

FUNDAMENTAL PRINCIPLES GOVERNING SOLVENTS USE

2.1 SOLVENT EFFECTS ON CHEMICAL SYSTEMS

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2.1.1 HISTORICAL OUTLINE

According to a story, a little fish asked a big fish about the ocean, since he had heard it being talked about but did not know where it was. Whilst the little fish's eyes turned bright and shiny full of surprise, the old fish told him that all that surrounded him was the ocean. This story illustrates in an eloquent way how difficult it is to get away from every day life, something of which the chemistry of solvents is not unaware.

The chemistry of living beings and that which we practice in laboratories and factories is generally a chemistry in solution, a solution which is generally aqueous. A daily routine such as this explains the difficulty which, throughout the history of chemistry, has been encountered in getting to know the effects of the solvent in chemical transformations, something which was not achieved in a precise way until well into the XX century. It was necessary to wait for the development of experimental techniques *in vacuo* to be able to separate the solvent and to compare the chemical processes in the presence and in the absence of this, with the purpose of getting to know its role in the chemical transformations which occur in its midst. But we ought to start from the beginning.

Although essential for the later cultural development, Greek philosophy was basically a work of the imagination, removed from experimentation, and something more than meditation is needed to reach an approach on what happens in a process of dissolution. However, in those remote times, any chemically active liquid was included under the name of "divine water", bearing in mind that the term "water" was used to refer to anything liquid or dissolved.¹

Parallel with the fanciful search for the philosopher's stone, the alchemists toiled away on another impossible search, that of a universal solvent which some called "alkahest" and others referred to as "menstruum universale", which term was used by the very Paracelsus (1493-1541), which gives an idea of the importance given to solvents during that dark and obscurantist period. Even though the "menstruum universale" proved just as elusive as the philosopher's stone, all the work carried out by the alchemists in search of these

illusionary materials opened the way to improving the work in the laboratory, the development of new methods, the discovery of compounds and the utilization of novel solvents. One of the tangible results of all that alchemy work was the discovery of one of the first experimental rules of chemistry: “*similia similibus solvuntor*”, which reminds us of the compatibility in solution of those substances of similar nature.

Even so, the alchemy only touched lightly on the subject of the role played by the solvent, with so many conceptual gulfs in those pre-scientific times in which the terms dissolution and solution referred to any process which led to a liquid product, without making any distinction between the fusion of a substance - such as the transformation of ice into liquid water -, mere physical dissolution - such as that of a sweetener in water - or the dissolution which takes place with a chemical transformation - such as could be the dissolution of a metal in an acid. This misdirected vision of the dissolution process led the alchemists down equally erroneous collateral paths which were prolonged in time. Some examples are worth quoting: Hermann Boerhaave (1688-1738) thought that dissolution and chemical reaction constituted the same reality; the solvent, (*menstruum*), habitually a liquid, he considered to be formed by diminutive particles moving around amongst those of the solute, leaving the interactions of these particles dependent on the mutual affinities of both substances.² This paved the way for Boerhaave to introduce the term affinity in a such a way as was conserved throughout the whole of the following century.³ This approach also enabled Boerhaave to conclude that combustion was accompanied by an increase of weight due to the capturing of “particles” of fire, which he considered to be provided with weight by the substance which was burned. This explanation, supported by the well known Boyle, eased the way to considering that fire, heat and light were material substances until when, in the XIX century, the modern concept of energy put things in their place.⁴

Even Bertollet (1748-1822) saw no difference between a dissolution and a chemical reaction, which prevented him from reaching the law of definite proportions. It was Proust, an experimenter who was more exacting and capable of differentiating between chemical reaction and dissolution, who made his opinion prevail:

“The dissolution of ammonia in water is not the same as that of hydrogen in azote (nitrogen), which gives rise to ammonia”⁵

There were also alchemists who defended the idea that the substances lost their nature when dissolved. Van Helmont (1577-1644) was one of the first to oppose this mistaken idea by defending that the substance dissolved remains in the solution in aqueous form, it being possible to recover it later. Later, the theories of osmotic pressure of van 't Hoff (1852-1911) and that of electrolytic dissociation of Arrhenius (1859-1927) took this approach even further.

Until almost the end of the XIX century the effects of the solvent on the different chemical processes did not become the object of systematic study by the experimenters. The effect of the solvent was assumed, without reaching the point of awakening the interest of the chemists. However, some chemists of the XIX century were soon capable of unraveling the role played by some solvents by carrying out experiments on different solvents, classified according to their physical properties; in this way the influence of the solvent both on chemical equilibrium and on the rate of reaction was brought to light. Thus, in 1862, Berthelot and Saint-Gilles, in their studies on the esterification of acetic acid with ethanol,

discovered that some solvents, which do not participate in the chemical reaction, are capable of slowing down the process.⁶ In 1890, Menshutkin, in a now classical study on the reaction of the trialkylamines with haloalkanes in 23 solvents, made it clear how the choice of one or the other could substantially affect the reaction rate.⁷ It was also Menshutkin who discovered that, in reactions between liquids, one of the reactants could constitute a solvent inadvisable for that reaction. Thus, in the reaction between aniline and acetic acid to produce acetanilide, it is better to use an excess of acetic acid than an excess of aniline, since the latter is a solvent which is not very favorable to this reaction.

The fruits of these experiments with series of solvents were the first rules regarding the participation of the solvent, such as those discovered by Hughes and Ingold for the rate of the nucleophilic reactions.⁸ Utilizing a simple electrostatic model of the solute - solvent interactions, Hughes and Ingold concluded that the state of transition is more polar than the initial state, that an increase of the polarity of the solvent will stabilize the state of transition with respect to the initial state, thus leading to an increase in the reaction rate. If, on the contrary, the state of transition is less polar, then the increase of the polarity of the solvent will lead to a decrease of the velocity of the process. The rules of Hughes-Ingold for the nucleophilic aliphatic reactions are summarized in Table 2.1.1.

Table 2.1.1. Rules of Hughes-Ingold on the effect of the increase of the polarity of the solvent on the rate of nucleophilic aliphatic reactions

Mechanism	Initial state	State of transition	Effect on the reaction rate
S_N2	$Y^- + RX$	$[Y^{\delta-} \cdots R \cdots X^{\delta-}]^{\ddagger}$	slight decrease
	$Y + RX$	$[Y^{\delta-} \cdots R \cdots X^{\delta-}]$	large increase
	$Y^- + RX^+$	$[Y^{\delta-} \cdots R \cdots X^{\delta-}]$	large decrease
	$Y + RX^+$	$[Y^{\delta-} \cdots R \cdots X^{\delta+}]^{\ddagger}$	slight decrease
S_N1	RX	$[R^{\delta-} \cdots X^{\delta-}]$	large increase
	RX^+	$[R^{\delta-} \cdots X^{\delta+}]^{\ddagger}$	slight decrease

In 1896 the first results about the role of the solvent on chemical equilibria were obtained, coinciding with the discovery of the keto-enolic tautomerism.⁹ Claisen identified the medium as one of the factors which, together with the temperature and the substituents, proved to be decisive in this equilibrium. Soon systematic studies began to be done on the effect of the solvent in the tautomeric equilibria. Wislicenus studied the keto-enolic equilibrium of ethylformylphenylacetate in eight solvents, concluding that the final proportion between the keto form and the enol form depended on the polarity of the solvent.¹⁰ This effect of the solvent also revealed itself in other types of equilibria: acid-base, conformational, those of isomerization and of electronic transfer. The acid-base equilibrium is of particular interest. The relative scales of basicity and acidity of different organic compounds and homologous families were established on the basis of measurements carried out in solution, fundamentally aqueous. These scales permitted establishing hypotheses regarding the effect of the substituents on the acidic and basic centers, but without being capable of separating this from the effect of the solvent. Thus, the scale obtained in solution for the acidity of

the α -substituted methyl alcohols $[(\text{CH}_3)_3\text{COH} > (\text{CH}_3)_2\text{CHOH} > \text{CH}_3\text{CH}_2\text{OH} > \text{CH}_3\text{OH}]$ ¹¹ came into conflict with the conclusions extracted from the measurements of movements by NMR.¹² The irregular order in the basicity of the methyl amines in aqueous solution also proved to be confusing $[\text{NH}_3 < \text{CH}_3\text{NH}_2 < (\text{CH}_3)_2\text{NH} > (\text{CH}_3)_3\text{N}]$,¹³ since it did not match any of the existing models on the effects of the substituents. These conflicts were only resolved when the scales of acidity-basicity were established in the gas phase. On carrying out the abstraction of the solvent an exact understanding began to be had of the real role it played.

The great technological development which arrived with the XIX century has brought us a set of techniques capable of giving accurate values in the study of chemical processes in the gas phase. The methods most widely used for these studies are:

- The High Pressure Mass Spectrometry, which uses a beam of electron pulses¹⁴
- The Ion Cyclotron Resonance and its corresponding Fourier Transform (FT-ICR)¹⁵
- The Chemical Ionization Mass Spectrometry, in which the analysis is made of the kinetic energy of the ions, after generating them by collisions¹⁶
- The techniques of Flowing Afterglow, where the flow of gases is submitted to ionization by electron bombardment¹⁷⁻¹⁹

All of these techniques give absolute values with an accuracy of $\pm(2-4)$ Kcal/mol and of ± 0.2 Kcal/mol for the relative values.²⁰

During the last decades of XX century the importance has also been made clear of the effects of the solvent in the behavior of the biomacromolecules. To give an example, the influence of the solvent over the proteins is made evident not only by its effects on the structure and the thermodynamics, but also on the dynamics of these, both at local as well as at global level.²¹ In the same way, the effect of the medium proves to be indispensable in explaining a large variety of biological processes, such as the rate of interchange of oxygen in myoglobin.²² Therefore, the actual state of development of chemistry, as much in its experimental aspect as in its theoretical one, allows us to identify and analyze the influence of the solvent on processes increasingly more complex, leaving the subject open for new challenges and investigating the scientific necessity of creating models with which to interpret such a wide range of phenomena as this. The little fish became aware of the ocean and began explorations.

2.1.2 CLASSIFICATION OF SOLUTE-SOLVENT INTERACTIONS

Fixing the limits of the different interactions between the solute and the solvent which envelops it is not a trivial task. In the first place, the liquid state, which is predominant in the majority of the solutions in use, is more difficult to comprehend than the solid state (which has its constitutive particles, atoms, molecules or ions, in fixed positions) or the gaseous state (in which the interactions between the constitutive particles are not so intense). Moreover, the solute-solvent interactions, which, as has already been pointed out, generally happen in the liquid phase, are half way between the predominant interactions in the solid phase and those which happen in the gas phase, too weak to be likened with the physics of the solid state but too strong to fit in with the kinetic theory of gases. In the second place, dissecting the solute-solvent interaction into different sub-interactions only serves to give us an approximate idea of the reality and we should not forget that, in the solute-solvent interaction, the all is not the sum of the parts. In the third place, the world of the solvents is very varied from those which have a very severe internal structure, as in the case of water, to those

whose molecules interact superficially, as in the case of the hydrocarbons. At all events, there is no alternative to meeting the challenge face to face.

If we mix a solute and a solvent, both being constituted by chemically saturated molecules, their molecules attract one another as they approach one another. This interaction can only be electrical in its nature, given that other known interactions are much more intense and of much shorter range of action (such as those which can be explained by means of nuclear forces) or much lighter and of longer range of action (such as the gravitational force). These intermolecular forces usually also receive the name of van der Waals forces, from the fact that it was this Dutch physicist, Johannes D. van der Waals (1837-1923), who recognized them as being the cause of the non-perfect behavior of the real gases, in a period in which the modern concept of the molecule still had to be consolidated. The intermolecular forces not only permit the interactions between solutes and solvents to be explained but also determine the properties of gases, liquids and solids; they are essential in the chemical transformations and are responsible for organizing the structure of biological molecules.

The analysis of solute-solvent interactions is usually based on the following partition scheme:

$$\Delta E = \Delta E_i + \Delta E_{ij} + \Delta E_{jj} \quad [2.1.1]$$

where *i* stands for the solute and *j* for the solvent. This approach can be maintained while the identities of the solute and solvent molecules are preserved. In some special cases (see below in specific interactions) it will be necessary to include some solvent molecules in the solute definition.

The first term in the above expression is the energy change of the solute due to the electronic and nuclear distortion induced by the solvent molecule and is usually given the name solute polarization. ΔE_{ij} is the interaction energy between the solute and solvent molecules. The last term is the energy difference between the solvent after and before the introduction of the solute. This term reflects the changes induced by the solute on the solvent structure. It is usually called cavitation energy in the framework of continuum solvent models and hydrophobic interaction when analyzing the solvation of nonpolar molecules.

