1   Chemistry in Alternative Reaction Media

Chemical reactions do not occur in isolation, but within an environment that is dictated by the surrounding molecules, atoms and ions. This environment can be called the *medium*, and may consist of other reactant molecules in the gas phase, or neighbours within a crystal lattice. In many cases, however, a *solvent* of some kind is used as the reaction medium, and the reactants are *solutes*. A solvent and a solute may be defined as follows:

Two compounds which mix together to give a single, homogeneous liquid phase.

In general, the compound present in greatest quantity is the solvent and the other is the solute. Although all compounds may behave as solvents, it is only those that are liquid at room temperature which are usually classed as such. Solvents are widely used in all aspects of chemistry: in synthesis, chromatographic separation, dilution, extraction, purification, analysis and spectroscopy, crystal growth and cleaning [1, 2]. Solvents may also be reactants; reaction of a solvent is known as *solvolysis*. Since any compound is a solvent, at least in principle, then the ability to select the right one for a particular task is essential. A solvent for a particular application might be selected on the following criteria:

1   The effect that the solvent has on the chemical reaction's products, mechanism, rate or equilibrium.
2   The stability of substrates, products and (often delicate) catalysts, transition states and intermediates, in the solvent.
3   Suitable liquid temperature range for useful reaction rates.
4   Sufficient solvent volatility for removal from the product by evaporation or distillation.
5   Cost, which is a particularly important consideration when scaling up for industrial applications.

This chapter outlines the major uses and characteristics of solvents, and discusses some of the problems associated with their use. The remainder of the book describes some of the alternative media in which chemistry may be conducted, and it is hoped that these alternatives will give advantages over conventional
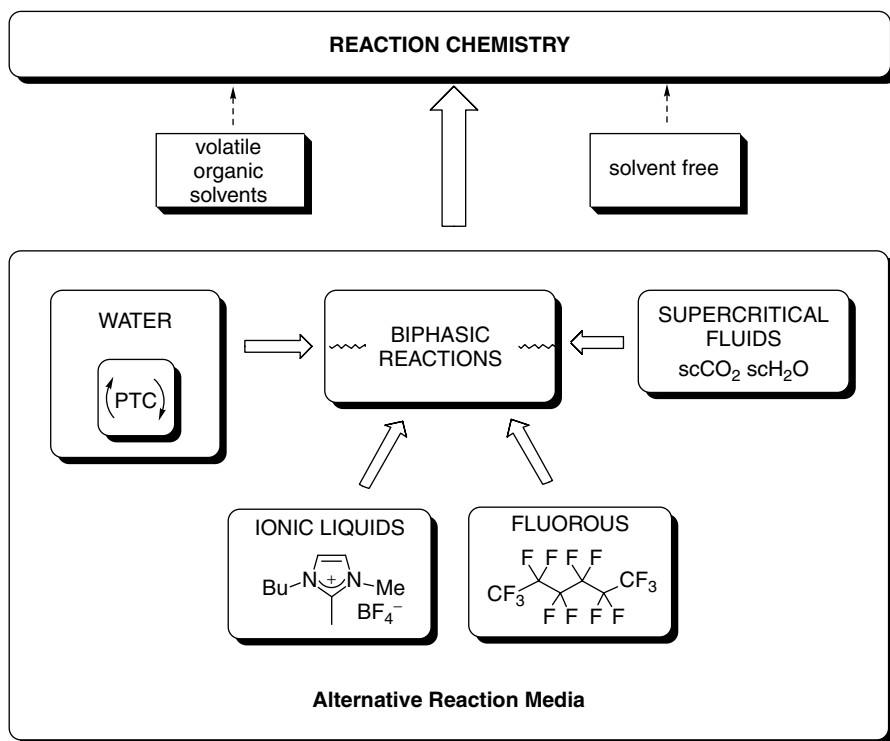
Figure 1.1   Summary of alternative reaction media

volatile organic solvents in terms of improved ease of separation, efficiency and yield. They may even open doors to new reaction chemistry. These alternatives may be used by themselves or in the multiphasic systems described in Chapter 2. Figure 1.1 outlines the solvent systems covered in this book.

1.1   ECONOMIC AND POLITICAL CONSIDERATIONS

Whilst this book focuses on the chemical uses of solvents, it should not be forgotten that, of an estimated 60 million tonnes of synthetic solvents used each year, a large proportion is used for non-chemical applications. Vapour degreasing, dry cleaning and immersion-cleaning of mechanical parts are amongst the largest of these. Figure 1.2 shows some of the major uses of solvents.

Despite their evident utility, the use of solvents in chemical processes must be scrutinized from environmental and economic points of view because solvent use is inherently wasteful. In a chemical process, a solvent is usually added to reactants to facilitate reaction, and is later removed from the chemical product prior to disposal or, preferably, recycling and reuse. Removal of residual solvent from
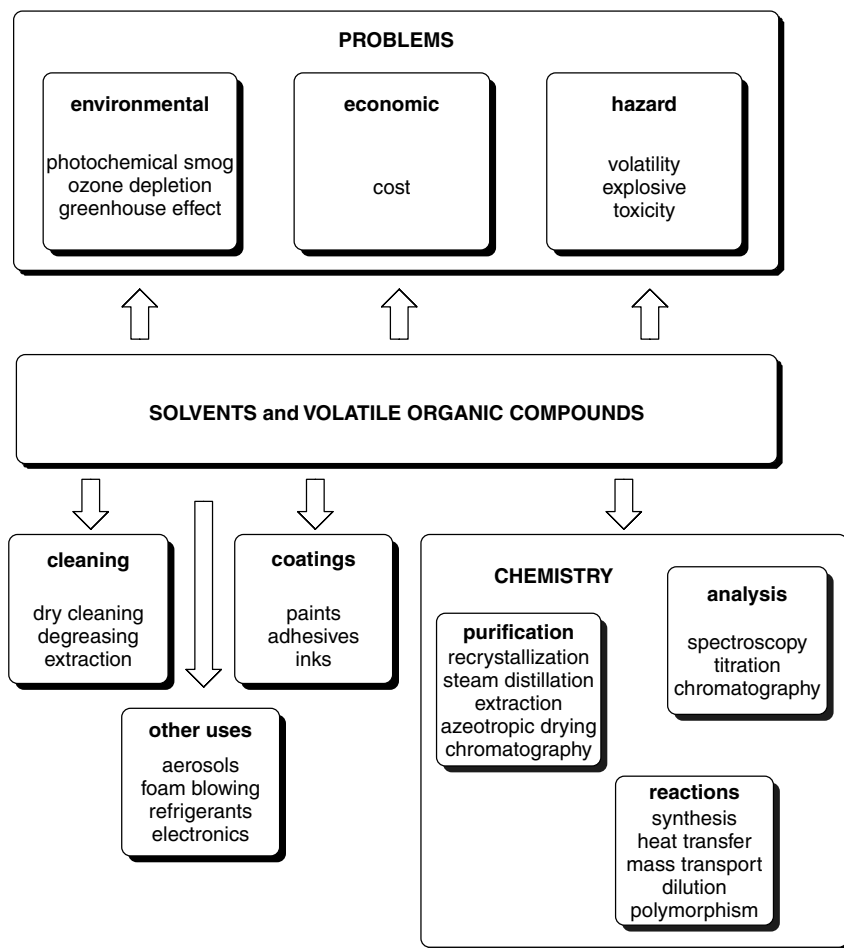
Figure 1.2 Summary of the major uses and problems associated with solvents

a chemical product is frequently achieved either by evaporation or distillation, and for this reason most popular solvents are highly volatile. This volatility has led to some major public concerns about solvent use, some of which appear in the 'problems' box in Figure 1.2. Leaks and spillage of volatile solvents inevitably lead to evaporation into the atmosphere. Atmospheric pollution has been one of the major global environmental issues of the late 20th and early 21st century, and emissions of some categories of volatile organic solvents have been implicated in the depletion of the Earth's ozone layer and in the greenhouse effect. On a local level, exposure to volatile organic compounds (VOCs) in the workplace may lead to dizziness, nausea and other, longer term effects including respiratory problems and cancer. In 1987, the Montreal Protocol set a timescale for the reduction

and eventual phasing out of greenhouse gases and ozone depleting compounds. In particular, the use of chlorofluorocarbons (CFCs), bromofluorochlorocarbons (halons) and carbon tetrachloride as solvents, refrigerants, fire extinguishers and aerosol propellants is now a thing of the past [3]. In the mid-1990s, the widely used cleaning agent and degreaser 1,1,1-trichloroethane was removed from use because of its ozone depleting effects. In 1991 the Geneva Protocol set a framework for the reduction of VOC emissions, and the Kyoto Protocol of 1997 set targets for the reduction of six more classes of emission believed responsible for climate change: CO_2, nitrogen oxides (NO_x), hydrofluorocarbons, volatile perfluorocarbons, methane and sulfur hexafluoride. More recent legislation in the United States and in Europe has centred around the emissions of VOCs. Other compounds have come under scrutiny because of their toxicity and carcinogenicity. Government bodies and environmental agencies are implementing these legislative measures with a carrot-and-stick approach. Funding initiatives to aid and promote the development of cleaner chemical technologies are balanced by fines and penalties to punish those responsible for emission of pollutants into the environment [4]. The principal of 'the polluter pays' is now in place both in Europe and in the USA [5]. Unfortunately, many of the compounds involved are exactly those that have desirable properties as solvents. The legislation process is ongoing and the chemical industry is accordingly looking for both short term replacements for controlled solvent substances, and long term strategies that will make manufacturing processes conform with future controls. It seems highly likely that, in the near future, all emissions of organic compounds to the environment will be strictly controlled, and the more cynical might classify organic solvents as the 'banned' and the 'soon-to-be-banned'. Table 1.1 shows a generalized guide to the acceptability of solvent types, although this should be viewed with caution. For example, methanol, an oxygenated solvent widely considered to be acceptable, is a suspected carcinogen.

