone included 2175 ionic liquids, which is much more than the number of molecular solvents (260) mentioned in Marcus' book [18] or than the number of common industrial solvents (600).[19]

In all of the mentioned CS, organic ions and salts are widely used as phase-forming components. This is related to green principles: the salts are non-volatile; therefore, the hazards of ignition and air contamination sharply decrease in comparison with those for molecular solvents. Aqueous biphasic systems mainly consist of water, which makes them even safer and environmentally more friendly. Combined solvents are the subjects of this review. There is a large body of literature addressing these solvents, which increases from day to day. This is illustrated in Fig. 2 created using the Web of Science statistics. There are already several monographs addressing this topic.[5, 20 – 22]

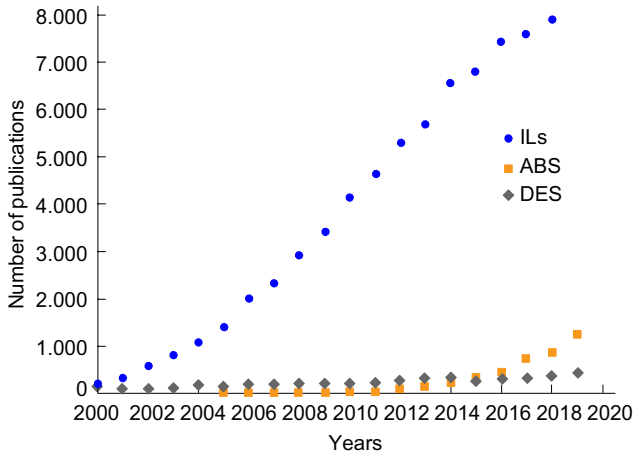


Figure 2. Variation of the number of publications on ILs, ABS and DES during the last 20 years [Web of Science data; requests: TOPIC: ('ionic liquid*'), TOPIC: ('deep eutectic*'), TOPIC: ('aqueous biphasic' or 'aqueous two-phase')].

We did not claim to give an exhaustive account of new extraction solvents; this is hardly possible, in view of the abundance of literature devoted to this topic. Our primary goal was to outline the important features, to give vivid examples and to make an attempt to, if not consider different systems from a unified point of view, then at least put them on a common platform hoping to see unexpected relationships and look more closely to stereotypical views.

2. Ionic liquids

2.1. Overview

Ionic liquids are salts with melting points of <100 °C. Certainly, the temperature threshold is conventional and intentionally generous: one can consider that this threshold separates 'ionic liquids' and 'salt melts'. There is a subclass of ILs that are liquid at room temperature (recently, room temperature has been most often taken to be 25 °C). Exactly

these ILs are of most interest for practical purposes and can be used as extraction solvents.

Most of ILs contain a large organic cation, usually with a positively charged heteroatom, coupled with one of the wide range of organic and inorganic anions.[23] Usually these are anions with delocalized or shielded charge. Often, ILs include fluorine-containing components, with readily available fluorinated anions being most common. Low polarizability of the fluorine atoms accounts for the decrease in the strength of the intermolecular contacts and for the 'liquefying' effect inherent in fluorinated compounds; for the same reason, the viscosity and water solubility are usually lower for fluorinated compounds than for non-fluorinated ones, which is important for extraction solvents.

Typical examples of IL cations are five- and six-membered heterocyclic cations such as *N*,*N*′-dialkylimidazolium, *N*,*N*′-dialkylpyrazolium, *N*-alkylpyridinium, *N*-alkylpyridazinium, *N*-alkylpyrimidinium, *N*-alkylpyrazinium and *N*-alkyl derivatives of ammonium, phosphonium, sulfonium, guanidinium, *etc*. The anions present in ILs can also represent inorganic anions such as BF_4^-, Cl^-, PF_6^-, $FeCl_4^-$, NO_3^-, $CF_3SO_3^-$, $(CF_3SO_2)_2N^-$, RCO_2^-, *etc*. The structural formulae of frequently encountered cations and anions are summarized in Table 1.

2.2. Principal features of ionic liquids

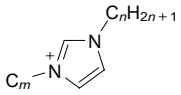
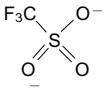
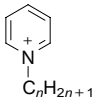
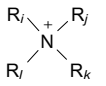
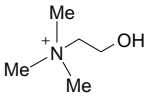
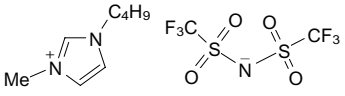
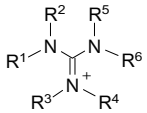
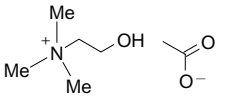
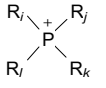
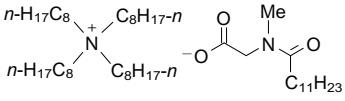
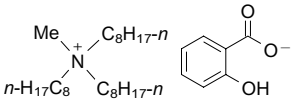
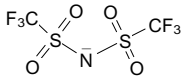
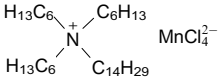
Despite the structural diversity and abundance of ILs, it is possible to distinguish a unique set of properties characteristic of this class of solvents: negligibly low vapour pressure, thermal and chemical stability and electrical conductivity.

Regarding the environmental friendliness, the most important feature is the lack of volatility (furthermore, over a wide range of temperatures), which sharply reduces the possibility of air pollution in comparison to that for conventional solvents. The long-range Coulomb forces between ions prevent their escape to the gas phase. Due to the lack of volatility, ILs are normally non-flammable, but it is quite possible that they decompose at elevated temperature to give fire-hazardous products.[24]

A key feature of ILs is electrical conductivity, which is determined by ionic conduction and depends on the chemical natures and sizes of the cation and the anion. However, it is necessary to take into account the relatively high viscosity and possible association of ions, which affect the ion mobility. These factors are probably responsible for the limited range of electrical conductivity (0.1 – 13.0 mS cm^{-1}) of the most widely used ILs.[25, 26]

It is often believed that ILs entirely consist of ions. This is true in the sense that the cation and the anion that form

Table 1. Structural formulae of typical cations and anions of ionic liquids and examples of the main types of ionic liquids.

Structural formula	Name and designation	Structural formula	Name and designation
Cations		***Anions***	
	Dialkylimidazolium, $C_nC_mIm^+$		Trifluoromethylsulfonate, TfO^-
			Dicyanamide, $N(CN)_2^-$
	Alkylpyridinium, C_nPy^+	Br^-	Bromide
		Cl^-	Chloride
		$FeCl_4^-$	Tetrachloroferrate(III)
	Tetraalkylammonium, N^+_{ijkl}	***Ionic liquids***	
	2-Hydroxyethyltrimethylammonium (choline)		1-Butyl-3-methylimidazolium bis(triflyl)imide (hydrophobic IL)
	Hexaalkylguanidinium, $(R^1R^2)(R^3R^4)(R^5R^6)Gu^+$		Choline acetate (hydrophilic IL)
	Tetraalkylphosphonium, P^+_{ijkl}		Tetraoctylammonium *N*-lauroylsarcosinate (hydrophilic-hydrophobic IL)
Anions			Trioctylmethylammonium salicylate (complexing IL)
	Bis(triflyl)imide, NTf_2^-	$Zn(OH_2)_6^{2+}ZnCl_4^{2-}$	Zinc chloride trihydrate (inorganic IL)
	Hexafluorophosphate, PF_6^-		Trihexyltetradecylphosphonium tetrachloromanganate (magnetic IL)
	Tetrafluoroborate, BF_4^-		

an IL are the smallest chemically discernable units, but this does not rule out the presence of noticeable amounts of ion pairs and more complex associates, including electrically neutral ones.

The IL structure may be characterized by local or dynamic inhomogeneity. A number of recent experimental (especially spectroscopic) and theoretical studies showed that ILs can possess local microheterogeneity and dynamic ordering at the nanoscale level. The high diversity and complexity of IL structures and interactions between IL components, which follow from the combined nature of these compounds, are considered to be the key factors responsible for these features.

Evidently, the presence of microheterogeneity or organization should strongly affect the solvent properties. However, it is not yet entirely clear how sure one can be about these extremely interesting effects, especially whether these effects are general. The information about the relevant theoretical and experimental studies can be gained from reviews.[27, 28]

In some cases, ILs are considered to have low toxicity, high biocompatibility and high biodegradability. Whether these statements are true depends on the properties of the cation and the anion. The widely used ILs based on dialkylimidazolium, especially those containing fluorinated anions, are potentially toxic[29] and are poorly biodegradable.[30] Ionic liquids containing 'biological' anions and cations — derivatives of biomolecules, *e.g.*, amino acids, choline, guanidinium, betaine, carbohydrates and so on — are much more beneficial in this respect.[31, 32] Choline chloride (vitamin B4), an inexpensive and biodegradable organic salt, is a very popular cationic component of biocompatible ILs.[33 – 38] [In this review, the word 'choline' is used to mean the (β-hydroxyethyl)trimethylammonium cation $(CH_3)_3N^+CH_2CH_2OH$[39] and not the hydroxide $(CH_3)_3N^+CH_2CH_2OH^{\bullet}OH^-$.]

Due to the high water solubility, which is usual for biocompatible ILs, they are most often used for extraction from non-aqueous media or solid samples, and also as parts of ABS.[40]

The most promising features of ILs are diversity and versatility. Ionic liquids are often called 'designer' solvents. The wide choice of cations and anions provides for the fabrication of a broad range of available ILs and offers opportunities for tuning their properties (volatility, conductivity, density, toxicity, viscosity, polarity, solvating capacity, hydrophilicity or hydrophobicity, *etc.*) and for the synthesis of tailor-made compounds for specific applications. This variability means that the benefits of ILs are far from being universal (common to the whole class). By deliberate choice of the cation or the anion, one can attain that any of the benefits considered to be inherent in the whole class would disappear (for example, not only just combustible ILs, but also those suitable as propellants have been described[41]).

Hydrolytically stable ILs immiscible with water can serve as extraction solvents. The versatility of this class accounts for the diversity of systems applicable for extraction.[42 – 45] Below we consider the most important of such systems.

2.3. Main classes of ionic liquids

Classical first-generation hydrophobic ionic liquids are solvents based on dialkylimidazolium cations and fluorinated anions. These compounds synthesized at the end of the 20th century were the first ILs to be tested for extraction.[14, 46] The presence of fluorinated anions ensured not only low melting points of imidazolium salts, but also their stability and immiscibility with water. One more benefit of classical ILs is the relatively low viscosity in comparison with other ILs.

The most typical representatives of first-generation hydrophobic ILs are 1-butyl-3-methylimidazolium hexafluorophosphate and bis(triflyl)imide ($C_4C_1ImPF_6$ and $C_4C_1ImTf_2N$, respectively). Ionic liquids with fluorinated anions are most often used in extraction as relatively inert diluents. They are described in more detail below, together with other classes of hydrophobic ILs.

Soon after ILs suitable as inert diluents, there also appeared specialized ILs possessing additional properties. Complexing and magnetic ILs are of most interest.

Complexing ionic liquids (CILs) historically appeared as task-specific ILs (TSILs). They contain functional groups that provide for the complex formation with metal ions and combine the properties of usual ILs with the properties of traditional extractants. The complexing ionic liquids can replace combinations of an extraction solvent with a complexing agent.

The selectivity of CILs is determined by the nature of functional groups and, hence, it can be rather readily controlled. Since functional groups are present in exceptionally high concentrations, the content of the proper IL cations and anions is usually several moles per litre. Among the advantages of these systems, note that they may possess high extraction capacity, which is convenient for the microextraction preconcentration (where the target component should be completely recovered into the smallest possible volume of the extract).

The first complexing ILs based on the dialkylimidazolium cation containing thioether, thiourea and urea functional groups covalently bound to the alkylimidazolium cation were specially synthesized for the extraction of Hg^{2+} and Cd^{2+} (Ref. 47). Many CILs contain functionalized cations and fluorinated anions. Currently, examples of selective metal extraction have been reported for CILs based on pyridinium,[48, 49] piperidinium,[49] pyrrolidinium,[49] quaternary ammonium[50, 51] and imidazolium cations;[52] the last mentioned CILs are most numerous.

The role of functional group can also be performed by coordinatively active IL anion such as carboxylate, salicylate, phthalate, oleate and other.[53 – 57] These ILs differ from fluorine-containing ones by more facile synthesis, ready accessibility, low toxicity and reasonable biodegradability.

Hydrophilic-hydrophobic ionic liquids (HHILs) adjoin the previous IL class and overlap with it. These ILs are immiscible with water, but are characterized by a high water content (up to 10 mass % and even more) and very low water solubility.

These properties are inherent in ammonium and phosphonium ILs with some anions, for example, trioctylmethylammonium salicylate (TOMAS), tetraoctylammonium *N*-lauroylsarcosinate (TOALS), and tetrahexylammonium dihexylsulfosuccinate (THADHSS) synthesized in our studies.[57, 58] The starting reactants for the synthesis of these ILs are relatively cheap and accessible; dihexyl sulfosuccinate and *N*-lauroyl sarcosinate are anions of the commercially manufactured surfactants. These non-toxic anions have good biodegradability and exhibit coordination activity towards some metal ions. Hydrophilic-hydrophobic ionic

liquids represent a more readily available alternative to the classical imidazolium CILs.

Magnetic ionic liquids (MILs) are obtained by insertion of a paramagnetic component into the IL cation or anion. Usually, MILs contain a transition metal or lanthanide ion. They possess the same physicochemical properties as conventional ILs, but also exhibit a strong response to an external magnetic field, which may be convenient, for example, in analytical chemistry to separate and transfer an extract.

The first MIL — 1-butyl-3-methylimidazolium tetrachloroferrate ($C_4C_1ImFeCl_4$) — was synthesized in 2001, but its paramagnetic properties were first demonstrated by Hayashi and Hamaguchi in 2004.[59] Unlike ferrofluids, which are colloidal solutions of ferromagnetic or ferrimagnetic nanoparticles dispersed in a carrier fluid, MILs are transparent and exist as pure magnetic solvents.[60] Higher magnetic susceptibility (effective magnetic moment of up to 10.6 μ_B) is inherent in MILs containing lanthanides, such as $C_6C_1Im_{5-x}Dy(SCN)_{8-x}(H_2O)_x$.[61]

High magnetic moments can be favourable for the use of these solvents in analytical extraction devices, microfluidic devices, magnetic field-based sensors and numerous other applications. For extraction, it is most important to ensure easy separation and collection of the extract with a magnet.[62 – 64]

Inorganic ionic liquids are unlikely to be suitable for extraction from aqueous solutions; however, they might be useful for the extraction from non-aqueous media and from solid materials. Publications addressing such ionic liquids are scarce.[65] As an example of an inorganic IL, consider zinc chloride trihydrate $ZnCl_2 \cdot 3\,H_2O$, which has a melting point of 6 °C and fully consists of $Zn(OH_2)_2^{2+}$ cations and $ZnCl_4^{2-}$ anions.[66]

2.4. Ionic liquids as extraction solvents

This publication does not claim to describe in detail characteristics of ILs and to exhaustively survey their extraction applications. This information can be found in monographs and specialized reviews.[42, 43, 45, 67 – 72] Here we well briefly consider the IL properties that are most important for extraction and the key trends of the extraction applications of ILs.

Properties of ionic liquids that are important for extraction. The density difference between the aqueous and non-aqueous phase is an important factor for extraction. Unlike most imidazolium ILs, which are usually heavier than water, the densities of ammonium and phosphonium liquids can be considerably variable,[73] with many of them being lighter than water. The density range of frequently used ILs is 0.9 – 1.6 g cm^{-3}.

A general problem faced when using ILs as solvents is their relatively high viscosity, which is significantly higher than the viscosity of water or organic solvents and ranges from several tens to thousands of millipascals per second. This may complicate the application of ILs in extraction due to hampered mass transfer. The ILs used in extraction have viscosity in the range of 40 – 300 mPa s (for comparison, the n-octanol viscosity is 7.3 mPa s).

The viscosity depends on the nature of ions that constitute the IL and the presence of foreign components; in the case of extraction, the major foreign component is water.[74] The viscosity of moderately viscous (50 – 100 MPa s) ILs decreases by 10 – 40% in the presence of water, while in the case of highly viscous phosphonium and ammonium ILs (100 to $n \times 10^3$ MPa s), the viscosity decreases by more than an order of magnitude.[75, 76] The decrease in viscosity is attributed to shielding of the electrostatic interactions between ions.

An extraction solvent should be immiscible with water and poorly water soluble. In the case of extraction from non-aqueous media, immiscibility with this liquid is required; popular fluorinated ILs such as dialkylimidazolium bis(triflyl)imides are quite suitable for the extraction from hydrocarbon media, fuels and so on.[77]

The decisive role for determining the IL solubility in water can belong to both the anion and the cation. The imidazolium ILs with relatively hydrophilic anions (halides, phosphate, acetate, salicylate, tetrafluoroborate, *etc*.) can be mixed with water in any ratio at room temperature, whereas hydrophobic bis(triflyl)imide forms ionic liquids immiscible with water even with highly hydrophilic cations [*e.g*., trimethyl(carboxymethyl)ammonium].[78] Elongation of the alkyl group in the IL cation can sharply decrease the miscibility with water: even halide salts with such substituents (*e.g*., trioctylmethylammonium chloride) are not miscible with water. In the general case, a combination of relatively low polarity and relatively weak coordination between the constituent ions makes many ILs immiscible with water and with low-polarity solvents (alkanes, arenes, ethers).