The calculation of the three energy terms needs analytical expressions for the different energy contributions but also requires knowledge of solvent molecules distribution around the solute which in turn depends on the balance between the potential and the kinetic energy of the molecules. This distribution can be obtained from diffraction experiments or more usually is calculated by means of different solvent modelling. In this section we will comment on the expression for evaluating the energy contributions. The first two terms in equation [2.1.1] can be considered together by means of the following energy partition :

$$\Delta E_i + \Delta E_{ij} = \Delta E_{el} + \Delta E_{pol} + \Delta E_{d-r} \quad [2.1.2]$$

Analytical expressions for the three terms (electrostatic, polarization and dispersion-repulsion energies) are obtained from the intermolecular interactions theory.

2.1.2.1 Electrostatic

The electrostatic contribution arises from the interaction of the unpolarized charge distribution of the molecules. This interaction can be analyzed using a multipolar expansion of the charge distribution of the interacting subsystems which usually is cut off in the first term

which is different from zero. If both the solute and the solvent are considered to be formed by neutral polar molecules (with a permanent dipolar moment different from zero), due to an asymmetric distribution of its charges, the electric interaction of the type dipole-dipole will normally be the most important term in the electrostatic interaction. The intensity of this interaction will depend on the relative orientation of the dipoles. If the molecular rotation is not restricted, we must consider the weighted average over different orientations

$$\langle E_{d-d} \rangle = -\frac{2}{3} \frac{\mu_1^2 \mu_2^2}{(4\pi\epsilon)^2 kTr^6} \quad [2.1.3]$$

where:

μ_i, μ_j	dipole moments
k	Boltzmann constant
ϵ	dielectric constant
T	absolute temperature
r	intermolecular distance

The most stable orientation is the antiparallel, except in the case that the molecules in play are very voluminous. Two dipoles in rapid thermal movement will be orientated sometimes in a way such that they are attracted and at other times in a way that they are repelled. On the average, the net energy turns out to be attractive. It also has to be borne in mind that the thermal energy of the molecules is a serious obstacle for the dipoles to be oriented in an optimum manner.

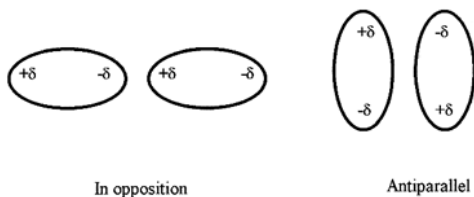


Figure 2.1.1. The dipoles of two molecules can approach one another under an infinite variety of attractive orientations, among which these two extreme orientations stand out.

The average potential energy of the dipole-dipole interaction, or of orientation, is, therefore, very dependent on the temperature.

In the event that one of the species involved were not neutral (for example an anionic or cationic solute) the predominant term in the series which gives the electrostatic interaction will be the ion-dipole which is given by the expression:

$$\langle E_{i-d} \rangle = -\frac{q_i^2 \mu_j^2}{6(4\pi\epsilon)^2 kTr^4} \quad [2.1.4]$$

2.1.2.2 Polarization

If we dissolve a polar substance in a nonpolar solvent, the molecular dipoles of the solute are capable of distorting the electronic clouds of the solvent molecules inducing the appearance in these of new dipoles. The dipoles of solute and those induced will line up and will be attracted and the energy of this interaction (also called interaction of polarization or induction) is:

$$\langle E_{d-id} \rangle = -\frac{\alpha_j \mu_i^2}{(4\pi\epsilon)^2 r^6} \quad [2.1.5]$$

where:

μ_i	dipole moment
α_j	polarizability
r	intermolecular distance

In a similar way, the dissolution of an ionic substance in a nonpolar solvent also will occur with the induction of the dipoles in the molecules of the solvent by the solute ions.

These equations make reference to the interactions between two molecules. Because the polarization energy (of the solute or of the solvent) is not pairwise additive magnitude, the consideration of a third molecule should be carried out simultaneously, it being impossible to decompose the interaction of the three bodies in a sum of the interactions of two bodies. The interactions between molecules in solution are different from those which take place between isolated molecules. For this reason, the dipolar moment of a molecule may vary considerably from the gas phase to the solution, and will depend in a complicated fashion on the interactions which may take place between the molecule of solute and its specific surroundings of molecules of solvent.

2.1.2.3 Dispersion

Even when solvent and solute are constituted by nonpolar molecules, there is interaction between them. It was F. London who was first to face up to this problem, for which reason these forces are known as London's forces, but also as dispersion forces, charge-fluctuations forces or electrodynamic forces. Their origin is as follows: when we say that a substance is nonpolar we are indicating that the distribution of the charges of its molecules is symmetrical throughout a wide average time span. But, without doubt, in an interval of time sufficiently restricted the molecular movements generate displacements of their charges which break that symmetry giving birth to instantaneous dipoles. Since the orientation of the dipolar moment vector is varying constantly due to the molecular movement, the average dipolar moment is zero, which does not prevent the existence of these interactions between momentary dipoles. Starting with two instantaneous dipoles, these will be oriented to reach a disposition which will favor them energetically. The energy of this dispersion interaction can be given, to a first approximation, by:

$$E_{disp} = -\frac{3I_i I_j}{2(4\pi\epsilon)^2 (I_i + I_j)} \frac{\alpha_i \alpha_j}{r^6} \quad [2.1.6]$$

where:

I_i, I_j	ionization potentials
α_i, α_j	polarizabilities
r	intermolecular distance

From equation [2.1.6] it becomes evident that dispersion is an interaction which is more noticeable the greater the volume of molecules involved. The dispersion forces are often more intense than the electrostatic forces and, in any case, are universal for all the atoms and molecules, given that they are not seen to be subjected to the requirement that permanent dipoles should exist beforehand. These forces are responsible for the aggregation of the substances which possess neither free charges nor permanent dipoles, and are also the

protagonists of phenomena such as surface tension, adhesion, flocculation, physical adsorption, etc. Although the origin of the dispersion forces may be understood intuitively, this is of a quantum mechanical nature.

2.1.2.4 Repulsion

Between two molecules where attractive forces are acting, which could cause them to be superimposed, it is evident that also repulsive forces exist which determine the distance to which the molecules (or the atoms) approach one another. These repulsive forces are a consequence of the overlapping of the electronic molecular clouds when these are nearing one another. These are also known as steric repulsion, hard core repulsion or exchange repulsion. They are forces of short range which grow rapidly when the molecules which interact approach one another, and which enter within the ambit of quantum mechanics. Throughout the years, different empirical potentials have been obtained with which the effect of these forces can be reproduced. In the model hard sphere potential, the molecules are supposed to be rigid spheres, such that the repulsive force becomes suddenly infinite, after a certain distance during the approach. Mathematically this potential is:

$$E_{rep} = \left(\frac{\sigma}{r} \right)^{\infty} \quad [2.1.7]$$

where:

r intermolecular distance
 σ hard sphere diameter

Other repulsion potentials are the power-law potential:

$$E_{rep} = \left(\frac{\sigma}{r} \right)^n \quad [2.1.8]$$

where:

r intermolecular distance
 n integer, usually between 9 and 16
 σ sphere diameter

and the exponential potential:

$$E_{rep} = C \exp \left(- \frac{r}{\sigma_0} \right) \quad [2.1.9]$$

where:

r intermolecular distance
 C adjustable constant
 σ₀ adjustable constant

These last two potentials allow a certain compressibility of the molecules, more in consonance with reality, and for this reason they are also known as soft repulsion.

If we represent the repulsion energy by a term proportional to r^{-12} , and given that the energy of attraction between molecules decreases in proportion to r^{-6} at distances above the molecular diameter, we can obtain the total potential of interaction:

$$E = -Ar^{-6} + Br^{-12} \quad [2.1.10]$$

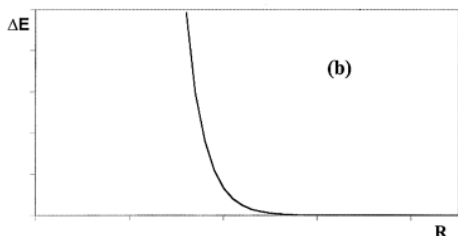
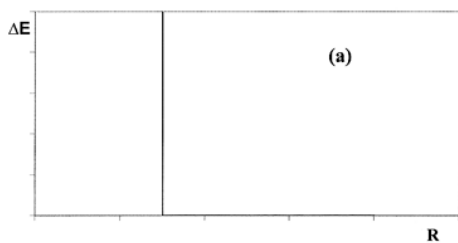


Figure 2.1.2. Hard-sphere repulsion (a) and soft repulsion (b) between two atoms.

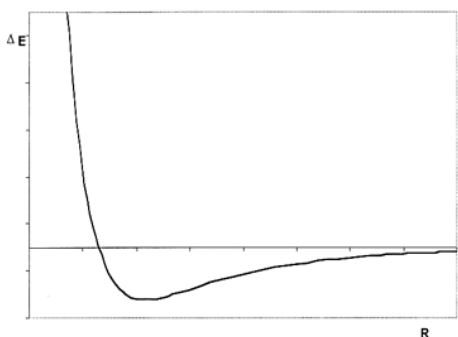


Figure 2.1.3. Lennard-Jones potential between two atoms.

where:

r	intermolecular distance
A	constant
B	constant

which receives the name of potential “6-12” or potential of Lennard-Jones,²³ widely used for its mathematical simplicity (Figure 2.1.3)

2.1.2.5 Specific interactions

Water, the most common liquid, the “universal solvent”, is just a little “extraordinary”, and this exceptional nature of the “liquid element” is essential for the world which has harbored us to keep on doing so. It is not normal that a substance in its solid state should be less dense than in the liquid, but if one ill-fated day a piece of ice spontaneously stopped floating on liquid water, all would be lost, the huge mass of ice which is floating in the colder seas could sink thus raising the level of water in the oceans.

For a liquid with such a small molecular mass, water has melting and boiling temperatures and a latent heat of vaporization which are unexpectedly high. Also unusual are its low compressibility, its high dipolar moment, its high dielectric constant and the fact that its density is maximum at 4 °C. All this proves that water is an extraordinarily complex liquid in which the intermolecular forces exhibit specific interactions, the so-called hydrogen bonds, about which it is necessary to know more.

Hydrogen bonds appear in substances where there is hydrogen united covalently to very electronegative elements (e.g., F, Cl, O and N), which is the case with water. The hydrogen bond can be either intermolecular (e.g., H₂O) or intramolecular (e.g., DNA). The protagonism of hydrogen is due to its small size and its tendency to become positively polarized, specifically to the elevated density of the charge which accumulates on the mentioned compounds. In this way, hydrogen is capable, such as in the case of water, of being doubly bonded: on the one hand it is united covalently to an atom of oxygen belonging to its molecule and, on the other, it electrostatically attracts another atom of oxygen belonging to another molecule, so strengthening the attractions between molecules. In this way, each atom of oxygen of a molecule of water can take part in four links with four more molecules of water, two of these links being through the hydrogen atoms covalently united to it and the other two links through hydrogen bonds thanks to the two pairs of solitary electrons which it

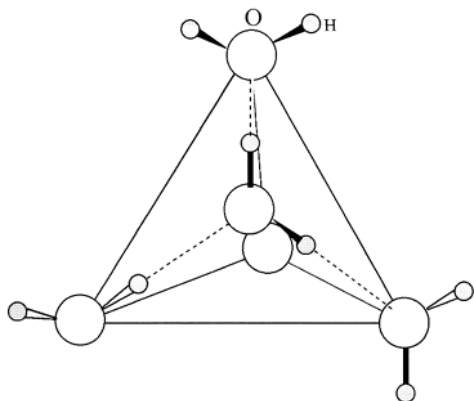


Figure 2.1.4. Tetrahedral structure of water in a crystal of ice. The dotted lines indicate the hydrogen bridges.

possesses. The presence of the hydrogen bonds together with this tetrahedral coordination of the molecule of water constitute the key to explaining its unusual properties.

The energy of this bond (10-40 KJ/mol) is found to be between that corresponding to the van der Waals forces (~ 1 KJ/mol) and that corresponding to the simple covalent bond (200-400 KJ/mol). An energetic analysis of the hydrogen bond interaction shows that the leading term is the electrostatic one which explains that strong hydrogen bonds are found between hydrogen atoms with a partial positive charge and a basic site. The second term in the energy decomposition of the hydrogen bond interaction is the charge transfer.²⁴

The hydrogen bonds are crucial in explaining the form of the large biological molecules, such as the proteins and the nucleic acids, as well as how to begin to understand more particular chemical phenomena.²⁵

Those solutes which are capable of forming hydrogen bonds have a well known affinity for the solvents with a similar characteristic, which is the case of water. The formation of hydrogen bonds between solute molecules and those of the solvent explains, for example, the good solubility in water of ammonia and of the short chain organic acids.

