

Reviews

Solvents and Solvent Effects: An Introduction

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Abstract:

Solution chemistry is carried out in solvents, that is in liquids under the conditions of application, which can exert a considerable influence on the properties of the dissolved solute species. A short historical overview on the influence of solvents on chemical processes (equilibria, reaction rates) and physical processes (absorption spectra, crystallization) is presented. The term “solvent polarity” is discussed, and a solvatochromic parameter for its empirical determination is mentioned. A classification of solvents according to their chemical bonds is given, with special attention to supercritical fluids, fluoruous solvents, and room temperature ionic liquids as promising new reaction media.

Introduction

Chemical reactions can be performed in the gaseous, liquid, or solid state, but, with good reasons, the vast majority of chemical transformations is usually carried out in the liquid phase in solution. *Solutions* are homogeneous liquid phases consisting of more than one component in variable ratios, when for convenience one of the components, which is called the *solvent* and may itself be a mixture, is treated differently from the other components which are called the *solutes*. Usually, the component which is in excess is called the *solvent* and the minor component(s) is(are) the *solute(s)*.

From the macroscopic point of view, a solvent is a continuum characterized by its macroscopic physical constants such as boiling point, vapor pressure, density, cohesive pressure, index of refraction, relative permittivity, thermal conductivity, surface tension, etc. It is the ideal medium to transport heat to and from endo- and exothermic chemical reactions. From the molecular–microscopic point of view, a solvent is a discontinuum which consists of individual, mutually interacting solvent molecules, characterized by molecular properties such as dipole moment, electronic polarizability, hydrogen-bond donor (HBD) and hydrogen-bond acceptor (HBA) capability, electron-pair donor (EPD) and electron-pair acceptor (EPA) capability, etc. According to the extent of these intermolecular solvent/solvent interactions, there exist highly structured solvents (e.g., water with its strong directional hydrogen bonds, forming an intermolecular network with cavities) and less structured solvents

(e.g., hydrocarbons with their weak nondirectional dispersion forces, filling the available space in a more regular manner).^{1–3} On dissolution of solutes, solvents break the crystal lattice of solid reactants, they dissolve liquid or gaseous reactants, and they can exert a considerable influence on reaction rates and on the positions of chemical equilibria, as well as on the position and intensity of absorption bands of dissolved solutes containing all kinds of chromophores (e.g., in IR, UV/vis, NMR, and ESR spectra).^{4,5}

These general observations were earlier often summarized by a familiar quotation of the famous ancient Greek philosopher Aristotle (384–322 B.C.), which reads in Latin “*Corpora non agunt nisi fluida (or liquida) seu soluta*”, and was translated into English as “*Compounds do not react unless fluid or if dissolved*”, or “*No reactions in the absence of solvent*”; for examples, see refs 5–7. However, according to Hedvall,⁷ this seems to be a misinterpretation of the original text given in Greek as “*Τά υγρά μικτά μάλιστα των σωμάτων*” (Ta hygra mikta malista ton somaton), which is probably taken from Aristotle’s work *De generatione et corruptione*.^{7–8} According to refs 7 and 8c, this statement should be better read as “...it is chiefly the liquid substances which ‘react’” or “...for instance, liquids are the type of

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bodies most liable to mixing".^{8c} In this softened version, Aristotle's statement is obviously considerably less distinct and didactic. In view of the many solid/solid reactions meanwhile known,^{6a,9} it is quite understandable that solid-state chemists were not very happy with the common first version of Aristotle's statement.⁷

The development of modern solution chemistry is embedded in the evolution of general physical chemistry.^{1–4,10,11} Two of the first Nobel prizes in chemistry were awarded to the Dutch physical chemist van't Hoff in 1901 and the Swedish scientist Arrhenius in 1903, mainly for their work in solution chemistry. Further developments in solution chemistry are above all connected with the pioneering work of Raoult, Ostwald, Nernst, Lewis, Debye, E. Hückel, and Bjerrum. More detailed reviews on the development of modern solution chemistry can be found in refs 10, 11.

Whenever a chemist wishes to perform a certain chemical reaction, she or he has to take into account not only the right reactants and their concentrations, the proper reaction vessel, an adequate reaction temperature, and if necessary a tailor-made, task-specific reaction catalyst but also the selection of an appropriate solvent or solvent mixture as the reaction medium. The solvent influence on chemical reactivity has been studied for more than a century, beginning with the work of Berthelot and Péan de Saint Gilles in Paris/France in 1862 on the esterification of acetic acid with ethanol¹² and the pioneering work of Menshutkin in St. Petersburg/Russia in 1890 on the quaternization of tertiary amines by haloalkanes,¹³ which led him to remark that "a reaction cannot be separated from the medium in which it is performed". He studied the S_N2 reaction between triethylamine and iodoethane at 100 °C in 23 solvents and found, for example, that the reaction in acetone proceeds 338 times faster and in benzyl alcohol proceeds 739 times faster than it does in a hexane solution.¹³ A more recent and detailed description of the solvent influence on Menshutkin reactions can be found in ref 14.