The industries involved in the manufacture of solvents and formulations which use them have been hit hard by antipollution legislation. Many solvent users have responded to these regulations by reformulating products to reduce their content of volatile organic components, or even eliminate them completely [6]. These

Table 1.1 General guide to the acceptability of solvents

Most acceptable	None (rarely possible)
	Water
	Oxygenated (e.g. alcohols, ethers, ketones and esters)
	Aliphatic hydrocarbons (e.g. cyclohexane, dodecane)
	Aromatic hydrocarbons (e.g. xylene, mesitylene)
	Dipolar aprotic (e.g. DMSO, DMF, NMP)
	Chlorinated solvents (e.g. dichloromethane)
	Ozone depleters (e.g. CFCs, 1,1,1-trichloroethane)
Least acceptable	Toxic and carcinogenic solvents (CCl_4, benzene)

new formulations include aqueous emulsions, high solids paints, and radiation-curable or powder based coatings. In addition, much more consideration is now given to the recycling of solvents within a manufacturing plant. Current forecasts predict a continuation of the recent trends seen in the USA and shown in Table 1.2: a decline in the demand for aromatic, aliphatic hydrocarbon and chlorinated solvents, and an increased demand for oxygenated alternatives [7]. Oxygenated solvents are more acceptable because they are believed to break down in the environment much more quickly than hydrocarbon and halogenated solvents. Sales of chlorinated solvents in Western Europe fell by 17 % between 1996 and 2001 (Figure 1.3), although this statistic discounts recycling and so

Table 1.2 Trends in solvent demand in the USA (10^3 tonnes per annum)

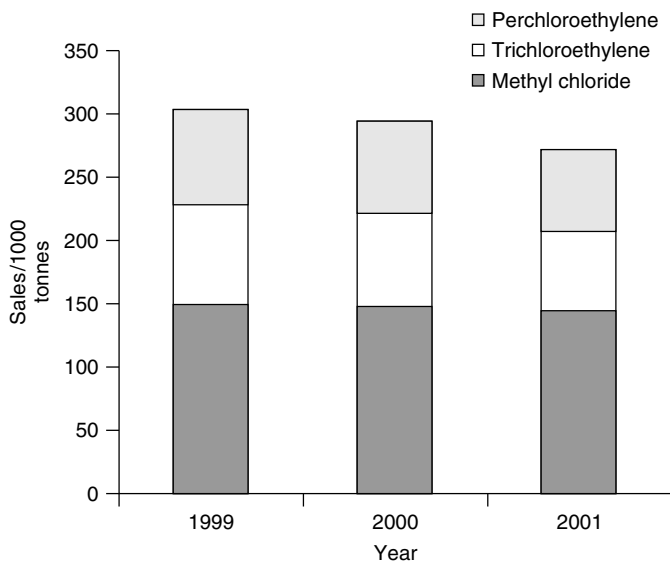| Solvent class	1987	2001
Hydrocarbons	3244	1372
Ethers	1239	1645
Alcohols	1124	1525
Ketones	506	480
Chlorinated	805	330
Esters	216	355
Other solvents	180	227
Total	7244	5934

Figure 1.3   Sales of chlorinated solvents in Western Europe 1996–2001 [10]

may represent improvements in efficiency as well as reduction in use [8]. These figures are based on solvent sales, and, when recycling and reuse are taken into account, it is estimated that the actual quantity of solvents used may be as high as 60 million tonnes per year for the USA alone [9].

1.2 WHY DO THINGS DISSOLVE?

A substance will dissolve, quite simply, if it is energetically favourable for it to do so. If the sum of the energies required to break apart those forces holding the potential solute together *and* to separate the solvent molecules from one another is outweighed by the energy released on solvation, then the substance will dissolve. However, dissolution is a kinetic as well as a thermodynamic process, and solutes that dissolve slowly may be accelerated greatly by the employment of heat or ultrasound.

To understand the dissolution of ionic solids in water, lattice energies must be considered. The lattice enthalpy, ΔH_l, of a crystalline ionic solid is defined as the energy released when one mole of solid is formed from its constituent ions in the gas phase. The hydration enthalpy, ΔH_h, of an ion is the energy released when one mole of the gas phase ion is dissolved in water. Comparison of the two values allows one to determine the enthalpy of solution, ΔH_s, and whether an ionic solid will dissolve endothermically or exothermically. Figure 1.4 shows a comparison of ΔH_l and ΔH_h, demonstrating that AgF dissolves exothermically.
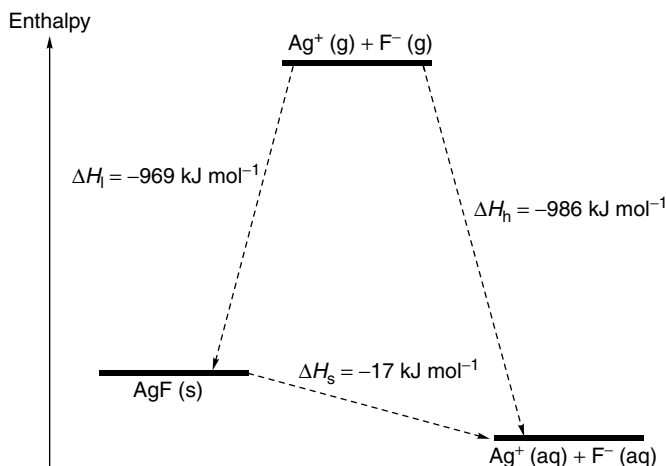

Figure 1.4 Thermodynamic cycle comparing the lattice enthalpy, ΔH_l, and the enthalpy of hydration, ΔH_h, for AgF. The enthalpy of solvation, ΔH_s, is equal to the difference between ΔH_l and ΔH_h
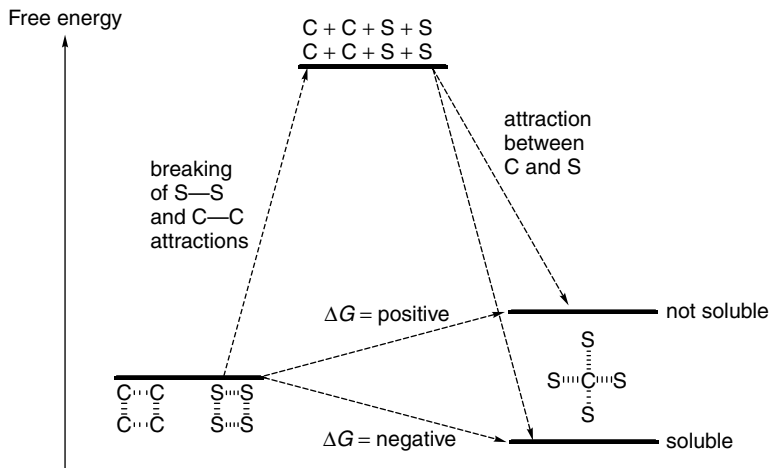
Figure 1.5 Thermodynamic cycle for the dissolution of compound C in solvent S. For dissolution to occur, the attractive forces between solute and solvent must outweigh the free energy required to separate solvent–solvent and solute–solute attractive forces

Figure 1.6 'Like dissolves like': perfluoroalkyl ponytails make phosphines more soluble in a fluorous solvent. These phosphines are suitable ligands for metal catalysts, and will therefore aid the solubility of these catalysts in fluorous solvents

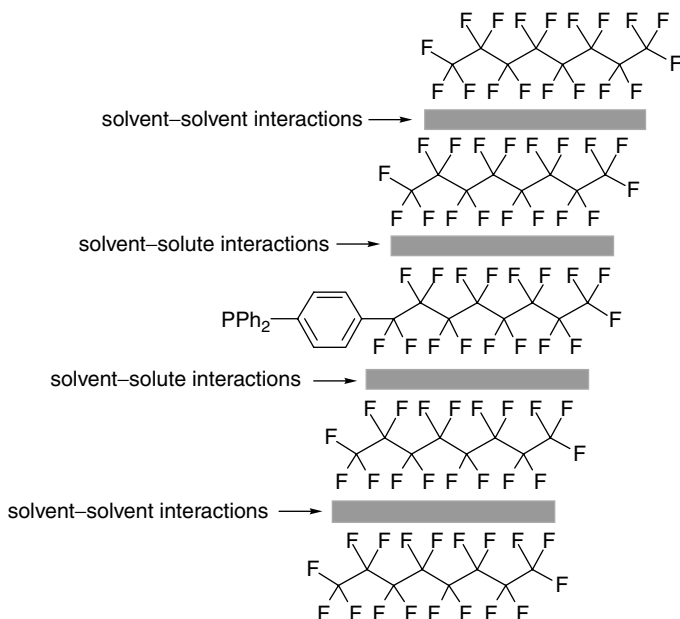For an ionic compound to be soluble in water, the free energy of solution, ΔG_s ($\Delta G = \Delta H - T\Delta S$), must be negative. In general, ΔH_s values are usually also negative, but there are exceptions. For example, NaCl has a small, positive value for ΔH_s (about $+2\,\text{kJ}\,\text{mol}^{-1}$). It dissolves endothermically, and dissolution of salt in water causes a cooling of the solution. Here, the entropy terms must be playing a significant role.