A low solubility of ILs in water does not always mean that water is also poorly soluble in ILs. The above-mentioned HHILs contain much water, which is favourable for the recovery of hydrophilic compounds. Among HHILs, mentioned should be made of ammonium and phosphonium ILs with anions containing carboxylate, sulfonate, phosphinate or amino acid group. Being poorly soluble in water ($< 2 \times 10^{-4}$ mol L^{-1}), ammonium-based hydrophilic-hydrophobic ionic liquids, TOALS, THADHSS and TOMAS, incorporate large amounts of water: from 4.8 to 13.2 mass %.[57, 58, 79] More than 20 mass % water is present, after saturation, in phosphonium ILs with amino acid anions[80] and in ammonium ILs with the phosphinate anion.[76] Indeed, the mole fraction of water in the phosphonium ionic liquid CYPHOS is 0.51 to 0.89.[81]

The mutual solubility of some extraction solvents and water (Fig. 3) demonstrates the unusual hydrophilic-hydrophobic nature of HHILs. It can be seen that TOALS, TOMAS and THADHSS are located in a separate area remote from both usual molecular solvents and classical ILs or aqueous biphasic systems.

Apparently, the hydrophilic nature of the HHIL anions accounts for the high content of water in these ionic liquids. The theoretical calculations[86] performed for the TOALS – water system showed the presence of two types of water: free and clustered water. The exact state of water in HHILs (water of hydration, water as clusters or other aggregates) remains obscure. High solubility of water in phosphonium ILs is sometimes attributed to the formation of reverse micelles.[75]

Estimation of the polarity of some ILs used for extraction in terms of the Dimroth – Reichardt parameters† demonstrated that they are less polar than ethanol, but more polar than molecular solvents such as acetone or

† Solvatochromic parameter $E_T(30)$ is determined from the absorption spectrum of the Reichardt's dye, 2,6-diphenyl-4-(2,4,6-triphenylpyridinium-1-yl)phenolate, in this solvent; it is equal to the electron transition energy of the dye in kcal mol^{-1}.

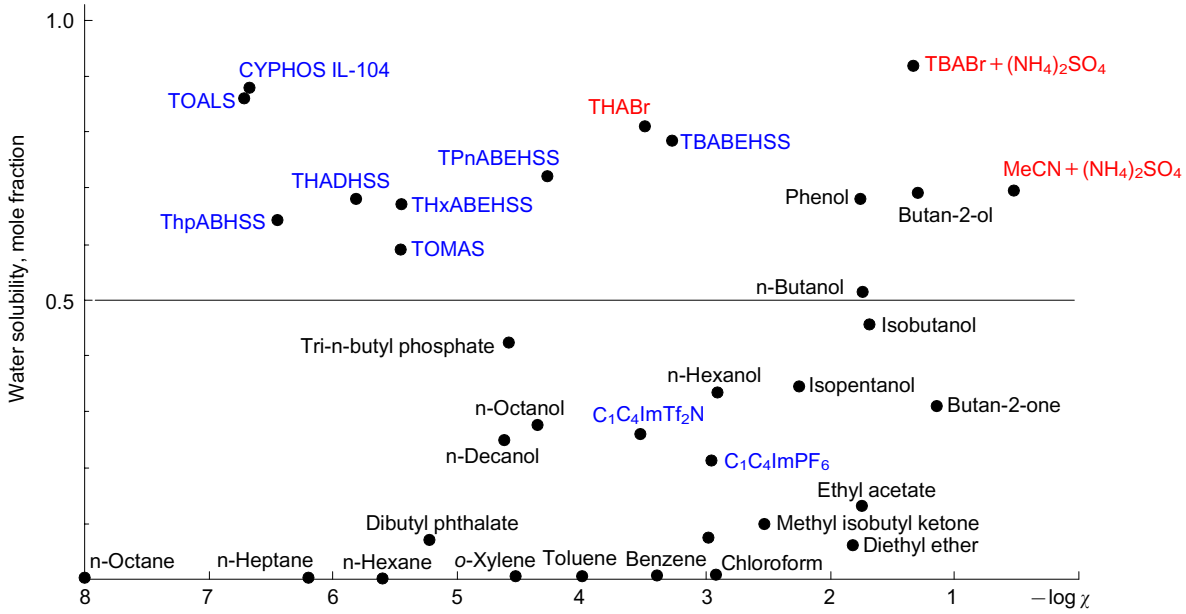


Figure 3. Mutual solubility of extraction solvents (χ is the mole fraction of the solvent in the saturated aqueous solution) and water. The following designations are used: CYPHOS IL 104 is trihexyltetradecylphosphonium bis(2,4,4-trimethylpentyl)phosphinate; TOMAS is trioctylmethylammonium salicylate; TOALS is tetraoctylammonium *N*-lauroylsarcosinate; THADHSS is tetrahexylammonium dihexylsulfosuccinate; TBABEHSS, TPnABEHSS, THxABEHSS, THpABEHSS are tetrabutyl-, tetrapentyl-, tetrahexyl-, tetraheptylammonium bis(2-ethylhexyl)sulfosuccinates, respectively; THABr is tetrahexylammonium bromide; TBABr is tetrabutylammonium bromide. The figure was created by the authors using published data in the Refs 18, 43, 58, 75, 79, 82–85.

acetonitrile. The $E_T(30)$ value increases in the series: dichloromethane (40.8) < chloroform (41.0) < acetone (42.2) < acetonitrile (45.4) < THADHSS (46.2) < TOALS (46.6) < TOMAS (46.8) < $C_4C_1ImTf_2N$ (51.8) < 1-hexyl-3-methylimidazolium bis(triflyl)imide (51.6) < ethanol (52.4). Imidazolium ILs are more polar than ammonium ILs, the polarity of which is close to that of acetonitrile.

Extraction of metal ions. The extraction of metal ions into ILs was first reported in 1999.[14] The authors observed unusually high distribution ratios of Sr^{II} ions (c_{Sr} = 0.0015 mol L^{-1}) during extraction from nitric acid solutions into hydrophobic 1,3-dialkylimidazolium ILs with fluorinated anions in the presence of 0.15 mol L^{-1} of dicyclohexyl-18-crown-6 as neutral extractant. The value $D_{Sr} = 1.1 \times 10^4$ found for 1-ethyl-3-methylimidazolium bis(triflyl)imide ($C_2C_1ImTf_2N$) was 3–4 orders of magnitude higher than the values inherent in extraction into usual organic solvents (*e.g.*, for example, normal alcohols), which naturally drew attention to ILs as a good alternative to molecular solvents. The subsequent experiments carried out independently by several research groups demonstrated the complexity and ambiguity of the phase transfer mechanisms and regular patterns of extraction. The applicability of ILs based on PF_6^- and BF_4^- turned out to be markedly restricted by hydrolysis of these anions in acid media to give HF.[87] One more feature of ILs is ion exchange between the IL cation and the metal–crown ether cationic complex, which is possible during highly efficient extraction [88, 89] and which, unfortunately, results in a loss of the solvent and contamination of the aqueous phase.

Large-scale research was undertaken to elucidate the factors responsible for occurrence of either the cation exchange or conventional (extraction of a metal–crown ether ion associate with nitrate) extraction mechanism. It was shown that cation exchange predominates when metals are recovered from solutions with low concentrations of acids and/or salts with relatively hydrophilic anions (*e.g.*, HCl, HNO_3) into ILs composed of relatively hydrophilic cations (*e.g.*, C_nC_1Im, where $n \leqslant 6$) and relatively hydrophobic anions. The distribution ratio of the metal decreases with increasing acidity.[71, 90, 91] The hydrophobization of the IL imidazolium cations by elongation of alkyl groups hampers the displacement of cations to the aqueous phase and results in switching from the cation exchange mechanism to the traditional extraction mechanism. However, the efficiency of extraction from acid media decreases.[92] A few studies demonstrated the possibility of extraction of metal complexes with crown ethers without the loss of ILs.[93] Under certain conditions, extraction of anionic metal complexes is possible.[94, 95]

In general, the predominance of either the ion exchange or the traditional (extraction of neutral chelates) extraction mechanism depends on the natures of the IL and the metal, the presence of co-solvent,[96] acidity and other conditions. A synergistic effect of mixed systems involving various extractants and ILs has been reported.[97, 98]

The above examples refer to the application of ILs as diluents for traditional complexing reagents (extractants). Ionic liquids containing weakly coordinating fluorinated anions are coordinatively inert and can dissolve extremely low amounts of metal salts of approximately 10^{-4} mass %.[99] Some exclusions to this rule have been reported.[100, 101]

Another type of extraction of metal ions is the extraction with CILs. Among the first ILs of this type synthesized by Rogers and co-workers,[47] high efficiency and selectivity to Hg^{2+} and Cd^{2+} ions were found for ILs with a thiocarbamide group attached to imidazolium by a covalent bond. Imidazolium ILs with aminodiacetate groups were used for the extraction of Cu^{2+}, Ni^{2+} and Co^{2+} ions.[102]

Ionic liquids capable of coordinating alkali and alkaline earth metal ions had a crown ether moiety in the imidazolium cation, but they showed only moderate efficiency.[103] An IL containing a crown ether moiety connected to two imidazolium cations was used for extraction of Ln^{3+} and Y^{3+}.[104]

It is noteworthy that along with benefits, CILs also have a number of drawbacks. They cannot be easily synthesized and are rather expensive. Most often, they have high viscosity and are not used neat, but are diluted, in particular with cheaper coordinatively inert ILs.[48, 103, 105] Generally, this line of research has not yet been a definite success.

An alternative to classical ILs is provided by less expensive and more available ILs based on quaternary ammonium and phosphonium cations with coordinating anions. Some of these compounds have been used as liquid anion exchangers for more than half a century. Trioctylmethylammonium chloride, widely commercially available as Aliquat 336 (a mixture of trioctylmethyl- and tridecylmethylammonium chlorides), have been actively used in hydrometallurgy, radiochemistry and analytical chemistry since the mid-20th century. Experimental data on the extraction of elements are systematized in numerous papers, reviews and monographs.[106, 107]

After the beginning of large-scale production of trihexyltetradecylphosphonium chloride (commercial brand CYPHOS IL 101) in 2003, phosphonium ILs have become commercially available.[108] Some examples of metal extraction with phosphonium ILs are covered in reviews.[69, 109] The extraction selectivity is largely determined by the choice of the IL anion.[110 – 112]

Due to the high viscosity of ILs [*e.g.*, 1450 (Ref. 113) and 1824 cP (Ref. 114) for Aliquiat 336 and CYPHOS IL 101, respectively], they are often diluted with molecular solvents (toluene, naphtha, chloroform, *etc.*). It should not go without mention that the benefits of neat ILs are lost upon the addition of diluents. Furthermore, in this case, the use of ILs virtually does not differ from the well-known extraction with amines or quaternary ammonium salts. The similarity to so-called binary extraction, which employs solutions of substituted ammonium and phosphonium salts with organic anions in molecular solvents, is especially evident (see, *e.g.*, Refs 115, 116).

Regarding the selectivity and efficiency of metal ion extraction, ILs with organic anions capable of complex formation appear most promising. Carboxylates are of interest for the preparation of readily available and cheap ILs. The extractants studied for this purpose[53 – 55, 57] include tetraalkyl ammonium and phosphonium salicylates, thiosalicylates, tosylates, benzoates, 2-(methyl)benzoates, hexanoates and oleates. Tsulatani *et al.*[117] used hydrophobic phosphonate and alkyl sulfosuccinate anions and anions of some surfactants.

Most often, CILs are used as extractants; however, they can also act as diluents. For example, TOMAS, THADHSS and TOALS solubilize complexing reagents and extract their metal complexes.[118 – 120]

Extraction of organic compounds into ILs is considered in quite a number of publications related to analytical, biotechnological and other applications.

The first publication on the use of hydrophobic ILs in extraction[46] considers the distribution of a number of substituted aromatic compounds between $C_4C_1ImPF_6$ and water. Comparison with the distribution of the same compounds in the n-octanol – water system revealed a correlation, but in the case of ILs, the distribution ratios were approximately an order of magnitude lower. According to Armstrong and co-workers,[121] the distribution ratios of a number of organic compounds in $C_4C_1ImPF_6$ are similar to those for octan-1-ol, and the highest recovery is attained for neutral forms of ionogenic compounds.

A systematic study of the distribution of organic compounds of various classes in ionic liquids based on substituted imidazolium cations [$C_4C_1ImPF_6$; 1-butyl-2,3-dimethylimidazolium hexafluorophosphate ($C_1C_1C_4ImPF_6$), $C_4C_1ImTf_2N$ and 1-butyl-2,3-dimethylimidazolium bis(triflyl)imide ($C_1C_1C_4ImTf_2N$)] demonstrated that most of the studied phenols, acids, amino acids and some polyfunctional compounds were extracted as non-charged species. The extraction mechanism of these compounds did not depend on the structure of imidazolium ILs.[42]

A comparison of the distribution ratios of neutral organic compounds between water and a popular hydrophobic ionic liquid, $C_4C_1ImPF_6$, and 48 other extraction solvents[42] showed that the extraction properties of ILs resemble most closely those of esters. The distribution ratios can be predicted with a good accuracy from the data for n-butyl acetate and *m*-xylene:

$$\log D_{C_4C_1ImPF_6} = 0.135 + 0.62 \log D_{\text{butyl acetate}} + 0.11 \log D_{m\text{-xylene}} \quad (1)$$

number of reference compounds: $n = 18$; correlation coefficient: $r^2 = 0.95$.

The ability to undergo ion exchange, which is inherent only in ILs, in particular, in two-phase extraction systems, was manifested in the extraction of amino acids and catecholamines. The $C_4C_1ImPF_6$ ionic liquid provided a quantitative extraction of amino acids as cationic complexes with dicyclohexyl-18-crown-6 (DCH18C6),[122] being exchanged with the 1-butyl-3-methylimidazolium cation. The efficiency of cation exchange extraction of catecholamines into ILs increases with increasing hydrophobicity of catecholamine.[123] We demonstrated[124] the benefits of combining the extraction recovery of phenols and catecholamines with their subsequent voltammetric determination in the extract without dilution with a supporting electrolyte or back extraction.

The hydrophilic-hydrophobic ILs based on quaternary ammonium cations, THADHSS, TOMAS and TOALS, are almost in all cases superior to the first-generation imidazolium ILs in the extraction of various classes of organic compounds.[58, 109] A distinctive feature of HHILs is the ability to solvate hydrophilic ionogenic compounds and to perform highly efficient ion exchange extraction. These ILs are able to quantitatively extract multicharged anions, for example, anions of synthetic azo dyes such as azorubine, tartrazine, sunset yellow and so on.[125]

An important application area of ILs as extraction solvents for the separation and determination of organic, inorganic and biologically active compounds is microextraction preconcentration, which means conduction of the extraction on a micro scale.

Microextraction preconcentration is inapplicable for an industrial process, but is very convenient for analytical chemistry. This approach eliminates serious drawbacks of ILs such as relatively high cost and high viscosity and takes full advantage of the almost unlimited possibilities of controlling the solvent properties.

Numerous publications, including reviews,[126 – 128] are devoted to the use of ILs in various types of liquid microextraction, particularly single-drop microextraction (SDME), dispersive liquid – liquid microextraction (DLLME) and hollow fibre liquid phase microextraction (HF-LPME). It is worth noting that the replacement of conventional solvents by ILs made it possible to overcome the limitations of some methods and to expand the range of analytes. The IL volumes required for microextraction are usually 1 – 200 μL.

High viscosity, high surface tension, low vapour pressure and low water solubility of ILs were favourable for the formation of higher-volume and stable microdrops in SDME and, hence, for the sensitivity and reproducibility of the analysis. The SDME procedure is well combined with gas chromatographic analysis (including GC/MS) and with high-performance liquid chromatography.[129 – 132]

In the hollow fibre microextraction, the diversity of ILs helped to solve the problem of narrow range of solvents suitable for this technique; HF-LPME is successfully used for preconcentration and analysis of organic compounds and metal ions.[126 – 128]

The use of ILs in DLLME made it possible to minimize the amount of organic solvents needed for dispersion and, in some cases, to completely avoid the use of such solvents.[70, 133] The new version of DLLME, in which the extraction solvents are obtained *in situ* from salts that supply both the cation and anion components,[134 – 136] vividly demonstrates the specific features of ILs.

A number of publications describes microextraction preconcentration using magnetic ionic liquids as extractants from both aqueous and non-aqueous media.[63, 126, 137] Magnetic ionic liquids proved to be highly efficient in the extraction of nucleic acids,[138] phenols,[139] fatty acids,[132] metal ions [140, 141] and some organic contaminants.[142, 143]

3. Aqueous biphasic systems

3.1. Overview

Aqueous biphasic systems, or aqueous two-phase systems (ABS, ATPS) contain two immiscible liquid phases based on water.[144] Most often, ABS are formed by two (rarely, more than two) compounds that are simultaneously present in the aqueous medium in concentrations above certain thershold. Separately, the ABS components are, most often, water-soluble, but when present simultaneously, they cause phase separation.

Both liquid phases mainly consist of water, but one is less aqueous and the other is more aqueous. The component that is mainly contained in the less aqueous phase is often called phase-forming agent.‡ The component that predominantly remains in the more aqueous phase is called phase-separating or salting-out agent.

The mixture of agar agar, gelatin and water described at the end of 19th century was probably the first ABS to be mentioned in the literature.[145] However, studies of systems of this type were not virtually developed up to the mid-20th century. The active research and application of ABS was initiated by the study of Albertsson published in 1956,[146] which addressed the distribution of unicellular algae and their components in a two-phase system based on water, polyethylene glycol (PEG) as the phase-forming agent and KH_2PO_4 and K_2HPO_4 salt mixture as the salting-out agent.

