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Classical and non–classical non–aqueous solvents–An overview about some recent developments

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Nonaqueous solvents have become versatile media in modern chemistry, offering tunable properties, sustainable processing, and access to reactivities challenging in water. Recent advances in the development and synthesis of classical and molecular solvents from renewable resources, particularly driven by sustainability considerations, have significantly expanded their range of applications.
These developments can be rationalized within a unified framework based on how solvent structure and dynamics govern mesoscale organization and function. **Structurally programmable solvents**, such as ionic liquids and deep eutectic solvents, provide tailored solvation landscapes through specific intermolecular interactions, enabling selective extraction, catalysis, and molecular recognition. **Stimuli-responsive systems** introduce dynamic control, where external triggers (e.g., temperature, pH, CO_2) modulate phase behavior, polarity, and interfacial properties, thereby coupling reaction and separation processes. **Self-organizing and transient solvent systems**, including microemulsions, nanostructured domains, and ephemeral solvents, generate compartmentalized environments that mimic soft-matter systems and allow spatial and temporal control over reactions. Finally, **bioinspired and hybrid solvents**, such as NADES (Natural Deep Eutectic Solvents) and CO_2-based mixtures, integrate multiple functionalities and enable the stabilization of complex biomolecules alongside efficient processing routes. Across these categories, a common paradigm emerges: solvent systems are no longer passive media but actively engineered components of chemical processes. Their ability to integrate functionality, responsiveness, and sustainability highlights their central role in advancing modern chemistry. In this context, environmental impact will remain a key criterion in the future development of next-generation solvents, complementing classical performance metrics.

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Introduction

Why do we need nonaqueous solvents? This is a good question. Hydrophobic substances can be dissolved in aqueous environments with appropriate solubilizers (surfactants, hydrotropes, anti-crystallization agents, etc.). More and more is known about such solutions, which are also applied in industrial processes and for products. Yet, water has a disadvantage: its high enthalpy of evaporation makes it quite cost intensive to purify it via distillation. So other methods like precipitation of impurities or solutes and phase separations in general should be considered as alternative separation processes.

Over the last decades, there have been many attempts to classify the different types of solvents, like the empirical solvent polarity parameters, the dipole moment, or the Hansen solubility parameters [1,2]. Also, criteria for the “greenness” of solvents have been established. Note that there is an increasing number of tools and programs to estimate the “greenness” of solvents [3].

In total, we can state that a good solvent must

- ensure a sufficient solubility of the targeted solute
- be stable (chemically inert, not flammable, and temperature stable)
- of low or best negligible corrosiveness
- fulfil economic requirements (price, availability in sufficient quantities, and best offered by different suppliers)
- have a good health, safety, and environment (HSE) profile
- be easily removable.

Of course, there are also various physical–chemical parameters that must fit to the individual application, for example, viscosity and surface tension.

A classical nonaqueous solvent is ethanol. It is easy to purify via distillation, but it is also inflammable and potentially explosive. Even mixed with water, its flash and explosion points are still low up to high concentrations of water [4]. All this is also true for other short-chain alcohols, to a certain extent. Therefore, still chlorinated solvents like dichloroethane or chloroform are widely used in industry. They can be easily removed by evaporation without being explosive. Although ethanol and 1,2-dichloroethane (DCE) exhibit similar flash points, their overall hazard profiles differ substantially. Chlorinated solvents such as DCE typically have higher vapor densities, narrower explosive limits, and reduced tendency to form highly flammable vapor—air mixtures, which can simplify process control despite their toxicity. Consequently, they are often preferred in practice due to their chemical inertness and more manageable flammability behavior under controlled conditions. Further, due to their C—Cl-bond, they present unique solubilization properties. As a consequence, they are still industrially used as cleaning solvents. Even in the synthesis of caffeine (or its extraction from coffee powder), they are preferably used [5]. A further reason for this is their selectivity. They are not totally hydrophobic; the C—Cl-bond confers them unique properties between hydrophobicity and polarizability. Particularly partially chlorinated compounds display a distinctive feature among solvent classes: they contain strongly CH-acidic bonds capable of hydrogen bonding. However, this property alone does not confer uniqueness. Their singularity stems from the minimal involvement of nonbonded interactions with chlorine atoms: the likelihood of (O/N)—H···Cl hydrogen bonds is limited to 6%, while halogen—halogen interactions occur with probabilities below 15% [6]. This combination enables these solvents to act as pure hydrogen-bond donors (HBDs) without exhibiting acceptor characteristics, allowing especially, but not exclusively, good interactions with electron-rich solutes. Consequently, only a few alternatives fulfil both criteria simultaneously. Unless the organic solvents are chlorinated, always a compromise must be found between an economically reasonable distillation and the costs of protection against inflammation and explosion [7].

But indeed, chlorinated solvents pose environmental problems and will be banned progressively form industrial application.

Dimethylsulfoxide (DMSO) is also a widespread solvent. It is a small molecule, which is advantageous for solvent performance. Small molecular size facilitates diffusion into large or dense structures, similar to the behavior of water. In addition, reduced molecular size is associated with a favorable entropic contribution to solvation and transport processes. Further, DMSO is highly polar and stable. It is widely used as a solvent due to its high polarity and slightly amphiphilic structure, which allows it to dissolve both polar and nonpolar compounds efficiently. This dual solubility makes DMSO particularly effective as a carrier for bioactive compounds, facilitating their transport across alternating hydrophilic and hydrophobic barriers, such as the skin. Additionally, its high dielectric constant stabilizes ionic and polar species in solution, further enhancing its utility in pharmaceutical formulations and chemical reactions [8,9]. Although petrol-based, it has an acceptable toxicity profile and it is rather cheap and an excellent solvent. dimethylformamide (DMF) with a high boiling point (yet low flash point) and N-methyl-2-pyrrolidone (NMP) are further industrial solvents, not to forget tetrahydrofurane [10], for which alternatives are searched. Besides their toxicity, they are all petrol-based and as such, and in a general attempt to transform the world of solvents to biobased ones, no longer well considered in industry. However, as long as no alternatives are presented for a decent price and at sufficiently high quantities, they are still tolerated.