Dissolution of non-ionic compounds may be considered in a similar manner. For a compound C to dissolve in solvent S, the free energy of mixing must be negative; it needs to outweigh the breaking of the attractive forces C–C and S–S, as shown in Figure 1.5. This applies to the mixing of liquids as well as the dissolution of solids and is the basis of the hydrophobic effect, which is discussed in Chapter 5 in the context of the use of water as a solvent for organic chemistry.

The general rule for solvation is that 'like dissolves like'. A compound which has a particular functional group attached will often dissolve well in a solvent that contains that functional group. Perfluorinated aliphatic solvents are good examples to mention here as they are being explored as solvents for multiphasic catalysis (see Chapter 3). In order to dissolve metal catalysts in these solvents, lengthy perfluorinated groups are attached to the ligands surrounding the catalyst. These groups should enable the solute–solvent interactions to be as similar as possible to solvent–solvent attractions, as shown in Figure 1.6.

1.3   SOLVENT PROPERTIES AND SOLVENT CLASSIFICATION

The diversity of solvents makes classification very complex and many different ways of classifying solvents are used. Solvents may be broadly classed according to their chemical type, i.e. aqueous, molecular-inorganic (composed of covalently bonded molecules, e.g. NH_3), molecular-organic, ionic (made up of cations and anions) or atomic (noble gases or metallic) liquids. Molecular organic solvents may be further divided according to their chemical composition – aliphatic, aromatic, alcohol or other functional group. Solvents are often classed according to their physical properties. Key properties include melting and boiling points, viscosity, density, dipole moment, dielectric constant, specific conductivity and cohesive pressure (see Table 1.3). The physical properties that are considered most important depend upon the application. For example, in a synthesis that involves conducting a reaction at elevated temperature, then boiling point may be the most important constant. However, knowing the dielectric constant of the solvent is also essential if microwave heating is to be used [11].

1.3.1   Density

Density (the mass of a compound per unit volume) is an important factor to consider for the separation of immiscible liquids. Two phases should have sufficient

Table 1.3 Properties used to classify solvents

Molecular physical property	Dipole moment
Bulk physical properties	Cohesive pressure
	Dielectric constant
	Refractive index
	Melting point and boiling point
Chemical properties	Donor numbers
	Acceptor numbers
Solvatochromic properties	E_T^N, α, β and π^*

density difference to ensure efficient separation, otherwise an emulsion may be formed. The relatively high density of bromoform (CHBr$_3$, $\rho = 2.9\,\mathrm{g\,cm^{-3}}$) and other halogenated solvents is utilized in the mining industry to separate crushed heavy ore-rich minerals from lighter gangue[1] material. Densities of liquids range from about $14\,\mathrm{g\,cm^{-3}}$ for liquids metals (Hg), through $1{-}3\,\mathrm{g\,cm^{-3}}$ for halogenated solvents, to under $1\,\mathrm{g\,cm^{-3}}$ for hydrocarbons.

1.3.2 Mass Transport

Solvents can increase reaction rates by dispersing reactant molecules and increasing the collision frequency (Figure 1.7a). In solution, all of the solutes are potential reactants. Reactions between solids, however, tend to be much slower than reactions in liquids as there is only a small amount of contact between the solid reactants. Even fine powders will have a relatively small surface area-to-mass ratio, so the bulk majority of the reactant is not in the right place to react (Figure 1.7b).

Exceptional solid–solid reactions with high rates have been observed, but many of these are condensation reactions which eliminate water [12] and it is likely that the reaction takes place in a thin, aqueous layer at the boundary between the solid surfaces, as shown schematically in Figure 1.7c. Other examples are those which produce a liquid product. For example, dimethylimidazolium tetrachloroaluminate, an ionic liquid, may be prepared simply by mixing together dimethylimidazolium chloride with aluminium trichloride [13]. The powdered reactants will collapse together to form a liquid product. This reaction is described further in Chapter 4, in the context of preparing ionic liquids for use as reaction solvents. Despite these inherent drawbacks, there is sometimes enough molecular motion within solids to give a useful rate of reaction, and a wide range of solid–solid reactions have been reported, including oxidations, reductions, additions, eliminations, substitutions and polymerizations [14].

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[1] *Gangue* is a term used in mining and geology to describe the rock in which a vein of mineral ore is imbedded.
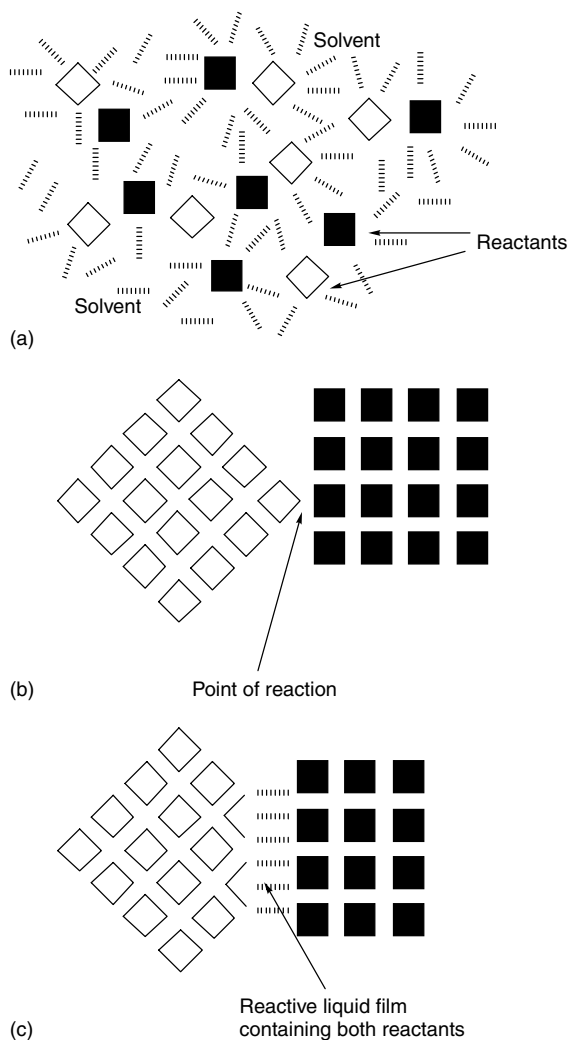
Figure 1.7 (a) In the liquid phase, molecules of both compounds are dispersed and all molecules are potentially reactive; (b) when two solids react, reaction can only occur at the point where the two crystallites are in direct contact; (c) reaction between solids may form a thin liquid layer which increases the rate of reaction

1.3.3 Boiling Point, Melting Point and Volatility

Melting points and boiling points are related to the strength of the intermolecular forces between solvent molecules, and to the molecular weight of the solvent. Dispersive forces, hydrogen bonding and permanent dipole moments all contribute. Typically, for molecules of similar mass, nonpolar compounds which

Table 1.4 Melting points and boiling points of four illustrative compounds

Solvent	RMM	Mp (°C)	Bp (°C)	Intermolecular forces
Propane	44	−188	−42	Dispersive
Acetonitrile	41	−44	82	Permanent dipole
Ethanol	46	−114	78	H-bonding
LiCl	42.4	605	>1300	Electrostatic/ionic

Source: *CRC Handbook of Chemistry and Physics*, 80th Edition, CRC Press, Florida, 2000.

display only dispersive interactions have lower melting and boiling points than those which exhibit permanent dipoles, electrostatic forces, and hydrogen bonding (Table 1.4).

1.3.4 Solvents as Heat-Transfer Media

Solvents play an important role as a heat transfer medium. They carry away heat liberated by an exothermic reaction, or can supply the thermal energy required to initiate an endothermic one. Diffusion and mobility of the solvent reduce the extent of thermal gradients within a reactor, allowing a reaction to proceed in a smooth and even fashion. The ability of a solvent to transfer heat in a reactor is illustrated by the familiar, yet ingenious, concept of reflux (Figure 1.8), in which the reaction temperature is held constant by allowing a portion of the solvent to boil away and condense on a cooled surface, before being returned to the main reservoir of the reactor. This prevents an exothermic reaction from 'running away' and overheating. Solvents with a large degree of intermolecular attraction, and in particular H-bonding solvents, have high heat capacities.