The influence of solvents on the position of chemical equilibria was simultaneously discovered in 1896 by Claisen¹⁵ in Aachen, Knorr¹⁶ in Jena, Wislicenus¹⁷ in Würzburg,

and Hantzsch¹⁸ in Würzburg, all in Germany. They studied independently of one another the keto–enol tautomerism of 1,3-dicarbonyl compounds (e.g., acetyl-dibenzoylmethane) and the nitro–isonitro tautomerism of primary and secondary aliphatic nitro compounds (e.g., phenyl-nitromethane). To give a more recent exemplary result, the enol content of pentane-2,4-dione decreases from 98 (32.3) → 55 (1.12) → 43 (0.763) cmol/mol (mol %) in going from cyclohexane to acetonitrile and dimethyl sulfoxide as solvent, respectively, measured IR spectroscopically at room temperature and infinite dilution.¹⁹ The values in parentheses are the corresponding equilibrium constants $K_T = c(\text{enol})/c(\text{keto})$. As expected, in more polar solvents the keto form with the larger dipole moment is favoured in the liquid phase.

The selection of an appropriate solvent or solvent mixture is of paramount importance for not only chemical but also for physical processes such as recrystallization, all kinds of extraction processes, chromatographic separations, phase-transfer catalytic reactions, etc.

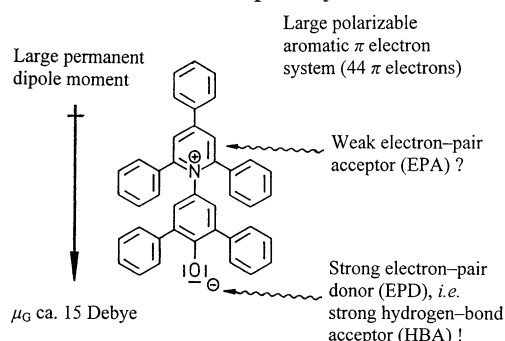
For example, the crystallization of 5-fluorouracil leads to different crystalline polymorphic forms depending on the solvent used: from water → form I and from nitromethane → form II is obtained.^{20a} The polymorphic outcome of this crystallization is obviously determined by the solvent–influenced initial aggregation or prenucleation self-assembly of 5-fluorouracil molecules in solution, mainly induced by intermolecular hydrogen bonding between solute and solvent molecules. The various external factors which determine crystallization processes have been recently reviewed, including the influence of the solvent in terms of solubility and its ability to form solute/solvent hydrogen bonds.^{20b}

Often solvent mixtures are more appropriate media than pure solvents.^{2b} Solvent mixtures compared with their neat components can have improved physical properties, e.g., with respect to their solvation power, density, viscosity, vapor pressure, relative permittivity, refractive index, and freezing or boiling point. For example, water freezes at 0.0 °C and dimethyl sulfoxide at 18.5 °C; however, a binary mixture containing 34 cmol/mol water and 66 cmol/mol dimethyl sulfoxide forms an eutectic freezing at –78.6 °C, which can be used as a cryosolvent.^{2b} A particular property of solvent mixtures must be always taken into account: the composition of the solute solvation shell can differ from that of the bulk solvent mixture. Solute molecules or ions are preferably surrounded by that component with which the larger negative Gibbs solvation enthalpy results. This observation is called *preferential solvation* and leads to molecular–microscopic solute–induced local inhomogeneities in multicomponent solvent systems.^{2b,4}

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Scheme 1. Molecular structure and some ground-state properties of the negatively solvatochromic standard pyridinium-*N*-phenolate betaine dye used for the determination of $E_T(30)$ and normalized E_T^N values as empirical measures of solvent polarity^{4,25,33}



Of particular interest is the influence of solvents on all types of physical light absorption processes, that is on UV/vis, IR, ESR, and NMR spectra, caused by differential solvation of the ground and first excited state of the dissolved absorbing species.⁴ Already in 1878, Kundt in Zürich/Switzerland proposed the rule that increasing solute/solvent dispersion interactions lead in general to a bathochromic shift of the solute's UV/vis absorption band.²¹ The solutes he studied were chlorophyll, fuchsin, aniline green, cyanine, quinizarin, and egg yolk, dissolved in 12 solvents with different indices of refraction. Later, in 1922, Hantzsch in Würzburg/Germany called the solvent dependence of UV/vis spectra *solvatochromism*.²²

Taking into account that UV/vis spectra of chromophores can be influenced not only by the surrounding solvent sphere but also by other surroundings such as micelles, vesicles, gels, polymers, glasses, solids, and surfaces, the use of the more general term *perichromism* (from Greek peri = around) has been recommended by Kosower.²³ Solvatochromic band shifts caused by dye inclusion into protein interiors have been called *enzymichromism*.²⁴