The best would be a low-toxic and bio-based solvent that is readily biodegradable and, very best, even comestible. Fortunately, there was some progress in this direction within the last years. Here are some examples:

- **γ-valerolactone** can be made from waste biomass (hemicellulose). It is readily biodegradable and is even comestible in small doses . Further, it is an excellent solvent for numerous important substances and could partly replace DMF and NMP in the future. It is fully water miscible (which can be an advantage and a disadvantage in applications) and it is a good graffiti remover. It even dissolves several industrially important polymers, a fact, which could be used for recycling processes. Further details about this solvent can be found in Reference [11]. Due to a significant industrial production starting in 2026 in Germany, it can be purchased in large quantities at a moderate price [12].
- **Solketal (Isopropylidenglycerin)** is an excellent glycerol-based solvent that is considered to be of very low harmfulness. It is based on glycerol, a by-product of biodiesel production and as such partially bio based [13]. However, it requires the use of acetone, and the ketal can open, under certain circumstances, and release acetone to the environment, which is not desirable. On the other hand, acetone is even used for certain plant extractions, e.g. ginkgo [14].
- **Ethyl acetate** is a common organic, relatively hydrophobic, yet a polar solvent that occurs naturally and can be produced from biomass. It is widely used for plant extraction processes. Yet, it is more and more considered to be harmful, if exposed to it over a longer time period, despite its low acute toxicity [15].
- **2-Methyltetrahydrofuran** or **2-methyl-THF** can be produced from biomass. Since 2023, it is allowed in the European Union as a solvent for plant extraction. Although it is not harmless, it can replace the even

more toxic hexane in such industrial processes [16]. Despite the slightly higher polarity, 2-methyl-THF has a boiling point similar to that of hexane.

- **Cyrene (dihydrolevoglucosenone)** is a bio-based promising alternative to DMF and NMP; however, it has not yet found its entrance to industry in large quantities.
- **Limonene** is a natural biosolvent, but it has a significant allergenic potential and is highly aqua toxic [17]. This is an example that shows that natural solvents are not automatically the better choice. Note, for example, that the bio-based furfuraldehyde is toxic and carcinogenic [18], whereas the petrol-based 3-methoxy-3-methyl-butan-1ol (MMB) is considered to be ecofriendly [19].
- **Glycerol-1,2-carbonate** is discussed as a potentially very promising biogenic solvent since a long time, but a convenient, cheap, and environmentally acceptable synthesis is still lacking [20].
- **Ethyl lactate** is biogenic, biodegradable, and of relatively low toxicity and has already found various industrial applications [21].
- Very recently, a Swiss group presented a new and very promising class of alternative aprotic solvents with medium polarity produced directly from agricultural waste biomass in up to 83 mol% yield (on xylan basis). The presented xylan acetals are easy to access from hemicellulose and have interesting properties [22].

Of course, in the future, new solvents should be always "green" meaning "greener" than existing solvents. Green does not necessarily mean biobased (although this is highly desired) but at least biodegradable and of low toxicity, both for humans and plants/animals. Here the aqua toxicity is the most crucial parameter. And, availability, REACH-approval (in Europe), and low price will always be further decisive criteria.

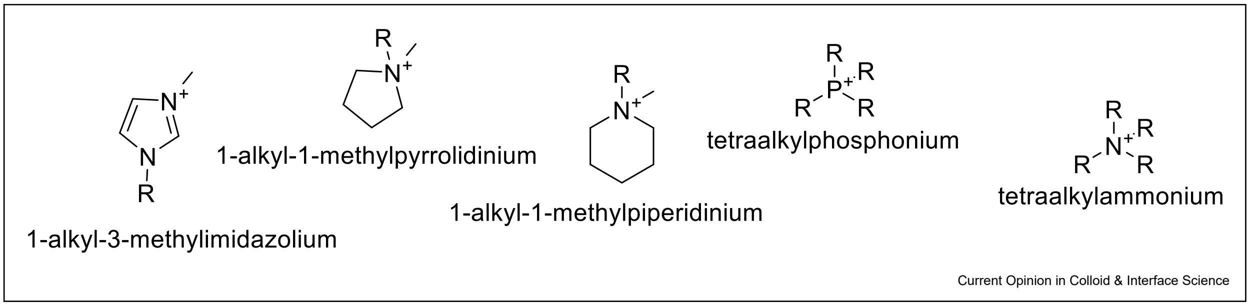
In a seminal paper in 2011, Jessop considered what are the real needs in the field of green solvents [23]. Even 15 years later, his conclusions are still relevant. Among them, it is still true that in industry, we are lacking easily removable polar aprotic solvents. Furthermore it is truer than ever that distillation processes cannot be the future for solvent separation since they require a lot of energy and precaution. It may well be that in future decades, the huge distillation towers will gradually disappear in industry and be replaced by installations of chromatography and phase separation, even at large scales.

In 2012, Aubry et al. published a landmark paper in Green Chemistry, entitled "panorama of sustainable solvents using the COSMO-RS approach" [24]. This work was an extension of an earlier study, in which COSMO-RS had been applied to classify 153 classical solvents and to subdivide them in a rigorous and unambiguous way into 10 classes [25]. In the 2012 paper, 138 green solvents have been chosen according to well-defined criteria such as flammability, toxicity, HSE profile, etc. The COSMO-RS approach was used to compare the solvent properties of these green solvents to those of the classical ones and to allocate each green solvent to one of the 10 solvent classes. The resulting classification is a very valuable starting point for any industrial application, for which more sustainable solvents are desired.