2.1.2.6 Hydrophobic interactions

On the other hand, those nonpolar solutes which are not capable of forming hydrogen bonds with water, such as the case of the hydrocarbons, interact with it in a particular way. Let us imagine a molecule of solute incapable of forming hydrogen bonds in the midst of the water. Those molecules of water which come close to that molecule of solute will lose some or all of the hydrogen bonds which they were sharing with the other molecules of water. This obliges the molecules of water which surround those of solute to arrange themselves in space so that there is a loss of the least number of hydrogen bonds with other molecules of water. Evidently, this rearrangement (solvation or hydration) of the water molecules around the nonpolar molecule of solute will be greatly conditioned by the form and the size of this latter. All this amounts to a low solubility of nonpolar substances in water, which is known as the hydrophobic effect. If we now imagine not one but two nonpolar molecules in the midst of the water, it emerges that the interaction between these two molecules is greater when they are interacting in a free space. This phenomenon, also related to the rearrangement of the molecules of water around those of the solute, receives the name of hydrophobic interaction.

The hydrophobic interaction term is used to describe the tendency of non-polar groups or molecules to aggregate in water solution.²⁶ Hydrophobic interactions are believed to play a very important role in a variety of processes, specially in the behavior of proteins in aqueous media. The origin of this solvent-induced interactions is still unclear. In 1945 Frank and Evans²⁷ proposed the so-called iceberg model where emphasis is made on the enhanced local structure of water around the non-polar solute. However, computational studies and ex-

perimental advances have yielded increasing evidence against the traditional interpretation,²⁸ and other alternative explanations, such as the reduced freedom of water molecules in the solvation shell,²⁹ have emerged.

To understand the hydrophobic interaction at the microscopic level molecular simulations of non-polar compounds in water have been carried out.³⁰ The potential of mean force between two non-polar molecules shows a contact minimum with an energy barrier. Computer simulations also usually predict the existence of a second solvent-separated minimum. Although molecular simulations provide valuable microscopic information on hydrophobic interactions they are computationally very expensive, specially for large systems, and normally make use of oversimplified potentials. The hydrophobic interaction can also be alternatively studied by means of continuum models.³¹ Using this approach a different but complementary view of the problem has been obtained. In the partition energy scheme used in the continuum models (see below and Chapter 8) the cavitation free energy (due to the change in the solvent-solvent interactions) is the most important contribution to the potential of mean force between two non-polar solutes in aqueous solution, being responsible for the energy barrier that separates the contact minimum. The electrostatic contribution to the potential of mean force for two non-polar molecules in water is close to zero and the dispersion-repulsion term remains approximately constant. The cavitation free energy only depends on the surface of the cavity where the solute is embedded and on the solvent physical properties (such as the surface tension and density).

2.1.3 MODELLING OF SOLVENT EFFECTS

A useful way of understanding the interaction between the molecules of solvent and those of solute can be done by reproducing it by means of an adequate model. This task of imitation of the dissolution process usually goes beyond the use of simple and intuitive structural models, such as “stick” models, which prove to be very useful both in labors of teaching as in those of research, and frequently require the performance of a very high number of complex mathematical operations.

Even though, in the first instance, we could think that a solution could be considered as a group of molecules united by relatively weak interactions, the reality is more complex, especially if we analyze the chemical reactivity in the midst of a solvent. The prediction of reaction mechanisms, the calculation of reaction rates, the obtaining of the structures of minimum energy and other precise aspects of the chemical processes in solution require the support of models with a very elaborated formalism and also of powerful computers.

Traditionally, the models which permit the reproduction of the solute-solvent interactions are classified into three groups:³²

- i Those based on the simulation of liquids by means of computers.
- ii Those of continuum.
- iii Those of the supermolecule type.

In the models classifiable into the first group, the system analyzed is represented by means of a group of interacting particles and the statistical distribution of any property is calculated as the average over the different configurations generated in the simulation. Especially notable among these models are those of Molecular Dynamics and those of the Monte Carlo type.

The continuum models center their attention on a microscopic description of the solute molecules, whilst the solvent is globally represented by means of its macroscopic properties, such as its density, its refractive index, or its dielectric constant.

Finally, the supermolecule type models restrict the analysis to the interaction among just a few molecules described at a quantum level which leads to a rigorous treatment of their interactions but does not allow us to have exact information about the global effect of the solvent on the solute molecules, which usually is a very long range effect.

The majority of these models have their origin in a physical analysis of the solutions but, with the passage of time, they have acquired a more chemical connotation, they have centered the analysis more on the molecular aspect. As well as this, recourse is more and more being made to combined strategies which use the best of each of the methods referred to in pursuit of a truer reproduction of the solute-disolvente interactions. Specially useful has been shown to be a combination of the supermolecular method, used to reproduce the specific interactions between the solute and one or two molecules of the solvent, with those of continuum or of simulation, used to reproduce the global properties of the medium.

2.1.3.1 Computer simulations

Obtaining the configuration or the conformation of minimum energy of a system provides us with a static view of this which may be sufficient to obtain many of its properties. However, direct comparison with experiments can be strictly be done only if average thermodynamic properties are obtained. Simulation methods are designed to calculate average properties of a system over many different configurations which are generated for being representative of the system behavior. These methods are based in the calculation of average properties as a sum over discrete events:

$$\langle F \rangle = \int dR_1 \dots dR_n P(R) F(R) \approx \sum_{i=1}^N P_i F_i \quad [2.1.11]$$

Two important difficulties arise in the computation of an average property as a sum. First, the number of molecules that can be handled in a computer is of the order of a few hundred. Secondly, the number of configurations needed to reach the convergency in the sum can be too great. The first problem can be solved by different computational strategies, such as the imposition of periodic boundary conditions.³³ The solution of the second problem differs among the main used techniques in computer simulations.

The two techniques most used in the dynamic study of the molecular systems are the Molecular Dynamics, whose origin dates back³⁴ to 1957, and the Monte Carlo methods, which came into being following the first simulation of fluids by computer,³⁵ which occurred in 1952.

Molecular Dynamics

In the Molecular Dynamic simulations, generation of new system configurations or sequence of events is made following the trajectory of the system which is dictated by the equations of motion. Thus, this methods leads to the computation of time averages and permits the calculation of not only equilibrium but also transport properties. Given a configuration of the system, a new configuration is obtained moving the molecules according to the total force exerted on them:

$$\frac{m d^2 R_j}{dt^2} = - \sum_{k=1}^n \nabla_j E(R_{jk}) \quad [2.1.12]$$

If we are capable of integrating the equations of movement of all the particles which constitute a system, we can find their paths and velocities and we can evaluate the properties of the system in determined time intervals. Thus, we can find how the system being studied evolved as time moves forward. In the first simulations by Molecular Dynamics of a condensed phase,³⁴ use was made of potentials as simple as the hard sphere potential, under which the constituent particles move in a straight line until colliding elastically. The collisions happen when the separation between the centers of the spheres is equal to the diameter of the sphere. After each collision, the new velocities are obtained by making use of the principle of conservation of the linear moments. But a chemical system requires more elaborate potentials under which the force, which at every instant acts between two atoms or molecules, changes in relation to the variation of the distance between them. This obliges us to integrate the equations of movement of the system in very small time intervals, in which it is assumed that the force which acts on each atom or molecule is constant, generally lying between 1 and 10 femtoseconds. For each of these intervals, the positions and velocities of each of the atoms is calculated, after which they are placed in their new positions and, once again, the forces are evaluated to obtain the parameters of a new interval, and so on, successively. This evolution in time, which usually requires the evaluation of hundreds of thousands of intervals of approximately 1 femtosecond each, allows us to know the properties of the system submitted to study during the elapse of time. In fact, the task commences by fixing the atoms which make up the system being studied in starting positions, and later move them continuously whilst the molecules being analysed rotate, the bond angles bend, the bonds vibrate, etc., and during which the dispositions of the atoms which make up the system are tabulated at regular intervals of time, and the energies and other properties which depend on each of the conformations, through which the molecular system makes its way with the passage of time, are evaluated. Molecular Dynamics is Chemistry scrutinized each femtosecond.

Monte Carlo methods

The first simulation by computer of a molecular system was carried out using this method. It consists of generating configurations of a system introducing random changes in the position of its constituents.

In order to obtain a good convergence in the sequence of configurations, Metropolis *et al.*³⁵ suggested an interesting approach. This approach avoids the generation of a very long random configurations as follows: instead of choosing random configurations and then weighing them according to the Boltzmann factor, one generates configurations with a probability equal to the Boltzmann factor and afterwards weigh them evenly. For this purpose once a new configuration is generated the difference in the potential energy with respect to the previous one is computed (ΔU) and a random number $0 \leq r \leq 1$ is selected. If the Boltzmann factor $\exp(-\Delta U/kT) > r$ then the new configuration is accepted, if $\exp(-\Delta U/kT) < r$ is rejected.

In the Monte Carlo method, every new configuration of the system being analysed can be generated starting from the random movement of one or more atoms or molecules, by rotation around a bond, etc. The energy of each new configuration is calculated starting from a potential energy function, and those configurations to which correspond the least energy are selected. Once a configuration has been accepted, the properties are calculated. At the end of the simulation, the mean values of these properties are also calculated over the ensemble of accepted configurations.

When the moment comes to face the task of modelling a dissolution process, certain doubts may arise about the convenience of using Molecular Dynamics or a Monte Carlo method. It must be accepted that a simulation with Molecular Dynamics is a succession of configurations which are linked together in time, in a similar way that a film is a collection of scenes which follow one after the other. When one of the configurations of the system analysed by Molecular Dynamics has been obtained, it is not possible to relate it to those which precede it or those which follow, which is something which does not occur in the Monte Carlo type of simulations. In these, the configurations are generated in a random way, without fixed timing, and each configuration is only related to that which immediately preceded it. It would therefore seem advisable to make use of Molecular Dynamics to study a system through a period of time. On the other hand, the Monte Carlo method is usually the most appropriate when we are able to do without the requirement of time. Even so, it is advisable to combine adequately the two techniques in the different parts of the simulation, using a hybrid arrangement. In this way, the evolution of the process of the dissolution of a macromolecule can be followed by Molecular Dynamics and make use of the Monte Carlo method to resolve some of the steps of the overall process. On the other hand, it is frequently made a distinction in the electronic description of solute and solvent. So, as the chemical attention is focused on the solute, a quantum treatment is used for it while the rest of the system is described at the molecular mechanics level.³⁶

2.1.3.2 Continuum models

In many dissolution processes the solvent merely acts to provide an enveloping surrounding for the solute molecules, the specific interactions with the solvent molecules are not of note but the dielectric of the solvent does significantly affect the solute molecules. This sort of situation can be confronted considering the solvent as a continuum, without including explicitly each of its molecules and concentrating on the behavior of the solute. A large number of models have been designed with this approach, either using quantum mechanics or resorting to empirical models. They are the continuum models.³² The continuum models have attached to their relative simplicity, and therefore a lesser degree of computational calculation, a favorable description of many chemical problems in dissolution, from the point of view of the chemical equilibrium, kinetics, thermochemistry, spectroscopy, etc.

Generally, the analysis of a chemical problem with a model of continuum begins by defining a cavity - in which a molecule of solute will be inserted - in the midst of the dielectric medium which represents the solvent. Differently to the simulation methods, where the solvent distribution function is obtained during the calculation, in the continuum models this distribution is usually assumed to be constant outside of the solute cavity and its value is taken to reproduce the macroscopic density of the solvent.

Although the continuum models were initially created with the aim of the calculation of the electrostatic contribution to the solvation free energy,³⁷ they have been nowadays extended for the consideration of other energy contributions. So, the solvation free energy is usually expressed in these models as the sum of three different terms:

$$\Delta G_{sol} = \Delta G_{ele} + \Delta G_{dis-rep} + \Delta G_{cav} \quad [2.1.13]$$

where the first term is the electrostatic contribution, the second one the sum of dispersion and repulsion energies and the third one the energy needed to create the solute cavity in the solvent. Specific interactions can be also added if necessary.

For the calculation of the electrostatic term the system under study is characterized by two dielectric constants, in the interior of the cavity the constant will have a value of unity, and in the exterior the value of the dielectric constant of the solvent. From this point the total electrostatic potential is evaluated. Beyond the mere classical outlining of the problem, Quantum Mechanics allows us to examine more deeply the analysis of the solute inserted in the field of reaction of the solvent, making the relevant modifications in the quantum mechanical equations of the system under study with a view to introducing a term due to the solvent reaction field.³⁸ This permits a widening of the benefits which the use of the continuum methods grant to other facilities provided for a quantical treatment of the system, such as the optimization of the solute geometry,³⁹ the analysis of its wave function,⁴⁰ the obtaining of its harmonic frequencies,⁴¹ etc.; all of which in the presence of the solvent. In this way a full analysis of the interaction solute-solvent can be reached at low computational cost.