During several decades, the studies were focused on ABS based on water-soluble polymers (mainly polyethylene glycols of various degrees of polymerization).[147] The phase separation was induced by adding salting-out agents (most commonly, alkali metal or ammonium phosphates, sulfates and carbonates), by cooling below the upper critical solution temperature of the polymer or by heating above the lower critical solution temperature. The major applications of these ABS were separation, isolation and purification of biological macromolecules.[147]

Currently, quite a few ABS based on non-polymeric phase-forming components have been reported in the literature. Among these, mention should be made of hydrophilic ionc liquids [15] and, generally, organic salts;[148] molecular solvents miscible with water (lower alcohols,[149] acetone,[150] acetonitrile,[151] *etc.*), surfactants [152] and, at least formally, deep eutectic solvents.[153]

Apart from the addition of salting-out compounds and temperature control, in some cases, phase separation of ABS is also achieved by changing pH,[154, 155] forming hydrophobic ion pairs,[156] introduction of sucrose (sugaring-out) [157] and so on. Examples of widely used ABS are depicted in Fig. 4. Aqueous biphasic systems can also be formed on the basis of surfactants or deep eutectic solvents; they can be magnetic or involve protolytic interactions. These types of ABS are described below in the corresponding parts of the review.

High content of water is the key benefit of aqueous biphasic systems. Water is an extremely cheap, readily available, biocompatible, non-toxic, non-flammable and versatile solvent (although this sounds strange, but water can also be called an ideal green solvent). Water has a relatively low volatility under ambient conditions and is odourless. However, if necessary, it can be easily removed by evaporation. The use of aqueous biphasic systems opens up the unique possibility to extract dissolved compounds into a water-like medium.

The presence of a large amount of water in the phase responsible for extraction allows the use of ABS for the recovery of highly hydrophilic compounds, including charged ones, such as dyes,[158] metal complexes,[148] *etc.* Aqueous biphasic systems are also efficient for the isolation of biological macromolecules in the native form, with their tertiary and quaternary structures being preserved.[147]

3.2. Nature and characteristic features of aqueous biphasic systems

Despite the active studies of the physicochemical properties, extraction capacity and applications of ABS, which have been in progress for more than half a century, it is still a challenge to give a clear and incontrovertible definition for these systems.

This situation is largely due to blurring of boundaries, which is natural for the permanently expanding field covering ever new systems and phase-forming compounds. Indeed, previously ABS were usually defined [159] as liquid – liquid two-phase systems based on combination of water and a polymer – polymer or polymer – salt mixture (often, without mentioning systems with hydrophilic solvents), but since the beginning of the 2000s this definition had to be expanded to cover ionic liquid – salt and ionic liquid – polymer mixtures. By now, it has become clear that the

‡ Of course, this is used in the narrow sense, meaning the formation of new, less aqueous phase. It would be better to call this component 'extract-forming', since, strictly speaking, all components including water are phase-forming.

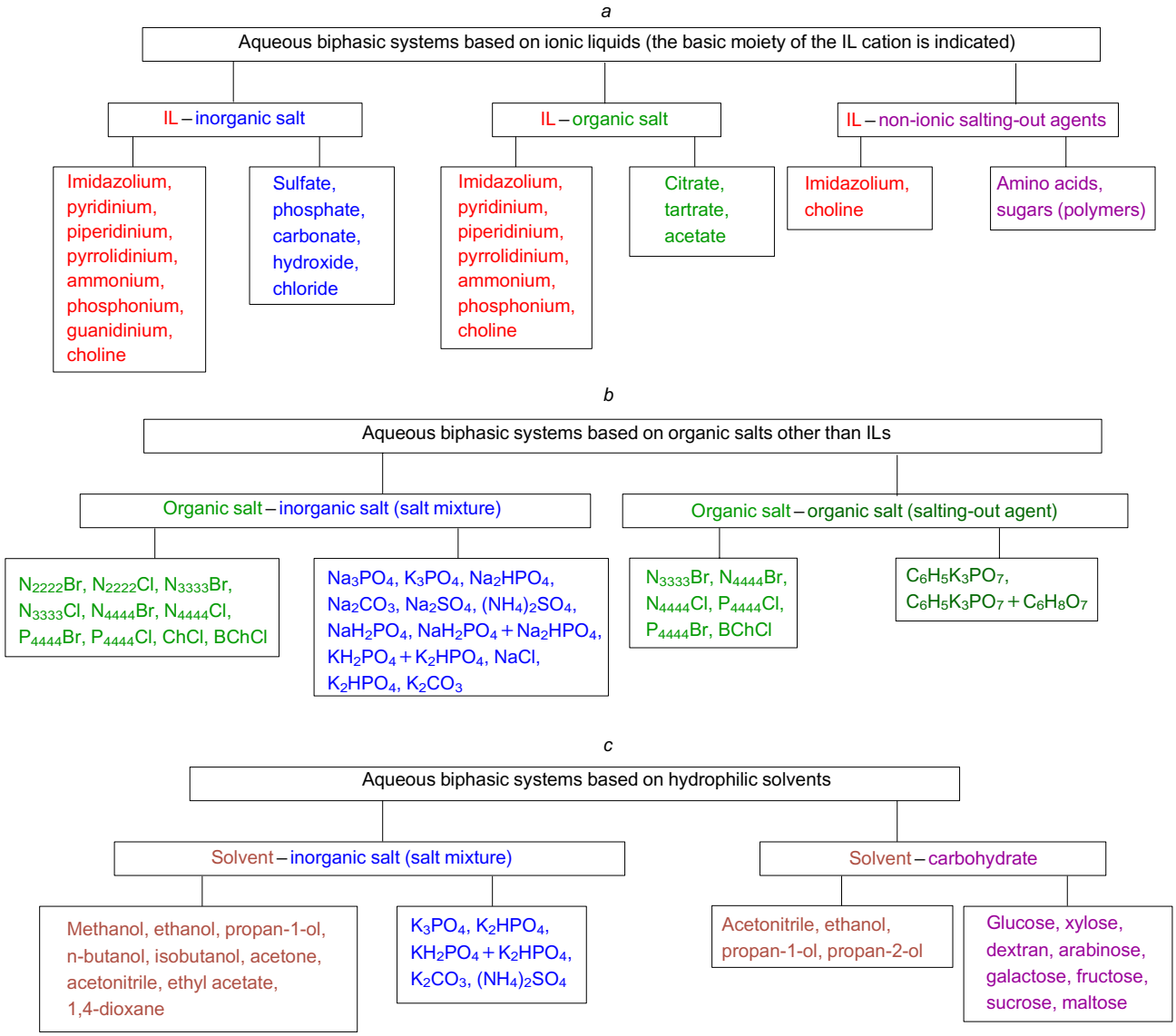


Figure 4. Widely used types of aqueous biphasic systems based on ILs (*a*), organic salts other than ILs (*b*) and hydrophilic solvents (*c*). The following designations are used: $N_{2222}Br$ is tetraethylammonium bromide, $N_{2222}Cl$ is tetraethylammonium chloride, $N_{3333}Br$ is tetra-n-propylammonium bromide, $N_{3333}Cl$ is tetra-n-propylammonium chloride, $N_{4444}Br$ is tetra-n-butylammonium bromide, $N_{4444}Cl$ is tetra-n-butylammonium chloride, $P_{4444}Br$ is tetra-n-butylphosphonium bromide, $P_{4444}Cl$ is tetra-n-butylphosphonium chloride, ChCl is choline chloride, BChCl is benzyldimethyl(2-hydroxyethyl)ammonium chloride.

notion 'ionic liquids' should be replaced by just 'organic salts' (considering systems based on organic salt – salt and organic salt – polymer mixtures [160]), because an arbitrary threshold in the IL melting point, whether it is 100 °C or 25 °C, can by no means be critical for phase separation. Furthermore, there is no guarantee that new classes of substances would not have to be added to the list of possible components.

It is often indicated that ABS contain two 'water-rich' phases; however, the minimum amount of water is usually not specified.

Finally, it is normally implied that ABS are formed only in the presence of a third compound (apart from water and the phase-forming component), *e.g.*, upon the addition of a salting-out inorganic salt to an aqueous solution of a polymer. However, note that the phrase 'aqueous biphasic system' does not itself point to the need to introduce a third component.

In our opinion, the following simple and broad definition would be the most appropriate: any heterogeneous liquid – liquid system in which both phases are more than half water (50 mol.%) can be termed aqueous biphasic system. This definition, which fully corresponds to the meaning of the words 'aqueous biphasic system', is not generally accepted and is not commonly used at all; however, in our opinion, it is a good alternative to the existing definitions.

It should be noted that, according to this definition, ABS can be considered to include not only customary systems with a salting-out agent for organic salts or hydrophilic solvents, but also a small number of systems containing single compounds immiscible with water (more precisely, those having limited mutual solubility with water), such as n-butanol or phenol (see Fig. 3), with no additional components. Moreover, liquid – liquid systems based on water and above-mentioned hydrophilic-hydro-

phobic ILs and tetrahexylammonium bromide (THABr) fall into the class of ABC (A similar definition, in the regard that it gives no indication of the necessity of salting-out agent or a similar additional agent, was proposed by Billard [161] in a book [162]).

In our opinion, the facts that this definition is somewhat unusual and fairly broad are benefits rather than drawbacks. This emphasizes the similarity of systems that are usually 'registered at different addresses' and demonstrates the ambiguity of boundaries within the large class of CS. Note that whereas butanol is a liquid, some HHILs and THABr are solids in the absence of water at room temperature. The fact that they are separated from water as liquids is not surprising: the same is true for phenol.

3.3. Main types of aqueous biphasic systems

Polymer-based aqueous biphasic systems (polymer – inorganic salt and polymer – polymer systems) have already become common and are only briefly mentioned in the review. They have been widely studied as a biocompatible and environmentally friendly alternative to the conventional liquid – liquid systems for the purification and recovery of biomolecules, blood cells, organelles [163] and metal ions.[164 – 166]

However, in the case of polymer – polymer systems, the difference in the polarity (more broadly, in the solvation capacity) of phases is usually moderate, which may result in insufficient efficiency of extraction of the target compounds. The polymer – salt systems are more promising in this respect; furthermore, they have lower cost and easier handling and disposal. The relatively high viscosity of polymer-containing systems can deteriorate mass transfer, retard the attainment of phase equilibrium and complicate practical use of the system. It is possible to use functionalized polymers and various additives to improve the rheological properties of polymer-based ABS and the separation efficiency; however, this would complicate the process and increase the cost. Furthermore, the introduction of additional components is often undesirable (for example, for the recovery of trace components). Several monographs are devoted to polymer-based ABS.[166 – 169]

Systems with hydrophilic solvents were seldom assigned to ABS previously, although this assignment seems quite appropriate. Hydrophilic solvents, in particular alcohols, ketones, ethers and esters, have been systematically used (especially since the second half of the 20th century) for the extraction of diverse hydrophilic compounds, including biologically active substances, from aqueous solutions. Russian researchers made a substantial contribution to this area.[170 – 176]

Most often, inorganic salts are used as salting-out agents. Among the solvents, mention should be made of acetonitrile, acetone and aliphatic alcohols, including ethanol, which are widely used in chromatography. These compounds represent cheap and readily available alternatives to ionic liquids or DES. Low viscosity of extraction systems based on hydrophilic solvents ensures a high rate of mass transfer, while high volatility provides for easy separation of the analyte by solvent evaporation. The biocompatibility and production from renewable sources are also significant benefits of these systems. However, one should bear in mind the fire hazard, flammability and some other drawbacks of alcohols and other hydrophilic solvents.

The number of publications addressing systems with salting-out of hydrophilic solvents has been markedly increasing in recent years, with these systems being more and more often assigned to ABS. A number of successful applications for the separation of biomolecules using not only inorganic salting-out agents, but also carbohydrates for phase separation have been described.[177 – 180]

The extraction into ABS based on acetonitrile, which is convenient for chromatography, and inorganic salts as salting-out agents is used in a popular analytical sample preparation method (QuECHERS meaning quick, easy, cheap, effective, rugged and safe). This method allows efficient recovery of organic compounds of various classes, especially pesticides.[181, 182] The phase separation was originally induced by a mixture of sodium chloride and magnesium sulfate; in modern procedures, other salts are used such as ammonium chloride [183] or formate [184] (this eliminates the metal salt-related problems, which arise when the procedure is followed by mass spectrometric determination).

Aqueous biphasic systems based on organic salts, including ionic liquids. A breakthrough in the development of extraction into ABS was made by Rogers and co-workers,[15] who obtained a liquid – liquid two-phase system based on 1-butyl-3-methylimidazolium chloride (C_4C_1ImCl), a water-soluble ionic liquid, in the presence of potassium phosphate.

It became clear that ABS can be obtained by salting-out of diverse hydrophilic ILs with inorganic salts. This sharply expanded the range of available ABS and stimulated numerous studies all over the world. An illustration is provided by the title of the review [160] published by a reputable Portuguese research team: 'Aqueous biphasic systems: a boost brought about by using ionic liquids'.

For the preparation of ABS, a phase-separating agent, or a salting-out agent, is required. The efficiency of salting-out agents is determined by the free energies of hydration of ionic components (usually the effect of anion is much more pronounced than the cation effect [185]). Multicharged small-sized ions and, generally, ions with a high charge density (*e.g.*, SO_4^{2-}, HPO_4^{2-}, Mg^{2+}, Ca^{2+}, Li^+, Na^+, H^+, OH^-) are favourable for this purpose.

It is believed that efficient salting-out agents are kosmotropic, that is, they enhance the degrees of ordering and structurization of water. The opposite are chaotropic compounds, which increase the disorder and entropy of the medium. The kosmotropic salting-out agents interact with water molecules more strongly than water molecules interact with one another and, hence, they can break hydrogen bonds between water molecules (water structuring/destructuring, chaotropicity and kosmotropicity issues are exceptionally interesting, but they require a separate discussion, see, for example, Refs 186 – 188).

The salting-out power of ions usually obeys the Hofmeister series, which was established more than a hundred years ago and evaluates the ability of salts to precipitate proteins and some other substances from aqueous solutions, expressed in terms of the minimum effective concentrations of these salts.[189, 190] Subsequently, it was repeatedly shown that this series is correlated with the order of variation of the effect of ions on diverse phenomena in heterogeneous systems involving water (*e.g.*, the interfering influence of foreign ions on the operation of ion selective electrodes [191]). The order of ions in the Hofmeister series is similar to the order of variation of free energies of hydration of anions.

For an invariable cation, the salting-out strength of salts usually decreases in the following series of anions:

$$CO_3^{2-} > SO_4^{2-} > S_2O_3^{2-} > H_2PO_4^- > OH^- > F^- > HCO_2^- > > CH_3CO_2^- > Cl^- > Br > NO_3^- > I^- > ClO_4^- > SCN^-$$

(minor variations are possible, for example, perchlorate and thiocyanate can change places [186]).

Data on aqueous biphasic systems based on imidazolium, pyridinium, phosphonium and ammonium ILs and correlations with the Hofmeister series can be found in the literature.[192–194]

Bridges *et al.*[194] noted that distribution and exchange of ions takes place between the ABS coexisting phases with retention of the electroneutrality of the whole system and particular phases. The more chaotropic cation and anion are mainly distributed to the less aqueous phase, while the salting-out kosmotropic ions are distributed to the more aqueous phase. As the amount of the salting-out agent increases, the more aqueous phase becomes more and more structured and, hence, the transfer of chaotropic components to the other phase is intensified.

The two-phase area decreases with increasing temperature. The higher the temperature, the greater the salt and IL concentrations that are needed for phase separation. Thus, lower temperatures are favourable for the formation of ABS. The types and physicochemical description of IL-based ABS were described in detail in the literature.[162, 195]

Hydrophilic ILs as imidazolium halides, sulfates, sulfonates, alkanoates, tetrafluoroborates and triflates are used most often as the main phase-forming components of ABS. Other widely used ILs are those based on quaternary ammonium and phosphonium salts, which are usually more prone to phase separation (this is attributed to higher charge localization on the heteroatom and shielding of the charge by alkyl substituents).

The advantages of IL-based ABS are due to the combined nature of ILs and the related possibility to vary the properties of the system. Aqueous biphasic systems can be formed only using hydrophilic ILs, the range of which is much wider than the range of hydrophobic ILs; furthermore, they are considered to be less toxic and more readily available than the hydrophobic ILs. The wide choice of IL cations and anions substantially expands the ranges of hydrophilicity–hydrophobicity and polarity of ABS phases.

A significant factor is that the viscosities of the 'organic' phases of IL-based ABS and polymers can be substantially different. Phases saturated with imidazolium, phosphonium or ammonium ILs are markedly less viscous (2–14 cP)[196, 197] than typical polymer-saturated phases (up to 96 cP), with the mass fractions of the ABS phase-forming components being similar.[198, 199] This is very important for fast mass transfer between the phases and for easier handling. Aqueous biphasic systems based on ILs usually do not tend to form emulsions and show fast separation into phases, in each of which water is the major component.[160]

Note that most inorganic salts that serve as salting-out agents are supposed to be used with moderately acidic aqueous solutions. At low pH, the salting-out strength decreases due to the protonation of salting-out anions (anions of weak acids). This reduces the number of ILs–salt combinations suitable for given conditions (meanwhile, extraction from particularly acidic solutions is often required for practical purposes). For the development of environmentally friendly ABS, inorganic salts are replaced by organic salts (citrates, tartrates, *etc.*) or even by milder agents that promote phase separation such as amino acids, carbohydrates and water-soluble polymers.