Ionic liquids

Since the beginning of this century, there has been a real hype with ionic liquids (ILs). People tried to sell them as the magic solution for many solvent problems in industry. Thousands of research papers appeared over the years containing detailed studies of cation—anion combinations with melting points below 100°C, a widely used criterion of ILs. Most of the studies concern dialkylimidazolium cations with a significant variety of counter anions [26]. But also pyridinium derivatives, quaternary ammonium ions, and other "bulky" cations are considered for ILs, see Figure 1. All have in common that the unsymmetrical structure of the cations prevents efficient packing and crystallization of the salts thus significantly reducing the melting points. Of course, the anions also play an important role but the main effect

Figure 1



Examples of common bulky cations found in ionic liquids.

usually comes from the cations. For example, 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide has a melting point below −15°C, whereas the classical NaCl has a melting point of 801°C [27]. Despite this huge difference in melting points, there is a common feature: the vapor pressure of both is extremely low [28]. These very low vapor pressure values are the main arguments for their initial classification as "green" solvent. Indeed, there is no risk of air contamination since ILs are certainly not "Volatile Organic Solvents". The downside is, however, that distillation is usually not an option to get rid of them for separation and purification of a solution. This is even a major disadvantage of ILs. Another drawback of ILs is their often high viscosity and sometimes their hygroscopy [29]. By contrast, a good property for application is the usually large temperature range, over which they are liquid. This feature may be useful in some cases. We should also note the high chemical and electrochemical stability of classical ILs.

The electrical conductivity of ILs can be high or low, depending on the dissociation of the ions and of course on the viscosity, which is usually shown by a so-called Walden plot. Walden started from the idea that the product of conductivity and viscosity is constant and that this product only varies with temperature. If negative deviations from such a straight line (as a function of temperature) occur, there is association of ions and consequently, the molar electrical conductivity is lower than expected from the ionic nature of the molten salt.

As far as the solubility of other salts in ILs is concerned, this solubility is usually rather low. However, it turned out that various industrial relevant chemicals can be solubilized in such ILs. Probably, the most prominent example is cellulose, which can be dissolved, for example, in ethyl methylimidazolium acetate with concentrations up to 15 wt% [30]. Of course, then the viscosity is even higher than in the case of the pure IL but nevertheless, such solutions can be interesting systems to replace the viscose process, which is problematic, especially from an environmental point of view. Even the even more hydrophobic natural polysugar chitin could be dissolved in an IL [31].

Despite the huge number of studies on ILs, their real applications are surprisingly rare. Most of the "applications" are limited to academic work and usually declared as "potential" applications. The reason is that ILs present a multitude of disadvantages. As Jessop [23] pointed out, they are not easy to synthesize (in fact several steps are necessary), they are difficult to purify, and finally, they may exhibit a significant toxicity. Note that alkylimidazolium salts are not biodegradable [32] because in nature, no enzyme exists that can cleave the N−C bonds in these cations. Altogether and against all "potential applications" suggested in academic literature, this considerably limits their usefulness to replace other solvents. The known industrial applications up to now of ILs are shown in Table 1. In the future, more large-scale applications probably will appear. For example, the use of dialkylimidazolium salts as excellent cellulose solubilizers in processes, in which textiles are to be recycled and this, despite all known shortcomings of these ILs, is as aforementioned.

A promising class of ILs is "comestible" ones. To prepare them, especially the cations must be harmless. For example, they can be derivatives of amino acids or most prominent, the natural cation choline (former vitamin B4) can be used in combination with various, also "edible" anions such as alkyl carboxylates or saccharinate [38,39]. However, it should be noted that industrially, choline is produced from ammonia and petrol-based sources, so it is not really biogenic. Of course, biogenic variations of choline, such as betaine or carnitine esters, can be also considered [40,41]. Choline-based ILs can for example be used to solubilize suberin, a natural polyester, which is prominent in various barks [42,43]. However, choline has also two shortcomings: first, as a quaternary ammonium ion, it is considered as a neurotransmitter and therefore excluded from any application in cosmetics, at least in the EU [44]. Second, when heating choline salts up to temperatures of 80°C and more (which is quite common to dissolve the desired components), choline can decompose into amines with a very unpleasant smell. As a result, no industrial applications of choline-based ILs are known, despite their undisputable advantages.

In the last years, another type of ILs came up. They are not based on the bulkiness of the cations to prevent crystallization, rather the anions bring in a very significant entropy in the liquid state, which favors this state over the solid one. This was sometimes called the "concept of melting point lowering due to ethoxylation" (COMPLET) [45], which is responsible for the liquefaction of the salts at room temperature. The first examples were so-called TOTO salts, see Figure 2.

Note that the liquid state is probably favored not only due to the high flexibility (and low crystallization energy) of the EO groups but also because of significant annihilation of the charges due to a very strong ion pairing. As a consequence, the electrical conductivity is low. On the other hand, it turned out that also divalent cations and even three-, four-, and five-valent cations can be liquefied by using appropriate counter anions, such as $C_xEO_yCH_2COO-$, which are commercially available in the form of acids (Akypos™). Therefore, these COMPLET-based ILs are easy and cheap to make, they are of low toxicity and they can be applied to liquefy numerous cations from the periodic table of

Table 1

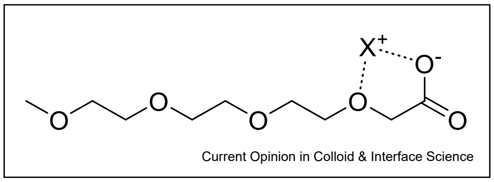
Known industrial applications of ionic liquids according to References [33–37].