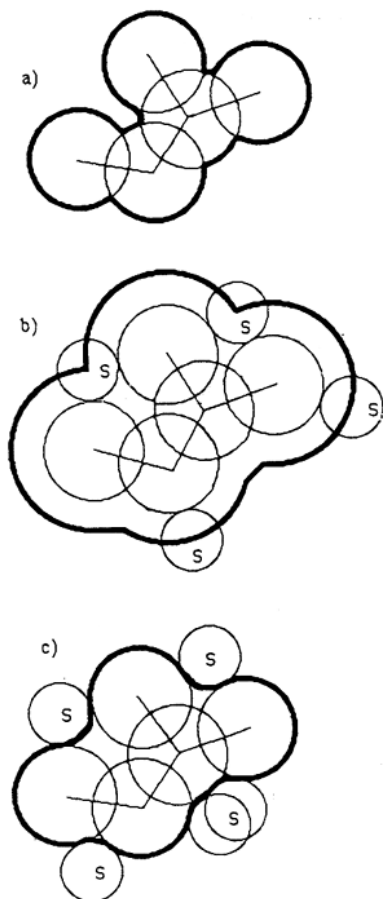


Figure 2.1.5. Molecular Surface models. (a) van der Waals Surface; (b) Accessible Surface and (c) Solvent Excluding Surface.

Continuum models essentially differ in:

- How the solute is described, either classically or quantumly
- How the solute charge distribution and its interaction with the dielectric are obtained
- How the solute cavity and its surface are described.

The first two topics are thoroughly considered in Chapter 8 by Prof. Tomasi, here we will consider in detail the last topic.

2.1.3.3. Cavity surfaces

Earliest continuum models made use of oversimplified cavities for the insertion of the solute in the dielectric medium such as spheres or ellipsoids. In the last decades, the concept of molecular surface as become more common. Thus, the surface has been used in microscopic models of solution.^{38,42} Linear relationships were also found between molecular surfaces and solvation free energies.⁴³ Moreover, given that molecular surfaces can help us in the calculation of the interaction of a solute molecule with surroundings of solvent molecules, they are one of the main tools in understanding the solution processes and solvent effects on chemical systems. Another popular application is the generation of graphic displays.⁴⁴

One may use different types of molecular cavities and surfaces definitions (e.g. equipotential surfaces, equidensity surfaces, van der Waals surfaces). Among them there is a subset that shares a common trait: they consider that a molecule may be represented as a set of rigid interlocking spheres. There are three such surfaces: a)

the van der Waals surface (WSURF), which is the external surface resulting from a set of spheres centered on the atoms or group of atoms forming the molecule (Figure 2.1.5a); b) the Accessible Surface (ASURF), defined by Richards and Lee⁴⁵ as the surface generated by the center of the solvent probe sphere, when it rolls around the van der Waals surface (Figure 2.1.5b); and c) the Solvent Excluding Surface (ESURF) which was defined by Richards⁴⁶ as the molecular surface and defined by him as composed of two parts: the contact surface and the reentrant surface. The contact surface is the part of the van der Waals surface of each atom which is accessible to a probe sphere of a given radius. The reentrant surface is defined as the inward-facing part of the probe sphere when this is simultaneously in contact with more than one atom (Figure 2.1.5c). We defined⁴⁷ ESURF as the surface envelope of the volume excluded to the solvent, considered as a rigid sphere, when it rolls around the van der Waals surface. This definition is equivalent to the definition given by Richards, but more concise and simple.

Each of these types of molecular surfaces is adequate for some applications. So, the van der Waals surface is widely used in graphic displays. However, for the representation of the solute cavity in a continuum model the

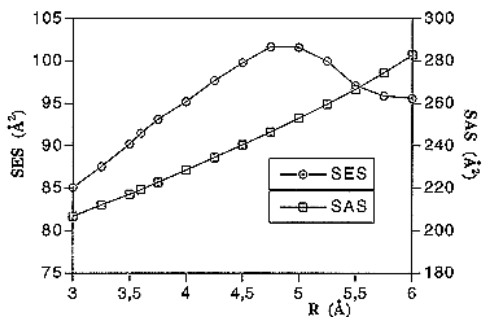


Figure 2.1.6. Variation of the area of the Solvent Accessible Surface and Solvent Excluding Surface of a methane dimer as a function of the intermolecular distance.

van der Waals surface is widely used in graphic displays. However, for the representation of the solute cavity in a continuum model the Accessible and the Excluding molecular surfaces are the adequate models as far as they take into account the solvent. The main relative difference between both molecular surface models appears when one considers the separation of two cavities in a continuum model and more precisely the cavitation contribution to the potential of mean force associated to this process (Figure 2.1.6). In fact, we have shown³¹ that only using the Excluding surface the correct shape of the potential of mean force is obtained. The cavitation term cannot be correctly represented by interactions among only one center by solvent molecule,

such as the construction of the Accessible surface implies. The Excluding surface, which gives the area of the cavity not accessible to the solvent whole sphere and which should be close to the true envelope of the volume inaccessible to the solvent charge distribution, would be a more appropriate model (Figure 2.1.7).

2.1.3.4 Supermolecule models

The study of the dissolution process can also be confronted in a direct manner analyzing the specific interactions between one or more molecules of solute with a large or larger group of solvent molecules. Quantum Mechanics is once again the ideal tool for dealing with this type of system. Paradoxically, whilst on the one hand the experimental study of a system becomes complicated when we try to make an abstraction of the solvent, the theoretical study becomes extraordinarily complicated when we include it. In this way, Quantum Mechanics has been, since its origins, a useful tool and relatively simple to use in the study of isolated molecules, with the behavior of a perfect gas. For this reason, Quantum Mechanics becomes so useful in the study of systems which are found in especially rarefied gaseous surroundings, such as the case of the study of the molecules present in the interstellar medium.⁴⁸ Nev-



Figure 2.1.7. The Solvent Excluding Surface of a particular solute is the envelope of the volume excluded to the solvent considered as a whole sphere that represents its charge density.

ertheless, when studying systems in solution, the goodness of the results grows with the number of solvent molecules included in the calculation, but so also does the computational effort. Because of this, the main limitation of the supermolecule model is that it requires computational possibilities which are not always accessible, especially if it is desired to carry out the quantum mechanical calculations with a high level of quality. This problem is sometimes resolved by severely limiting the number of solvent molecules which are taken into account. However, this alternative will limit our hopes to know what is the global effect of the solvent over the molecules of solute, specifically the far reaching interactions solute-solvent. Where the supermolecule model is effective is in the analysis of short distance interactions between the molecules of the solute and those of the solvent, provided a sufficient number of solvent molecules are included in the system being studied to reproduce the effect being studied and provided that the calculation can be tackled computationally.⁴⁹ In this manner the supermolecule model takes the advantage over other models of modelling the solute-solvent interaction, which is the case of the continuum models. Recent advances are removing the boundaries between the different computational strategies that deal with solvent effects. A clear example is given by the Car-Parrinello approach where a quantum treatment of the solute and solvent molecules is used in a dynamic study of the system.⁵⁰

2.1.3.5 Application example: glycine in solution

A practical case to compare the advantages obtained with the utilization of the different models can be found in the autoionization of the aminoacids in aqueous solution. The chemistry of the aminoacids in an aqueous medium has been at the forefront of numerous studies,⁵¹⁻⁵⁷ due to its self-evident biological interest. Thanks to these studies, it is well known that, whilst in the gas phase the aminoacids exist as non-autoionized structures, in aqueous solution it is the zwitterionic form which is prevailing (Figure 2.1.8).

This transformation suggests that when an aminoacid molecule is introduced from vacuum into the middle of a polar medium, which is the case of the physiological cellular media, a severe change is produced in its properties, its geometry, its energy, the charges which its atoms support, the dipolar molecular moment, etc., set off and conditioned by the presence of the solvent.

Utilizing Quantum Mechanics to analyze the geometry of the glycine in the absence of solvent, two energy minima are obtained (Figure 2.1.9), differentiated essentially by the rotation of the acid group. One of them is the absolute energy minimum in the gas phase (I), and the other is the conformation directly related with the ionic structure (II): The structure which is furthest from the zwitterionic form, I, is 0.7 Kcal/mol more stable than II, which

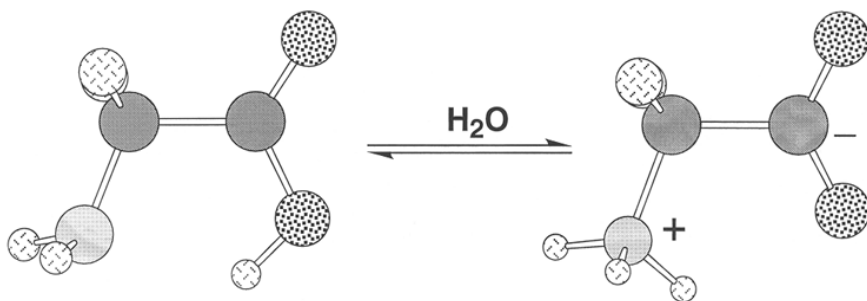


Figure 2.1.8. Neutral and zwitterionic form of glycine.

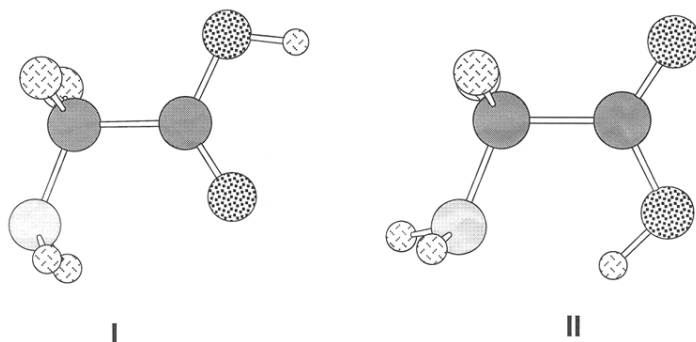


Figure 2.1.9. Quantum Mechanics predicts the existence of two conformers of glycine in the gas phase whose main difference is the rotation of the acid group around the axis which joins the two carbons. The structure I, the furthest from the zwitterionic geometry, is revealed to be the most stable in gas phase.

highlights the importance of the solvent for the autoionized form of the aminoacids to prevail.

An analysis of the specific effects of the solvent in the formation and the stability of the zwitterion can be addressed carrying out the calculations of the reaction path with and without a molecule of water (Figure 2.1.10), this being within the philosophy of the supermolecule calculations. This discrete molecule of solvent has been located such that it actively participates in the migration of the proton from the oxygen to the nitrogen.⁵⁵

That molecule of water forms two hydrogen bonds so much with the neutral glycine as zwitterionic, and when the glycine is transformed from the neutral configuration to the zwitterion the interchange of two atoms of hydrogen is produced between the aminoacid and the molecule of solvent. Thus, we reproduce from a theoretical point of view the process of protonic Table transfer of an aminoacid with the participation of the solvent (intermolecular mechanism). Table 2.1.2 shows the relative energies of the three solute-solvent structures analysed, as well as that of the system formed by the amino acid and the molecule of solvent individually.

The table shows that the neutral glycine - molecule of water complex is the most stable. Moreover, the energy barrier which drives the state of transition is much greater than that which is obtained when Quantum Mechanics is used to reproduce the autoionization of the glycine with the presence of the solvent by means of an intramolecular process.⁵⁵ This data suggests that even in the case where a larger number of water molecules are included in

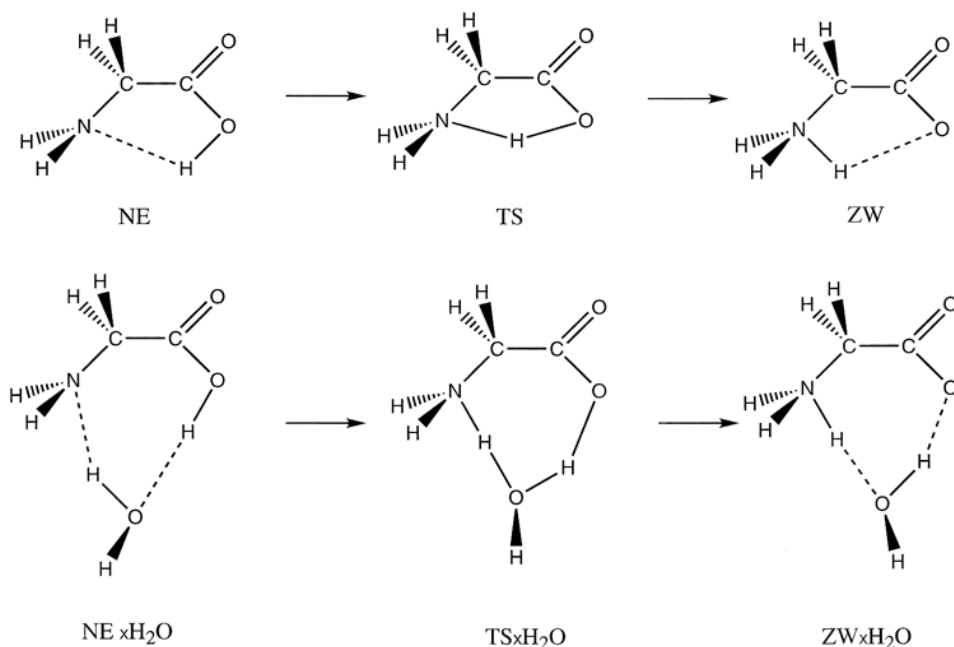


Figure 2.1.10. Intramolecular and intermolecular proton transfer in glycine, leading from the neutral form to the zwitterionic one.