Instead of inorganic salts, sugars, amino acids or other highly hydrated compounds can be used for phase separation. Almost half a century ago, Matkovich and Christian [157] described the phase separation in the water–acetone system induced by sucrose and extraction of hydroxyquinolinate metal complexes in this ABS (the authors also reported that the attempt they made to separate phases in the ethanol–water system with sucrose was unsuccessful).

By analogy with salting-out, this phenomenon was called sugaring-out; however, in some cases, 'salting-out with sugars' is considered.

At a qualitative level, it is clear that, owing to the presence of several hydroxy groups, sugars, like inorganic salts, can efficiently bind water and decrease the water activity, which induces phase separation (by the way, the use of dextran, a polymer of glucose, in polymeric ABS with PEG is well-known [200]). Carbohydrates, which are milder agents than inorganic salts, are well suited for the preparation of biocompatible ABS and isolation of biomolecules. They represent a large and diverse group of biodegradable and non-toxic compounds obtained from renewable feed. As a drawback of carbohydrates, one can mention the need for high concentrations of the sugaring-out agent (a few moles per litre [201]), which implies a very high viscosity of the sugared phase (syrup).

Sugaring-out of acetonitrile with glucose and xylose was reported;[151] starch and dextran did not induce phase separation. The distribution of a number of organic compounds (furfural, syringic acid, *etc.*) was studied. The distribution ratios obtained at sugar concentrations of 15–50 g L^{-1} were not very high (at the level of a few units). In the subsequent publications, phase diagrams of ABS based on acetonitrile and dextran were presented and the effect of dextran molecular mass on the phase separation ability of the system was studied.[202]

Sugaring-out of propanol and hydrophilic ILs was also reported.[179] However, since carbohydrates are less potent phase-separating agents than inorganic salts, the number of ILs able to form ABS with them is limited. Imidazolium ILs with fluorinated anions showed the ability to form ABS on mixing with aqueous solutions of sucrose, glucose, fructose, xylose, maltose, galactose, mannose, arabinose, maltitol, sorbitol and xylitol. It was shown that the crucial role in the formation of ABS is played by carbohydrate–water complex formation: the number of hydroxy groups in the carbohydrate and its stereochemistry.[201] The phase separation capacity in the IL–amino acid–water ABS increases with increasing solubility of the amino acid in water.[203]

Both hydrophilic ILs and organic salts can serve as salting-out agents. It is quite reasonable, although somewhat unusual, that organic salts, in particular many ILs, can themselves act as salting-out agents with respect to appropriate phase-forming components. Hirayama *et al.*[204] described the application of the hydrophilic ionic liquid C_4C_1ImCl for salting-out of tetrahydrofuran. This ABS was used for the extraction of thymol blue (in the neutral red form).

It is known that quaternary ammonium salts can be salted-out with inorganic salts. Meanwhile, they can themselves act as salting-out agents in ABS based on PEG or polypropylene glycol (PPG) (*e.g.*, tetramethyl- to tetrabutylammonium bromides [205]). It was noted [162] that the replacement of an inorganic salt in a polymer system by IL

virtually eliminates the crystallization problem, which arises when inorganic salts are used, and extends the range of phase polarity. The formation of polymer – IL – water ABS is determined by not merely the hydration capability of particular components, but this is a result of a subtle interplay of competing interactions between the components.[206]

Yet another vivid example of the possible dual role of an organic salt (phase-forming and sallting-out component) may be provided by choline-based ABS. Biocompatible ABS based on choline ionic liquids (Ch-ILs) in combination with inorganic salts or various polymers have been studied in considerable detail. Ionic liquids based on the choline cation are easily prepared, inexpensive, stable in aqueous solutions, biodegradable and less toxic than other ILs. Choline chloride is non-toxic and biodegradable; it is widely used as a livestock feed supplement. Of course, formulation of a really environmentally safe system requires also the appropriate choice of other components — polymers, biopolymers, sugars and/or salts.

Unlike conventional IL-based ABS, in most choline-based ABS, the ionic liquid serves for salting-out of the phase-forming component — water-soluble polymer (usually PEG or PPG).

The first application of ABS based on various choline ILs (choline formate, acetate, propionate, butyrate, glycolate, lactate, benzoate, oxalate or citrate) and polypropylene glycol PPG-400 was demonstrated for the extraction of proteins: bovine serum albumin (BSA), trypsin, papain and lysozyme (Fig. 5 *a*).[207] In the subsequent studies the range of choline ILs and phase-separating agents has considerably expanded.[208 – 210] Detailed information on the mechanisms controlling the formation of ABS based on Ch-ILs can be found in the literature.[162, 211]

While considering a series of choline ILs with organic acid anions, Li *et al.*[207] found that their ability to form ABS with PPG-400 is determined by the nature and capacity for hydration of the IL anion. Highly hydrated anions reduce the number of water molecules available for the hydration of the polymer, which results in the polymer salting-out. This is confirmed by the trend followed by some choline ILs: the capacity for phase separation decreases in the following series of anions (Fig. 5 *b*):

citrate > > oxalate > glycolate > propionate ≈
≈ lactate ≈ acetate > formate > butyrate.

A study of the influence of the nature of the Ch-IL dicarboxylate anions on the formation of ABS demonstrated that the longer the alkyl chain of the anion, the greater the biphasic region. However, the effect of the alkyl chain length is less pronounced than in the case where inorganic salts are used to salt-out imidazolium ILs.[212] The original views on the salting-out of ILs by more hydrophilic polyethylene glycol were inconsistent with the fact that the most hydrophilic IL, choline glutarate, showed the greatest ability to form ABS.[208] Furthermore, most of monocarboxylate Ch-ILs do not form ABS with PEG (especially with low molecular weights), unlike di- and tricarboxylic acid anions, which can induce phase separation. One of the possible explanations for these observations is as follows: the interaction between PEG-600 and Ch-ILs predominates over the water – Ch-IL and water – PEG-600 interactions. The relative contributions to solvation of all possible interactions (PEG – water, PEG – ions, water – ions) between the system components can be roughly equal.[199, 202]

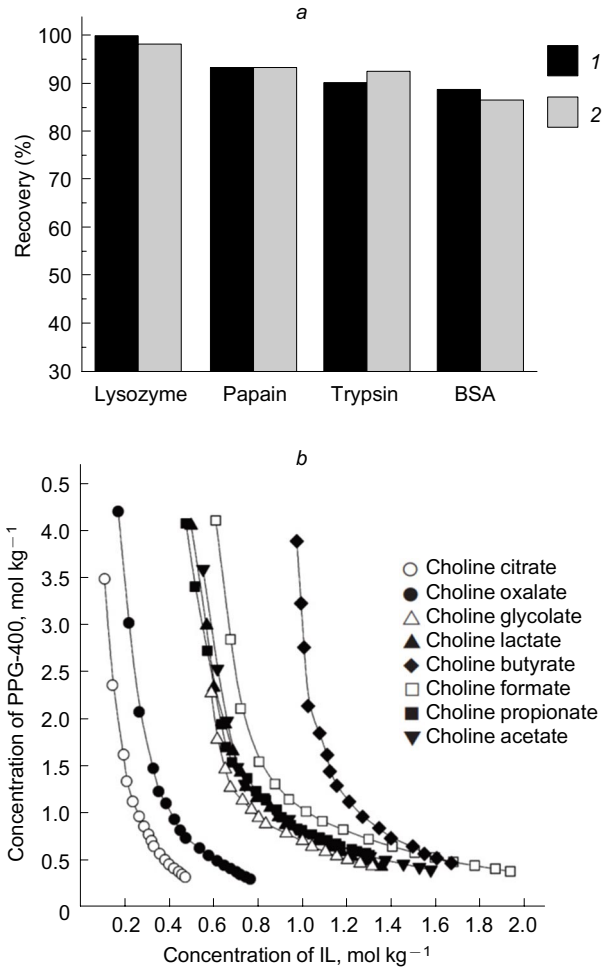


Figure 5. Diagram of protein extraction into ABS based on PPG-400 and choline lactate (*1*) and choline citrate (*2*) ILs at pH 7.0 and 25°C (*a*) and binodal curves for ABS based on several Ch-ILs and PPG-400 at 25°C (*b*).[207] Published with permission from the Royal Society of Chemistry.

Consider salting-out of choline salts with inorganic salts. Choline salicylate forms ABS on mixing with aqueous solutions of potassium phosphate, aqueous solutions of citrate or phosphate buffers or potassium carbonate solution.[209, 210] This feature is also inherent in other salts, but to a lesser extent. The ability of choline ILs to form ABS in the presence of K_3PO_4 decreases in the following series of anions: salicylate > levulinate > glutarate ≈ succinate ≈ acetate > chloride (Fig. 6 *a*).

More hydrophobic choline ILs are more easily salted-out, like imidazolium ILs.[212] Nevertheless, for some analytes such as antibiotics, the highest distribution ratios are observed for ABS based on hydrophilic Ch-ILs (Fig. 6 *b*). Generally, the ability of choline ILs to form ABS with inorganic salts is lower than that of usual imidazolium, ammonium or phosphonium salts.[209]

Pereira *et al.*[213] integrated the principal conclusions drawn from analysis of reported phase diagrams of the Ch-ILs – K_3PO_4, Ch-ILs – PPG and Ch-ILs – PEG systems. As Ch-ILs is mixed with K_3PO_4, a strong salting-out agent, the ABS formation is driven by the predominant solvation of inorganic salt. Meanwhile, the formation of ABS in the

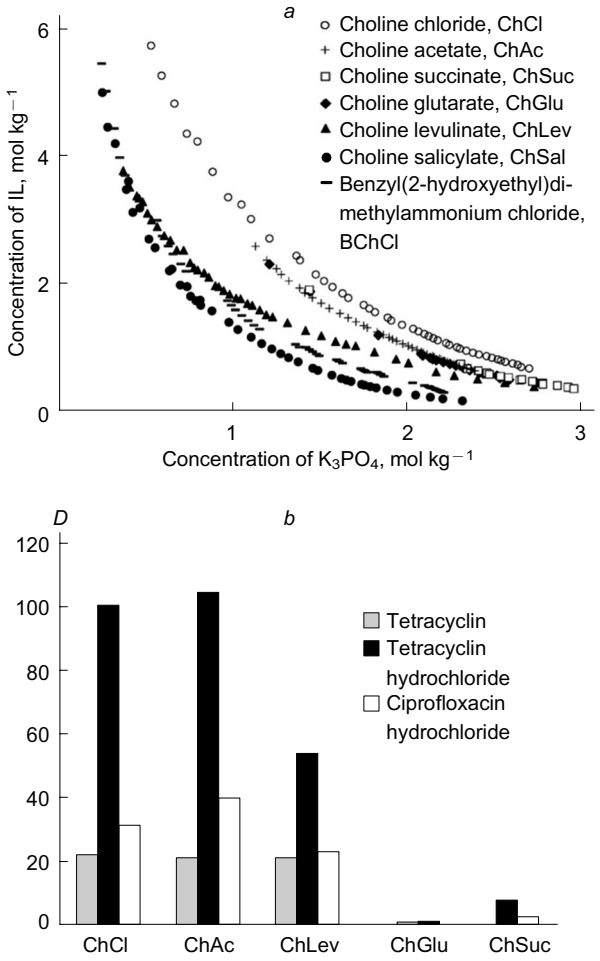


Figure 6. Binodal curves for several ABS based on Ch-ILs and K_3PO_4 (*a*) and distribution ratios of antibiotics in ABS (30 mass % ChCl – ChAc – ChLev + 20 mass % K_3PO_4; 30 mass % ChGlu – ChSuc + 27 mass % K_3PO_4) (*b*).[210] Published with permission from the RSC Publishing.

systems composed of Ch-ILs and polymers, *e.g.*, relatively hydrophobic polypropylene glycol, is due to higher affinity of IL ions for water molecules. However, it was noted that in polymer-containing systems, the phase separation is controlled by a complex interplay of factors, because all components can make a significant contribution to solvation processes and compete with one another for hydrogen bonding.

From the practical standpoint, extensive use of Ch-IL-based systems is hampered by relatively low preconcentration factors and, in the case of extraction from solid samples, also by difficulties associated with the relatively low 'penetration power' of ILs. Potent salting-out agents such as K_3PO_4, K_2HPO_4 or K_2CO_3 are applicable in alkaline aqueous solutions, which significantly limits the range of analytes. In addition, the formation of ABS requires large amounts of Ch-ILs.[37] Nevertheless, choline-based ABS have a number of benefits such as low toxicity and viscosity, biocompatibility, easy and fast extraction (compared to traditional liquid – liquid extraction) and relatively low cost.

Aqueous biphasic systems based on organic salts other than ionic liquids. Initially, only hydrophilic ILs, *i.e.*, liquid water-soluble salts, were considered as organic phase-forming components of ABS. However, the liquid state of the original organic salt is by no means a necessary condition for ABS formation. Many solid salts are also capable of forming aqueous biphasic systems in the presence of a salting-out agent.

One of the two salts that make up the ABS combination acts as the phase-separating agent. Usually this is an inorganic salt; it is hydrated to a higher extent than the second salt, which is organic and serve as the phase-forming (extracting) component. The organic salt may be solid at room temperature and, if its melting point is at least slightly lower than 100 °C, it formally fits into the broad definition of ionic liquids.

The salt – salt aqueous biphasic systems are often easily prepared by just adding one or several salts to an aqueous solution of the analyte or to water; they can have low viscosity and a wide phase separation region. These properties are characteristic of some systems based on quaternary ammonium salts, which are described below.

Salts with multicharged anions are more efficient as salting-out agents. The studies of TBABr-based ABS showed that the shift of the binodal curves towards lower contents of components for the formation of the phase separation region corresponds to the Hofmeister series: $Na_3PO_4 \gg K_3Cit$ (potassium citrate, $K_3C_6H_5O_7$) > $Na_2HPO_4 > Na_2CO_3 > Na_2SO_4 \gg NaH_2PO_4$ (Fig. 7 *a*).[214]

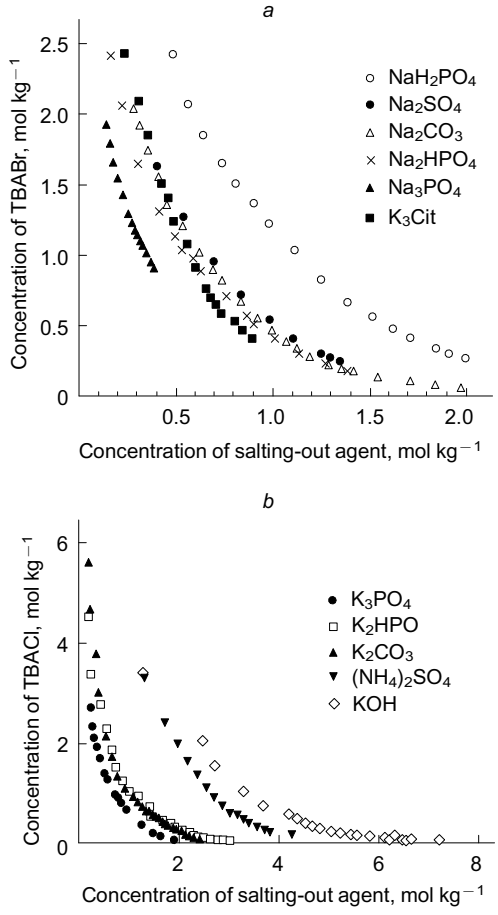


Figure 7. Binodal curves for ABS based on TBABr (*a*)[214] and TBACl (*b*)[194] in combination with various salting-out agents. Figure 7 *a* published with permission from the Royal Chemical Society, Figure 7 *b* published with permission from Elsevier.

Similar results were obtained for TBACl-based ABS (Fig. 7 *b*).[194] It is worth noting that the use of different inorganic salting-out agents leads to different pH values of coexisting phases. Generally, it was shown that ABS are formed more easily under alkaline conditions.[209] The effect of pH is more pronounced for quaternary ammonium compounds than for imidazolium and pyridinium ILs.

Capela *et al.*[215] used amino acids as the separating components of ABS based on ammonium and phosphonium salts. The tetrabutylphosphonium – L-lysine chloride system at pH of 10 – 11 was used to separate aromatic and aliphatic amino acids.

The hydrophobicity of the organic salt is the crucial factor for the formation of ABS. As can be seen from comparison of phase diagrams (Fig. 8 *a*) for tetrabutylammonium and choline salts in the presence of K_3PO_4, a potent salting-out agent,[216] binodals are located closer to the origin of coordinates for tetrabutylammonium-based systems than for choline systems, *i.e.*, the phase separation region is wider. The lowest capacity for phase separation (*i.e.*, the greatest amount of salting-out agent is required) was found for choline chloride. In this case, the hydrophilic nature of the cation plays some role. When chloride is replaced by carboxylates (from butanoate to octanoate), the hydrophobicity and the phase separation capacity increase (see Fig. 8 *a*). The elongation of the anion alkyl chain in tetrabutylammonium salts expands the region of existence of the biphasic system (see Fig. 8 *b*).