Process/application	Ionic liquid/technology	Industrial user	Description
Epoxybutene isomerization	Tetraalkylphosphonium iodide IL	Texas Eastman/Cytec (Solvay)	Isomerization of 3,4-epoxybut-1-ene to 2,5-dihydrofuran, a THF intermediate.
BASIL™ acid scavenging	1-Methylimidazolium chloride (PIL)	BASF	Biphasic acid scavenging with facile phase separation and improved yields.
Toxic gas capture & storage	Lewis-acidic ILs	Air Products/Versum Materials	Reversible complexation and safe handling of toxic gases (e.g., BF_3).
HycaPure™ mercury removal	SILP (Supported Ionic Liquid Phase) with chlorocuprate(II) IL	Clariant/QUILL/ PETRONAS	Removal of mercury from natural gas streams at low concentrations.
SCILL catalysts	Solid catalyst with ionic liquid layer	Clariant	Improved selectivity and lifetime in hydrogenation processes.
Antistatic polymer additives	Quaternary ammonium ILs	3M	Antistatic additives for polymers and coatings.
Pigment dispersion additives	Ammonium/heterocyclic ILs	Evonik (TEGO®)	Improved pigment dispersion in paints and coatings.
Functional additives	Various IL formulations	IoLiTec	Additives for cleaning agents, particle synthesis, and optical materials.
Natural Fibre Welding®	$[C_2mim][OAc]$	Natural Fibre Welding, Inc.	IL-based processing and welding of natural fibers.
PET (poly(ethylene terephthalate)) recycling	IL-assisted depolymerization	Ioniqa	Chemical recycling of PET to monomers.
High-temperature cooling	Thermally stable ILs	Mettop/Proionic	Heat transfer fluids for high-temperature industrial processes.
Lubricants and heat transfer	IL additives	Klüber Lubrication/ Proionic	Improved lubrication and thermal/electrical dissipation.
Ionic liquid piston compressor	Specialized IL	Linde gas	IL used as a liquid piston in gas compressors.
Fluorination catalysis	Antimony-based ILs	Arkema	Catalysts for selective fluorination reactions.
Rare-earth extraction (pilot)	Imidazolium-based ILs	BASF	Selective extraction of rare-earth elements.
Carboxylic acid extraction	Phosphonium ILs	Eastman Chemical Company	Extraction of carboxylic acids from aqueous streams.
Cellulose dissolution & shaping [a]	Imidazolium-based ILs	BASF (licensed)	Dissolution and shaping of cellulose materials.

IL, ionic liquid.

[a] Industrial implementation demonstrated at the pilot scale.

Figure 2



General structure of TOTO salts, with X^+ being a monovalent cation.

elements, for example, rare earth metals. Another advantage of tuning the IL properties via the anions is the fact that these anions can be chosen to function as surfactants. Alkali or multivalent ions just as ammonium ions are possible counterparts [45]. The surface tensions of these surfactants are in the range of comparable charged surfactants [46]. In this case, it is even possible to make an IL that entirely consists of direct micelles in their pure state. Possible applications are not yet explored [45]. Furthermore, catanionic mixtures based on this concept have been explored, which, in aqueous media, are able to overcome the drawback of precipitation under equimolar conditions due to the high flexibility and hydration of the inserted ethylene oxide units [47].

Probably, this concept can be extended to other cation—anion pairs with anionic headgroups that might overcome some drawbacks, like low conductivities or high viscosities, due to very strong carboxylate—cation interactions, which make these ILs currently less attractive for catalytic or electrolyte applications. It can be speculated that in the case of adjusted anions the cations might be very active.

Deep eutectic solvents

As the current applications of ILs are a bit disappointing, many research groups turned to so-called deep eutectic solvents. These are mixtures of two solids or a solid and a liquid with a significantly reduced melting point compared to the melting points of each component. For example, the salt choline chloride has a melting point of 302°C and urea of 133°C. When mixing them at a molar ratio of 1:2, the melting point of the mixture drops to 12°C, so even below room temperature, and a new, thermodynamic stable liquid is formed. The reason is a complex and energetically very favourable hydrogen-bonding network, which has been studied in detail [48].

In contrast to ILs, such a deep eutectic solvent can be made by simple mixing the solid components and the components can be even fully biobased or even completely of biological origin thus reducing their toxicity compared to classical ILs. However, in many publications, concentrated salt solutions in a solvent that is already liquid at room temperature are also called deep eutectic solvents (DESs), without the proof that the melting point of the mixture is really far below the melting point of both components and is lower than expected for a typical eutectic mixture. Unfortunately, this is widely accepted today, despite the fact that it is often against the definition of a deep eutectic point.

Note that ILs and DES are similar in some respects. Per definition, ILs are made of ions, although they can be strongly associated. Many DES form, because of the strong interaction between one ion of the salt and a hydrogen donor (e.g. urea in the aforementioned case) or acceptor. Another example is given in Figure 3.

Mixtures of lactic acid and choline chloride are liquid at room temperature because they form low-melting mixtures (not necessarily a deep eutectic, an expression that would be valid only for the composition with the lowest melting point of the mixture), but the IL choline lactate is also liquid at room temperature [50].

Note that there can be even a continuous cross-over from an IL to a deep eutectic (or at least low-melting) mixture (see Figure 4).

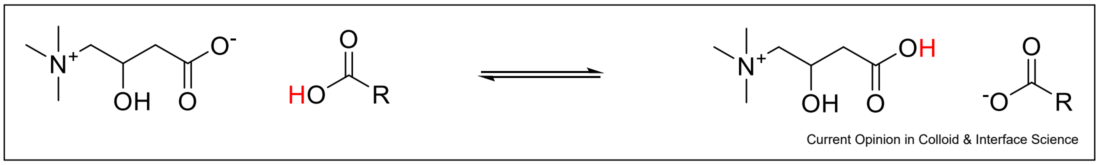
This is possible when one of the two components of the eutectic mixture is a zwitterion and the proton can more or less freely move from one anionic species to the other one.