1.3.5 Cohesive Pressure, Internal Pressure, and Solubility Parameter

The *cohesive pressure* (*c*) of a solvent, otherwise known as *cohesive energy density* (CED), is a measure of the attractive forces acting in a liquid, including dispersive, dipolar and H-bonding contributions, and is related to the energy of vaporization and the molar volume (Equation 1.1):

$$c = \frac{\Delta U_{vap}}{V_{molar}} \tag{1.1}$$

Like other measures of pressure, *c* has units of MPa. In theory, a liquid will break all solvent–solvent interactions on vaporization, and so *c* is a measure of the sum of all the attractive intermolecular forces acting in that liquid. Hydrogen-bonding and dipolar solvents therefore have high *c* values. Water has a large value for *c*, and fluorocarbons very low values (Table 1.5).
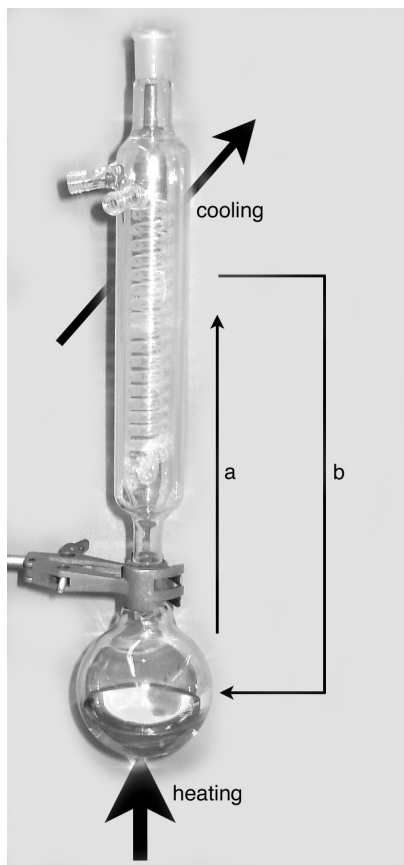
Figure 1.8   Heat transfer via reflux. Solvent evaporates on heating (a) and condenses in a cooler part of the reactor. The cooled liquid is returned to the reservoir (b) and the net effect is the removal of heat from the reservoir

The square route of the cohesive pressure is termed *Hildebrand's solubility parameter* (δ). Hildebrand observed that two liquids are miscible if the difference in δ is less than 3.4 units, and this is a useful rule of thumb. However, it is worth mentioning that the inverse of this statement is not always correct, and that some solvents with differences larger than 3.4 are miscible. For example, water and ethanol have values for δ of 47.9 and 26.0 $MPa^{0.5}$, respectively, but are miscible in all proportions. The values in the table are measured at 25 °C. In general, liquids become more miscible with one another as temperature increases, because the intermolecular forces are disrupted by vibrational motion, reducing the strength of the solvent–solvent interactions. Some solvents that are immiscible at room temperature may become miscible at higher temperature, a phenomenon used advantageously in multiphasic reactions.

Table 1.5 Cohesive pressures (c), Hildebrand's solubility parameter (δ), and internal pressures (π) for a range of representative solvents [1, 2]

Solvent	c (MPa)	δ (MPa$^{0.5}$)	π (MPa)
Water	2302	47.9	151
Methanol	887	29.6	285
Ethanol	703	26.0	291
Acetonitrile	590	24.3	379
Dichloromethane	414	20.3	408
Acetone	398	20.2	337
Chloroform	362	19.0	370
Benzene	357	18.8	379
Ethyl acetate	347	18.6	354
Toluene	337	18.4	379
Cyclohexane	285	17.6	326
Diethyl ether	251	15.8	264
n-Hexane	225	14.9	239
Perfluoroheptane	136	11.9	220

The *internal pressure* (π) of a solvent represents the energy change that the liquid must undergo during a very small increase in volume at constant temperature. This small expansion does not disrupt the H-bonding network of the solvent, and so it is a good indication of the dipolar and dispersive attractions. The data in Table 1.5 show a trend of increasing π value as polarity increases, except for strongly H-bonding liquids such as water and alcohols, which indicates just how strongly the H-bonds contribute to the properties of these solvents. Internal pressure can have an effect on the rates of chemical reactions that display a significant change in the volume, $\Delta V^{\ddagger}$ (*volume of activation*), of the transition state. This is discussed further in Chapter 7.

1.4 SOLVENT POLARITY

It is perhaps obvious that consideration of physical properties such as melting point, boiling point and viscosity of a solvent are essential when choosing a solvent for a particular application. For a chemical reaction, it is also vital that one has some understanding of how well the substrates, reagents and products will dissolve. This is governed by a number of factors, which together make up the character of the solvent. This general character of the solvent is frequently termed *polarity* but, unfortunately, the concept of solvent polarity is not a simple one. For example, methanol is clearly more polar than cyclohexane, but what about dichloromethane, diethyl ether and benzene? We know empirically that these solvents behave differently, but which is most polar? The answer depends on which property we look at: the dielectric constants follow the order

dichloromethane > diethyl ether > benzene, but the order of ability to accept an electron pair is dichloromethane > benzene > diethyl ether. Solvent polarity might best be defined as the solvation power of a solvent, and depends on the interplay of electrostatic, inductive, dispersive, charge-transfer and H-bonding forces [15]. Despite the problems of quantifying solvent polarity, numerous methods have been devised to assess polarity based on various physical and chemical properties. These include dielectric constant, electron pair acceptor and donor ability, and the ability to stabilize charge separation in an indicator dye.

1.4.1 Dipole Moment and Dispersive Forces

Any compound with a nonsymmetrical distribution of charge or electron density will possess a permanent *dipole moment*, μ, whereas a molecule with a centre of symmetry will have no permanent dipole moment. Dipole moment is proportional to the magnitude of the separated charges, z, and also the distance between those charges, l.

$$\mu = zl \tag{1.2}$$

Dipolar molecules will form localized structures in a bulk solvent by orientation of these permanent dipoles, and Figure 1.9 shows two different ways in which two molecules with permanent dipoles may align with one another. With several molecules and three dimensions, a wide range of localized structures are possible. Dipole moments have units of coulomb metres (C m) or Debyes (D, $1\,D = 3.34 \times 10^{-30}\,C\,m$).

As well as these permanent dipole moments, random motion of electron density in a molecule leads to a tiny, instantaneous dipole, which can also induce an opposing dipole in neighbouring molecules. This leads to weak intermolecular attractions which are known as *dispersive forces* or *London forces*, and are present in all molecules, ions and atoms – even those with no permanent dipole moment. Dispersive forces decrease rapidly with distance, and the attractions are in proportion to $1/r^6$, where r is the distance between attracting species.

1.4.2 Dielectric Constant

Dielectric constant (or *relative permittivity*), ε_r, is an indication of the polarity of a solvent, and is measured by applying an electric field across the solvent between
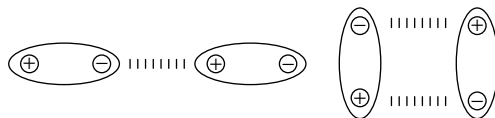

Figure 1.9 Possible alignments of two dipolar molecules that can lead to attraction and short-range structuring of liquids
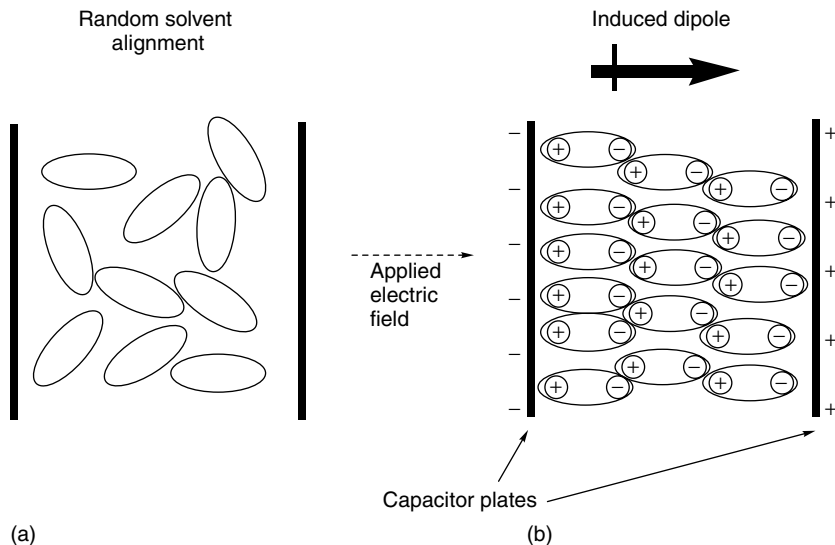
Figure 1.10 Polarization of molecules in an electric field. In the absence of an applied electrical field (a), molecules are aligned randomly, with no net dipole. When the field is applied (b), the solvent molecules are polarized and align themselves to reduce the strength of the field

two plates of a capacitor. The electric field will induce a dipole opposite to the applied field, even in solvents with no permanent dipole of their own, as shown in Figure 1.10. This phenomenon is often referred to as *polarizability*. Because this behaviour is similar to the orientation of a solvent around an electrolyte, ε_r is usually a good indicator of the ability of the solvent to dissolve ionic compounds. The dielectric constant is measured relative to the effect of the same applied field when applied to a vacuum (Equation 1.3), where ε_o is the permittivity of a vacuum.