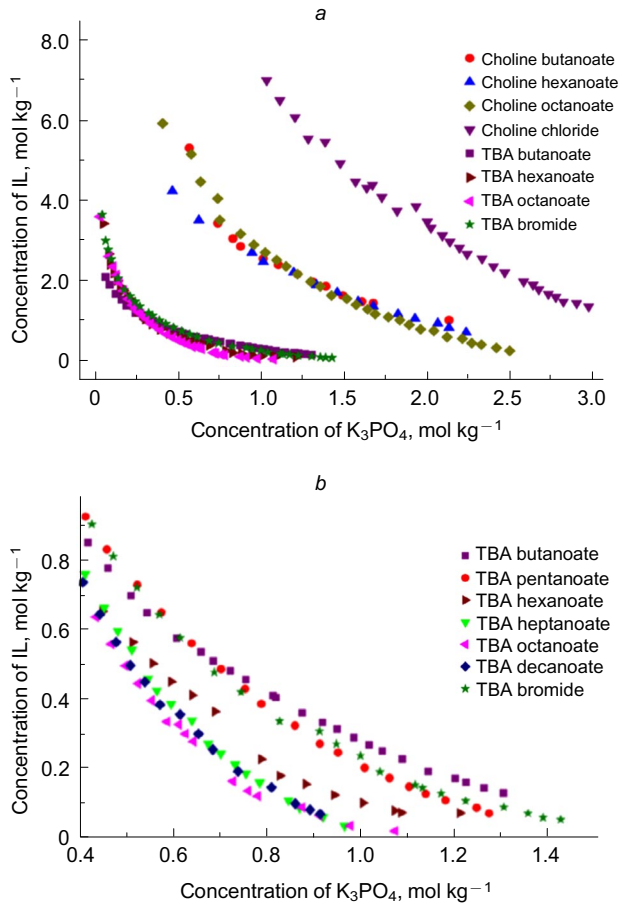


Figure 8. Phase diagrams of ternary systems based on choline (*a*) and tetrabutylammonium ILs (*b*) with K_3PO_4 as the salting-out agent at atmospheric pressure and $T = 298.15$ K.[216] Published with permission from Elsevier.

Irrespective of the nature of the inorganic salt (salting-out agent), the capacity of quaternary ammonium salts for phase separation increases with the elongation of alkyl chains. This correlates with the water solubility and hydrophobicity of the salts.[209] Organic salts with aliphatic and aromatic cations were investigated for the ability to form ABS in the presence of a $C_6H_5K_3O_7$ and $C_6H_8O_7$ mixture at pH 7.[209] The series of the ability to form ABS

$$P_{4444}Cl \approx TBACl > C_4C_1pyCl > BChCl > C_4C_1ImCl$$

(C_4C_1pyCl is 1-butyl-3-methylpyridinium chloride) was in good agreement with the chaotropicity series for the cations of the same chloride salts, with K_3PO_4, K_2HPO_4 and K_2CO_3 used as salting-out agents.[160,194]

Tetrabutylammonium bromide (TBABr) is a readily available non-volatile and non-toxic phase-forming component of salt-based ABS. Akama[148] used TBABr-based aqueous biphasic systems for the selective separation of Cd^{II} from Co^{II}, Cu^{II}, Fe^{III} and Zn^{II} in the presence of $(NH_4)_2SO_4$ as the salting-out agent. Cadmium ions were quantitatively extracted into the TBABr-saturated phase as $[TBA]^+[CdBr_4]^{2-}$ ion pairs at pH of 1.0 – 9.0. The same system was successfully used to separate Cr^{III} and Cr^{VI}.[217] Extraction of dyes was used to demonstrate the applicability of ABS in a microfluidic device.[218,219] Phase separation can also be attained by adding other salts: Na_3PO_4, K_3Cit, Na_2HPO_4, Na_2CO_3, Na_2SO_4, and NaH_2PO_4.[214]

When $(NH_4)_2SO_4$ is used as the salting-out agent, ABS is formed at a TBABr concentration of 55 mmol L^{-1} and a content of $(NH_4)_2SO_4$ not lower than 27.3 mass %. The system is characterized by fast phase separation and low viscosity of the extract (1.55 mPa s), which is lower than the viscosity of most known ABS. Owing to the broad range of accessible concentrations of phase-forming components, it is possible to attain a high volume ratio between the initial phase and the extract. Extraction in this system provides high preconcentration factors (up to 150) and low limits of detection of heavy metals in the subsequent determination by inductively coupled plasma atomic emission spectrometry.[220]

A drawback of ABS formed in the presence of salting-out agents regarding their extraction applications is the necessity of adding large amount of a salting-out agent, which is highly undesirable for determination of traces of elements. In addition, the high content of salts restricts the range of methods suitable for the subsequent determination of analytes in the concentrate.

Aqueous biphasic systems based on organic salts without a salting-out agent. A very curious and little known feature of some quaternary ammonium salts is the ability to be separated from water into an independent liquid phase even in the absence of a salting-out agent. For example, this takes place when solid tetrahexylammonium bromide (THABr) is mixed with water. Nakayama[85] carried out a physicochemical study of such systems and constructed their phase diagrams. The THABr-enriched liquid phase consisted mainly of water. Since the mole fraction of water was much higher than 0.5, this liquid – liquid system can be assigned with confidence to the class of ABS. The melting point of tetrahexylammonium bromide is somewhat lower than 100 °C; hence, it can be classified (though formally) as an ionic liquid.

As can be seen from Fig. 3, the THABr – water system is located at the border between the regions of classical aqueous biphasic systems and hydrophilic-hydrophobic ionic liquids. From the practical standpoint, this system combines the benefits of ILs (non-volatility and capacity for ion exchange) and ABS (high content of water in the extracting phase and efficiency of mass transfer as a result of formation *in situ* during extraction). Unlike traditional ABS, preparation of the THABr – H_2O system requires the addition of only one organic salt to water. Since the volume of the arising phase is much smaller than the initial volume, this system is particularly suited for preconcentration. After the extraction preconcentration in this system, the limits of determination of heavy metals in samples with high contents of salts (including seawater) by microwave plasma atomic emission spectrometry decreased 60 – 500-fold.[221]

Other aqueous biphasic systems. In addition to the well-studied ABS based on polymers, ionic liquids, organic salts and hydrophilic solvents, mention should be made of systems that are formed upon mixing of other phase-forming components and systems with specific properties. Examples of such ABS are aqueous systems based on pyrazolone derivatives that are phase-separated as a result of protolytic interaction;[222] micellar biphasic systems; magnetic ABS, including those in which organic free-radical groups rather than metals serve as paramagnetic centres;[223, 224] ABS based on eutectic solvents (these are considered in the Section devoted to deep eutectic solvents).

Apparently, the micellar extraction systems were described for the first time by Japanese researchers.[152] The formation of ABS from aqueous solutions of surfactants of various natures (especially oxyethylated ones,[225] which obviously resemble PEG) takes place when the surfactant content is above the critical micelle concentration due to variation of temperature, ionic strength, pH, *etc*. For example, it was reported that two immiscible phases are formed in solutions of nonionic surfactants when the lower critical solution temperature is exceeded or in solutions of zwitter-ionic surfactants at temperatures below the upper critical solution temperature. As a rule, one phase has a markedly smaller volume and is enriched in the surfactant, while the other phase is depleted of the surfactant. Phase separation can be affected not only by temperature (and the surfactant nature determining the separation point), but also by the presence of various additives, including salting-out agents.[226, 227]

In this review, we restricted ourselves to only mentioning this extensive field, which is evidently related to some of the systems considered here. Extraction into surfactant-based ABS of various types and under various names, *e.g.*, 'cloud point extraction', 'coacervate extraction', 'gel extraction' and 'supramolecular solvent extraction', are actively used by analytical chemists for preconcentration and determination of organic and inorganic compounds. Details can be found in several reviews.[226, 228 – 232]

3.4. Application of aqueous biphasic systems in extraction

Aqueous biphasic systems are widely used for the recovery, separation and purification of compounds of various nature. According to Pereira and Coutinho,[195] ~100 original papers on ABS have been published every year in the last decade. These studies mainly address extraction of biologically active compounds ranging from small molecules[233 – 235] to macromolecules and even cells[160, 236 – 238] and also metals (see review[239]).

In the vast majority of papers on the separation of enzymes, proteins, amino acids and antibiotics, ILs based on imidazolium and inorganic salts or biocompatible and biodegradable organic salts are used as phase-forming components.[160, 236, 240] These systems were applied, in particular, for the extraction of BSA, lysozyme, trypsin, myoglobin, peroxidase, cytochrome c, globulins, haemoglobin and ovalbumin.[37, 160] The selective separation of protein molecules depended on their affinity to water-rich phases, composition of the system and also on the pH and temperature.

For protein purification processes, it is highly important to maintain the native structure and functional stability of proteins. Two water-rich phases of ABS create a biocompatible medium for such processes. The versatility of the proposed ABS is provided by the wide choice of alternative phase-forming components. It was found that the application of ammonium and phosphonium salts as components of extraction systems stabilizes enzymes and increases the solubility of hydrophobic proteins.[241 – 243] The use of an aqueous biphasic system with the Ammoeng110 IL based on the ammonium cation with polyethylene oxide groups in the presence of $K_2HPO_4 - KH_2PO_4$ salting-out system ensured virtually quantitative recovery of two alcohol dehydrogenases in high yield and with retained stability of the enzyme.[240] A quantitative extraction of BSA (up to 10 g L^{-1}) was observed for ABS based on phosphonium or ammonium ILs and citrate salt.[206, 244] An increase in the IL hydrophobicity proved to be favourable for the separation of ovalbumin and lysozyme.[238] Aqueous biphasic systems based on ILs were used to extract and purify proteins and enzymes such as BSA[244] and extracellular media from real matrices.[245]

Choline-based ILs were used to prepare ABS with biocompatible polymers for the quantitative recovery of antibodies from real matrices.[246] Tial *et al*.[37] discussed in detail the use of choline-based ABS for the extraction of proteins, nucleic acids, amino acids, alkaloids, antibiotics, flavonoids, polyphenols and dyes. The factors influencing the extraction potential of ABS consisting of hydrophilic ILs towards amino acids are considered in the literature.[162, 215]

Generally, phosphonium- or ammonium-based ABS containing biodegradable organic salting-out agents can be considered as a cost-effective alternative to systems based on polymers or other ILs for the separation and purification of protein molecules. In addition, these ABSs are thermally and chemically more stable than imidazolium-based analogues.

Aqueous biphasic systems are widely used not only for the separation, isolation and purification of chemically diverse compounds for preparative purposes, but also in analytical chemistry for preconcentration of residual drugs, pesticides, dyes and other contaminants in natural and waste waters and food products, in particular of animal origin.[247]

The application of ABS for the isolation and preconcentration of metal ions started ~40 years ago (if studies on extraction into hydrophilic solvents with salting-out are taken into account, then even earlier[170]). The first paper devoted to the extraction of metal ions into ABS based on polyethylene glycol with ammonium sulfate as the salting-out agent was published by Zolotov and co-workers in the USSR.[164] Later, systems of this type were used, for example, for group extraction of lanthanides and actinides as

complexes with Arsenazo III (3,6-bis[(2-arsonophenyl)azo]-4,5-dihydroxy-2,7-naphthalenedisulfonic acid), which is widely used as a reagent for photometric and extraction photometric determination.[165]

Metal ions can be extracted into ABS as negatively charged complexes with inorganic anions. This type of extraction is characteristic of metal ions that form halide or pseudohalide complexes.[248, 249] The efficiency of extraction depends on the hydrophobicity of the organic phase and stability of complexes formed in the extraction system. Metals are often extracted as complexes with water-soluble or insoluble extractants.[220, 221] A more rare case is the reagent-free extraction of metal ions, which is possible for a limited range of systems (*e.g.*, extraction of anions containing metals in high oxidation states such as TcO_4^-, $Cr_2O_7^{2-}$).[217]

In most applications describing the extraction and separation and metal ions, extraction is carried out from acid media, which prevents hydrolysis and precipitation of metal ions and simultaneously promotes the formation of metal complexes. More detailed data on metal extraction can be found in reviews.[161, 239]

Owing to peculiar physicochemical properties, biphasic systems based on quaternary ammonium salts have a number of obvious advantages, which extend and facilitate their applicability as new extraction systems. Aqueous biphasic systems are actually obtained *in situ* by mixing two salts or even by dissolving one salt in water, which makes it possible to intensify mass transfer between phases and to reduce the extraction time. Furthermore, ABS can be obtained from inexpensive, readily available and non-toxic components. In some ABS, the concentrate obtained after the extraction and phase separation can be diluted with water to the volume optimal for analysis, which is unrealistic in conventional extraction systems. Therefore, extraction of metal ions into ABS can be combined with subsequent analysis without back extraction[221] and without the necessity of dilution with organic solvents.[220]

4. Combined solvents: deep eutectic systems

4.1. Overview

Deep eutectic solvents (systems) (DES), more rarely called low transition temperature mixtures (LTTMs) or low-melting mixtures (LMMs), are mixtures of compounds that are liquid at room or somewhat higher temperature. As the temperature boundaries, it is reasonable to use the same values of 25 °C and 100 °C that were proposed for ionic liquids (see Section 2.1).

The first study on the modern DES was reported by Abbott *et al.*[250] While looking for new hydrolytically stable ionic liquids, the authors found that choline chloride forms eutectic mixtures with zinc chloride in a relatively broad range of molar ratios (the values in parentheses are melting points): 1 : 1 (65 °C), 2 : 1 (25 °C), 3 : 1 (45 °C). This range is not typical of previously studied mixtures of a similar nature such as chloroaluminate ILs (and, generally, ionic liquids), in which an excess of the source of organic cations over the equimolar amount leads to an increase in the melting temperature of the mixture. The authors attributed the specific features of the new systems to the important role of complex formation and the stoichiometry, which provide the maximum charge delocalization and, as a consequence, the greatest possible decrease in the melting point of the mixture.[250]

Later, Abbott *et al.*[16] reported the results of studying the properties of mixtures of quaternary ammonium salts with amides, and, instead of the term 'ionic liquids', they used the terms 'eutectic mixtures' and 'deep eutectics'. The authors focused attention on the choline chloride – urea system, which exists as a homogeneous liquid at room temperature over a certain range of component ratios. The minimum melting temperature (12 °C) corresponds to the melting point of the 2 : 1 urea – ChCl mixture and is much lower than the melting points of single components[251] (Fig. 9; for detailed discussion, see Section 4.3).

The considerable decrease in the melting temperature of mixtures in comparison with pure components (302 and 133 °C for choline chloride and urea, respectively) was attributed[16] to the formation of hydrogen bonds between amide group protons and chloride ions within ChCl and to low symmetry of the choline ion. This explanation implies that chloride, which is a small anion with a high charge density, becomes a large 'complex' anion with a shielded charge, and this leads to 'liquefaction' of the organic salt. The role of these factors was illustrated by replacing urea by amides with different proton donor properties or by replacing choline by quaternary ammonium salts composed of anions characterized by different hydrogen bond acceptor properties and structurally different cations.

In the same study, the properties of DES as solvents were also addressed for the first time. The authors demonstrated that the liquid 2 : 1 urea – ChCl mixture can dissolve hydrogen bond donor (carboxylic acid) and acceptor (metal halides) compounds and metal oxides (apparently due to the high chloride concentration).[16]

The subsequent publication of Abbott *et al.*,[252] which summarized and continued the earlier studies, has the term 'deep eutectic solvents' as the headline. According to the authors, the introduction of a new term was required to distinguish between the class of ILs (single compounds) and the class of deep eutectics (mixtures of compounds) composed of hydrogen bond donors and acceptors. This authors demonstrated the possibility of fabricating DES using choline chloride in combination with carboxylic acids and the possibility of varying the physicochemical properties of the obtained liquid phases (phase transition temperatures, viscosity, electrical conductivity, dissolving capacity), depending on the nature of the initial mixture components. The similarity of these properties of ILs and DES was emphasized. In particular, the specific electrical conductivities of deep eutectic solvents such as ChCl – urea and ChCl – oxalic acid, which varied in the range of 0.1 – 10 mS cm^{-1} depending on the component ratio, proved to be very similar to those for some imidazolium ILs.[252]

4.2. Range of possible components

Classification. Abbott and co-workers[253] proposed classification of DES into four types I – IV, depending on the nature of components (Table 2). Types I – III correspond to the general formula Cat^+X^-zY, where Cat^+ is the organic cation (substituted ammonium, phosphonium, sulfonium, *etc.*); X^- is the Lewis base (most often, halide anion); Y is a Lewis or Brønsted acid; z is the number of molecules Y linked to the X^- anion.