A more recent example of an extraordinarily large *negative solvatochromism* (that is a hypsochromic band shift with increasing solvent polarity) is the intramolecular charge-transfer vis absorption of the zwitterionic betaine dye 2,6-diphenyl-4-(2,4,6-triphenylpyridinium-1-yl)phenolate (Scheme 1). According to its molecular structure, this betaine dye (i) exhibits a large permanent dipole moment, suitable for the registration of dipole/dipole and dipole/induced dipole solute/solvent interactions; (ii) it possesses a large polarizable π -electron system, suitable for the registration of dispersion interactions; and (iii) the phenolate oxygen atom represents

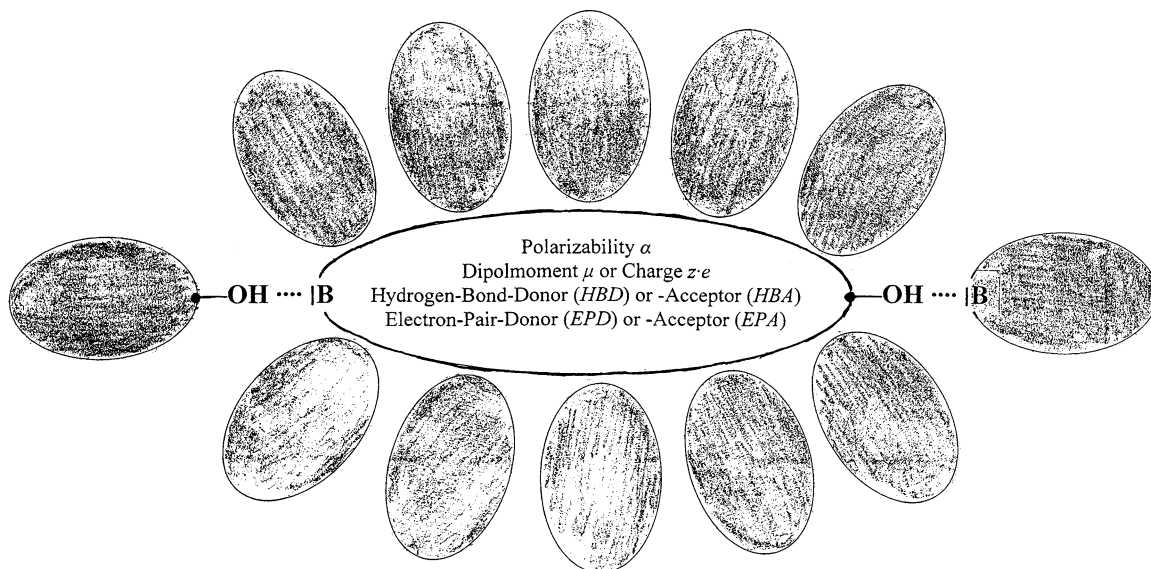
a highly basic EPD centre, suitable for the interaction with HBD solvents and Lewis acids. Because the positive charge is delocalized and sterically shielded, interactions with EPD solvents (Lewis bases) are small and practically not registered. With increasing solvent polarity, the highly dipolar electronic ground state is more stabilized by solvation than the less dipolar Franck–Condon excited state. As result, its long-wavelength CT absorption band is shifted from $\lambda_{\max} = 810$ nm to $\lambda_{\max} = 453$ nm when diphenyl ether is replaced by water as solvent, which corresponds to a solvent-induced band shift of $\Delta\lambda = -357$ nm (or $\Delta\nu = +9730$ cm⁻¹ or $\Delta E_T = 28$ kcal/mol).^{4,25,33} Such solvatochromic dyes can be used as indicators for the empirical determination of solvent polarity. Using this betaine dye as a solvatochromic probe, a comprehensive vis spectroscopically derived solvent polarity scale called $E_T(30)$ ^{25,33a}—also normalized as the E_T^N scale^{25,33b}—has been empirically developed and has found manifold applications.^{25c,26}

The $E_T(30)$ values are simply defined as the molar transition energies (in kcal/mol) of the standard betaine dye shown in Scheme 1, according to $E_T(30)$ (kcal/mol) = $h \cdot c \cdot \tilde{\nu}_{\max} \cdot N_A = 28\,591/\lambda_{\max}$ (nm), where $\tilde{\nu}_{\max}$ is the wave-number and λ_{\max} is the wavelength of the long-wavelength absorption maximum of betaine no. 30,^{33a} and h , c , and N_A are Planck's constant, the speed of light, and Avogadro's constant, respectively. High $E_T(30)$ values correspond to high solvent polarity. E_T^N values are dimensionless and vary between 0.00 (tetramethylsilane) and 1.00 (water).^{33b}

All these solvent effects originate from the nonspecific and specific intermolecular interactions between solute and solvent, as schematically illustrated in Figure 1. The neutral or ionic solute species can have an electronic polarizability α , a permanent dipole moment μ , or a charge $z \cdot e$, which are responsible for the nonspecific interaction forces. They also can act as hydrogen-bond donors (HBD; right-hand side) and/or hydrogen-bond acceptors (HBA; left-hand side) and