Table 2.1.2. Relative energies (in Kcal/mol) for the complexes formed between a molecule of water with the neutral glycine (NE·H₂O), the zwitterion (ZW·H₂O), and the state of transition (TS·H₂O), as well as for the neutral glycine system and independent molecule of water (NE+H₂O), obtained with a base HF/6-31+G**

NE·H ₂ O	TS·H ₂ O	ZW·H ₂ O	NE+H ₂ O
0	29.04	16.40	4.32

the supermolecule calculation, the intramolecular mechanism will still continue as the preferred in the autoionization of the glycine. The model of supermolecule has been useful to us, along with the competition of other models,^{54,55} to shed light on the mechanism by which an amino acid is autoionized in aqueous solution.

If the calculations are done again but this time including the presence of the solvent by means of a continuum model (implemented by means of a dielectric constant = 78.4; for the water), the situation becomes different.^{55,58-60} Now it is the conformation closest to the zwitterionic (II) which is the most stable, by some 2.7 Kcal/mol. This could be explained on the basis of the greater dipolar moment of the structure (6.3 Debyes for the conformation II compared to 1.3 of the conformation I).

The next step was to reproduce the formation of the zwitterion starting with the most stable initial structure in the midst of the solvent (II). Using the continuum model, we observe how the structure II evolves towards a state of transition which, once overcome, leads

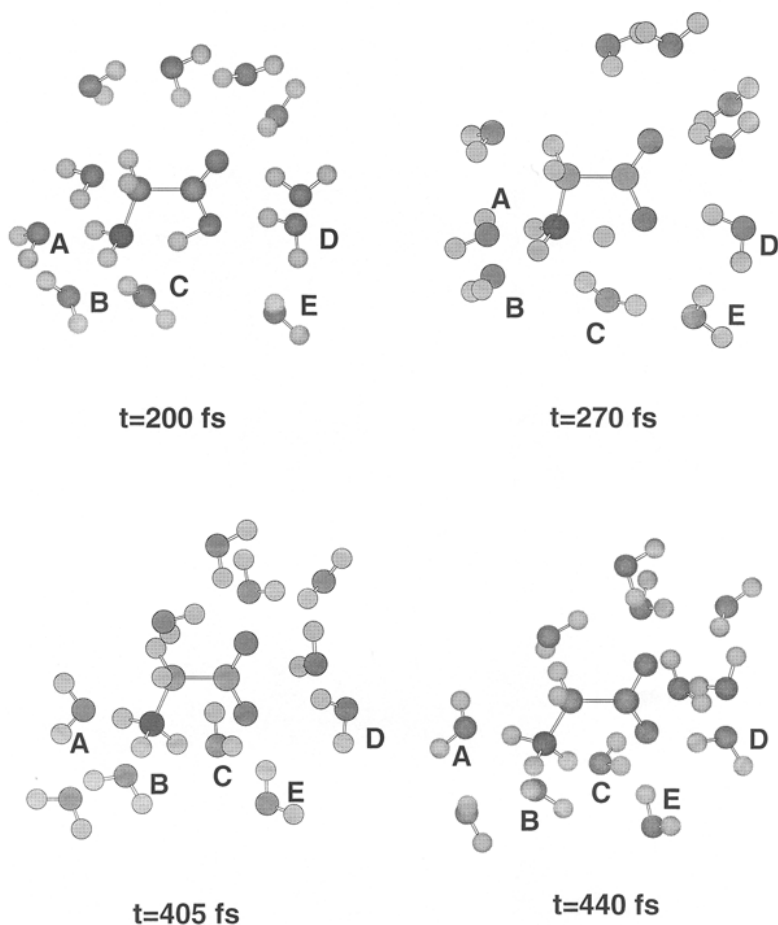


Figure 2.1.11. The microscopic environment in which the formation of zwitterion takes place is exhibited in these four “snapshots”. It is possible to see the re-ordering of the structure of the molecule of glycine, along with the re-ordering of the shell of molecules of water which surround it, at 200, 270, 405 and 440 femtoseconds from the beginning of the simulation of the process by Molecular Dynamics.

to the zwitterion (Figure 2.1.7). This transition structure corresponds, then, to an intramolecular protonic transfer from the initial form to the zwitterionic form of the aminoacid. The calculations carried out reveal an activation energy of 2.39 Kcal/mol, and a reaction energy of -1.15 Kcal/mol at the MP2/6-31+G** level.

A more visual check of the process submitted to study is achieved by means of hybrid QM/MM Molecular Dynamics,⁵⁸ which permits “snapshots” to be obtained which reproduce the geometry of the aminoacid surrounded by the solvent. In Figure 2.1.11 are shown four of these snapshots, corresponding to times of 200, 270, 405 and 440 femtoseconds after commencement of the process.

In the first of these, the glycine has still not been autoionized. Two molecules of water (identified as A and B) form hydrogen bonds with the nitrogen of the amine group, whilst

only one (D) joins by hydrogen bond with the O_2 . Two more molecules of water (C and E) appear to stabilize electrostatically the hydrogen of the acid (H_1). The second snapshot has been chosen whilst the protonic transfer was happening. In this, the proton (H_1) appears jumping from the acid group to the amine group. However, the description of the first shell of hydration around the nitrogen atoms, oxygen (O_2) and of the proton in transit remain essentially unaltered with respect to the first snapshot. In the third snapshot the amino acid has now reached the zwitterionic form, although the solvent still has not relaxed to its surroundings. Now the molecules of water A and B have moved closer to the atom of nitrogen, and a third molecule of water appears imposed between them. At the same time, two molecules of water (D and E) are detected united clearly by bridges of hydrogen with the atom of oxygen (O_2). All of these changes could be attributed to the charges which have been placed on the atoms of nitrogen and oxygen. The molecule of water (C) has followed a proton in its transit and has fitted in between this and the atom of oxygen (O_2). In the fourth snapshot of the Figure 2.1.8 the relaxing of the solvent, after the protonic transfer, is now observed, permitting the molecule of water (C) to appear better orientated between the proton transferred (H_1) and the atom of oxygen (O_2), and this now makes this molecule of solvent strongly attached to the zwitterion inducing into it appreciable geometrical distortions.

From the theoretical analysis carried out it can be inferred that the neutral conformer of the glycine II, has a brief life in aqueous solution, rapidly evolving to the zwitterionic species. The process appears to happen through an intramolecular mechanism and comes accompanied by a soft energetic barrier. For its part, the solvent plays a role which is crucial both to the stabilization of the zwitterion as well as to the protonic transfer. This latter is favored by the fluctuations which take place in the surroundings.

2.1.4 THERMODYNAMIC AND KINETIC CHARACTERISTICS OF CHEMICAL REACTIONS IN SOLUTION

It is very difficult for a chemical equilibrium not to be altered when passing from gas phase to solution. The free energy standard of reaction, ΔG° , is usually different in the gas phase compared with the solution, because the solute-solvent interactions usually affect the reactants and the products with different results. This provokes a displacement of the equilibrium on passing from the gas phase to the midst of the solution.

In the same way, and as was foreseen in section 2.1.1, the process of dissolution may alter both the rate and the order of the chemical reaction. For this reason it is possible to use the solvent as a tool both to speed up and to slow down the development of a chemical process.

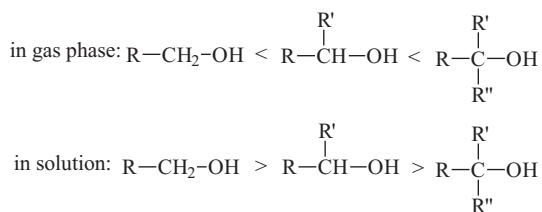
Unfortunately, little experimental information is available on how the chemical equilibria and the kinetics of the reactions become altered on passing from the gas phase to the solution, since as commented previously, the techniques which enable this kind of analysis are relatively recent. It is true that there is abundant experimental information, nevertheless, on how the chemical equilibrium and the velocity of the reaction are altered when one same process occurs in the midst of different solvents.

2.1.4.1 Solvent effects on chemical equilibria

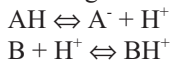
The presence of the solvent is known to have proven influences in such a variety of chemical equilibria: acid-base, tautomerism, isomerization, association, dissociation, conformational, rotational, condensation reactions, phase-transfer processes, etc.,¹ that its detailed analysis is outside the reach of a text such as this. We will limit ourselves to analyz-

ing superficially the influence that the solvent has on one of the equilibria of greatest relevance, the acid-base equilibrium.

The solvent can alter an acid-base equilibrium not only through the acid or basic character of the solvent itself, but also by its dielectric effect and its capacity to solvate the different species which participate in the process. Whilst the acid or basic force of a substance in the gas phase is an intrinsic characteristic of the substance, in solution this force is also a reflection of the acid or basic character of the solvent and of the actual process of solvation. For this reason the scales of acidity or basicity in solution are clearly different from those corresponding to the gas phase. Thus, toluene is more acid than water in the gas phase but less acid in solution. These differences between the scales of intrinsic acidity-basicity and in solution have an evident repercussion on the order of acidity of some series of chemical substances. Thus, the order of acidity of the aliphatic alcohols becomes inverted on passing from the gas phase to solution:



The protonation free energies of MeOH to t-ButOH have been calculated in gas phase and with a continuum model of the solvent.⁶¹ It has been shown that in this case continuum models gives solvation energies which are good enough to correctly predict the acidity ordering of alcohols in solution. Simple electrostatic arguments based on the charge delocalization concept, were used to rationalize the progressive acidity of the alcohols when hydrogen atoms are substituted by methyl groups in the gas phase, with the effect on the solution energies being just the opposite. Thus, both the methyl stabilizing effect and the electrostatic interaction with the solvent can explain the acid scale in solution. As both terms are related to the molecular size, this explanation could be generalized for acid and base equilibria of homologous series of organic compounds:



In vacuo, as the size becomes greater by adding methyl groups, displacement of the equilibria takes place toward the charged species. In solution, the electrostatic stabilization is lower when the size increases, favoring the displacement of the equilibria toward the neutral species. The balance between these two tendencies gives the final acidity or basicity ordering in solution. Irregular ordering in homologous series are thus not unexpected taking into account the delicate balance between these factors in some cases.⁶²

2.1.4.2 Solvent effects on the rate of chemical reactions

When a chemical reaction takes place in the midst of a solution this is because, prior to this, the molecules of the reactants have diffused throughout the medium until they have met. This prior step of the diffusion of the reactants can reach the point of conditioning the performance of the reaction, especially in particularly dense and/or viscous surroundings. This is the consequence of the liquid phase having a certain microscopic order which, although

much less than that of the solid state, is not depreciable. Thus, in a solution, each molecule of solute finds itself surrounded by a certain number of molecules of solvent which envelope it forming what has been denominated as the solvent cage. Before being able to escape from the solvent cage each molecule of solute collides many times with the molecules of solvent which surround it.

In the case of a dilute solution of two reactants, A and B, their molecules remain for a certain time in a solvent cage. If the time needed to escape the solvent cage by the molecules A and B is larger than the time needed to suffer a bimolecular reaction, we can say that this will not find itself limited by the requirement to overcome an energetic barrier, but that the reaction is controlled by the diffusion of the reactants. The corresponding reaction rate will, therefore, have a maximum value, known as diffusion-controlled rate. It can be demonstrated that the diffusion-limited bimolecular rate constants are of the order of 10^{10} - 10^{11} $\text{M}^{-1}\text{s}^{-1}$, when A and B are ions with opposite charges.⁶³ For this reason, if a rate constant is of this order of magnitude, we must wait for the reaction to be controlled by the diffusion of the reactants. But, if the rate constant of a reaction is clearly less than the diffusion-limited value, the corresponding reaction rate is said to be chemically controlled.

Focusing on the chemical aspects of the reactivity, the rupture of bonds which goes along with a chemical reaction usually occurs in a homolytic manner in the gas phase. For this reason, the reactions which tend to prevail in this phase are those which do not involve a separation of electric charge, such as those which take place with the production of radicals. In solution, the rupture of bonds tends to take place in a heterolytic manner, and the solvent is one of the factors which determines the velocity with which the process takes place. This explains that the reactions which involve a separation or a dispersion of the electric charge can take place in the condensed phase. The effects of the solvent on the reactions which involve a separation of charge will be very drawn to the polar nature of the state of transition of the reaction, whether this be a state of dipolar transition, isopolar or of the free-radical type. The influence of the solvent, based on the electric nature of the substances which are reacting, will also be essential, and reactions may occur between neutral nonpolar molecules, between neutral dipolar molecules, between ions and neutral nonpolar molecules, between ions and neutral polar molecules, ions with ions, etc. Moreover, we should bear in mind that alongside the non specific solute-solvent interactions (electrostatic, polarization, dispersion and repulsion), specific interactions may be present, such as the hydrogen bonds.