As can be seen from Table 2, every DES of types I – IV contains at least one ionic component. However, quite a few recent publications describe DES obtained by combining non-ionogenic (but capable of hydrogen bonding) com-

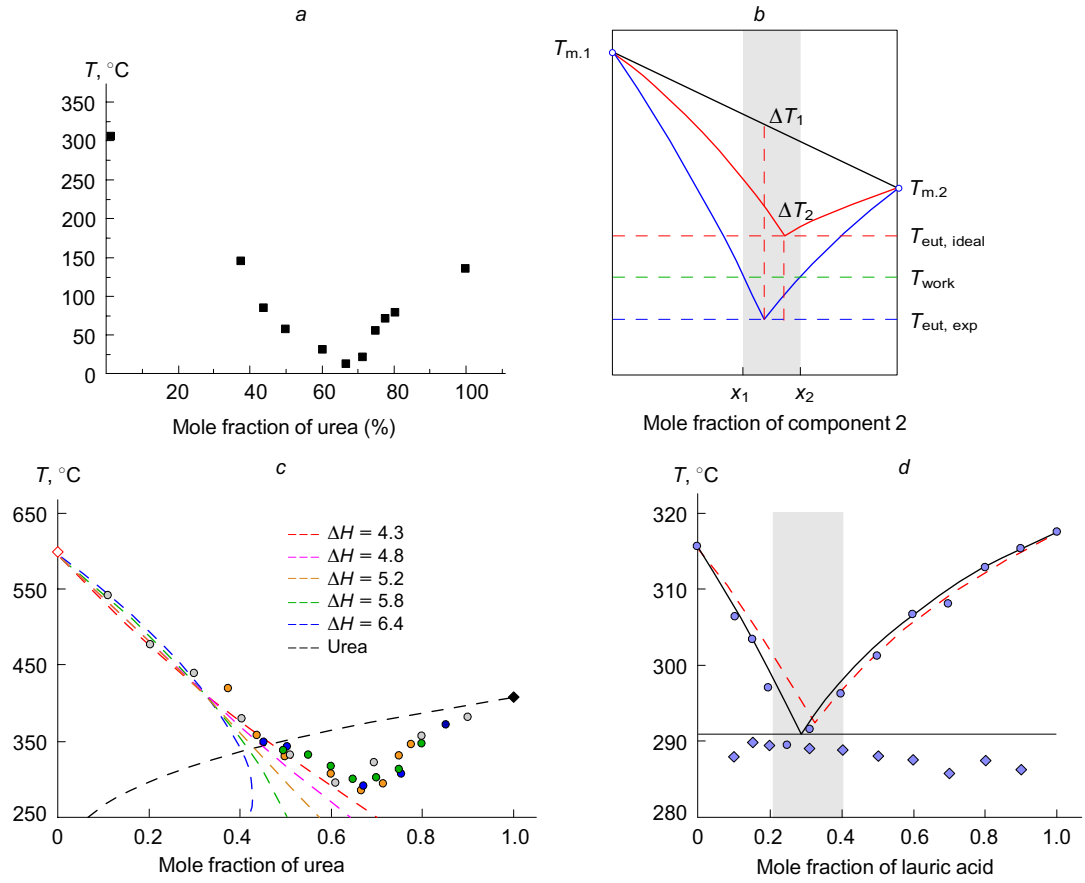


Figure 9. Solid – liquid equilibria in binary systems: freezing temperature of the urea – ChCl mixture *versus* mole fraction of urea (*a*),[16] schematic phase diagram of a binary mixture (red lines show the solubility curves for an ideal mixture and blue lines show the case of deep eutectics) (*b*),[251] comparison of the experimental (symbols) and calculated (for an ideal mixture, dashed line) phase diagram of urea – ChCl (*c*) and L-menthol – lauric acid mixtures (*d*) (see Ref. 251 and references therein). $T_{m.1}$ and $T_{m.2}$ are the melting points of mixture components; $T_{eut., ideal}$ is the theoretical eutectic temperature calculated in the ideal mixture approximation; $T_{eut. exp.}$ is the experimentally determined eutectic temperature; T_{work} is the temperature at which the physicochemical properties of DES are investigated; x_1 and x_2 are the boundaries of the range of DES compositions corresponding to the liquid state at the working temperature; ΔT_1 is the difference between the linear combination of the melting points of mixture components and the real eutectic temperature; ΔT_2 is the difference between the theoretical and experimental eutectic temperatures; ΔH is the enthalpy of melting of ChCl, kJ mol^{-1}. Figure 9 *a* published with permission from Royal Society of Chemistry, Figs 9 *b* – *d* published with permission from Springer Nature.

Table 2. Types of eutectic solvents (eutectic liquids).[253, 254]

Type	General formula
I	$Cat^+X^- \, z\,MCl_x$ (M = Zn, Sn, Fe, Al, Ga, In)
II	$Cat^+X^- \, z\,MCl_x \cdot y\,H_2O$ (M = Cr, Co, Cu, Ni, Fe)
III	$Cat^+X^- \, z\,RZ$ (Z = OH, CO_2H, $C(O)NH_2$)
IV	MCl_x + RZ (M = Al, Zn; Z = OH, $C(O)NH_2$)
V	Non-ionic organic compounds (thymol – menthol mixture and so on)

Note. RZ are alcohols, carboxylic acids, amides; R are alkyls or aryls (including substituted ones).

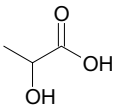
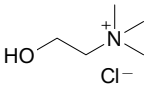
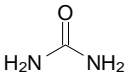
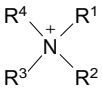
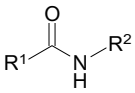
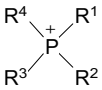
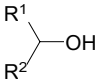
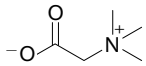
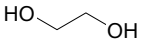
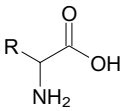
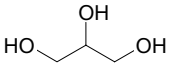
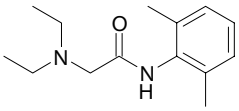
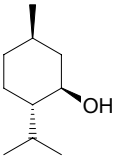
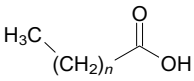
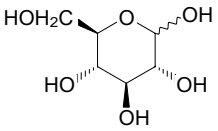
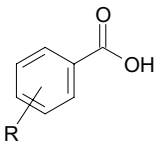
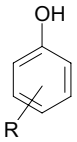
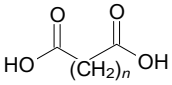
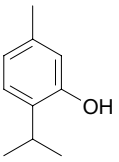
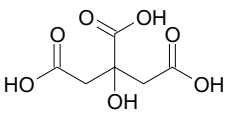
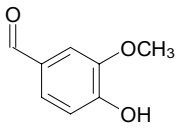
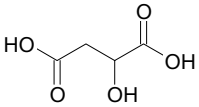
pounds. In 2019, Coutinho and co-workers[254] proposed to extend the existing classification by including such compounds as type V. As the parent system, they took the thymol – menthol deep eutectics.

The eutectic solvents of types I, II and IV contain metal salts. Evidently, these DES resemble the corresponding well-known ionic liquids and, in some cases, they are actually ionic liquids, with the only differences being deviation from the exact stoichiometry and the absence of product isolation from the reaction mixture. The 'purely organic' systems of types III and V have been less studied and, therefore, they are more interesting.

Component diversity. The diversity of combinations of potential components of eutectic solvents, as in the case of ILs, provides the possibility of varying the physicochemical properties of liquids over a wide range, which conceptually makes it possible to obtain solvents with an optimal set of characteristics to address particular problems. Meanwhile, DES favourably compare with ILs, as they are cheaper due to the readily available starting components and simple preparation: as a rule, they are prepared by merely mixing the components with moderate heating without a solvent and, moreover, the final product is not purified but is used as is.

In the literature, the possible DES components are usually subdivided into hydrogen bond proton donors and acceptors. This classification is convenient for practice, but is rather arbitrary. The existing data concerning actual hydrogen bonds in particular systems are only hypothetical or there are no data at all (in some cases, the existence of

Table 3. Widely used components of eutectic solvents.

Structural formula	Name	Structural formula	Name
MCl_x $MCl_x \cdot y\,H_2O$	Transition metal chlorides and their hydrates		Lactic acid
	Choline chloride		Urea
	Quaternary ammonium salts		Carboxylic acid amides and their derivatives
	Quaternary phosphonium salts		Aliphatic alicyclic alcohols
	Betaine		Ethylene glycol
	α-Amino acids		Glycerol
	Lidocaine		Menthol
	Linear aliphatic acids		D-glucose
	Aromatic acids		Phenols
	Dibasic aliphatic acids		Thymol
	Citric acid		Vanillin
	Malic acid		

hydrogen bonds is doubtful). Choline chloride, a popular component and the parent for the whole series of DES, is traditionally assigned to proton acceptors regarding the hydrogen bond between the chloride ion and a second component of the mixture (*e.g.*, urea). However, it is clear that the situation is at least more complicated: the choline hydroxy group can also participate in hydrogen bonding as a proton donor.[255] In the case of carboxylic acids classified as DES,[256] it is impossible to unambiguously distinguish the hydrogen bond donor and acceptor (the known tendency of carboxylic acids to dimerization leaves no doubt in their dual donor-acceptor nature).

The diversity of components that are now actively used for DES preparation is illustrated by Table 3.

The typical components include transition metal chlorides and their hydrates,[253] amines (lidocaine[257]), amino acids,[258] quaternary ammonium salts, including choline salts (ChCl,[16] betaine,[258] tetraalkylammonium halides[259]) and phosphonium salts.[260] These compounds are usually referred to as potential hydrogen bond acceptors (however, indication of a particular functional group or ion is usually avoided).

Eutectic mixture components that are potential hydrogen bond donors are much more diverse. Such components used frequently include carboxylic acids, both monobasic (aliphatic,[261] lactic,[258] glycolic, levulinic[262] and salicylic[263] acids) and polybasic acids (oxalic, malonic, glutaric,[262] malic and citric[258] acids). Popular components of DES are amides (urea and its alkyl-substituted derivatives, thiourea, acetamide and benzamide[16]) and alcohols including simple alcohols (linear and cyclic monofunctional)[264] and polyols [ethylene glycol, butanediol(s),[265] glycerol[258]] and also mono- and oligosaccharides and related sugar alcohols (sorbitol, xylitol, *etc.*).[258]

Phenolic compounds represent one more fairly broad class of organic components of DES (the parent phenol[266] and its substituted analogues: chlorophenols,[267] cresols, xylenes[268]). However, it is noteworthy that due to toxicity of these compounds,[269] their practical use does not comply with green chemistry principles. A promising trend is replacement of phenol and its halogen and alkyl derivatives by safer analogues such as thymol[270] and vanillin.[271]

A number of DES have been prepared using menthol and other terpenoids.[272–275] Menthol and related compounds are relatively hydrophobic [for menthol, the decimal logarithm of the octanol–water partition coefficient (lipophilicity) is 3.38];[276] therefore, the corresponding DES are considered to be promising extraction solvents. Furthermore, the ability of menthol to form liquid eutectics has been well-known for long (in particular, in pharmacology). A textbook example is the menthol–camphor mixture. It is by no means unimportant, although not always taken into account, that the melt of menthol itself can be very easily supercooled.[277] Perhaps some DES are also supercooled melts.

Choi *et al.*[278] considered natural deep eutectics (Natural DES, NADES). The authors introduced this term to describe mixtures produced by living organisms and serving as media for biochemical reactions, transport of metabolites, stabilization of macromolecules, *etc.*[279] An example is maple syrup consisting mainly of sucrose, glucose and malic acid.[278] All of the three listed compounds are solids, but their mixtures are liquids (even after evaporation in order to remove the residual water). These systems are used for extraction and especially for extraction of various compounds from solid matrices.[280, 281] However, subsequently this term was used in relation to not only natural, but also artificially obtained eutectic mixtures the components of which can be isolated from natural sources.[251] These DES are often considered to be safe and biodegradable, in view of the fact that these features are inherent in their components.

Magnetic deep eutectic solvents (MDES). Only a few examples of magnetic DES have been reported in the literature. In particular, magnetic deep eutectic solvents based on choline chloride — [choline chloride–phenol][$FeCl_4$] and [choline chloride–ethylene glycol][$FeCl_4$] — were prepared, characterized and used to extract thiophene from a heptane solution. Microextraction was carried out by adding 20 μL of MDES to 1.5 mL of heptane using ultrasound for dispersion. The microdrops of MDES concentrate with thiophene were collected by a magnet (a cubic magnet was immersed into the system) and the concentration of thiohene remaining in the heptane phase was determined by gas chromatography with a flame ionization detector. It was shown that the phenol mixture provides a higher extraction efficiency than the ethylene glycol mixture.[282]

4.3. Definition of deep eutectic solvents

Investigation of deep eutectic solvents is a new area, which naturally has some 'teething problems', ranging from fuzzy terminology to uncertainty of fundamental concepts, *e.g.*, views on the driving forces of formation of eutectic systems.

The name 'deep eutectic solvents/systems', which has already been established in the literature, is also far from being perfect.

According to the generally accepted interpretation, the eutectic (from Greek ευτηκτος meaning low-melting) temperature is the lowest possible melting point for a given mixture that corresponds to a strictly definite composition.[283] Meanwhile, it the case of solvents, there is no need to maintain the component ratio that strictly corresponds to the eutectic composition. In this case, chemists deal with some range of the ratios in which the mixture is liquid and choose a particular value from this range considering the target physicochemical properties (which naturally depend on the mixture composition). Thus, the word 'eutectic' in this term does not seem completely appropriate, being too restrictive.

The adjective 'deep' is also ambiguous. The studies devoted to the nature of the class of 'deep eutectics' and to comparison of these systems with other eutectic systems make up only a minor part of all publications on this subject. Coutinho and co-workers[251] proposed to characterize the 'depth' of eutectics by the deviation of the experimental eutectic temperature (T_{eut}) from the temperature expected for an ideal mixture (see Fig. 9 *b*). Thus, only systems with a clear-cut deviation from ideality should be referred to as deep eutectics (it is not clear, however, what is the quantitative threshold for the necessary deviation).

This approach is almost perfect from the standpoint of physical chemistry. However, it implies that phase diagrams are drawn and compared, which is far from being always done in the studies focused on practical issues (which means most of studies). In addition, analysis of phase diagrams for a broad range of mixtures that were classified as deep eutectic mixtures in the literature showed that they are nearly ideal, which eliminates these systems from the class of deep eutectics (see, for example, data for a menthol–

carboxylic acid system in Fig. 9 *d*). (all the more attention is drawn to systems that actually significantly deviate from ideality, like, for example, choline chloride – urea mixture, see Fig. 9 *c*).

Thus, a great part of the described deep eutectic solvents are not necessarily eutectic (the composition does not always correspond to the eutectic point) and are not always deep.

In our opinion, these mixtures would be better called 'low-melting mixtures' (which is sometimes done) or 'low-melting combined solvents.' These terms emphasize the combined nature of solvents, the presence of several components (not necessarily two). The world 'low-melting' points to the solid state of the initial components, without reference to the eutectic composition, the degree of lowering of the melting point and, the more so, structural details of the compounds, the ability to form hydrogen bonds and so on. Deep eutectic solvents occupy their own niche, although important but much more narrow.

The solvents immiscible with water and suitable for extraction from aqueous solutions would be appropriately termed 'low-melting combined extractants.'

Some historical background: low-melting extractants. The term 'low-melting extractants' was formerly used to designate low-melting organic compounds and sometimes their mixtures employed for extraction at temperatures slightly above room temperature.[284–286] Among the known low-melting solvents, mention may be made of paraffin wax, carboxylic acids,[287] naphthalene,[285] biphenyl, *p*-terphenyl, 8-hydroxyquinoline[288] and other.[284] A melt can serve as an inert diluent or as a coordination-active extractant, for example, for metal ions. A melt may either contain an added extractant dissolved in the inert component or be 100% extractant. Metal ions can be extracted as chelate complexes with organic ligands, complexes with anionic ligands or salts solvated with neutral organophosphorus compounds.[284]

These studies were extensively carried out at the end of the 20th century, especially in the USSR and in Japan. Unfortunately, now they are undeservedly forgotten so completely that in 2017, an 'innovative' extraction system using molten paraffin wax for preconcentration and analysis was reported in a reputable journal.[289] As the analytical tool, the authors used the modern laser-induced breakdown spectroscopy; however, the chemical extraction procedure was approximately the same as was previously used for low-melting extractants.

In the context of current studies on DES, data on the use of molten mixtures, for example, naphthalene – biphenyl eutectic mixture, as extractants are of special interest. The melting points of separate components of this mixture are 80 and 69 °C, respectively. Meanwhile the mixture containing 55.5 mol.% biphenyl melts at 39 °C. This combined low-melting extractant in the presence of β-diketones was used to recover Ti, Zr, Hf, Nb, Cr and Mo from aqueous solutions; after the extract solidified, the metals were determined by X-ray fluorescence spectrometry.[290]

Melts of C_7–C_9 carboxylic acids in paraffin wax,[287] C_{11}–C_{17} carboxylic acids and molten mixtures of these acids, including technical products,[291] were also used for extraction. There is an obvious analogy between these systems and modern eutectic mixtures of carboxylic acids[256, 292] and mixtures of carboxylic acids with compounds of other classes.[257, 270, 293]

4.4. Driving forces of formation of deep eutectic solvents

There is not always clear as yet what driving forces are responsible for the formation of DES and how the balance of interactions in the known effective systems looks like.

In particular, the role of hydrogen bonds in the formation of DES is far from being as obvious as is commonly believed. The main body of publications on DES address their practical applications, while the percentage of studies dealing with their structure is moderate. Nevertheless, the issues of internal organization of the liquids have been touched upon from the very beginning. Indeed, in an early paper, Abbott *et al.*[16] established the presence of hydrogen bonding between the amide protons of urea and the fluoride in the urea – choline fluoride (2 : 1) DES using NMR technique (HOESY). According to the same publication, the mass spectrum of urea – ChCl (2 : 1) DES contained peaks for Cl^- ions bound to one or two urea molecules (determined by fast atom bombardment mass spectrometry).

According to the results of modelling,[294] the formation of anionic urea within DES *via* proton transfer is unlikely. Subsequently, the 2 : 1 urea – ChCl system served as a sort of benchmark for studying properties of this class of CS. Hammond *et al.*,[295] who carried out a neutron diffraction study, determined more precisely the structure of hydrogen bond network between the constituent parts of this DES. Apart from the strong hydrogen bond between the chloride anions and urea molecules, which was confirmed earlier by NMR experiments, the authors found strong hydrogen bonds between chloride anions and choline cations and some weaker hydrogen bonds between the constituent parts of the system. The DES components exist as a spatial structure the unit cell of which is a chloride anion in the central position connected to one choline cation and two urea molecules. According to Sun *et al.*,[296] the composition of 66.7 mol.% urea and 33.3 mol.% ChCl corresponds to the shortest lifetimes of hydrogen bonds between DES components, which provides the highest mobility of the system components and, as a result, the minimum melting point.