$$\varepsilon_r = \frac{\varepsilon_{\text{solvent}}}{\varepsilon_o} \tag{1.3}$$

1.4.3 Electron Pair Donor and Acceptor Numbers

1.4.3.1 Donor Number, DN

The *donor number*, DN, of a solvent, proposed by Gutmann, is a measure of the Lewis basicity of the solvent, i.e. its ability to donate a pair of electrons [16]. The DN is determined by measuring the negative enthalpy for the reaction of equimolar quantities of the solvent with the standard Lewis acid, $SbCl_5$, at room temperature in 1,2-dichloroethane (Scheme 1.1), and reflects the ability of the solvent to solvate Lewis acids. $SbCl_5$ reacts with protic solvents such as alcohols

Polar and Nonpolar Solvents

The terms polar, apolar and dipolar are frequently used to describe solvents and other molecules, but there is a certain amount of confusion and inconsistency in their application. *Dipolar* is used to describe molecules with a permanent dipole moment. *Apolar* should only be used to refer to solvents with a spherical charge distribution. All other solvents should be considered polar. Strictly speaking, by this definition, compounds such as carbon tetrachloride and benzene which are not spherical and may be polarized in an electrical field (see section on dielectric constant), are polar, and this polarizability is important when explaining the properties of those solvents. However, they do not have a permanent net dipole moment and give low values on most scales of solvent polarity. They are widely, if erroneously, termed *nonpolar*, and, although misleading, this name is useful in distinguishing solvents of low polarity from those with permanent dipoles. Solvents that are able to donate an acidic hydrogen to form a H-bond are termed *protic*, and those that cannot are called *aprotic*.

Solvent Classes and Examples

Apolar	liquid xenon, neon, argon
Nonpolar/polarizable	carbon tetrachloride, benzene, cyclohexane
Dipolar aprotic	chloroform, dimethylformamide, dimethyl sulfoxide
Dipolar protic	ethanol, methanol, water, liquid ammonia

and water, and the DN for these must be estimated by indirect methods. As the DN scale uses non-SI units, values of DN are usually normalized using 1,2-dichloroethane (DN = 0 kcal mol^{-1}) and hexamethylphosphoramide (HMPA, DN = 38.8 kcal mol^{-1}) as reference solvents for the scale. This generates the parameter DN^N (which corresponds to DN/38.8), thereby giving a unitless scale on which most solvents fall between 0 and 1 [17][2]. Table 1.6 shows values of donor number and other properties for some representative solvents.

Solvent: $+ SbCl_5$ ⟶ solvent —— $SbCl_5$
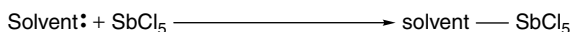
Scheme 1.1

[2] In fact, tris(pyrrolidino)phosphane oxide has a donor number of 1.22.

Table 1.6 Dipole moments (μ), dielectric constants (ε_r), normalized donor numbers (DN^N) and acceptor numbers (AN) for some common solvents [1, 2]

Solvent	$\mu(10^{-30}\,C\,m)$	ε_r	DN^N	AN
Water	5.9	78.3	0.46	54.8
Methanol	5.7	32.7	0.77	41.5
Ethanol	5.8	24.6	0.82	37.9
Dimethyl sulfoxide	13.5	46.5	0.77	19.3
N,N-dimethylformamide	12.4	37.8	0.69	16.0
Acetonitrile	11.8	35.9	0.36	18.9
Acetone	9.0	20.6	0.44	12.5
Ethyl acetate	6.1	6.0	0.44	9.3
Tetrahydrofuran	5.8	7.6	0.52	8.0
Diethyl ether	3.8	4.2	0.49	3.9
Dichloromethane	5.2	8.9	0.03	20.4
Chloroform	3.8	4.8	0.10	23.1
Carbon tetrachloride	0.0	2.2	0	8.6
Benzene	0.0	2.3	<0.01	8.2
Toluene	1.0	2.4	<0.01	–
Cyclohexane	0.0	2.0	0	0
n-Hexane	0.0	1.9	0	0

1.4.3.2 Acceptor number, AN

The *acceptor number*, AN, of a solvent is a measure of the power of the solvent to accept a pair of electrons [18]. Experimental evaluation of AN involves observing the frequency changes induced by a solvent on the ^{31}P NMR spectrum when triethylphosphine oxide, $Et_3P{=}O$, is dissolved in the solvent. Donation of an electron pair from the oxygen atom of $Et_3P{=}O$, as shown in Scheme 1.2, reduces the electron density around the phosphorus, causing a deshielding effect which leads to an increase in chemical shift. Hexane (AN = 0) and $SbCl_5$ (AN = 100) were used as fixed points to define this scale.

1.4.4 Empirical Polarity Scales

Quantitative determination of solvent polarity is difficult, and quantitative methods rely on physical properties such as dielectric constant, dipole moment and refractive index. It is not possible to determine the solvent polarity by measuring an individual solvent property, due to the complexity of solute–solvent interactions, and for this reason empirical scales of solvent polarity based on chemical
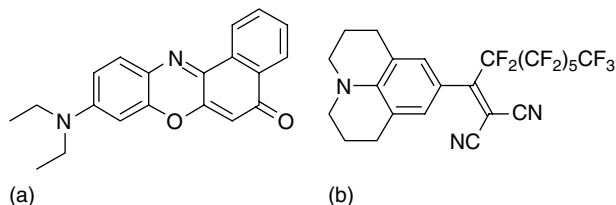
$$Et_3P{=}O + Solvent \longrightarrow Et_3P{-}O{-}Solvent$$

Scheme 1.2

Figure 1.11 Solvatochromic dyes: Nile Red (a) and an α-perfluoroalky-β,β-dicyanovinyl compound (b)

properties are widely used instead. It is preferable that these methods are easy to conduct from an experimental point of view. The most common method is to dissolve a compound with some solvent sensitive spectroscopic characteristic, a phenomenon known as *solvatochroism*. The use of solvatochromic dyes, which undergo a change in their UV spectrum in different solvents, has become a very popular way of achieving this. Some of these empirical methods are discussed below, but it should be noted that many other indicators of solvent polarity have been proposed and used with success [1]. Nile Red has been used to measure the polarity of some ionic liquids (see Chapter 4), and an α-perfluoroalky-β,β-dicyanovinyl dye was successfully used to produce a spectral polarity index (P_s) for fluorinated solvents in which other, more widely known probe molecules were not sufficiently soluble to be used (see Chapter 3) [19]. These dyes are shown in Figure 1.11.

1.4.5 E_T^N and $E_T(30)$ Parameters

Dimroth and Reichardt devised a polarity scale based on the solvatochromic behaviour of the pyridinium-N-phenoxide betaine dye shown in Figure 1.12 [20]. This dye is the most solvatochromic compound reported to date, showing a range of transition energies for the $\pi \rightarrow \pi^*$ absorption band from $147\,\mathrm{kJ\,mol^{-1}}$ ($810\,\mathrm{nm}$) in diphenyl ether to $264\,\mathrm{kJ\,mol^{-1}}$ ($453\,\mathrm{nm}$) in water [1, 21]. This exceptional behaviour makes the dye a useful indicator of solvent polarity, with the measurement being made by human eye (the absorption range is almost entirely within the visible region), or, more quantitatively, by UV-vis spectroscopy. The dye is green in dichloromethane, purple in ethanol and red in methanol, as shown in Figure 1.13.

The original solvent polarity scale, known as the $E_T(30)$ scale, was defined simply as the energy of the longest wavelength adsorption band for the dye, measured in $\mathrm{kcal\,mol^{-1}}$. This scale has now been revised and normalized because of the introduction of SI units, and E_T^N is defined in Equation 1.4.

$$E_T^N = \frac{E_T(\text{solvent}) - E_T(\text{TMS})}{E_T(\text{water}) - E_T(\text{TMS})} \tag{1.4}$$
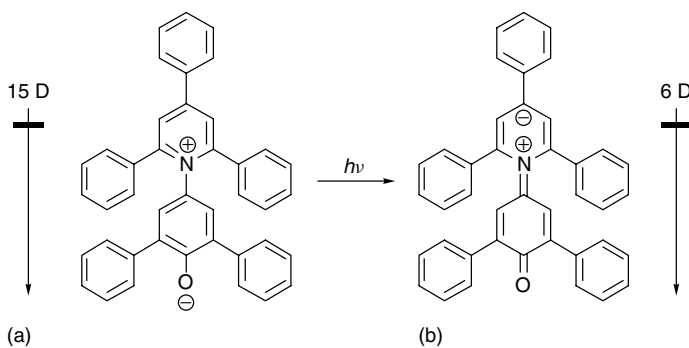
Figure 1.12 Reichardt's betaine dye in its zwitterionic ground state (a) and first excited state (b). The ground state has a larger dipole moment (15 D) than the excited state (6 D). Measurement of the energy of the transition between these two states ($\pi \to \pi^*$) is the basis for the E_T^N scale of solvent polarity
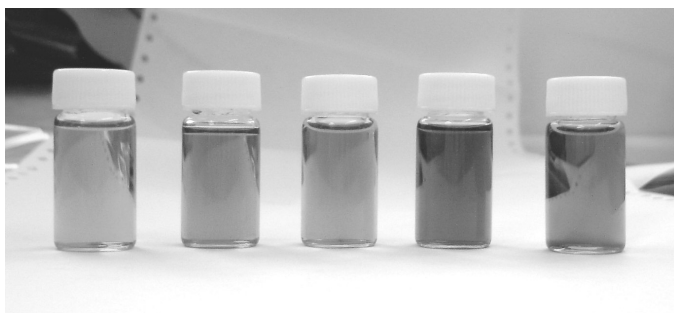
Figure 1.13 (Plate 1)   Solvatochromic behaviour of Reichardt's dye, in (from left to right) dichloromethane, acetone, acetonitrile, ethanol and methanol

where E_T is the energy for the $\pi \to \pi^*$ transition of the dye in a given solvent. Tetramethylsilane (TMS), by definition, has a E_T^N value of zero. Some E_T^N values for common solvents are given in Table 1.7.