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Nonspecific Interaction Forces:

- Instantaneous Dipole/Induced Dipole Forces (Dispersion or London Forces)
- Dipole/Induced Dipole Forces (Induction or Debye Forces)
- Dipole/Dipole Forces (Orientation or Keesom Forces)
- Ion/Dipole Forces (Coulomb Forces)

Specific Interaction Forces:

- HBD or/and HBA Interactions
- EPD/EPA or Charge-Transfer Interactions
- Solvophobic Interactions (only in highly structured solvents such as water)

Figure 1. Schematic two-dimensional illustration of nonspecific and specific intermolecular interaction forces between a solute species (neutral molecule or ion) and 12 solvent molecules in the first solvation shell (taken from ref 52a and reproduced by permission of The Royal Society of Chemistry, London).

as electron-pair acceptors (EPA; Lewis acid) and electron-pair donors (EPD; Lewis base). In highly structured solvents such as water, hydrophobic or more general solvophobic interactions are additionally possible. Because of this multitude of various solute/solvent interactions, it is rather difficult to use single macroscopic physical solvent parameters (or functions thereof) in correlating and predicting solvent effects qualitatively and quantitatively. Interpretation and correlation of solvent effects are much more complex than those of substituent effects, which are only determined by inductive, mesomeric (= resonance), and steric effects, and can be quantitatively correlated by means of the famous Hammett equation,²⁷ a prominent example of so-called *Linear Free Energy Relationships*.²⁸

Chemists usually attempt to understand solvent effects in terms of the so-called solvent polarity. The expression *solvent polarity* can be found in nearly all chemistry text books, but what does solvent polarity really mean? The simplicity of electrostatic solvation models, considering solvents as a nonstructured continuum, has led us to the use of relative permittivities, dipole moments, and refractive indices (or functions thereof) as macroscopic physical parameters of solvent polarity. However, as already mentioned, solute/solvent interactions take place on a molecular-microscopic level, with individual solvent molecules surrounding the ions or molecules of the solute in a noncontinuous, usually highly structured medium (Figure 1). Therefore, in correlating solvent effects, the pure electrostatic approach often failed.

From a more pragmatic point of view, it seems reasonable to define solvent polarity simply as the solvent's *overall*

solvation capability (or *solvation power*). This pragmatic definition was already proposed in 1965,^{29a} but only in 1994 was this definition accepted by the IUPAC committee responsible for the edition of the *Glossary of Terms Used in Physical Organic Chemistry*.³⁰ Accordingly, solvent polarity is simply defined as the “overall solvation capability for (i) educts and products, which influence chemical equilibria; (ii) reactants and activated complexes (transition states), which determine reaction rates; and (iii) ions or molecules in their ground and first excited state, which are responsible for light absorptions in the various wavelength regions. This overall solvation capability depends on the action of *all*, nonspecific and specific, intermolecular solute/solvent interactions, excluding such interactions leading to definite chemical alterations of the ions or molecules of the solute”.^{29,30}

Solvent polarity so defined cannot be measured by means of macroscopic physical solvent parameters such as relative permittivities, dipole moments, etc. Solvent polarity is better measured empirically by means of convenient, well-known, solvent-sensitive reference processes such as, for example, the solvolysis of 2-chloro-2-methylpropane (leading to Winstein's *Y* values³¹) or the UV/vis absorption of solvatochromic functional dyes [leading to Kosower's *Z* values³² or Reichardt's $E_T(30)$ and E_T^N values^{25,33}]. If one carefully selects an appropriate, sufficiently solvent-sensitive reference process, one can assume that this process reflects all possible solute/solvent interactions that are also present in related other solvent-influenced processes. Such reference processes can be considered as a probe of the solvation of the selected standard solute, a probe that sums up a wide variety of

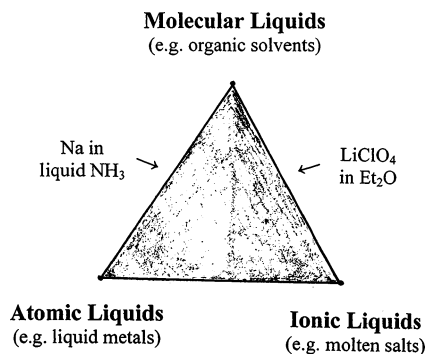


Figure 2. Classification of solvents according to their characteristic chemical bonds (taken from refs 4, 52a and reproduced by permission of The Royal Chemical Society, London).

possible intermolecular solute/solvent interactions (see Figure 1). Probe molecules and model processes used to establish empirical scales of solvent polarity in various ways have been reviewed.^{4,5,25,29}