Table 2.1.3. Relative rate constants of the Menschutkin reaction between triethylamine and iodoethane in twelve solvents at 50°C. In 1,1,1-trichloroethane the rate constant is $1.80 \times 10^{-5} \text{ l mol}^{-1} \text{ s}^{-1}$. Data taken from reference 40

Solvent	Relative rate constant	Solvent	Relative rate constant
1,1,1-Trichloroethane	1	Acetone	17.61
Chlorocyclohexane	1.72	Cyclohexanone	18.72
Chlorobenzene	5.17	Propionitrile	33.11
Chloroform	8.56	Benzonitrile	42.50
1,2-Dichlorobenzene	10.06		

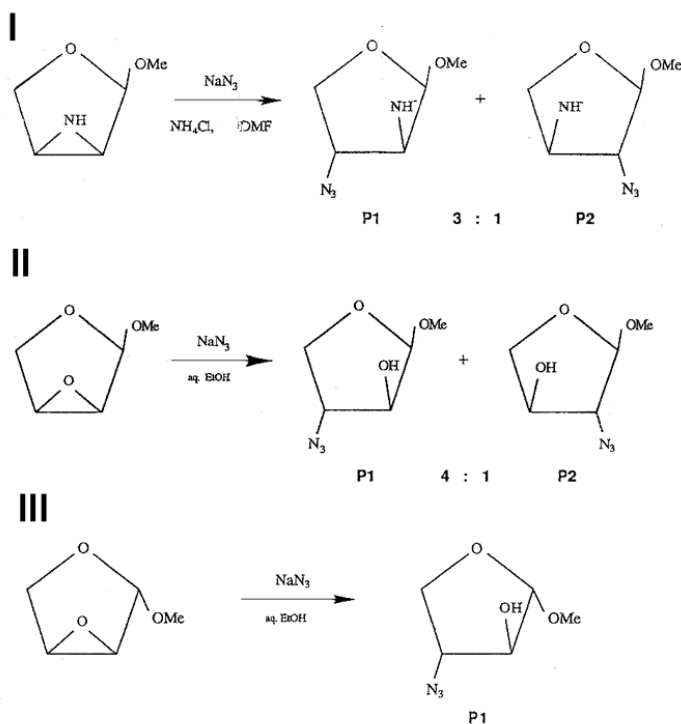


Figure 2.1.12. Models of the reaction studied for the addition of azide anion to tetrafuranosides. The experimental product ratio is also given.

The influence of the solvent on the rate at which a chemical reaction takes place was already made clear, in the final stages of the XIX century, with the reaction of Menshutkin between tertiary amines and primary haloalkanes to obtain quaternary ammonium salts.⁶⁴ The reaction of Menshutkin between triethylamine and iodoethane carried out in different media shows this effect (Table 2.1.3):

2.1.4.3 Example of application: addition of azide anion to tetrafuranosides

The capacity of the solvent to modify both the thermodynamic and also the kinetic aspects of a chemical reaction are observed in a transparent manner on studying the stationary structures of the addition of azide anion to tetrafuranosides, particularly: methyl 2,3-dideoxy-2,3-epimino- α -L-erythrofuranoside (I), methyl 2,3-anhydro- α -L-erythrofuranoside (II), and 2,3-anhydro- β -L-erythrofuranoside (III). An analysis with molecular orbital methods at the HF/3-21G level permits the potential energy surface in vacuo to be characterized, to locate the stationary points and the possible reaction pathways.⁶⁵ The effect of the solvent can be implemented with the aid of a polarizable continuum model. Figure 2.1.12 shows the three tetrafuranosides and the respective products obtained when azide anion attacks in C_3 (P1) or in C_4 (P2).

The first aim of a theoretical study of a chemical reaction is to determine the reaction mechanism that corresponds to the minimum energy path that connects the minima of reactant and products and passes through the transition state (TS) structures on the potential en-

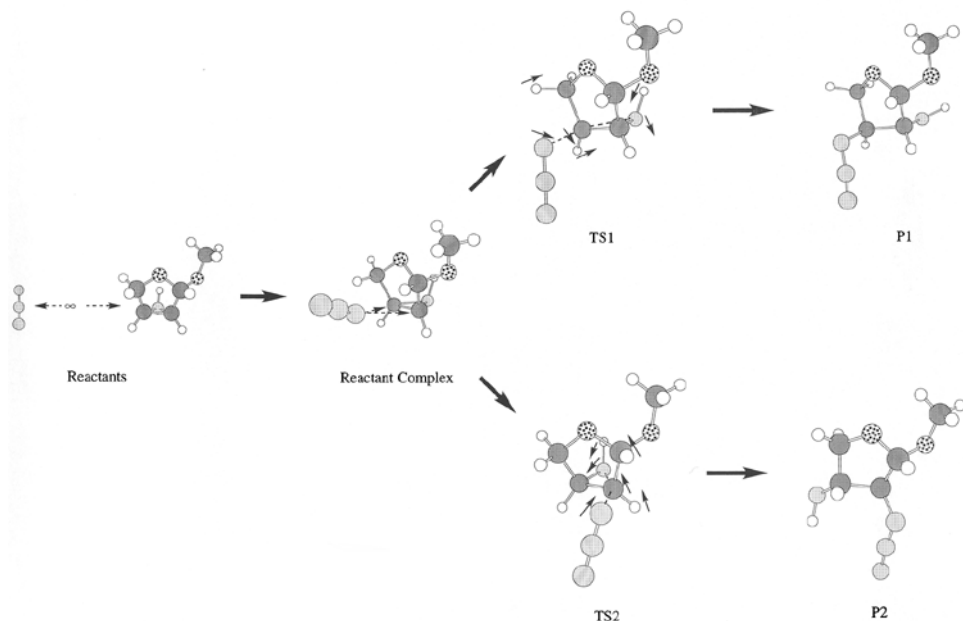


Figure 2.1.13. Representation of the stationary points (reactants, reactant complex, transition states, and products) for the molecular mechanism of compound I. For the TS's the components of the transition vectors are depicted by arrows.

ergy surface. In this path the height of the barrier that exists between the reactant and TS is correlated to the rate of each different pathway (kinetic control), while the relative energy of reactants and products is correlated to equilibrium parameters (thermodynamic control). The second aim is how the solute-solvent interactions affect the different barrier heights and relative energies of products, mainly when charged or highly polar structures appear along the reaction path. In fact, the differential stabilization of the different stationary points in the reaction paths can treat one of them favorably, sometimes altering the relative energy order found in vacuo and, consequently, possibly changing the ratio of products of the reaction. An analysis of the potential energy surface for the molecular model I led to the location of the stationary points showed in Figure 2.1.13.

The results obtained for the addition of azide anion to tetrafuranosides with different molecular models and in different solvents can be summarized as follows:⁶⁵

- For compound I, in vacuo, P1 corresponds to the path with the minimum activation energy, while P2 is the more stable product (Figures 2.1.14 and 2.1.15). When the solvent effect is included, P1 corresponds to the path with the minimum activation energy and it is also the more stable product. For compound II, in vacuo, P2 is the more stable product and also presents the smallest activation energy. The inclusion of the solvent effect in this case changes the order of products and transition states stability. For compound III, P1 is the more stable product and presents the smallest activation energy both in vacuo and in solution.
- A common solvent effect for the three reactions is obtained: as far as the dielectric constant of the solvent is augmented, the energy difference between P1 and P2

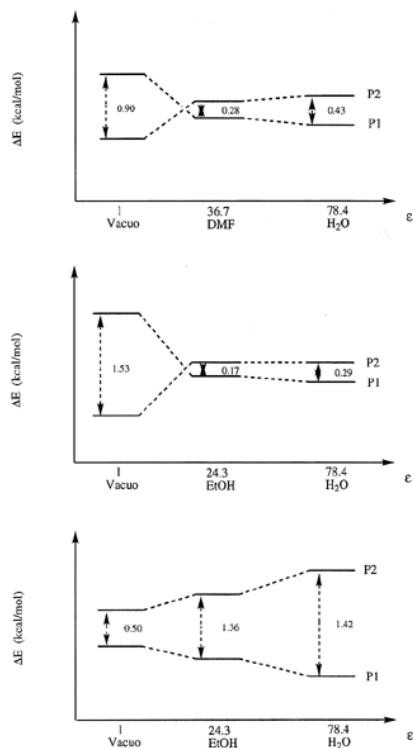


Figure 2.1.14. Schematic representation of the relative energies (in Kcal/mol) for the products P1 and P2, in vacuo ($\epsilon = 1$), DMF ($\epsilon = 36.7$), or EtOH ($\epsilon = 24.3$), and in water ($\epsilon = 78.4$).

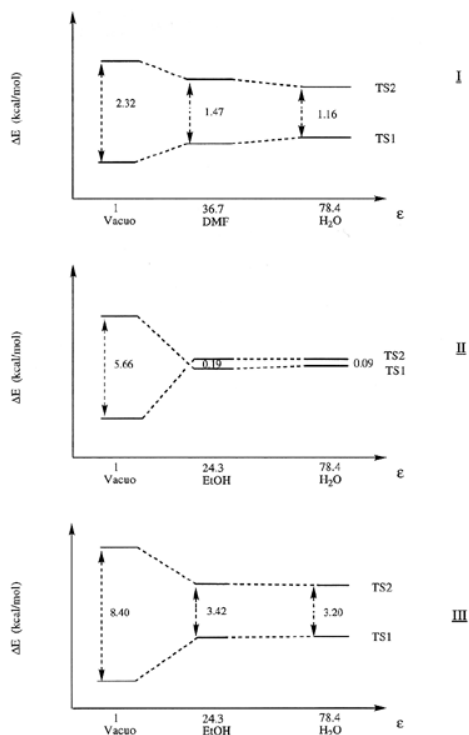


Figure 2.1.15. Schematic representation of the relative energies of activation (in Kcal/mol) for the transition states TS1 and TS2, in vacuo ($\epsilon = 1$), DMF ($\epsilon = 36.7$), or EtOH ($\epsilon = 24.3$), and in water ($\epsilon = 78.4$).

increases, favoring thermodynamically the path leading to P1. On the other hand, an opposite influence is evident in the case of the transition states, so an increase of the dielectric constant kinetically favors the path leading to P2.

All this data makes evident the crucial role which the solvent plays both in the thermodynamics and in the kinetics of the chemical reaction analysed.

2.1.5 SOLVENT CATALYTIC EFFECTS

Beyond the solvent as merely making possible an alternative scenery to the gas phase, beyond its capacity to alter the thermodynamics of a process, the solvent can also act as a catalyst of some reactions, and can reach the point of altering the mechanism by which the reaction comes about.

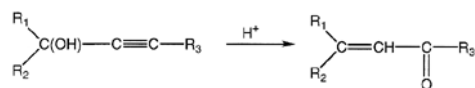


Figure 2.1.16. Reaction of Meyer-Schuster.

An example of a reaction in which the solvent is capable of altering the mechanism through which the reaction takes place is that of Meyer-Schuster, which is much utilized in organic synthesis.⁶⁶⁻⁷¹ This consists of the isomerization in an acid medium

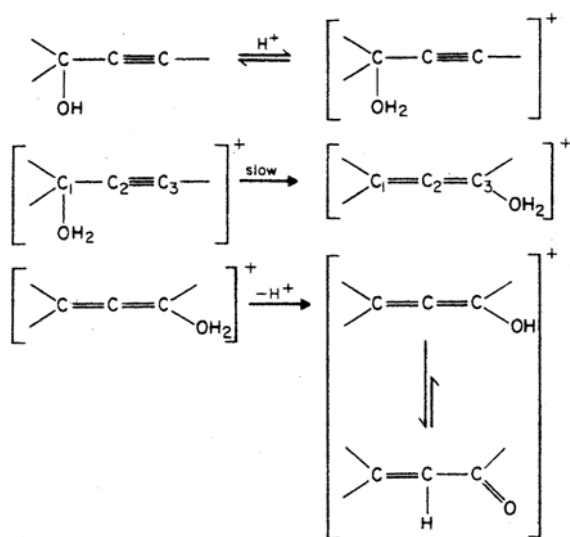


Figure 2.1.17. Steps of the reaction of Meyer-Schuster.

of secondary and tertiary α -acetylenic alcohols to carbon-ylc α,β -unsaturated compounds (Figure 2.1.16).

Its mechanism consists of three steps (Figure 2.1.17). The first one is the protonation of the oxygen atom. The second, which determines the reaction rate, is that in which the 1.3 shift from the protonated hydroxyl group is produced through the triple bond to give way to the structure of alenol. The last stage corresponds to the deprotonation of the alenol, producing a keto-enolic tautomerism which displaces towards the ketonic form.