Ashworth *et al.*[297] carried out modelling and calculated parameters for 172 variants of hydrogen bonds of various types (OH···O=C, NH···O=C, OH···Cl, NH···Cl, CH···Cl, CH···O=C, NH···OH, NH···NH, *etc.*), which can be expected to exist in the 2 : 1 urea – ChCl system. According to the calculation results, although the bond strengths were significantly variable, many of hydrogen bonds exising in the DES fell into fairly narrow energy ranges, which implies their high competitiveness within this range and, as a consequence, a diversity of thermodynamically feasible variants of the structure and high total entropy of the system.

Araujo *et al.*,[255] who used a combination of neutron diffraction and computer simulation, identified the structural changes underwent by the system components upon the formation of the 2 : 1 urea – ChCl DES from the solid starting components. In the crystal of pure ChCl, the Cl^- anion is surrounded by the methyl groups of the choline cation and, hence, serves as the linking unit between the neighbouring cations in the lattice and simultaneously suppresses the mobility of their methyl groups. During the formation of DES, the Cl^- anion is removed from the cation centre, which leads to weakening of the Coulomb interactions and to decrease in the rotation barrier for the methyl groups. The Cl^- anion forms a strong hydrogen bond with the hydroxyl proton of the choline cation. The

urea molecule, which has a planar structure (sp^2) in the crystal and a pyramidal structure (sp^3) in a single molecule, adopts an intermediate configuration within DES. The transition from the planar to non-planar state destabilizes the crystal structure of urea, on the one hand, and provides the configuration optimal for the formation of hydrogen bond network, on the other hand. The discovered 'stretchability' of the N – H bond in the urea molecule accounts for the fact that hydrogen bonds of different strength are formed between the urea molecules. In the smallest structural unit sufficient for description of all possible interactions between the system components (four urea molecules and two ChCl molecules), a strong N – H···O – C hydrogen bond is formed only between the two urea molecules, while the other such bonds (head-to-tail) between urea molecules are substantially weaker.

Migliorati *et al.*[298] compared the structural features obtained by modelling for the 2 : 1 urea – ChCl DES and for a similar system in which ChCl was replaced by butyltrimethylammonium chloride, a close analogue of choline without the OH group. It was shown that the absence of hydrogen bond between the butyltrimethylammonium cation and the chloride anion accounts for their fundamentally different relative arrangement (Cl^- anion is located near the CH_2 units of the butyl substituent) compared to that in ChCl-based DES. Thus, the replacement of the choline cation by the butyltrimethylammonium cation induces pronounced changes in the structure of the medium and, as a consequence, gives rise to differences between some properties of DES (*e.g.*, the melting point of the eutectic composition is 55 °C *versus* 12 °C in the case of ChCl).

Silva *et al.*[299] studied the influence of structural modifications of urea on the properties of DES containing also choline chloride. The results of this study partially overlap with the results of Abbott *et al.*,[16] but include not only data on the melting points of 2 : 1 mixtures but also full phase diagrams. The authors showed that the replacement of urea by close analogues that are less active towards the formation of hydrogen bonds (thiourea, methyl-, 1,1-dimethyl- and 1,3-dimethylurea) leads to an increase in the temperature corresponding to the eutectic point and to minor changes in the component ratio corresponding to this point. Two methyl groups increase the eutectic point to a greater extent than one methyl group; the substituents located at the same nitrogen atom induce a greater change than those located at different atoms.

4.5. Characteristic features of deep eutectic solvents

The combined nature of DES leads to specific features and complications (that are absent in the case of one-component molecular solvents), which must be borne in mind while interpreting the behaviour and predicting the properties of liquid systems. This is especially important for extraction and analytical chemistry applications in which the attention is rather focused on optimization of the recovery of target compounds than on the physical chemistry of the involved processes. Some frequently encountered pitfalls are described below (the given examples also illustrate how the chemistry of DES is diverse and interesting).

In the presence of water, eutectic solvents can decompose into components. Since many DES contain extensive networks of hydrogen bonds[300] and their components can be soluble in water, it is reasonable to wonde how water affects the structure and properties of solvents. The amount of these data is yet moderate, but new experimental and calculation results continue to appear. As was to be expected, water as a highly active hydrogen bond donor and acceptor usually present in very high concentration ($\sim$55 mol L^{-1}) often destroys DES.

Hammond *et al.*[301] used neutron diffraction to analyze the structure of 2 : 1 urea – ChCl DES. The results were presented as dependences of the coordination numbers (C.N.) of the components (*i.e.*, the number of the nearest species 'tightly connected' to a given species) on the content of water. It turned out that the addition of water is accompanied by gradual and non-linear decrease in the C.N. of components up to a water content of 10 mass % (77 mol %) where approximately half of the initially present bonds between the components are retained. When the water content is 15 mass % (83 mol.%), the C.N. for choline – choline interactions sharply increases, while the choline – water C.N. sharply decreases. Apparently, this is due to the decomposition of the hydrated aggregates of components; simultaneously, the water – water C.N. reaches a peak value corresponding to pure water. In other words, transition from the 'water in DES' system to the 'DES components in water' system takes place.

According to DFT molecular dynamics simulation data,[302] the destruction of the hydrogen bond network in the 2 : 1 urea – ChCl DES starts with the cleavage of solvate bonds with the chloride and continues as new hydrogen bonds between the DES components and water molecules are formed. Shas and Mjalli,[303] who performed modelling (together with experimental study) of the hydration of 2 : 1 urea – ChCl DES, reported that the number of urea – urea and urea – choline hydrogen bonds somewhat increased upon the addition of small amounts of water ($\sim$2 mass %) to pure DES. As this took place, the number of urea – chloride hydrogen bonds decreased, which also indicates the priority hydration of chloride, the binding of which enhances the interaction between the other DES components. Further addition of water (5 mass % and more) resulted in the hydration of not only the chloride anion, but also the other DES components with a decrease in the number of all types of hydrogen bonds within the DES (urea – urea, urea – chloride and urea – choline).

Passos *et al.*[153] discussed the question of how many components are present in an ABS based on DES. In other words, whether DES behaves as a real independen component of ABS or, being in equilibrium with water, it would split into a mixture of components. The authors considered DES based on ChCl in combination with urea and some carboxylic acids (acetic, hydroxyacetic, lactic and citric acids) in 2 : 1, 1 : 1 and 1 : 2 molar ratios. The compositions of ABS phases formed upon mixing of DES, PPG-400 and water were determined. It was found that in all cases, the components of the initial DES are distributed between two phases without retention of stoichiometry; therefore, DES are not exist as stable units, but dissociate on contact with water.

Farias *et al.*[304] carried out a comparative analysis of ABS based on DES composed of ChCl and a carbohydrate (glucose, fructose and sucrose in 1 : 2, 1 : 1 and 2 : 1 molar ratios to ChCl, respectively) using K_2HPO_4 as the salting-out agent and a similar ABS based on ChCl, but without the second DES component (carbohydrate). The formation of DES-based ABS is accompanied by destruction of the combined solvent, with ChCl being mainly distributed to the upper phase, while carbohydrates are in the lower phase

saturated with the salting-out agent. The phase diagrams for systems with and without carbohydrates differ insignificantly: a carbohydrate acts only as a modifying agent that narrows down the existence region of the biphasic system.

On going to more hydrophobic components, the stability of DES varies in a quite predictable manner. For DES composed from one hydrophobic and hydrophilic components, the latter was shown [261] to be lost on contact with an aqueous phase; the loss of components was clearly correlated with their water solubility. The stoichiometry specified by the synthesis was retained only for DES composed of highly hydrophobic components.

Generally, dissociation of relatively hydrophilic DES with subsequent distribution of components between the phases according to their polarity seems to be a rather general phenomenon. Nevertheless, until recently, little attention was paid to this issue. Only in rare cases, DES destruction with water was deliberately used, for example, for more efficient dispersion of the extracting phase.[305]

If one of the DES components is liquid, it can also act as the solvent (*extractant*) *by itself*. In this case, it is necessary to clearly understand whether the use of knowingly more complex and expensive combined solvent (which, moreover, may lose integrity on contact with water) would give any benefits (and what particular benefits it would give). Meanwhile, researchers still use combined liquids in those cases where a simpler system may have demonstrated equivalent or better extraction characteristics.

These cases can be conveniently illustrated in relation to carboxylic acids, which are widespread components of combined eutectic extractants.[306] Acids containing up to 9 carbon atoms in the chain are liquid at room temperature [the melting point of octanoic acid is 16 – 16.5 °C; that of nonanoic acid is 12.2 – 12.5 °C (Ref. 307)], which makes them potentially applicable for extraction in a pure state. Some acids that are solid when taken separately form mixtures liquid at room temperature. The eutectic composed of C_{10} and C_{12} acids in 2 : 1 ratio melts at 19.6 °C (Ref. 308) (in other studies,[256, 292] it was also classified as a deep eutectic solvent).

Schaeffer *et al.*[270] described extraction of copper(II) and some other transition metal ions into DES based on carboxylic acids $C_{n-1}H_{2n-1}CO_2H$ (n are even numbers ranging from 8 to 18) and menthol or thymol. The greater the carboxylic acid content (*i.e.*, the lower the menthol or thymol content) in the mixture, the better was the copper recovery. As the chain length in the acid molecule increased, the extraction decreased in parallel with the percentage of the acid in the mixture (from 0.4 for $n = 8$ to 0.1 for $n = 18$ when the composition was close to the eutectics; recall that acids with $n = 8-9$ are liquids). However, the water solubility of acids decreases, which is favourable for extraction. The best properties were found for DES based on decanoic (capric, C_{10}) acid. In some experiments, extraction was carried out at 50 °C and, what is especially important, decanoic acid, which is liquid at room temperature was directly used as the extractant (the melting point of this acid is 31.0 – 31.9 °C, Ref. 307). This favourably distinguishes this publication [270] from many other studies in which extraction by single components of the mixture was not considered. It turned out that the single acid shows a higher efficiency of extraction than when it is used as a part of eutectic solvent (easier subsequent separation of the phases was noted as an advantage of using the mixture).

Farajzadeh *et al.*[309] used a deep eutectic solvent comprising a mixture of dichloroacetic acid, n-butanol and L-menthol in 4 : 1 : 1 ratio for dispersive microextraction of pesticides. Since two components of this mixture are liquid in a pure state and, furthermore, n-butanol is only partly miscible with water, it is an open question whether all three components together are needed for extraction.

Even an originally solid component of DES may become liquid on contact with water and act as the extraction medium. The presence of other components in the initial DES may be useless or even detrimental. For example, in a study of microextraction recovery of Al^{III} from aqueous solutions, Panhwar *et al.*[310] used a mixture of choline chloride with phenol as a solvent immiscible with water. However, it is well known (see, for example, book [311] and Fig. 3.16 therein) that phenol by itself forms a liquid – liquid two-phase system with water. When the content of water is 27 mass %, the melting point of phenol decreases from 41 to 12 °C;[312] the upper critical solution temperature is 66.15 °C.[313] Biochemists have been using phenol-based multicomponent systems for the isolation and separation of macromolecules for many years.[314] Meanwhile, as noted above, DES often dissociate on contact with water. Thus, it is quite probable that in the cited study,[310] extraction into water-saturated phenol took place; the role of ChCl is at least problematic and requires a special investigation. Indeed, the authors noted that upon variation of the ChCl : phenol ratio (1 : 1, 1 : 2, 1 : 3, 1 : 4), the best analyte recovery was attained at the highest content of phenol. In other words, the lower the choline chloride content, the better (however, the authors did not attempt to carry out extraction with pure phenol without choline)!

A similar result was obtained in another study:[315] a ChCl – phenol mixture showed the highest efficiency of extraction of malachite green when the content of phenol was the highest among the tested contents. In a recent study,[316] the authors studied the composition of phases in the ChCl – phenol – tetrahydrofuran system and found that the initial ChCl – phenol DES was completely disintegrated (the 'organic' phase contained only phenol, tetrahydrofuran and water, but did not contain choline chloride). The studies on extraction with choline chloride – phenol mixtures were reasonably criticized by Shishov *et al.*[316] As an additional critical remark, note that the nature of phenol-containing systems is far from being in line with green chemistry principles.

Thus, it is always recommended to check the possibility of extraction using not only the complete ABS, but also its particular components.

In some cases, unexpected interactions are possible between DES components up to chemical reactions with cleavage or formation of covalent bonds. Naturally, this may cause variability and uncertainty of the actual composition of DES, which in turn may result in the lack of reproducibility of the physicochemical and extraction properties and to incorrect conclusions drawn from experiments. The unexpected events are especially probable on long-term storage, on heating of the mixture, in the presence of possible catalysts and so on. A good example is the formation of esters, which is probable for mixtures consisting of carboxylic acids and hydroxyl-containing compounds. The latter compounds, *e.g.*, choline, menthol, hydroxy acids and so on, are often used as DES components. The conceptual possibility of esterification in such systems has been confirmed.[317 – 319]

It is noteworthy that some reactions between the components that are undesirable for extraction may prove to be useful for organic synthesis. A number of studies are devoted to lipase-catalyzed reaction of menthol with fatty acids within DES.[318, 320]

4.6. Extraction systems based on deep eutectic solvents

Deep eutectic solvents are used as extraction solvents (extractants) in the separation and preconcentration methods, including liquid – liquid and gas extraction and especially extraction from solid matrices (leaching).[321 – 324]

The number of publications dealing with the extraction from solid matrices is still markedly greater. Indeed, out of the 123 papers published in 2019 with words 'deep eutectics' and 'extraction' present in the titles (Web of Science, request 'TITLE: (deep and eutectic* and extraction) AND YEAR PUBLISHED: (2019))'), only one-fourth (34 papers) are devoted to liquid – liquid extraction and out of them, 12 papers address extraction from non-aqueous media.

Depending on the goals and objectives, extraction can be implemented on a scale ranging from microextraction (sample preparation in chemical analysis [325]) to industrial processes (purification, separation and preparative isolation of target products [326]).

The potential of task-specific tuning of the physicochemical properties of DES (viscosity, density, polarity, miscibility with other liquids, *etc*.) determines the versatility of this class of combined extractants.

Extraction from aqueous solutions. The recovery of target compounds from aqueous solutions is performed using both hydrophobic water-immiscible DES and water-soluble DES, which form aqueous biphasic systems in the presence of phase separating agents.[327] Apart from traditional two-component DES, three component DES [309, 328] and DES mixed with a molecular solvent (diluent to decrease viscosity and facilitate dosing [329]) were reported. In addition, DES can serve as dispersive solvents, auxiliary components of an extraction system.[330, 331]

Procedures for microextraction preconcentration of target compounds using DES are actively developing in relation to new sample preparation approaches in chemical analysis. A number of procedures can be found in the literature: microextraction with solvent dispersion,[266] hollow fibre microextraction,[332] single-drop microextraction [333] and microextraction into *in situ* forming DES.[334] The microextraction procedures involving solvent dispersion include both classical dispersive liquid – liquid microextraction [328] and alternative procedures involving ultrasonic dispersion,[306] temperature-controlled dispersion [335] and vortex-assisted dispersion.[264]

Extraction of metal ions. The extraction of metal ions from various media into DES is widely used, first of all, for sample preparation in chemical analysis. New approaches to this process mainly refer to this field.

Other important fields are application of DES for isolation of valuable components from secondary raw materials [336] and removal of metal ion contamination.[324] In order to attain high efficiency and/or selectivity of extraction, complexing reagents and, in some cases, ion pair reagents [263] are employed. However, DES components are often able to act as ligands by themselves (DES containing carboxy, hydroxy and other functional groups with electron-donating atoms); in these cases, no additional reagents are needed.

The first paper dealing with metal ion distribution in the DES – water system was reported by van Osch *et al*.[257] The authors studied the reagent-free extraction of a number of alkali and heavy metals into 1 : 2, 1 : 3 and 1 : 4 lidocaine – decanoic acid eutectic systems. It was shown that under optimal conditions, Fe^{II}, Co^{II}, Ni^{II}, Cu^{II}, Mn^{II} and Zn^{II} are extracted quantitatively (> 99%). The recovery of other ions such as Li^{I}, Na^{I} and K^{I} is lower being < 50%. The following scheme was proposed for extraction: decanoic acid forms complexes with metal ions, while the protons thus released add to lidocaine, which migrates to the aqueous phase as a cation (it is clear that this means destruction of the initial DES). In relation to Co^{II} extraction, the possibility of extractant regeneration was demonstrated. An identical 2 : 1 lidocaide – decanoic acid mixture was employed [337] for selective recovery of Ni^{II} from an aqueous solution containing Li^{I} (while describing the mechanism of extraction, the authors referred to Ref. 257).