The number of solvents generally available to chemists working in academia and industry is between 250 and 300^{2–4} (with an infinite number of solvent mixtures), and this number is increasing. According to their chemical bonds, solvents can be classified into three groups (Figure 2): (i) molecular liquids (molecule melts; covalent bonds only), (ii) ionic liquids (molten salts; only ionic bonds), and (iii) atomic liquids (low-melting metals like mercury or liquid sodium; metallic bonds). Many interesting transitions are possible by mixing solvents of these three classes. For example, a 5 M solution of lithium perchlorate in diethyl ether (LPDE), a medium at the borderline between ionic and molecular liquids, is a highly electrophilic reaction medium because of the only partially coordinated reactive lithium cations and can be used for many organic reactions requiring electrophilic catalysis.³⁴ Reactions with concentrated solutions of lithium perchlorate in various organic solvents are commonly carried out under very mild conditions, often at room temperature, but nevertheless, care should be taken because of the oxidative power of perchlorates. Chemical reactions in liquid alkali metals and other metallic melts have been reviewed.³⁵

However, up to now, the vast majority of solvents used in academic and industrial laboratories are molecular liquids, belonging to the group of volatile organic compounds (VOCs), which account for a great proportion of environmental pollution and waste material.

According to their toxicity, volatility, flammability, and environmental hazards, their use is often problematic. Therefore, the development of environmentally more friendly solvents or even solvent-free reactions^{6a,9} is at present of great interest as one of the steps in the direction of “Green Chemistry”.³⁶

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The increasing awareness of the need for more sustainable technologies for the manufacture of fine chemicals and pharmaceuticals has focused attention on the use of alternative reaction media, where an alternative does not necessarily mean new or newly discovered solvents.³⁷

Amongst these alternative solvents, i.e., alternative to common organic solvents, are plain water and a group of so-called neoteric solvents such as supercritical fluid (scf) solvents; perfluorinated (fluorous) solvents; and nonaqueous, at room temperature liquid, (fully) ionic solvents (NART-LIS), also called room temperature ionic liquids (RTIL); see Figure 3.

Since the pioneering work of Breslow et al.,³⁸ using water as solvent in some Diels–Alder cycloaddition reactions, a remarkable renaissance of water as a useful and green solvent for many organic reactions has taken place.³⁹ Even simple organic reactions carried out in aqueous solution can show hydrophobic effects on rates and selectivities if nonpolar parts of the reactant molecules are brought together in the activated complex. The often large rate accelerations observed in water are mainly due to hydrogen-bond stabilization of the polarized activated complex and a decrease of the hydrophobic surface of the reactant molecules during the activation process.^{38c}

In addition to water, some other environmentally benign alternative solvents (Figure 3) such as supercritical fluid (scf) solvents have recently met with growing interest. They are favoured solvents for all kinds of separations (extraction, chromatography) and as reaction media.⁴⁰

Supercritical fluids have the advantage that their properties can be readily tuned by changes in pressure and temperature—and hence in density. By releasing the pressure, they can be

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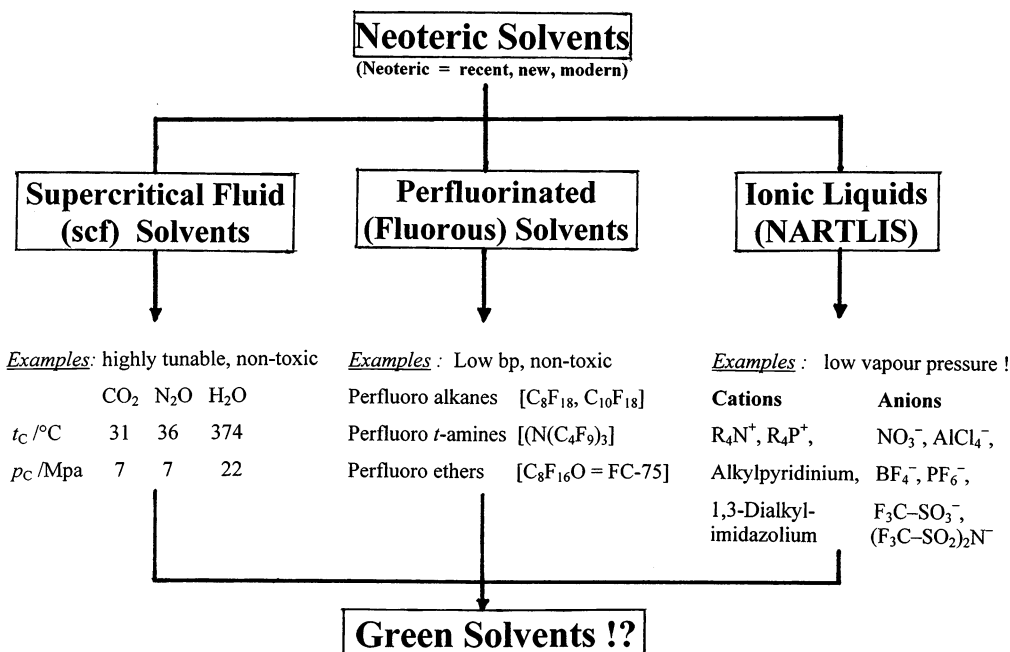


Figure 3. Neoteric solvents as potential green solvents.

easily removed (and recycled), leaving behind the separated solutes or the desired reaction products.