For the step which limits the reaction rate (rate limiting step), three mechanisms have been proposed,

two of which are intramolecular - denominated intramolecular, as such, and solvolytic - and the other intermolecular (Figure 2.1.18). The first of these implies a covalent bond between water and the atoms of carbon during the whole of the transposition. In the solvolytic mechanism there is an initial rupture from the O-C₁ bond, followed by a nucleophilic attack of the H₂O on the C₃. Whilst the intermolecular mechanism corresponds to a nucleophilic attack of H₂O on the terminal carbon C₃ and the loss of the hydroxyl group protonated of the C₁.

The analysis of the first two mechanisms showed⁷² the solvolytic mechanism as the most favorable localizing itself during the reaction path to an alquinylic carbocation interacting electrostatically with a molecule of water. This fact has been supported by the experimental detection of alquinylic carbocations in solvolytic conditions. Things being like that, two alternatives remain for the slow stage of the Meyer-Schuster reaction, the solvolytic and the intermolecular mechanism, and it seems that the solvent has a lot to say in this.

Although both mechanisms evolve in two steps, these are notably different. In the intermolecular mechanism, the first transition state can be described as an almost pure electrostatic interaction of the entrant molecule of water with the C₃, whilst the C₁ remains united covalently to the protonated hydroxyl group. This first transition state leads to an intermediate in which the two molecules of water are covalently bonded to the C₁ and C₃ atoms. The step from the intermediate to the product takes place through a second transition state, in which the C₃ is covalently bonded to the molecule of entrant water and there is an electrostatic interaction of the other water molecule. In the mechanism which we call solvolytic, the first transition state corresponds to the pass from covalent to electrostatic interaction of the H₂O united to the C₁, that is to say, to a process of solvolysis, so, the water molecule remains interacting electrostatically with the carbons C₁ and C₃.

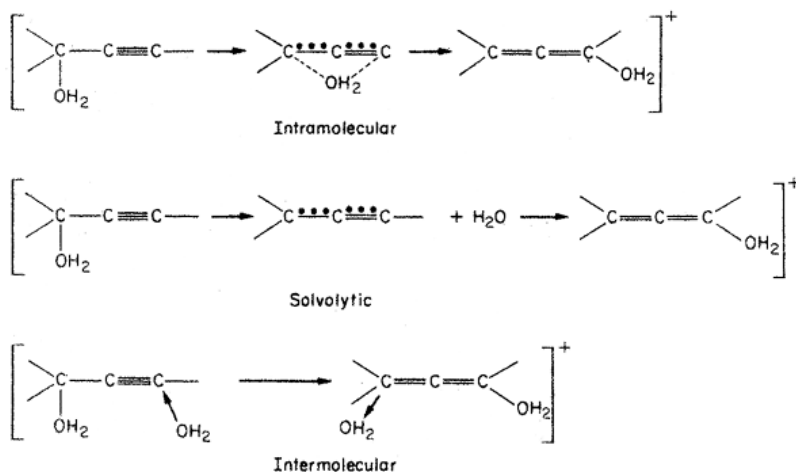


Figure 2.1.18. Three different mechanism for the rate-limiting step of the reaction of Meyer-Schuster.

On comparing the solvolytic and intermolecular processes a smaller potential barrier is observed for the latter, thus the solvent plays an active part in the Meyer-Schuster reaction, being capable of changing radically the mechanism through which this takes place. It seems clear that in the presence of aqueous solvents the nucleophilic attack on the C_3 precedes the loss of the water (solvolysis): a lesser activation energy corresponds to the intermolecular process than to the solvolytic. Moreover, if we analyze the intermolecular mechanism we can verify that the solvent stabilizes both the reactants as well as the products by the formation of hydrogen bridges.

Epilogue

As a fish in the midst of the ocean, the reactants are usually found in the midst of a solution in our laboratory tests. In the same way as in the ocean where there is both danger and a heaven for the fish, in the internal scenery of a solution the chemical reactions can be speeded up or slowed down, favored thermodynamically or prejudiced. In this way, on passing from vacuum to a solution, the molecules of the reactants can experience alterations in their geometry, the distribution of their charges, or their energy, which can have an effect on the outcome of the reaction. In the preceding pages we have attempted to make clear these solute-solvent influences, and to achieve this we have plunged, hand in hand with theoretical chemistry, into the microscopic and recondite environment of the solutions.

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2.2 MOLECULAR DESIGN OF SOLVENTS

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2.2.1 MOLECULAR DESIGN AND MOLECULAR ENSEMBLE DESIGN

Many of chemists seem to conjecture that the success in developing so-called high-functional materials is the key to recover social responsibility. These materials are often composed of complex molecules, contain many functional groups and their structure is of complex nature. Before establishing the final target compound, we are forced to consider many factors, and we are expected to minimize the process of screening these factors effectively.

At present, such a screening is called “design”. If the object of screening is each molecule, then it is called “molecular design”. In similar contexts are available “material design”, “solvent design”, “chemical reaction design”, etc. We hope that the term “molecular ensemble design” could have the citizenship in chemistry. The reason for this is as below.

Definition of “molecular design” may be expressed as to find out the molecule which has appropriate properties for a specific purpose and to predict accurately via theoretical ap-

proach the properties of the molecule. If the molecular system in question consists of an isolated free molecule, then it is “molecular design”. If the properties are of complex macroscopic nature, then it is “material design”. Problem remains in the intermediate between the above two. Because fundamental properties shown by the ensemble of molecules are not always covered properly by the above two types of design. This is because the molecular design is almost always based on quantum chemistry of free molecule and the material design relies too much on empirical factor at the present stage. When we proceed to molecular ensemble (mainly liquid phase), as the matter of fact, we must use statistical mechanics as the basis of theoretical approach.

Unfortunately, statistical mechanics is not familiar even for the large majority of chemists and chemical engineers. Moreover, fundamental equations in statistical mechanics cannot often be solved rigorously for complex systems and the introduction of approximation becomes necessary to obtain useful results for real systems. In any theoretical approach for molecular ensemble, we must confront with so-called many-body problems and two-body approximations must be applied. Even in the frameworks of this approximation, our knowledge on the intermolecular interaction, which is necessary in statistical mechanical treatment is still poor.

Under such a circumstance, numerical method should often be useful. In the case of statistical mechanics of fluids, we have Monte Carlo (MC) simulation based on the Metropolis scheme. All the static properties can be numerically calculated in principle by the MC method.

Another numerical method to supplement the MC method should be the numerical integration of the equations of motion. This kind of calculation for simple molecular systems is called molecular dynamics (MD) method where Newton or Newton-Euler equation of motion is solved numerically and some dynamic properties of the molecule involved can be obtained.

These two methods are invented, respectively, by the Metropolis group (MC, Metropolis et al., 1953)¹ and Alder’s group (MD, Alder et al., 1957)² and they are the molecular versions of computer experiments and therefore called now molecular simulation.³ Molecular simulation plays a central role in “molecular ensemble design”. They can reproduce thermodynamics properties, structure and dynamics of a group of molecules by using high speed supercomputer. Certainly any reasonable calculations on molecular ensemble need long computer times, but the advance in computer makes it possible that this problem becomes gradually less serious.

Rather, the assignment is more serious with intermolecular interaction potential used. For simple molecules, empirical model potential such as those based on Lennard-Jones potential and even hard-sphere potential can be used. But, for complex molecules, potential function and related parameter value should be determined by some theoretical calculations. For example, contribution of hydrogen-bond interaction is highly large to the total interaction for such molecules as H₂O, alcohols etc., one can produce semi-empirical potential based on quantum-chemical molecular orbital calculation. Molecular ensemble design is now complex unified method, which contains both quantum chemical and statistical mechanical calculations.

2.2.2 FROM PREDICTION TO DESIGN

It is not new that the concept of “design” is brought into the field of chemistry. Moreover, essentially the same process as the above has been widely used earlier in chemical engineer-

ing. It is known as the prediction and correlation methods of physical properties, that is, the method to calculate empirically or semi-empirically the physical properties, which is to be used in chemical engineering process design. The objects in this calculation include thermodynamic functions, critical constant, phase equilibria (vapor pressure, etc.) for one-component systems as well as the transport properties and the equation of state. Also included are physical properties of two-components (solute + pure solvent) and even of three-components (solute + mixed solvent) systems. Standard reference, "The properties of Gases and Liquids; Their Estimation and Prediction",⁴ is given by Sherwood and Reid. It was revised once about ten years interval by Reid and others. The latest 4th edition was published in 1987. This series of books contain excellent and useful compilation of "prediction" method. However, in order to establish the method for molecular ensemble design we need to follow three more stages.

- (1) Calculate physical properties of any given substance. This is just the establishment and improvement of presently available "prediction" method.
- (2) Calculate physical properties of model-substance. This is to calculate physical properties not for each real molecule but for "model". This can be done by computer simulation. On this stage, compilation of model substance data base will be important.
- (3) Predict real substance (or corresponding "model") to obtain required physical properties. This is just the reverse of the stage (1) or (2). But, an answer in this stage is not limited to one particular substance.

The scheme to execute these three stages for a large variety of physical properties and substances has been established only to a limited range. Especially, important is the establishment of the third stage, and after that, "molecular ensemble design" will be worth to discuss.

2.2.3 IMPROVEMENT IN PREDICTION METHOD

Thus, the development of "molecular ensemble design" is almost completely future assignment. In this section, we discuss some attempts to improve prediction at the level of stage (1). It is taken for the convenience's sake from our own effort. This is an example of repeated improvements of prediction method from empirical to molecular level.

The diffusion coefficient D_1 of solute 1 in solvent 2 at infinitely dilute solution is a fundamental property. This is different from the self-diffusion coefficient D_0 in pure liquid. Both D_1 and D_0 are important properties. The classical approach to D_1 can be done based on Stokes and Einstein relation to give the following equation

$$D_1\eta_2 = kT / 6\pi r_1 \quad [2.2.1]$$

where D_1 at constant temperature T can be determined by the radius r_1 of solute molecule and solvent viscosity η_2 (k is the Boltzmann constant). However, this equation is valid only when the size of solvent molecule is infinitely small, namely, for the diffusion in continuous medium. It is then clear that this equation is inappropriate for molecular mixtures. The well known Wilke-Chang equation,⁵ which corrects comprehensively this point, can be used for practical purposes. However, average error of about 10% is inevitable in the comparison with experimental data.

One attempt⁶ to improve the agreement with experimental data is to use Hammond-Stokes relation in which the product $D_1\eta_2$ is plotted against the molar volume ratio of solvent to solute V_r . The slope is influenced by the following few factors, namely,

- (1) self-association of solvent,
- (2) asymmetry of solvent shape, and
- (3) strong solute-solvent interactions.

If these factors can be taken properly into account, the following equation is obtained.

$$D_1\eta_2 / T = K_1 / V_0^{1/3} + K_2 V_r / T \quad [2.2.2]$$

Here constants K_1 and K_2 contain the parameters coming from the above factors and V_0 is the molar volume of solute.

This type of equation [2.2.2] cannot be always the best in prediction, but physical image is clearer than with other purely empirical correlations. This is an example of the stage (1) procedure and in order to develop a stage (2) method, we need MD simulation data for appropriate model.

2.2.4 ROLE OF MOLECULAR SIMULATION

We have already pointed out that statistical mechanical method is indispensable in “molecular ensemble design”. Full account of molecular simulation is given in some books³ and will not be reproduced here. Two types of approaches can be classified in applying this method.

The first one makes every effort to establish and use as real as exact intermolecular interaction in MC and MD simulation. It may be limited to a specific type of compounds. The second is to use simple model, which is an example of so-called Occam’s razor. We may obtain a wide bird-view from there.

In the first type of the method, intermolecular interaction potential is obtained based on quantum-chemical calculation. The method takes the following steps.

- (1) Geometry (interatomic distances and angles) of molecules involved is determined. For fundamental molecules, it is often available from electron diffraction studies. Otherwise, the energy gradient method in molecular orbital calculation can be utilized.
- (2) The electronic energy for monomer E_1 and those for dimers of various mutual configurations E_2 are calculated by the so-called *ab initio* molecular orbital method, and the intermolecular energy $E_2 - 2E_1$ is obtained.
- (3) By assuming appropriate molecular model and semi-empirical equation, parameters are optimized to reproduce intermolecular potential energy function.

Representative example of preparation of such potential energy function, called now *ab initio* potential would be MCY potential for water-dimer by Clementi et al.⁷ Later, similar potentials have been proposed for hetero-dimer such as water-methanol.⁸ In the case of such hydrogen-bonded dimers, the intermolecular energy $E_2 - 2E_1$ can be fairly large value and determination of fitted parameters is successful. In the case of weak interaction, *ab initio* calculation needs long computer time and optimization of parameter becomes difficult. In spite of such a situation, some attempts are made for potential preparation, e.g., for benzene and carbon dioxide with limited success.