More polar solvents, such as water and acetonitrile, stabilize the charged zwitterionic ground state of the dye more than the less dipolar excited state, which leads to a larger energy change for the $\pi \to \pi^*$ transition than in less polar media, as shown in Figure 1.14. In this application the dye is acting as a *reporter* molecule, revealing information about its local environment via an easy-to-measure property.

Although Reichardt's dye itself is not soluble in solvents of very low polarity (diphenyl ether is the lower limit), a related dye functionalized with *t*-butyl groups which has increased solubility in hydrocarbons, shown in Figure 1.15, has been used to extend the scale. However, attempts to use a similar approach to gain

Table 1.7 $E_T(30)$ and E_T^N values for some common solvents

Solvent	$E_T(30)(\text{kcal mol}^{-1})$	E_T^N
Water	63.1	1.000 (defined)
Methanol	55.4	0.762
Ethanol	51.9	0.654
Acetonitrile	45.6	0.460
Dimethyl sulfoxide	45.1	0.444
N,N-dimethylformamide	43.8	0.404
Acetone	42.2	0.355
Dichloromethane	40.7	0.309
Chloroform	39.1	0.259
Ethyl acetate	38.1	0.228
Tetrahydrofuran	37.4	0.207
Diethyl ether	34.5	0.117
Benzene	34.3	0.111
Toluene	33.9	0.099
Carbon tetrachloride	32.4	0.052
n-Hexane[a]	31.0	0.009
Cyclohexane[a]	30.9	0.006
Tetramethylsilane[a]	30.7	0.000 (defined)

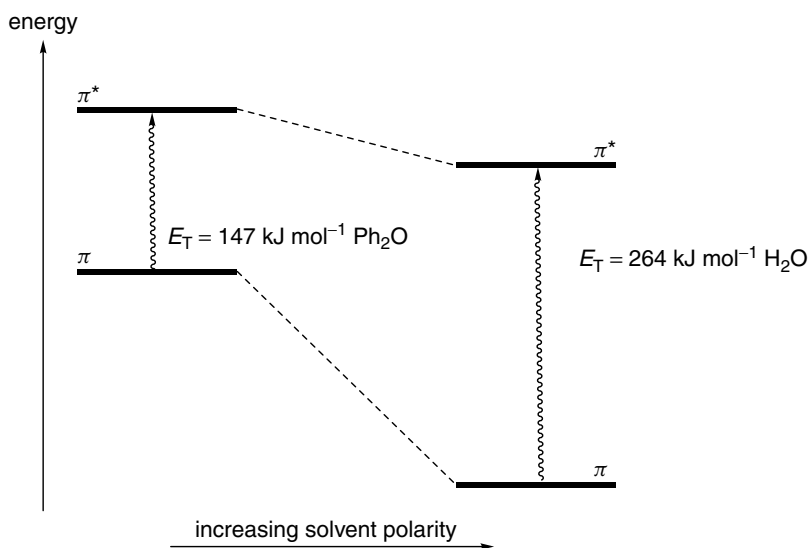[a] Measured using the t-butyl-substituted dye shown in Figure 1.15.

Figure 1.14 Increasing solvent polarity stabilizes the zwitterionic ground state (π) of Reichardt's dye relative to the first excited state (π^*), leading to an increase in the transition energy
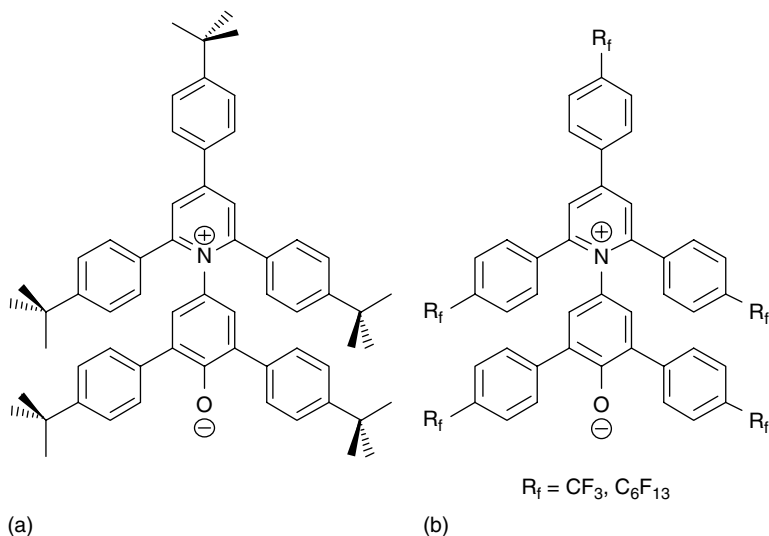
Figure 1.15 *t*-Butyl- (a) and perfluoroalkyl- (b) substituted betaine dyes for polarity measurements in less polar or highly fluorous solvents

useful measurements of fluorinated solvents by attaching fluorinated chains to the dye have proved largely unsuccessful [22].

As the E_T^N value is related to the ability of a solvent to stabilize charge separation in the dye, a correlation between E_T^N and dielectric constant, ε_r might be expected. Figure 1.16 shows a plot of E_T^N against ε_r for the solvents shown in Table 1.7. Not all solvents show a good correlation, which highlights the difficulty of producing a single parameter capable of describing solvent polarity. Dipolar, aprotic solvents appear to give a lower E_T^N value than would be expected on the basis of their dielectric constants. It should be remembered that the dye might form specific Lewis acid/base interactions with solvent molecules, as well as being sensitive to bulk, nonspecific solvent 'polarity'. A more detailed discussion of the relationships between empirical solvent scales may be found elsewhere [2].

1.4.6 Kamlet–Taft Parameters

From a practical viewpoint, E_T^N values are quickly and easily obtained, giving a very useful and convenient scale. However, a general polarity scale based on a single probe molecule has its limitations because a single compound cannot experience the diversity of interactions that the whole range of solvents can offer. The Kamlet–Taft parameters α, β and π^* tackle this problem by using a series of seven dyes to produce a scale for specific and nonspecific polarity of liquids [23]. Whilst it undoubtedly gives a more detailed description of the solvents properties,
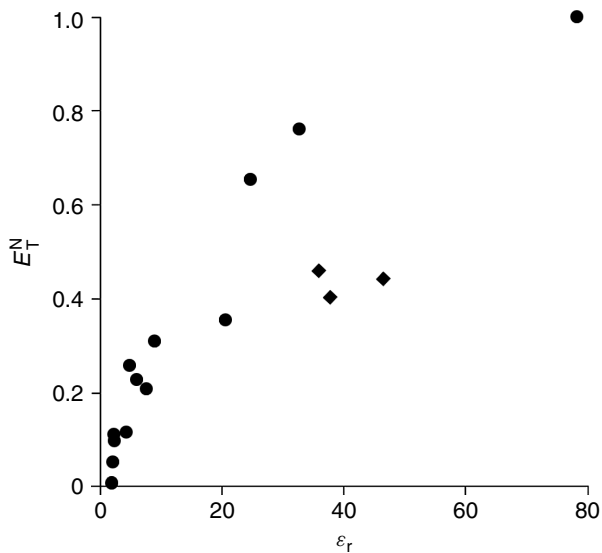
Figure 1.16   Relationship between E_T^N and ε_r for the solvents listed in Table 1.7. ◆, dimethyl sulfoxide, N,N-dimethylformamide and acetonitrile; ●, other solvents

Table 1.8   Kamlet–Taft α, β and π^* parameters for selected solvents [1, 2]

Solvent	α	β	π^*
Water	1.17	0.47	1.09
Methanol	0.98	0.66	0.60
Ethanol	0.86	0.75	0.54
Dimethyl sulfoxide	0.00	0.76	1.00 (defined)
N,N-dimethylformamide	0.00	0.69	0.88
Acetonitrile	0.19	0.40	0.75
Acetone	0.08	0.43	0.71
Ethyl acetate	0.00	0.45	0.55
Tetrahydrofuran	0.00	0.55	0.58
Diethyl ether	0.00	0.47	0.27
Dichloromethane	0.13	0.10	0.82
Chloroform	0.20	0.10	0.58
Carbon tetrachloride	0.00	0.10	0.28
Benzene	0.00	0.10	0.59
Toluene	0.00	0.11	0.54
n-Hexane	0.00	0.00	−0.04
Cyclohexane	0.00	0.00	0.00 (defined)
Perfluoromethylcyclohexane	0.00	−0.06	−0.40

this approach is more time consuming and requires extra measurements and calculations. The Kamlet–Taft equation is generally represented as follows:

$$X = X_o + a\alpha + b\beta + s\pi^*$$ (1.5)

where X_o, a b and s are solvent-independent constants for the solvatochromic indicator under study. X is the empirical measurement, i.e. the solvatochromic shift of the dye. α is the *hydrogen bond donor* (HBD) ability of the solvent and β is the *hydrogen bond acceptor* (HBA) ability. HBD and HBA solvents are discussed briefly below in Section 1.4.7. The parameter π^* is therefore a measure of the residual general polarity/polarizability of the solvent after H-bonding effects have been removed. Values for α, β and π^* have been obtained for a wide range of solvents which makes it an extremely useful scale for comparative purposes [1, 2]. Some Kamlet–Taft values for common solvents are given in Table 1.8.