Amongst supercritical fluids, particularly scf carbon dioxide has found many industrial applications.⁴⁰ The solvency of supercritical fluids, i.e., their ability to dissolve the mixtures to be separated or the reactants and products of reactions, depends on their solvent polarity or solvation power. Again, solvatochromic probe dyes have been used to determine this solvent polarity empirically.⁴¹ For example, the $E_T(30)$ or E_T^N values of scf CO₂ correspond to those of hydrocarbons such as cyclohexane.^{41a} This low polarity of scf CO₂ is a disadvantage, but it can be improved by addition of small amounts of more polar cosolvents (protic or fluorous solvents), called modifiers or entrainers.

Another benign solvent of interest is supercritical fluid (scf) water or even simple high-temperature water (HTW) and near-critical water (NCW) in the temperature range 200–350 °C.⁴² As the temperature rises from 25 to 300 °C, the density of water decreases from $\rho = 0.997$ to 0.713 g/cm³, its relative permittivity decreases from $\epsilon_r = 78.4$ to 19.7, its solubility parameter decreases from $\delta = 47.9$ to 29.7 MPa^{1/2}, and its ion product increases by 3 orders of magnitude from $K_w = 10^{-14.0}$ to $10^{-11.3}$. That means that water becomes a stronger acid and a stronger base as the temperature increases and can act as a powerful acid/base catalyst. The change in the relative permittivity makes the solvent polarity of water at 300 °C equivalent to that of acetone at 25 °C ($\epsilon_r = 20.6$).

Consequently, small organic compounds are completely miscible with scf water, whereas ions generally exist as contact ion pairs, resulting in reduced solubility for inorganic salts.⁴²

In analogy to *aqueous* solvents, the term *fluorous* solvents was introduced for perfluoro-substituted alkanes, dialkyl ethers, and trialkylamines by Horváth et al.^{43a} Fluorous solvents are nonpolar, hydrophobic, chemically inert, and nontoxic, with a higher density than the corresponding non-fluorinated solvents (Figure 3). They usually have a limited, temperature-dependent miscibility with conventional organic solvents, forming biphasic solvent systems with such solvents at ambient temperature. With different solubilities for reactants, catalysts, and products, such biphasic organic/fluorous solvent combinations can facilitate the separation of the product from the reaction mixture. Some organic/fluorous biphasic systems can become a single phase at elevated temperatures, which can then serve as a homogeneous reaction medium. After completion of the reaction, cooling down the reaction mixture leads again to the formation of two separate phases. In the ideal case, the product is dissolved in one phase, and the remaining reaction partners in the other, making the isolation of the product very easy. This new experimental technique, using *fluorous biphasic systems* (FBS) with *fluorous biphasic catalysis* (FBC), has already found many applications in synthetic organic chemistry and has been already repeatedly reviewed.⁴³ A variety of fluorous solvents are meanwhile

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commercially available. Because of the comparatively good solubility of gases in fluoruous solvents [e.g., up to 57 mL of O₂ can be dissolved in 100 mL of perfluoro(methylcyclohexane), in contrast to only 3 mL of O₂ in 100 mL of water at standard conditions], they are also good media for aerobic oxidation reactions and have even been tested as artificial blood substitutes.^{43e}

Water, supercritical fluids, and fluoruous solvents belong to the well-known class of molecular liquids (Figure 2). In addition to atomic liquids, ionic liquids represent a quite different group of solvents, consisting entirely of ions in the crystalline and fluid state (Figure 3). Because of its autoprotolysis reaction $2 \text{H}_2\text{O} \rightarrow \text{H}_3\text{O}^+ + \text{HO}^-$, water is in a way also an ionic liquid, however, with rather low ion concentrations of only 10^{-7} mol/L at 25 °C.

In contrast, the ion concentration in ionic liquids such as 1-(1-butyl)-3-methylimidazolium hexafluorophosphate, [bmim]⁺ [PF₆]⁻ (mp 12 °C), is with $c(\text{bmim}^+) = c(\text{PF}_6^-) \approx 4.8$ mol/L, more than 10^7 times larger. There is a continuous transition from pure water via aqueous ionophore (electrolyte) solutions to fully ionic liquids. The increasing electrostatic Coulomb interaction between the solvent particles leads to an increase of the cohesive pressure and the related Hildebrand solubility parameter and to a corresponding decrease of the vapor pressure, which is for fully ionic solvents smaller than the lower detection limit of usual vapor pressure measurements.