The reason of the formation of a deep eutectic with a salt and a hydrogen-bond donor (HBD) is well understood today: the anion, for example, the chloride, strongly interacts with the HBD and prevents the crystallization of the salt (and of the HBD itself, of course).

Figure 3

Samples of the LTTM lactic acid/choline chloride with corresponding structure (2:1; photo right) and the IL choline lactate (photo middle) and corresponding structure (left) and the components before mixing (photo left) at room temperature. Photo reproduced from Ref. [49] with permission from the Royal Society of Chemistry. IL, ionic liquid; LTTM, low-transition-temperature mixture.

Figure 4



Equilibrium between an eutectic solvent (two overall neutral species), where the HBA is part of the zwitterion (left) and an ionic liquid, composed of two ions, in the case where the proton is shifted from the HBD to the HBA [51]. HBD, hydrogen-bond donor. HBA, hydrogenbond acceptor.

When the DESs are made entirely of bio-based substances, they are often called Natural Deep Eutectic Solvents" (NADES). Like DES in general, they form new types of solvents that are widely studied today for possible applications. However, the exact composition of the DES/NADES is not necessarily the best one for an optimal solubilization power. We will come back to this point in the section about liquefied solubilizers. Note that most likely nature also takes profit of this concept to liquefy, solubilize, store, and transport solid substances in animals and plants [52].

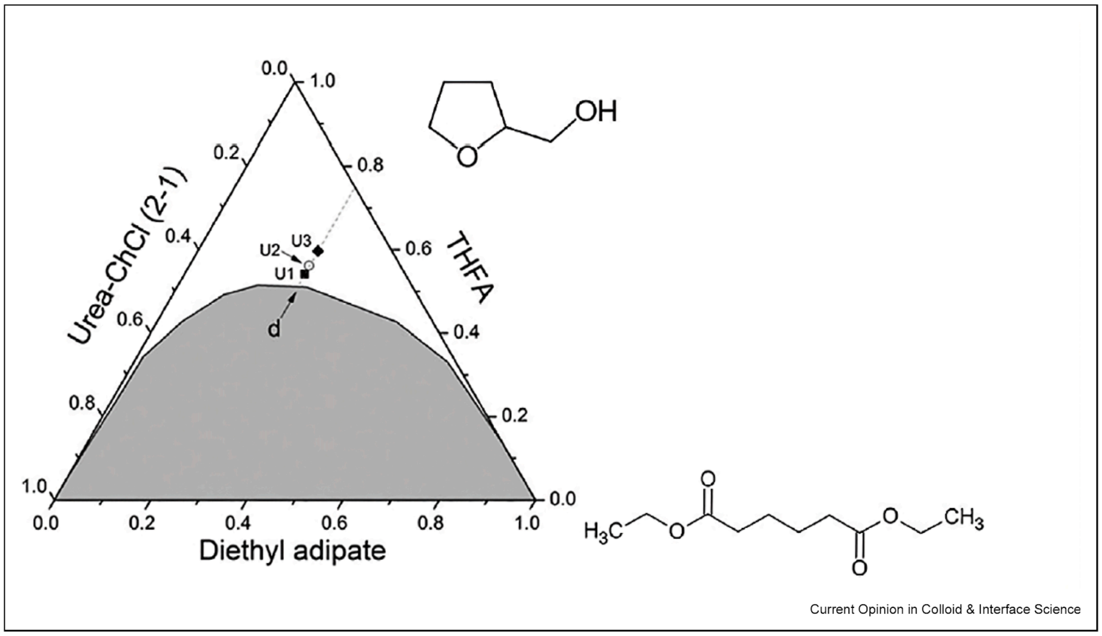
In that sense, the human application of NADES would be "simply" a biomimetic process that nature uses since a long time. In turn, it is possible that the concept of NADES gives new insights into biological processes. It is thought that water-insoluble and at room temperature solid substances in living cells are made liquid and even water soluble by the presence of secondary metabolites that form a NADES [51].

DESs are not always composed of one salt plus an HBD. Nevertheless, this type is widespread in research today. And consequently, these DESs are quite hydrophilic and as such are readily mixing with water. To make them miscible with a hydrophobic solvent, the concept of hydrotropy can be extended to find convenient solvotropes. For example, choline chloride can be mixed with the green solvent diethyl adipate by adding the bio-based solvotrope tetrahydrofurfuryl alcohol, see Figure 5.

In some cases, a hydrophobic DES or even NADES is desired. A good example is the mixture of menthol with lauric acid. Depending on the composition, the mixtures of these two components are liquid at room temperature. However, the melting point of both components (menthol: T_m = 33 °C, lauric acid: T_m = 44 °C) are only slightly above room temperature, so that it is not sure that these mixtures can really be called "deep" eutectics [54]. Note that even the mixtures of fatty acids can exhibit low melting points. For example, fatty acid combinations of C8—10 acids with lauric acid are liquid at room temperature and of low viscosity, giving them desirable characteristics of commonly known solvents [55]. In this case, the melting point lowering of the mixture (melting point around 18 °C) compared to the pure substances is less than 30 °C (the melting point of lauric acid is around 43 °C and that of decanoic acid is only 32 °C); however, this can be sufficient to substitute more toxic, petrol-based solvents. So, a "deep" eutectic mixture is not always necessary.