1.4.7 Hydrogen Bond Donor (HBD) and Hydrogen Bond Acceptor (HBA) Solvents

Hydrogen bond donor solvents are simply those containing a hydrogen atom bound to an electronegative atom. These are often referred to as protic solvents, and the class includes water, carboxylic acids, alcohols and amines. For chemical reactions that involve the use of easily hydrolysed or solvolysed compounds, such as $AlCl_3$, it is important to avoid protic solvents. Hydrogen bond acceptors are solvents that have a lone pair available for donation, and include acetonitrile, pyridine and acetone. Kamlet–Taft α and β parameters are solvatochromic measurements of the HBD and HBA properties of solvents, i.e. acidity and basicity, respectively [24]. These measurements use the solvatochromic probe molecules N,N-diethyl-4-nitroaniline, which acts as a HBA, and 4-nitroaniline, which is a HBA *and* a HBD (Figure 1.17).
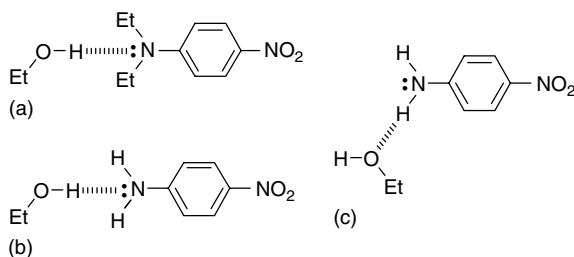

Figure 1.17 Hydrogen-bond formation between nitroanilines and ethanol. (a) N,N-diethyl-4-nitroaniline is a HBA only; (b) 4-nitroaniline is a HBA and (c) a HBD

1.5 THE EFFECT OF SOLVENT POLARITY ON CHEMICAL SYSTEMS

The main principles and concepts of the effect of solvent polarity on chemical reactions and equilibria are outlined in the following sections. However, this is a vast subject area beyond the scope of this work and the interested reader will find a detailed discussion elsewhere [1].

1.5.1 The Effect of Solvent Polarity on Chemical Reactions

Generally, the effect of changing the solvent in which a chemical reaction is conducted may be understood by considering the charge distribution of the reactants and transition states. In each case, a more polar solvent will lead to stabilization of species with dipoles or charge separation, relative to nonpolar species. For example, in a typical S_N1 nucleophilic substitution reaction, where an uncharged reactant forms a charged transition state, a more polar solvent will stabilize the transition state complex relative to the reactant, lowering the activation enthalpy, $\Delta H^{\ddagger}$, as shown in Figure 1.18. For example, the S_N1 solvolysis of t-butyl chloride (2-chloro-2-methylpropane), in which the rate limiting step is the heterolytic breaking of the C–Cl bond, is 3.4×10^5 times faster in water than in less polar ethanol [25].

By contrast, in an S_N2 reaction, a charged nucleophile reacts with an uncharged substrate to form a transition state in which the negative charge of the nucleophile
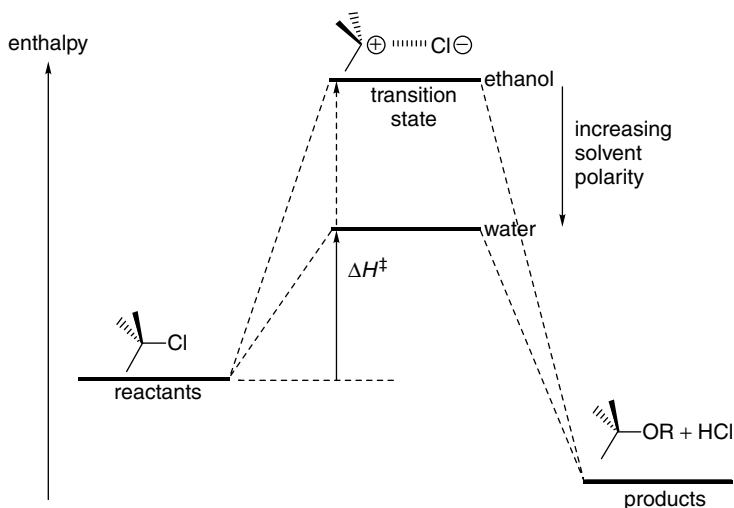

Figure 1.18 Solvent polarity effect in an S_N1 reaction. Increasing the polarity of the solvent stabilizes the charge separation formed in the transition state, lowering the activation energy and increasing the rate of reaction

is dispersed over the entire complex. The charge separation in the transition state is reduced compared with the reactants. In this situation, the use of a polar solvent will stabilize the starting material relative to the transition state, as shown in Figure 1.19. The reaction will thus proceed more slowly in solvents of higher polarity.

The direction and extent of the effect of solvent polarity on reaction rates of nucleophilic substitution reactions are summarized by the Hughes–Ingold rules, shown in Table 1.9 [26]. These rules do not account for the entropic effects or any specific solvent–solute interactions such as H-bonding, which may lead to extra stabilization of reactants or transition states [27].
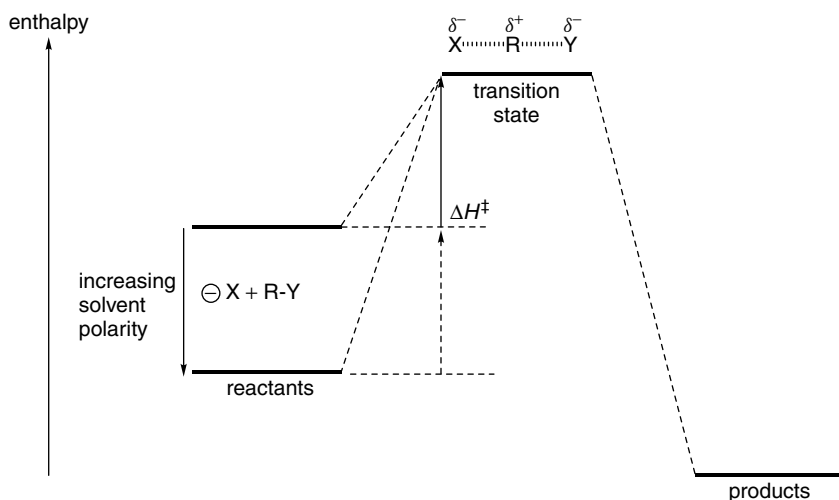
Figure 1.19 The effect of solvent polarity in an S_N2 reaction. Increasing the polarity of the solvent stabilizes reactants relative to the transition state, raising the activation energy and decreasing the rate of reaction

Table 1.9   Hughes–Ingold rules for solvent effects in nucleophilic substitution reactions [27, 28]

Reaction	Reactants	Transition state	Change in charge distribution	Effect of increasing solvent polarity	Size of effect
S_N2	$Y^- + R–X$	$^{\delta-}$ Y…. R…. $X^{\delta-}$	Dispersed	Decrease	Small
S_N2	$Y + R–X$	$^{\delta+}$ Y…. R…. $X^{\delta-}$	Increased	Increase	Large
S_N2	$Y^- + R–X^+$	$^{\delta-}$ Y…. R…. $X^{\delta+}$	Decreased	Decrease	Large
S_N2	$Y + R–X^+$	$^{\delta+}$ Y…. R…. $X^{\delta+}$	Dispersed	Decrease	Small
S_N1	$R–X$	$^{\delta+}$ R……. $X^{\delta-}$	Increased	Increase	Large
S_N1	$R–X^+$	$^{\delta+}$ R……. $X^{\delta+}$	Dispersed	Decrease	Small

Neutral reactants that form neutral products by passing through an uncharged transition state are expected to show little or no solvent polarity-dependent changes in reaction rate. This category of reaction includes pericyclic reactions and rearrangements, including the Diels–Alder reaction. However, dramatic changes in reaction rates for such reactions have been reported for such reactions when using either very polar *or* very nonpolar solvents. Although the solvent has no charge-stabilizing effect on the transition state in these cases, other solvent phenomena, including the *hydrophobic effect*, can lead to enhanced rates. These ideas are discussed further in Chapters 5 and 7.