One more example of reagent-free extraction of metal ions into hydrophobic DES based on a carboxylic acid was reported by Schaeffer *et al*.[270] The authors studied the extraction of Cu^{II}, Fe^{III}, Zn^{II} Co^{II}, Ni^{II}, Cr^{III}, Ca^{II} and Mg^{II} ion into a 7 : 3 capric acid – thymol mixture. This extraction proved to be relatively selective: only Cu^{II} and Fe^{III} were quantitatively recovered to the organic phase, Zn^{II} was partly extracted to the organic phase, and other metals were almost not extracted. The dependence of the extraction of Cu^{II} on the pH of the aqueous phase is shown in Fig. 10 *a*. The possibility of separation of Cu^{II} from Co^{II}

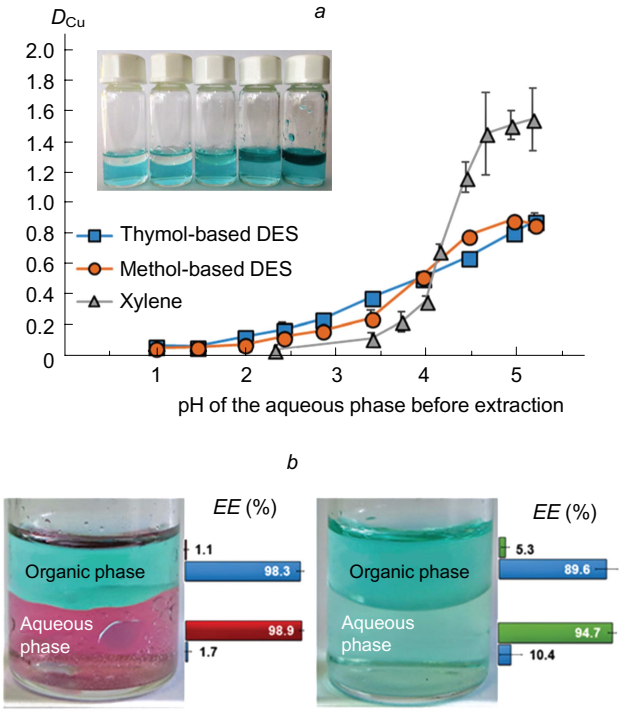


Figure 10. pH dependences of the distribution ratios of copper(II) ions (D_{Cu}) upon the extraction with 0.5 M capric acid in xylene, 7 : 3 capric acid – thymol DES, 7 : 3 capric acid – menthol DES; the inset shows the extraction of 0.1 M Cu^{II} into 7 : 3 capric acid – thymol DES at pH 1 – 5 (the aqueous phase is below) (*a*). Extent of extraction [*EE* (%)] for the 7 : 3 capric acid – thymol DES: separation of 0.01 M Cu^{II} (highlighted in blue), 0.1 M Co^{II} (highlighted in red) and 0.1 M Ni^{II} (highlighted in green) (pH 4.9, 20 °C) (*b*).[270] Published with permission from the Royal Society of Chemistry.

and Ni^{II} was demonstrated (Fig. 10 *b*). The separation factors for the $Cu^{II}-Co^{II}$ and $Cu^{II}-Ni^{II}$ pairs were 500 and 154, respectively.

The possibility of recovery of metals in high oxidation states as oxygen-containing anions was demonstrated[338] in relation to extraction of the pertechnetate anion TcO_4^- into hydrophobic DES based on quaternary ammonium (or phosphonium) halides and monobasic fatty carboxylic acids in 1 : 2 ratio. Under optimal conditions, pertechnetate anions were quantitatively recovered without additional reagents. It was assumed that extraction occurs *via* ion exchange between TcO_4^- and halide anions present in the combined solvents. Geng *et al.*[339] studied extraction of Au^{III} from hydrochloric acid solutions into a 1 : 1 mixture consisting of tetraalkylammonium (tetrapropyl-, tetrabutyl- and trioctylmethylammonium) bromide and hexanoic acid. The best results were attained for the most hydrophobic trimethyloctylammonium bromide: quantitative extraction took place under optimal conditions. Gold was selectively recovered as an anionic chloride complex from a solution containing Mg^{II}, Al^{III}, Mn^{II}, Co^{II}, Cu^{II}, Ni^{II} and Ce^{II}. The presence of $AuCl_4^-$ in the organic phase was confirmed by the absorption spectrum of the extract, which coincided with the spectrum of aqueous solution of $AuCl_4^-$ with a minor shift of the absorption maximum. Presumably, in this case, the extraction mechanism was also anion exchange between tetrachloroauate $AuCl_4^-$ and bromide anions. Tereshatov *et al.*[293] studied the extraction of metal ions as complexes with organic ligands. It was shown that In^{III} can be extracted from oxalic acid media with distribution ratios of $n \times 10^3$ into hydrophobic 1 : 2 tetraheptylammonium bromide – ibuprofen and 1 : 2 tetraheptylammonium bromide – decanoic acid DES. In the absence of oxalic acid, the metal distribution ratios decreased by two (or more) orders of magnitude. The mechanism proposed for extraction is anion exchange of the $[In(C_2O_4)_2]^-$ and $[In(C_2O_4)_3]^{3-}$ with bromide anions.

Deep eutectic solvents are actively used in the microextraction preconcentration to isolate metal ions from aqueous matrices. In the resulting concentrate, the analytes are determined, most often, by spectral methods (flame atomization[266] and electrothermal atomization[340] atomic absorption spectroscopy and spectrophotometry[341]) and also by chromatography.[342]

Relevant publications that appeared over the last five years describe microextraction and determination of Al^{III},[310] V^{V},[343] Cr^{III} and Cr^{VI}, Fe^{II} and Fe^{III}, Co^{II},[266,342] Ni^{II},[342–346] Cu^{II},[328,347,348] Cd^{II},[328,342,347–349] Pb^{II},[328,332,342,347,348] Hg^{II},[348,350] Th^{IV}.[263] Most of the listed publications are devoted to extraction of a single element.

Several papers[328,342,347,348] illustrate approaches to group preconcentration. In those cases where an element is present in the sample as two different species, determination procedures for both species are proposed. Yilmaz and Soylak[344] extracted Cr^{VI} as diethyldithiocarbamate complex in the presence of Cr^{III}, which was almost not extracted. The total content of chromium was determined after preliminary oxidation of Cr^{III} with potassium permanganate. Dareh Door *et al.*[335] reported selective extraction of Fe^{II} as a 2,4,6-tri(2′-pyridyl)-1,3,5-triazine complex in the presence of Fe^{III}. For determination of the total iron content, Fe^{III} was first reduced to Fe^{II} with hydroxylamine hydrochloride. The extraction of Hg^{II} as methyl derivatives reached a quantitative level without additional reagents,[350] while free Hg^{II} ions were almost not extracted. In the presence of dithizone (diphenylthiocarbazone), all Hg^{II} species were extracted quantitatively. In all three mentioned studies, the total content of the element and the content of element species that was quantitatively extracted without additional operations or reagents were found; other species of the element were determined as the difference between the two mentioned values.

Extraction of organic compounds. Water-immiscible hydrophobic DES are efficient, first of all, for extraction of non-polar and moderately polar organic compounds, especially compounds able to form hydrogen bonds with extracting phase components.

In an early study of extraction into hydrophobic DES from aqueous media,[259] a mixture of decanoic acid and quaternary ammonium salts was used to extract volatile carboxylic acids (acetic, propionic and butyric acids). Verma *et al.*[274] extracted lower alcohols (ethanol, propan-1-ol and n-butanol) into hydrophobic mixtures based on menthol combined with decanoic and lauric acids in a definite proportion. Extraction of a number of phenols into menthol – fatty acid (C_8, C_{10}, C_{12}) deep eutectic solvent[351] and a liquid mixture of C_8-C_{12} fatty acids was described.[292] The extraction technique used in the last-mentioned paper is notable: the solvent (acid mixture) was converted, by increasing pH, into a dispersion of the corresponding salts in the sample bulk and then the initial liquid mixture of acids was regenerated by acidifying the sample.

Kaul *et al.*[275] reported the extraction of some aromatic compounds with various substituents (toluene, chlorobenzene, aniline, phenol and benzoic, toluic, salicylic and phthalic acids) into DES based on decanoic acid in combination with menthol and quaternary ammonium salts. The extraction of polyfunctional organic compounds into hydrophobic DES was also described in the literature. Neonicotinoid pesticides were extracted into DES based on fatty acids in combination with menthol or with tetrabutylammonium chloride;[261] and the antibiotic ciprofloxacin was extracted into a liquid mixture of C_{10} and C_{12} carboxylic acids.[352] Apart from being used in a pure state as an extraction solvent, hydrophobic DES were used to impregnate polymer membranes.[353]

Aqueous biphasic systems based on eutectic mixtures. Aqueous biphasic systems are efficient, first of all, for extraction of highly hydrophilic compounds.

As noted above, the composition of phases responsible for extraction in these systems can crucially differ from the composition of the initial DES due to its dissociation in the presence of water. Many authors still do not pay attention to this circumstance and describe extraction into ABS based on DES, although they actually deal with extraction into a four- (and more) component ABS, the true components of which are water, salting-out agent and the participants of the initial eutectic solvent. On the one hand, from the practical standpoint, it is not very important whether DES has been retained in the aqueous biphasic system as long as the desired recovery is attained. On the other hand, ignoring the actual composition of ABS hampers the understanding of the essence of the involved processes, and therefore, interferes with the rational choice and design of new extraction systems.

Aqueous biphasic systems based on DES were employed for the extraction of biological macromolecules such as DNA (TBABr — ethylene glycol and Na_2SO_4 as a salting-out agent)[354] and proteins: BSA (a ChCl mixture with

polyols, and K_2HPO_4 as a salting-out agent),[355] trypsin, ovalbumin (urea – betaine and a K_3PO_4 and K_2HPO_4 mixture as a salting-out agent),[356] papain [ChCl – polyethylene glycol (20 : 1) and Na_2CO_3 as a salting-out agent].[357]

Efficient extraction of a broad range of water-soluble low-molecular-weight organic compounds (amino acids, alkaloids, phenolic compounds) was reported by Farias *et al.*[265, 358] The authors described extraction in the ChCl – glucose – polypropylene glycol system [358] and the application of DES based on ChCl and a number of alcohols (with K_2HPO_4 as the salting-out agent).[265] Dyes of various structures meant for various purposes, which are often ionogenic, can also be efficiently isolated (separated) using ABS based on DES (composed of ChCl and several alcohols with K_2HPO_4 as the salting-out agent).[265] Zhang *et al.*[359] extracted the Sudan III, amaranth and sunset yellow dyes into a 1 : 2 TBABr – polypropylene glycol mixture with betaine as the salting-out agent. Passos *et al.*[153] demonstrated highly efficient separation of Sudan III and PB29 ultramarine pigment (ChCl – carboxylic acids – propylene glycol).

Microextraction preconcentration. Microextraction with DES is utilized for the isolation and subsequent determination of a wide range of organic compounds (usually pollutants) in aqueous matrices.

Compounds of various classes can be extracted: biologically active compounds,[360] active ingredients of pharmaceutical products [361, 362] (including antibiotics,[264] narcotic drugs [363] and antibacterial agents [364]), dyes,[365 – 368] aromatic hydrocarbons and their substituted derivatives [306, 333, 369] (in particular, polycyclic [267]), phenols,[370] phthalates,[371] organophosphous compounds [372] and pesticides.[309, 329, 373] The analyte determination in the concentrate phase is mainly performed chromatographically, using high-performance liquid chromatography [369] and gas chromatography,[363] with various types of detection, as well as using spectrophotometry.[366]

Extraction from non-aqueous media. Liquid – liquid extraction into DES from non-aqueous media is currently actively developing. Considerable attention is paid to extraction from vegetable oils. Among the target components, the first mention should be made of biologically active compounds (antioxidants,[374] vitamins [375] and so on), dyes [376] and metal ions.[377] Many studies on extraction from non-aqueous media are devoted to the application of DES for purification of oil refining products (removal of nitrogen and sulfur compounds, dearomatization) and biodiesel (removal of glycerol and other undesirable impurities);[378] DES were also used to isolate compounds of various classes from coal tar.[379] A number of studies address the application of DES for separating mixtures of molecular solvents [380] (including azeotropes [381]) and removal of minor amounts of water.[382, 383]

Extraction from solid materials (leaching). Extraction from solid materials is one of the key existing DES applications. The greatest number of studies are concerned with isolation of valuable components and component groups from the biomass. DES extraction of plant biomass was used to isolate biologically active compounds [384] (mainly antioxidants, a number of which was described by Ramón and Guilenna [279]), (poly)saccharides,[385, 386] dyes,[387] lipids,[388] various contaminants (mycotoxins,[389] pesticides,[390] herbicides [391] and inorganic contaminants, metal ions [392]). Special mention should be made of the actively developing use of DES for wood delignification.[393]

Along with the use of DES for primary processing of plant raw materials, an important application of DES is isolation of valuable products from secondary sources such as biomass processing waste.[394] The DES extraction of animal sources is used to isolate peptides,[395] proteins,[396] chitin [397] and organic [398] and inorganic [399] toxicants.

The number of publications on DES extraction of other solids is moderate in comparison with the number of papers on biomass extraction. Note studies on metal leaching from natural sources [400] and from secondary raw materials.[336, 401]

Extraction (absorption) of gases. The use of DES for gas extraction is mainly described in the publications on the isolation of carbon dioxide from gas mixtures (see, *e.g.*, Ref. 402). However, there are also publications on the use of DES for absorption of sulfur dioxide,[403] hydrogen sulfide,[404] ammonia,[405] nitrogen oxides [406] and other gases. Details of various approaches and the current state of studies in this field are summarized in reviews.[407,408]

5. Conclusion

The interest of chemists in combined solvents has spread beyond the field of liquid organic salts (ionic liquids). The range of available combined solvents has sharply extended in the last decade and continues to grow owing to the use of organic salts in aqueous biphasic systems and expanding the field of eutectic mixtures.

Currently, the most studied CS are ionic liquids, especially those with fluorinated anions and substituted imidazolium cations. In most cases, they are relatively chemically inert and are not prone to specific solvation of the extracted substances or to complexation with metal ions. Frequently used alternatives to these ILs are salts of substituted ammonium and phosphonium cations with readily available anions, particularly, carboxylate anions and their derivatives and surfactant anions (with are usually cheaper). Complexing ILs are being actively studied; most often, these are ILs with complexing anions. An adjacent type of ionic liquids is the series of unusual hydrophilic-hydrophobic ILs, which are immiscible with water and are poorly soluble in water, but contain large amounts of water (> 50 mol.%). These solvents are suitable for the extraction of highly hydrophilic compounds and metal ion complexes. Analytical chemists often use microextraction, which neutralizes the drawbacks inherent in many ILs, that is, relatively high cost and excessively high viscosity.

Aqueous biphasic systems based on ionic liquids revolutionized the field of ABS and expanded the scope of applicability of ILs in extraction due to application of water-soluble ILs. Currently, it is clear that ABS can be obtained from various organic salts, which should not necessarily be liquid; therefore, the range of available and effective ABS is extended.

Of particular note are ABS based on organic salts that are formed without a salting-out agent and, hence, are free from the drawbacks associated with its use. In the future, the attention to these systems should be expected to increase. Apart from organic salts, ABS based on hydrophilic solvents are used more and more often. Organic salting-out agents and other phase-separating agents (sugars, amino acids), which are more advantageous for many applications than inorganic salts, started to be widely used.

Another vigorously developing field of research is concerned with combined solvents called deep eutectic solvents, which expanded the possibilities of obtaining liquids based

on organic salts beyond the range of ionic liquids. The studies in this field are still mainly carried out by the trial-and-error method, with the number of combinations of components to be studied being almost unlimited. However, some theoretical concepts have already been formed and the most important available classes of DES have been defined, including those composed of biocompatible and renewable raw material-based substances. Deep eutectic solvents containing no organic salts also appeared (so-called type V,[253, 254] *e.g.*, menthol – thymol).

The major problem associated with the use of DES in extraction is the possibility of their dissociation on contact with water due to the destruction of hydrogen bonds between components. This problem does not arise when extraction is carried out from non-aqueous media; studies addressing this issue are already rather numerous.[279, 378, 407] This also refers, to some extent, to the extraction from solid materials. One can hope that new eutectic liquids more suitable for extraction from aqueous media would appear; the search for such DES is an important current task.

A common feature of CS is the relatively high molecular weight of the components compared to conventional solvents. The latter are rather easily purified and can be obtained in highly pure state. The amount (concentration) of impurities usually increases with increasing molecular weight of the major component of the solvent. In the case of preconcentration of micro quantities of target compounds that are not chemically inert towards impurities, this can result in non-linearity of the distribution isotherms. Thus, the development and advancement of approaches to the preparation of high-purity CS and their components is of interest for research.

Generally, combined liquids opened up broad opportunities for the preparation of extraction solvents with diverse and unusual properties. The application of organic salts, especially the salts composed of biocompatible cations and anions, gives hope for green nature of these solvents, which is an important benefit. The large number of possible combinations, the potential chemical diversity of the class and the wide opportunities for tuning the properties are, perhaps, even more important advantages of the combined solvents.

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6. List of acronyms and designations

ABS — aqueous biphasic systems,
TSIL — task-specific ionic liquid,
BChCl — benzyldimethyl(2-hydroxyethyl)ammonium chloride,
$C_2C_1ImTf_2N$ —1-ethyl-3-methylimidazolium bis(triflyl)imide,
$C_4C_1ImPF_6$ — 1-butyl-3-methylimidazolium hexafluorophosphate,
$C_4C_1ImTf_2N$ —1-butyl-3-methylimidazolium bis(triflyl)imide,
$C_1C_1C_4ImTf_2N$ — 1-butyl-2,3-dimethylimidazolium bis(triflyl)imide,
Ch — choline,
ChCl — choline chloride,
CIL — complexing ionic liquid,
Ch-IL — choline ionic liquid,
CS — combined solvents,
CYPHOS IL 104 — trihexyl(tetradecyl)phosphonium bis(2,4,4,trimethylpentyl)phosphinate,
EL — eutectic liquid,
DES — deep eutectic solvents,
DLLME — dispersive liquid – liquid microextraction,
HF-LPME — hollow fibre liquid phase microextraction,
HHIL — hydrophilic-hydrophobic ionic liquid,
IL — ionic liquid,
LME — low-melting extractant,
LMM — low-melting mixture,
MDES — magnetic deep eutectic solvents,
MIL — magnetic ionic liquids,
SDME — single-drop microextraction,
THADHSS — tetrahexylammonium dihexylsulfosuccinate,
TOALS — tetraoctylammonium *N*-lauroylsarcosinate,
TOMAS — trioctylmethylammonium salicylate.

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