Compounds which are already fully ionic in the crystalline and liquid state are called *ionophores*, whereas compounds with molecular crystal lattices which form ions in solution by reaction with the solvent or with itself (autoprotolysis) are described as *ionogens* (e.g., chlorotriphenylmethane and water).⁴⁴

Nonaqueous, at room-temperature liquid ionic solvents are not a recent discovery; they have been known since 1914 when Paul Walden in St. Petersburg/Russia published his seminal paper “Über die Molekulargröße und elektrische Leitfähigkeit einiger geschmolzener Salze”, in which he described the properties of ethylammonium nitrate (EtNH₃⁺ NO₃⁻, EAN; mp 13–14 °C) as the first ionic liquid, purposely prepared for electric conductivity measurements.⁴⁵ He wrote in 1914 (translated from German into English): “The study of molten salts concerning conductivity, density, viscosity, etc., has been thoroughly pursued during the last years. ... Water-free salts were selected, which melt at relatively low temperatures, about up to 100 °C.”⁴⁵ The latter definition is still used today: ionic liquids are defined as materials (ionophores⁴⁴) that are composed entirely of cations and anions and that melt around 100 °C or below as a convenient, arbitrary temperature limit.⁴⁶

These first ionic liquids seem to have been forgotten for a long time. In the meantime, the chemistry of high-melting inorganic molten salts and salt mixtures (eutectics) has been

developed.⁴⁷ However, the application of these purely inorganic ionic liquids as reaction media suffered from the necessary high working temperatures (ca. 150–1000 °C; the lowest-melting inorganic salt eutectics melt at ca. 150 °C) and their often corrosive properties with respect to the reaction vessels.

Over the past decades the use of ionic liquids as reaction media has experienced a renaissance with the introduction of highly asymmetric, diffusely charged organic cations and water-stable, noncoordinating, bulky inorganic anions (Figure 3), which frustrate molecular packing in the crystal lattice.⁴⁶ Amongst them are tetraalkylammonium and phosphonium salts, 1,3-di- and 1,2,3-trialkylimidazolium salts, 1-alkyl- as well as 1,3- and 1,4-dialkylpyridinium salts, and 1,1-dialkylpyrrolidinium salts, to mention only a few. Since the first report on air- and water-stable imidazolium based ionic liquids such as 1-ethyl-3-methylimidazolium tetrafluoroborate, [emim]⁺ [BF₄]⁻ (mp = 15 °C), by Wilkes and Zaworotko in 1992,⁴⁸ a plethora of further ionic liquids has been described in the literature; for a compilation, see ref 49. More recently, so-called *functionalized, task-specific* ionic liquids (TSILs) have been developed by incorporation of additional functional groups in the cations and/or anions, leading to tailor-made ionophores with desired specific properties.⁵⁰

Even ionic liquids with chiral cations and/or anions are already available and have been successfully applied as catalysts and as reaction media for stereoselective syntheses.⁵¹ Because of strong electrostatic Coulomb interactions between the ions of the chiral ionic medium and the reactants as well as activated complexes, enantiomeric excesses up to ee = 44%,^{51b} 84%,^{51c} and 85%^{51d} (ionic liquid as solvent) and ee = 99%^{51e} (ionic liquid as catalyst) have been achieved.

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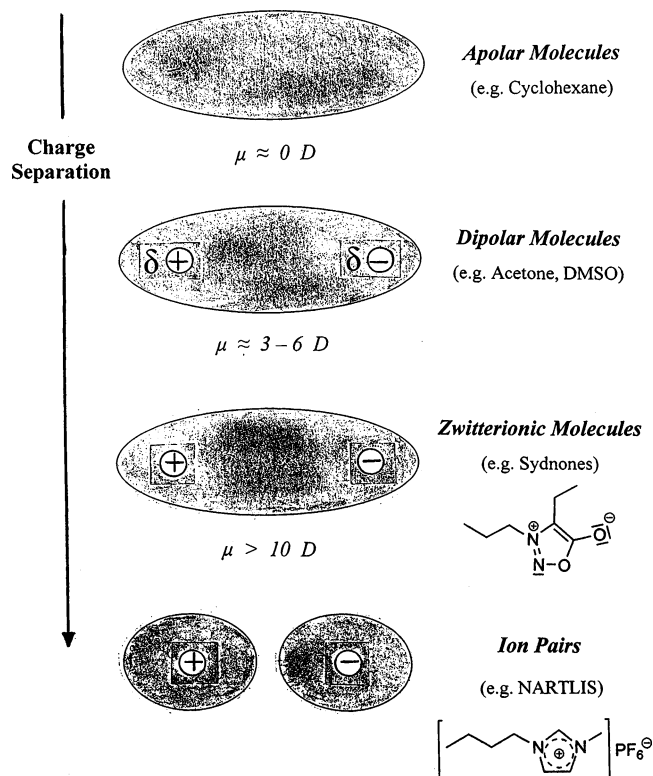


Figure 4. Sequence of solvents with increasing charge separation on going from neutral molecular solvents to molten salts (taken from ref 42a and reproduced by permission of The Royal Chemical Society, London).

What about the polarity of NARTLIS in comparison to conventional molecular liquids? Are they superpolar, equally polar, or even less polar than the commonly used molecular solvents?