In any case, DES and especially NADES are interesting potential solvents. To make them compatible with water, this can be done, as usual, by adding a significant amount of hydrotropes, for example, ethanol, to the menthol-lauric acid mixture, further to the classical use of surfactants. Of course, even a hydrophilic DES and a hydrophobic DES can be made miscible by adding a solvotrope (usually an alcohol) [56,57]. DESs, as well as their individual components, can also exhibit hydrotropic behavior. This has been demonstrated, for example,

Figure 5



Making the NADES urea-choline chloride miscible with the green solvent diethyl adipate with the help of the hydrotrope tetrahydrofurfuryl alcohol (THFA). The upper white part of the diagram is the monophasic region, the lower gray part is the diphasic one. Reproduced from Reference [53] with permission.

in the dissolution of Kraft lignin, where DES constituents promote solubilization through specific, non-micellar interactions. However, the often strong intermolecular interactions between DES components themselves may compete with solute—solvent interactions, thereby reducing the availability of favorable interactions with the solute and, consequently, diminishing the overall solubilization efficiency [58]. But in this case, it can be advantageous to work at rations different to the eutectic mixture so that the most solubilizing component of the DES is in access.

Note that even surfactants can be dissolved in the usually hydrophilic, neat DES and can form micelles that help organic substances incorporate into these structures [59,60]. Furthermore, the concepts of ILs and DES can be combined. For example, choline glutarate—choline chloride mixtures are liquids at room temperature even at compositions containing 95—98wt% of choline glutarate. To reduce even further the melting point of this mixture, the HBD urea can be added [61].

As far as possible applications are concerned, the literature is already quite large. For example, it was found that various metal oxides and other metal salts are readily soluble in DES even at significant concentrations [62] and that phosphorous compounds could be extracted from incinerated sewage sludge ash with low energy cost.

In recent literature, there are some interesting reviews about the "potential" use of DES and NADES, especially for plant extraction, in cosmetics and pharmaceutics. And in some of these reviews, also the problems with DES are clearly mentioned. Despite their promising properties, the large-scale application of NADES remains limited by several unresolved challenges. Key bottlenecks include insufficient process efficiency, difficulties in product separation, limited recyclability of the solvent systems, and significant constraints in process scalability [63—66]. Nevertheless, several companies like Gattefossé in France, Des Solutio in Portugal, or BioEutectics in the USA already commercialize or offer formulations based on NADES.

Liquefied solubilizers

The concept of deep eutectic mixtures is very versatile and their possible fields of applications are far beyond the present mainstream research. Currently, we work on two applications that are still only rarely considered:

i) We make DES so that promising (or) already industrially applied solvents that are liquid only at high temperatures can be used at room temperature. As was stated above, working at temperatures significantly above room temperature costs a lot of energy and bears the risk of inflammation or explosion. Here, the DES composition is not necessarily the best composition because on the one hand, a maximum concentration of the—initially solid—component is favourable and on the other hand, a too strong interaction between the two components forming the DES can weaken the solubilizing power of the "solvent" part of the liquid mixture. With this concept, the range of possible solvents can be expanded to chemicals that are solid at room temperature.

An example would be an alternative to 2,5-dimethyl isosorbide (DMI), which is an ether of the bicyclic diol isosorbide. It is a very promising solvent, bio-based and of low toxicity and it is liquid at room temperature, with a melting point around −70°C. However, despite its biogenic nature, it is not biodegradable. A valuable alternative could be 2,5-diacetyl-isosorbide (DAI), which is an ester and as such is readily biodegradable. However, its melting point is 57—58°C [67]. Now imagine a second component which brings down the melting point of the mixture to room temperature but at a low concentration of this second component (not necessarily at the eutectic point). Then, it could be expected that the high concentration of DAI in the mixtures allows for an excellent solubility of several interesting components, just as with DMI, but now in a low-toxic and biodegradable solvent (system).

A second example comes from the perfume and extraction industry. In former times, the so-called "enfleurage" was used to extract the original and mostly total scent from rose petals. To this purpose, the petals were pressed into odorless waxes of biological origin. Over several days, the rose scent molecules diffused into the waxes and could be recovered at the end (after saturation of the wax) by distillation. It is not difficult to imagine that the yield was extremely low and, consequently, the whole process is no longer profitable today. Other processes like steam distillation and solvent extraction (with hexane) turned out to be much more cost effective, however, at the expense of a loss of certain scents that are not or only partially extracted by these alternative processes. And the use of hexane is certainly not a green process, although this solvent can be readily separated from the scents by distillation [68]. Now, a valuable alternative would be to liquefy the waxes, for example, by mixing several long-chain fatty acids so that the melting point of the mixtures drops down to room temperature or at least close to it. Choosing the appropriate fatty acids, the mixture does not inhibit an unpleasant own odor. With this, the old and classical enfleurage process could be transformed to a liquid extraction process or "liquid enfleurage", which industrially is by far better to handle than a process involving a "solid" extractive (the wax), the latter being always handmade and cost intensive.

ii) We can combine the concepts of facilitated hydrotropy and of DES: in facilitated hydrotropy, one hydrotrope (i.e. solubilizer) can significantly enhance the solubility of a hydrophobic component in water. However, the hydrotrope itself is only scarcely soluble in water. Therefore, a second hydrotrope is added that solubilized the first hydrotrope, which in turn then solubilizes the desired hydrophobic compound. If the first hydrotrope makes a DES with the hydrophobic compound or the second hydrotrope transforms the hydrophobic substance and the first hydrotrope to a low melting mixture, the crystallization energy of the mixture is already "paid" and then the mixture of an aqueous solution with this low melting mixture is energetically much easier. For example, valuable plant second metabolites such as polyphenols can be solubilized (and even stabilized, e.g., against oxidation) in water at much higher concentrations.

Concrete promising examples of both directions just as the DES's typical drawbacks in these processes like product separation, recyclability, and constraints in process scalability are currently under examination to clarify whether these concepts are real future options and will be published soon.