1.5.2 The Effect of Solvent Polarity on Equilibria

Like reaction rates, the effect of solvent polarity on equilibria may be rationalized by consideration of the relative polarities of the species on each side of the equilibrium. A polar solvent will therefore favour polar species. A good example is the *keto–enol* tautomerization of ethyl acetoacetate, in which the 1,3-dicarbonyl, or *keto*, form is more polar than the *enol* form, which is stabilized by an intramolecular H-bond. The equilibrium is shown in Scheme 1.3. In cyclohexane, the *enol* form is slightly more abundant. Increasing the polarity of the solvent moves the equilibrium towards the *keto* form [28]. In this example, H-bonding solvents will compete with the intramolecular H-bond, destabilizing the *enol* form of the compound.

Solvent polarity effects are also seen in the formation of isomers of transition metal complexes. Reactions that give a mixture of *cis* and *trans* isomers can be tuned by careful choice of solvent to give one isomer in preference to the other. For example, with *cis* and *trans*-[Pt(H$_2$L-S)$_2$Cl$_2$] (where H$_2$L = *N*-benzoyl-*N'*-propylthiourea), shown in Scheme 1.4 [29], the *cis* isomer is favoured in solvents of high polarity whereas the *trans* isomer is dominant in solvents of low polarity. These observations are in accordance with other related observations [30], and

Solvent	K
Cyclohexane	1.07
Diethylether	0.54
Tetrahydrofuran	0.33
Ethanol	0.18
Water	0.06

$$K = \frac{[enol]}{[keto]}$$

Scheme 1.3 The effect of solvent polarity on *keto–enol* tautomerization of ethyl acetoacetate

Scheme 1.4 The more polar *cis* form of the platinum complex is dominant in polar solvents

represent a case of 'like yielding like' since the resulting *cis* complex is more polar than the *trans* complex. From the data in Table 1.10, it is apparent that the position of the equilibrium is highly solvent dependent. The relative rates of isomerization are greatest in nonpolar solvents and as polarity is increased the rate of isomerization decreases. With complexes that exist in solution as an equilibrium *cis–trans* mixture, it has been possible to crystallize the *cis* isomer from a low polarity solvent and the *trans* isomer from a polar solvent [31].

Table 1.10 Dependence of equilibrium from Scheme 1.4 on solvent polarity [31]

Solvent	ε_r	E_T^N	Equilibrium constant K
Benzene	2.27	0.111	0.88
Chloroform	4.70	0.259	0.47
Tetrahydrofuran	7.39	0.207	0.39
Acetone	20.5	0.355	0.28
N,N-dimethylformamide	36.7	0.404	0.23
Nitromethane	38.6	0.481	0.16

1.6   WHAT IS REQUIRED FROM ALTERNATIVE SOLVENT STRATEGIES?

The problem with solvents is not so much their use, but the inefficiencies associated with their recovery and reuse. High volatility, whilst being an extremely useful property, leads to solvent losses to the environment. If a process consists of a reaction stage and a purification stage, solvents may be used and lost at each stage, as shown schematically in Figure 1.20a. Real chemical processes may include several separation steps, with further opportunities for solvent loss.

Alternative solvent strategies should allow efficient recovery and reuse of the solvent if environmental damage is to be avoided. Because there is a huge variety of solvents with a wide spectrum of physical properties, a range of alternatives to cover the full range of these different physical characteristics is required. It is unlikely that there is one, simple approach that will work in all applications, and what might be economically appropriate for a high value pharmaceutical might prove impractical for a bulk commodity.

Exceptions to this rule of high recovery may be made for CO_2 and water, which are non-toxic and may be returned to the environment providing that
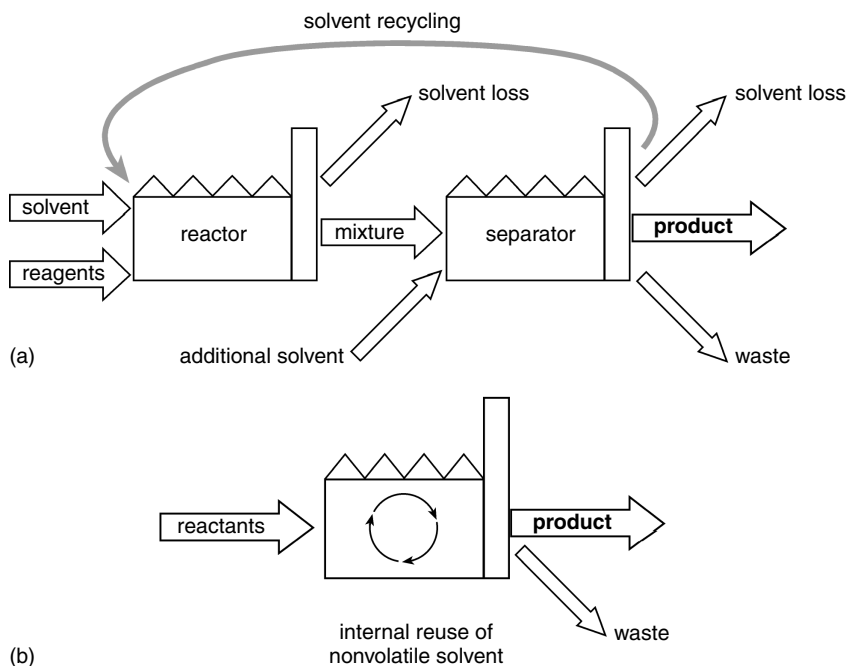

Figure 1.20   Schematic diagrams showing (a) solvent flow in a two-stage chemical process, where volatile organic solvents may be lost in both the reaction and separation steps; (b) improved efficiency in a process using a nonvolatile replacement solvent to reduce losses and improve separation

they are not contaminated by other, less benign chemicals. Although CO_2 is a greenhouse gas, and guidelines for the reduction of its emission have been set in law, its use as a solvent is not viewed as damaging. When used as a solvent, CO_2 is collected from air (or as a by-product of fermentation), converted to a liquid or supercritical fluid, and then returned to the atmosphere after use, giving a net change of zero. Of course, energy is required to compress the CO_2 and perform the phase change (which, ironically, may come from the burning of fossil fuels which *does* produce a net gain in CO_2), but this may be offset against the improvement in efficiency of any separation steps involved in the process. As CO_2 is a gas at ambient temperature and pressure, it can be removed simply by releasing the pressure from the reactor, to leave reaction products completely free of solvent and no energy is required to distil the solvent. The use of supercritical CO_2 and other supercritical fluids as reaction media is covered in Chapter 6.

If nonvolatile liquids are to be used to avoid the problems associated with volatile organic solvents, then it is very desirable that there is some convenient way of recovering the reaction products from the liquid. This approach is used in the biphasic systems described in Chapters 2–5. In the fluorous biphase (Chapter 3), reagents and catalysts are fine-tuned by adding perfluoroalkyl chains, known as 'ponytails', to ensure that only those chemicals will mix with the fluorous layer. Purification is simply a matter of separating the two phases. Transition metal catalysts with fluorous ligands will remain in the fluorous phase, and the whole catalyst–solvent mixture may be reused for another batch of reactions, as shown schematically in Figure 1.20b.

Ionic liquids may be used in a similar fashion, but in contrast to the extremely nonpolar fluorous solvents, ionic liquids are polar. They are completely nonvolatile and so cannot be lost to the atmosphere. A range of ionic compounds that are liquid at room temperature and their use in synthetic chemistry are described in Chapter 4.

Water is abundant and nontoxic and is therefore a desirable solvent in environmental terms. However, cleaning up water that is contaminated with trace amounts of organic or metal catalyst impurities is very expensive. Water may be used as the sole solvent for some organic reaction chemistry, or in biphasic reactions alongside organic, fluorous, or ionic liquid solvents. Phase transfer catalysis (PTC) allows the use of inorganic reagents for reactions with organic substrates without the need for a polar, nonaqueous mutual solvent. The use of water as a solvent and PTC are covered in Chapter 5.

If these new solvent technologies are to be implemented for real industrial scale chemical synthesis, they must give some genuine advantage over existing methods, in terms of overall cost, safety, product quality, or some other improvement. PTC is already in use in manufacturing processes [32], because it allows the use of cheap, inorganic reagents and reduces or eliminates the need for additional organic solvent. Water is used as a solvent for industrial hydroformylation reactions [33]. Supercritical carbon dioxide (sc CO_2) is used for decaffeination of coffee beans and for the extraction of bioactive molecules from crops [34].

A large scale supercritical reactor for chemical synthesis has recently been built in the UK and it seems likely that more synthetic processes using CO_2 as a solvent will appear in the near future [35].

At the time of writing, neither ionic liquids nor fluorous solvents have been used as solvents for commercial processes, although BASF use an ionic liquid as a proton scavenger in phosphine manufacture [36]. These are relatively new technologies and time will tell whether or not they will fulfil current high expectations.

Whilst the first part of this book deals mainly with concepts and theories of alternatives to the use of organic solvents as reaction media, the later Chapters (Chapters 7–11) look at some applications of these methods and compare their strengths and limitations as illustrated by these case studies.

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