The polarity of ionic liquids (i.e., their overall solvation capability^{29,30,52}) has been determined, amongst other methods, by means of kinetic measurements^{52b,c} and solvatochromic probe dyes.^{52a,d,e} In particular, the negatively solvatochromic standard pyridinium-*N*-phenolate betaine dye used to establish the $E_T(30)$ or E_T^N polarity scale (Scheme 1) has been used to characterize ionic liquids empirically.^{25,33} The available $E_T(30)$ and E_T^N values of ionic liquids have been reviewed.^{52a} According to these measurements, the polarity of most ionic liquids is comparable to that of molecular dipolar non-HBD (“aprotic”) and dipolar HBD (“protic”) solvents (HBD = hydrogen-bond donating). That means they behave not as superpolar but as quite normal polar solvents. This is not unexpected if one compares the continuously increasing intramolecular charge separation on going from neutral apolar solvents via dipolar and zwitterionic molecular solvents to the ion pairs of molten salts, as illustrated in Figure 4. Ionic liquids appear as the logical end of this sequence of solvent groups. Each solvent ion is surrounded

by a sphere of oppositely charged other solvent ions with complete dissociation, because an imaginary ion pair lacks stability as the electrostatic attractive forces between the ions of an ion pair is nullified by the equal attractions of each ion with all its surrounding ions.

This estimate of the polarity of ionic liquids is at least qualitatively supported by their comparatively low relative permittivities (“dielectric constants”), which are for five 1-alkyl-3-methylimidazolium-based solvents in the range of $\epsilon_r = 9–15$ at 25 °C,^{53b} with ethylammonium nitrate (EAN) as an exception ($\epsilon_r = 26$).^{53a} Because of the high intrinsic electrical conductance of ionic liquids, their ϵ_r values were indirectly determined by means of microwave dielectric spectroscopy (MDS) in the MHz/GHz wavelength regime.⁵³

Being for a long time more or less a subject for academic research only, ionic liquids are now commercially available and are going to find their way into a wide variety of industrial applications,⁵⁴ as described recently in an essay entitled “Out of the Ivory Tower”.^{54e}

The range of interesting properties such as chemical stability within a large temperature range, nonvolatility, nonflammability, high electrical conductance, broad electrochemical window (up to 4 V in some cases), etc. makes NARTLIS valuable alternative solvents for the replacement of environmentally less benign conventional molecular solvents^{36,46} as well as for electrical batteries.³ However, their mostly unknown short- and long-term toxicity and their biodegradability have still to be explored. First systematic studies of the clinical and environmental risks associated with ionic liquids have already been made, with altogether encouraging results up to now.⁵⁵ Their nonflammability has been recently questioned: despite their low vapor pressure, many organic ionic liquids are indeed combustible under certain conditions due to their positive heats of formation, oxygen content, and decomposition products.⁵⁶

The first commercial large-scale use of an ionic liquid has been introduced by BASF AG, Ludwigshafen/Germany, in 2002, using 1-methylimidazole to scavenge hydrogen chloride that is formed in the manufacture of alkoxyphenylphosphanes (= precursor for photoinitiators) from chlorophenylphosphanes and alcohols in the so-called BASIL process (= Biphasic Acid Scavenger utilizing Ionic Liq-

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uids).⁵⁷ The substitution reaction results in the *in situ* formation of the ionic liquid 1-methylimidazolium chloride, [Hmim]⁺Cl⁻ (mp = 75 °C), which separates as a clear liquid phase from the pure product and is recycled. 1-Methylimidazole simultaneously acts as a catalyst accelerating the rate of the substitution reaction.^{57c}

In summary, the full utilization of the possibilities included in the solvent triangle of Figure 2 for the selection of appropriate non-VOC media for chemical or physical processes under consideration has opened up, in academia and industry, rapidly increasing research in the field of old and new, environmentally more benign solvents, particularly with respect to their use as media for phase separations and chemical reactions.⁴ For the development of a sustainable green chemistry⁵⁸ the best solvent would certainly be no solvent at all. Therefore, considerable efforts have recently been made to design reactions that proceed under solvent-free conditions, using modern techniques such as reactions on solid mineral supports (e.g., alumina, silica, clays); solid-state reactions without any solvent, support, or catalyst between neat reactants; and solid–liquid phase-transfer catalysed and microwave-activated reactions, as well as gas-phase reactions.⁹ However, most organic reactions cannot

be carried out in the absence of a solvent; some exothermic reactions would even proceed explosively without the moderating influence of a surrounding reaction medium. Therefore, the search for new solvents and their specific solvation properties as well as the study of solvent effects on reaction rates and chemical equilibria will certainly not become superfluous in the foreseeable future. This special issue devoted to solvent effects in *Organic Process Research & Development* is aimed at describing topical research in this field from the point of view of an industrial chemist, who is daily confronted with the question: Which solvent should I use for the planned process under study? For this selection, he needs not only his subjective sure instinct but also an additional reliance on many objective, qualitative, and quantitative rules and facts.^{1–5} As ever, an intelligent choice of the proper solvent or solvent mixture is essential for the realization of certain chemical transformations or physical processes.

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