Surfactant-free nonaqueous microemulsions

Since a couple of years, so-called surfactant-free microemulsions (SFMEs) with water have raised some interest. To form micellar-like structures, surfactants can sometimes be replaced by hydrotropes. Then, loose aggregates of a hydrophobic solvent in water form that are stabilized by a surrounding higher concentration of the hydrotropes, e.g. ethanol. The advantage is that no surfactants are used that are possibly difficult to be separated after the use of classical microemulsions. It turned out that such SFMEs can even be formed without water. It seems to be a universal concept. Just as it is possible to form micellar systems even in ILs without water, it is possible to build water-free SFME [53]. In recent studies, it was shown that in (micro-)emulsion polymerization, the surfactants remain in the synthesized polymers. By contrast, the structure-stabilizing alcohols in SFMEs can be easily removed by distillation. This type of structuring—often referred to as "pre-Ouzo" structuring—has been utilized to regulate polymer particle size during synthesis. In this context, surfactant-free swollen aggregates act as nanoscale compartments that restrict polymer growth.

Building on this idea, a mesostructured, surfactant-free reaction medium was established for the free-radical polymerization of industrially relevant vinyl monomers. The system consists of water, methyl methacrylate, and small alcohols (ethanol, n-propanol, isopropanol, and tert-butanol) serving as hydrotropes. These SFMEs enable polymerization using either oil-soluble thermal or photoinitiators, as well as water-soluble redox initiators. With the exception of ethanol, which produces a homogeneous phase, all investigated alcohols induce mesostructuring that significantly impacts polymerization kinetics, molar mass, and final morphology.

In such systems, both the partitioning of alcohol into the organic domains and the presence of alcohol-enriched interfacial regions, which exhibit repulsive interactions, play a key role in controlling reactivity. Depending on the resulting mesophase, the polymer morphology can vary widely. [69]. In another example, IL-based surfactant-free microemulsions have been shown to function as soft templates for polymerization and nanomaterial synthesis, such as for the preparation of visible-light-active poly(methyl methacrylate)/TiO_2 nanocomposites, thereby again confirming their utility as polymerization templates [70].

Overall, SFME-based polymerization occupies an intermediate position between conventional solution polymerization and processes based on microemulsions or microsuspensions. Comprehensive overviews of both current and potential applications of SFMEs are available in a recent review article [71].

Of course, the formed micellar-like structures are not as well defined as in the case of classical microemulsions with true surfactants as they lack a distinct interfacial layer. This can be advantageous because mass transfer between the interior and exterior is not hindered and follows simple diffusion. This is comparable to the protein drops in living cells that spontaneously form and built their own, nonaqueous phase in cells [72]. This is quite well studied today, although still widely ignored in biology. However, the lacking distinct interface also entails limitations in terms of structural stability and control over domain size and lifetime. In particular, SFMEs may exhibit a narrower compositional window of stability and a stronger sensitivity to temperature or concentration fluctuations. Systems without water can further lack the pronounced polarity contrast typical of aqueous microemulsions, potentially reducing solubilization capacity for highly polar species and limiting tunability of interfacial properties.

Time will tell whether the SFME concept will ultimately establish itself and prove its broader applicability. It is likely that, depending on the process, conventional surfactant-based systems will remain preferred where well-defined interfaces are required—for example, in certain enzymatic transformations. In contrast, SFMEs may become advantageous in applications where straightforward separation and the avoidance of residual impurities are the primary concerns.

Ephemeral solvents

It is still valid that the best solvent is no solvent. Consequently, dry media reactions or solid–state reactions or solventless reactions are more and more considered. An alternative is ephemeral solvents, which are only made temporarily and vanish after they have completed their task. One example is Jessop's idea of switchable solvents. For example, in his switchable hydrophilicity solvents, the addition (or removal) of CO_2 can unify immiscible hydrophobic and hydrophilic phases in equilibrium (or back). This means, an organic phase can be built and then disappear without adding an organic solvent and the phases' recovery can be made without distillation. In addition, these systems have been shown to stabilize transient colloidal structures such as emulsions or vesicles, highlighting their ability to generate dynamic interfacial environments rather than behaving as simple bulk solvents. Notably, the formation, stability, and eventual disassembly of these structures can be reversibly controlled by the external trigger, allowing interfaces to be created and removed on demand.

Quite a long list of CO_2-switchable properties materials have been studied in the recent past [73]. Some of the most interesting concerning compartmentalization in media are switchable surfactants. These surfactants are mainly cationic and can be activated by the protonation of a nitrogen-containing group, like acetamidines or amines, upon sparging CO_2 gas. Here, dynamic interfacial behavior was shown not only to influence solubilization pathways but also to enable control over mass transport, reactivity, and phase behavior, placing such systems at the boundary among conventional solvents, hydrotropes, and surfactant-based formulations. The phase behavior and thus the aggregate form of the hydrophobic compartment of classical dodecyl sulfate (DS) can be triggered with CO_2 if it was mixed with N,N,N ′-tetra methyl-1,3-propanediamine (TMPDA). CO_2 protonates TMPDA, which noncovalently binds to two DS molecules forming a pseudo gemini surfactant, which tends to shape wormlike micelles. Bubbling N_2 recovers the original state which tends to form spherical micelles.

CO_2-switchable systems are not limited to predominantly aqueous environments but can also operate in nonaqueous media, where the CO_2-induced formation of ionic species triggers aggregation and even reverse micelle formation in organic solvents. For instance, CO_2-switchable amidine systems such as N′-dodecyl-N,N-dimethylacetamidine in mixtures of heptane, *n*-hexanol, and hexamethyldisilathiane form reverse (water-in-oil) micelles upon CO_2 addition, enabling the confined formation of CdS nanoparticles within the aggregates. Subsequent CO_2 removal (e.g., by N_2 bubbling at an elevated temperature) induces micellar disassembly, yielding surfactant-free nanoparticles. Yet, reversible structuring and interfacial organization was also demonstrated in fully nonaqueous systems: CO_2-switchable tertiary amines such as N,N-dimethylcyclohexylamine in nonaqueous mixtures with alcohols (e.g., octanol) exhibit a reversible polarity switch upon CO_2 addition, leading to the formation of ionic species and mesoscale aggregation in otherwise homogeneous organic media. Removal of CO_2 regenerates the neutral amine and disrupts these transient domains.

While some applications are still mainly academic, some industrial processes have already been designed. The mentioned fields of application include here emulsion polymerization, catalysis, soil washing, drug delivery, extraction, viscosity control, and oil transportation [74]. A known process based on a CO_2-switchable system that has been successfully applied industrially is the extraction of oil from soybean flakes, which could be made in such to avoid hexane as a toxic solvent [75].

However, even seemingly optimal solutions must be critically evaluated. CO_2-switchable surfactants and solvents offer attractive reversibility but they also come with several limitations. The need for continuous CO_2 addition and removal introduces process complexity, energy demand, and potential scalability issues, particularly in closed or large-scale systems. Incomplete switching or slow kinetics can lead to residual ionic species, affecting reproducibility and separation efficiency. Moreover, repeated switching cycles may cause chemical degradation or accumulation of impurities, compromising long-term stability. In some cases, the presence of CO_2-derived species (e.g., bicarbonates or carbamates) can interfere with sensitive reactions or catalysts and the requirement for specific amine-based structures may limit the chemical scope and applicability of these systems.

Another example is the formation of an ephemeral low-melting mixture, for example, in the case of the acid-catalyzed esterification of caffeic acid with phenethyl alcohol. In this particular, yet generalizable, example, one of the reactants, here caffeic acid, can be liquefied by the addition of choline chloride. In this mixture, the alcohol is soluble and the esterification reaction can take place. After the reaction has finished, water can be added, in which the added salt is soluble and the product, i.e., the ester, precipitates out of the aqueous solution [76].

A third example is a salt that is soluble in water only at elevated temperatures but then forming immediately a phase separation between one concentrated solution and one diluted solution in water. Note that polymers can also be used for a water—water phase separation [77]. In the case of tetrapentylammonium bromide, the upper phase separation temperature is only slightly above 30°C and as such easily accessible with low energy efforts [78]. At those temperatures, the salt-concentrated aqueous phase widely behaves as an organic solvent. After its use, it is sufficient to cool down the whole system so that at room temperature, the salt precipitates again nearly quantitatively and is therefore easily separated from water without any distillation process. The product, if hydrophobic and floating on top of the water phase, may then be recovered just by decanting it from water.

Another easy to separate solvent medium that is, due to its unique properties and easy accessibility, already widely applied in industrial processes is supercritical carbon dioxide (scCO_2). Its combination of gas-like diffusivity and liquid-like density allows scCO_2 to dissolve a wide range of nonpolar or weakly polar compounds while leaving no residual solvent after depressurization, making it an ideal medium for sustainable chemical processes [79]. The solvent power and selectivity of scCO_2 can be fine-tuned through temperature and pressure adjustments, enabling the targeted extraction of bioactive compounds such as carotenoids, vitamins, and essential oils from natural matrices [79,80].

Recent studies extend the role of scCO_2 beyond classical extraction. It has been successfully applied as a reaction medium for polymerizations and catalytic transformations where traditional organic solvents are typically used. For example, scCO_2 facilitates biomass conversion, chemical modification of cellulosic fibers, and preparation of battery cathode materials, providing high efficiency while eliminating the environmental burden associated with volatile organic solvents [80]. Moreover, cosolvents such as ethanol are sometimes combined with scCO_2 to enhance solubility of more polar substrates, demonstrating its flexibility as a green, tunable, nonaqueous reaction medium [80,81].

However, even approaches often regarded as highly promising, such as the use of supercritical carbon dioxide as an ephemeral solvent, merit a more nuanced assessment. While many technical challenges associated with high-pressure operation have been largely overcome at industrial scale, limitations remain in terms of solvent power, particularly for polar or highly functionalized compounds, often necessitating cosolvents or modifiers. In addition, the strong dependence on precise pressure and temperature control can complicate process windows and reproducibility, and the dynamic changes in density and solvating properties may influence reaction pathways or product selectivity. Consequently, despite its clear advantages, supercritical CO_2 is not universally applicable and must be carefully matched to the specific requirements of a given process.

Conclusion

Nonaqueous solvents have developed into a broad and highly diverse toolbox that reaches far beyond classical ILs and deep eutectic solvents. The systems discussed in this review—ranging from switchable and ephemeral solvents to biomimetic NADES, CO_2-controlled phases, thermoresponsive salt solutions, and self-assembled nanostructures—demonstrate how fundamentally solvent design has evolved. They allow reactivities, separations, and process strategies that would be impossible or prohibitively energy intensive in water or in volatile organic solvents.

Yet despite these advances, the field is far from mature. Many systems remain conceptually promising but are technologically underexplored. Key challenges such as viscosity, recyclability, phase control, long-term stability, and large-scale compatibility still limit their industrial relevance. Addressing these issues will require a shift from discovering ever more exotic solvent classes to understanding how these media actually behave in real processes, under real constraints, and at real scale and how their structuring actively participates in their application power.

If the community succeeds in bridging this gap, nonaqueous solvents will not just complement classical media—they will redefine what a solvent can be.

Declaration of competing interest

There are no competing interests to disclose.

Data availability

No data was used for the research described in the article.

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