To avoid repeated use of long time MO calculation, Jorgensen et al.⁹ has proposed MO-based transferable potential parameters called TIPS potential. This is a potential ver-

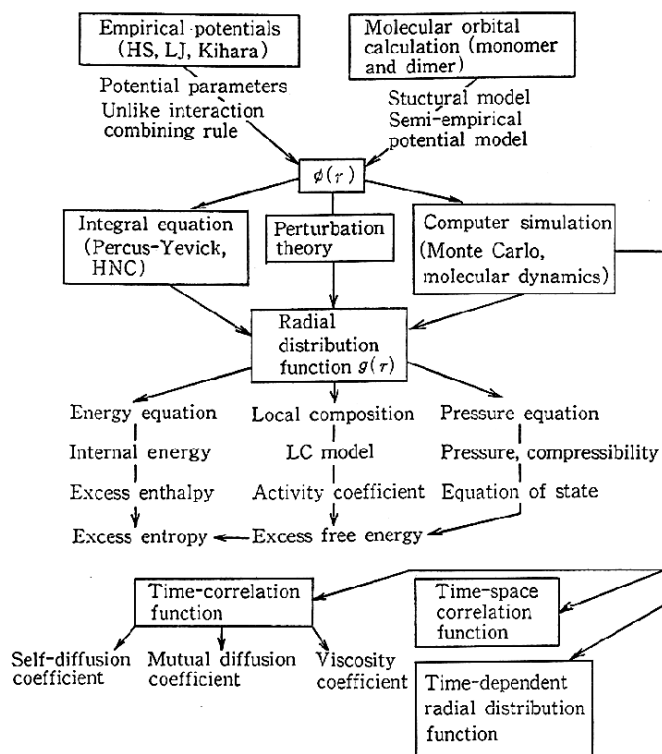


Figure 2.2.1. A scheme for the design of molecular ensembles.

sion of additivity rule, which has now an empirical character. It is however useful for practical purposes.

2.2.5 MODEL SYSTEM AND PARADIGM FOR DESIGN

The method described above is so to speak an orthodox approach and the ability of present-day's supercomputer is still a high wall in the application of molecular simulation. Then the role of the second method given in the last section is highly expected.

It is the method with empirical potential model. As the model, the approximation that any molecule can behave as if obeying Lennard-Jones potential seems to be satisfactory. This (one-center) LJ model is valid only for rare gases and simple spherical molecules. But this model may also be valid for other simple molecules as a zeroth approximation. We may also use two-center LJ model where interatomic interactions are concentrated to the major two atoms in the molecule. We expect that these one-center and two-center LJ models will play a role of Occam's razor.

We propose a paradigm for physical properties prediction as shown in Figure 2.2.1. This corresponds to the stage (2) and may be used to prepare the process of stage (3), namely, the molecular ensemble design for solvents.

Main procedures in this paradigm are as follows; we first adopt target molecule or mixture and determine their LJ parameters. At present stage, LJ parameters are available only for limited cases. Thus we must have method to predict effective LJ parameters.

For any kinds of mixtures, in addition to LJ parameters for each component, combining rule (or mixing rule) for unlike interaction should be prepared. Even for simple liquid mixtures, conventional Lorentz-Berthelot rule is not good answer.

Once potential parameters have been determined, we can start calculation downward following arrow in the figure. The first key quantity is radial distribution function $g(r)$ which can be calculated by the use of theoretical relation such as Percus-Yevick (PY) or Hypernetted chain (HNC) integral equation. However, these equations are an approximations. Exact values can be obtained by molecular simulation. If $g(r)$ is obtained accurately as functions of temperature and pressure, then all the equilibrium properties of fluids and fluid mixtures can be calculated. Moreover, information on fluid structure is contained in $g(r)$ itself.

On the other hand, we have, for non-equilibrium dynamic property, the time correlation function TCF, which is dynamic counterpart to $g(r)$. One can define various TCF's for each purpose. However, at the present stage, no extensive theoretical relation has been derived between TCF and $\phi(r)$. Therefore, direct determination of self-diffusion coefficient, viscosity coefficient by the molecular simulation gives significant contribution in dynamics studies.

Concluding Remarks

Of presently available methods for the prediction of solvent physical properties, the solubility parameter theory by Hildebrand¹⁰ may still supply one of the most accurate and comprehensive results. However, the solubility parameter used there has no purely molecular character. Many other methods are more or less of empirical character.

We expect that the 21th century could see more computational results on solvent properties.

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APPENDIX

PREDICTIVE EQUATION FOR THE DIFFUSION COEFFICIENT IN DILUTE SOLUTION

Experimental evidence is given in Figure 2.2.2 for the prediction based on equation [2.2.1]. The diffusion coefficient D_0 of solute A in solvent B at an infinite dilution can be calculated using the following equation:

$$D_0 = \left(\frac{9.97 \times 10^{-8}}{[I_A V_A]^{1/3}} + \frac{2.40 \times 10^{-8} A_B S_B V_B}{I_A S_A V_A} \right) \frac{T}{\eta_B} \quad [2.2.3]$$

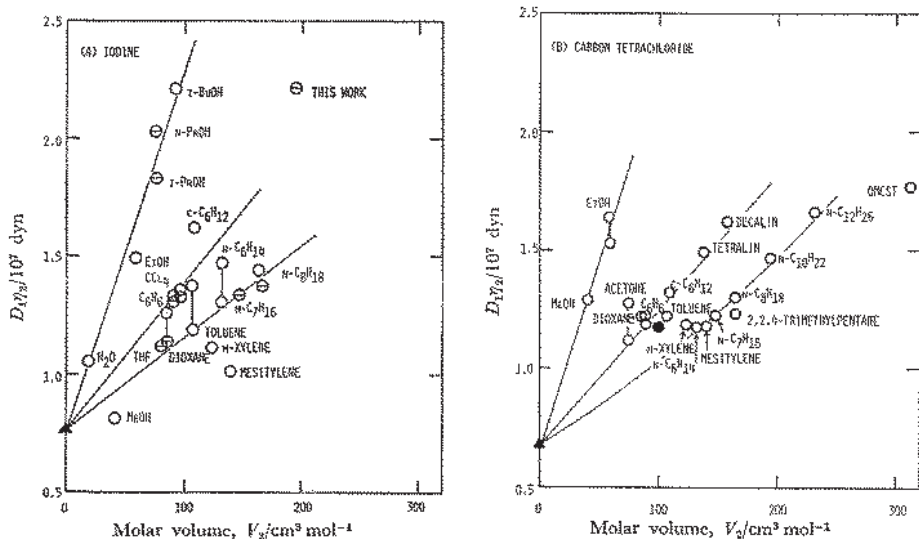


Figure 2.2.2. Hammond-Stokes plot for diffusion of iodine and carbon tetrachloride in various solvents at 298.15K. O, ⊙: D_{12} ; ●: $(D_1)_{self}\eta_B$; ▲: $D_1\eta_B$ at the Stokes-Einstein limit. Perpendicular lines connect two or more data for the same solvent from different sources. [Adapted, by permission, from K. Nakanishi, *Bull. Chem. Soc. Japan*, **51**, 713 (1978).

where D_0 is in $\text{cm}^2 \text{s}^{-1}$. V_A and V_B are the liquid molar volumes in $\text{cm}^3 \text{mol}^{-1}$ of A and B at the temperature T in K, and the factors I , S , and A are given in original publications,^{4,6} and η is the solvent viscosity, in cP.

Should the pure solute not be a liquid at 298 K, it is recommended that the liquid volume at the boiling point be obtained either from data or from correlations.⁴ Values of D_0 were estimated for many (149) solute-solvent systems and average error was 9.1 %.

2.3 BASIC PHYSICAL AND CHEMICAL PROPERTIES OF SOLVENTS

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This section contains information on the basic relationships characterizing the physical and chemical properties of solvents and some suggestions regarding their use in solvent evaluation and selection. The methods of testing which allow us to determine some of physical and chemical properties are found in Chapter 15. The differences between solvents of various chemical origin are discussed in Chapter 3, Section 3.3. The fundamental relationships in this chapter and the discussion of different groups of solvents are based on extensive CD-ROM database of solvents which can be obtained from ChemTec Publishing. The database has 110 fields which contain various data on solvent properties which are discussed below. The database can be searched by the chemical name, empirical formula, molecular weight, CAS number and property. In the first case, full information on a particular solvent

is returned. In the second case, a list of solvents and their values for the selected property are given in tabular form in ascending order of the property in question.

2.3.1 MOLECULAR WEIGHT AND MOLAR VOLUME

The molecular weight of a solvent is a standard but underutilized component of the information on properties of solvents. Many solvent properties depend directly on their molecular weights. The hypothesis of Hildebrand-Scratchard states that solvent-solute interaction occurs when solvent and polymer segment have similar molecular weights. This is related to the hole theory according to which a solvent occupying a certain volume leaves the same volume free when it is displaced. This free volume should be sufficient to fit the polymer segment which takes over the position formerly occupied by the solvent molecule.

Based on this same principle, the diffusion coefficient of a solvent depends on its molecular mass (see equations [6.2] and [6.3]). As the molecular weight of a solvent increases its diffusion rate also increases. If there were no interactions between solvent and solute, the evaporation rate of the solvent would depend on the molecular weight of the solvent. Because of various interactions, this relationship is more complicated but solvent molecular weight does play an essential role in solvent diffusion. This is illustrated best by membranes which have pores sizes which limit the size of molecules which may pass through. The resistance of a material to solvents will be partially controlled by the molecular weight of the solvent since solvent molecules have to migrate to the location of the interactive material in order to interact with it.

The chemical potential of a solvent also depends on its molecular weight (see eq. [6.6]). If all other influences and properties are equal, the solvent having the lower molecular weight is more efficiently dissolving materials, readily forms gels, and swells materials. All this is controlled by the molecular interactions between solvent and solute. In other words, at least one molecule of solvent involved must be available to interact with a particular segment of solute, gel, or network. If solvent molecular weight is low more molecules per unit weight are available to affect such changes. Molecular surface area and molecular volume are part of various theoretical estimations of solvent properties and they are in part dependent on the molecular mass of the solvent.

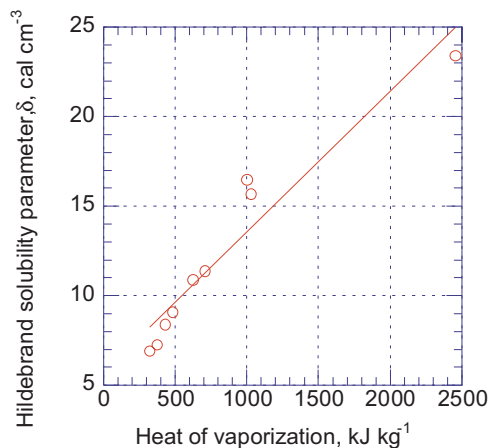


Figure 2.3.1. Hildebrand solubility parameter vs. heat of vaporization of selected solvents.

Many physical properties of solvents depend on their molecular weight, such as boiling and freezing points, density, heat of evaporation, flash point, and viscosity. The relationship between these properties and molecular weight for a large number of solvents of different chemical composition is affected by numerous other influences but within the same chemical group (or similar structure) molecular weight of solvent correlates well with its physical properties.

Figure 2.3.1 gives an example of interrelation of seemingly unrelated parameters: Hildebrand solubility parameter and heat of vaporization (see more on the sub-

ject in the Section 2.3.19). As heat of vaporization increases, the solubility parameter also increases.

Molar volume is a rather speculative, theoretical term. It can be calculated from Avogadro's number but it is temperature dependent. In addition, free volume is not taken into consideration. Molar volume can be expressed as molecular diameter but solvent molecules are rather non-spherical therefore diameter is often misrepresentation of the real dimension. It can be measured from the studies on interaction but results differ widely depending on the model used to interpret results.

2.3.2 BOILING AND FREEZING POINTS

Boiling and freezing points are two basic properties of solvents often included in specifications. Based on their boiling points, solvents can be divided to low (below 100°C), medium (100-150°C) and high boiling solvents (above 150°C).

The boiling point of liquid is frequently used to estimate the purity of the liquid. A similar approach is taken for solvents. Impurities cause the boiling point of solvents to increase but this increase is very small (in the order of 0.01°C per 0.01% impurity). Considering that the error of boiling point can be large, contaminated solvents may be undetected by boiling point measurement. If purity is important it should be evaluated by some other, more sensitive methods. The difference between boiling point and vapor condensation temperature is usually more sensitive to admixtures. If this difference is more than 0.1°C, the presence of admixtures can be suspected.

The boiling point can also be used to evaluate interactions due to the association among molecules of solvents. For solvents with low association, Trouton's rule, given by the following equation, is fulfilled:

$$\Delta S_{bp}^{\circ} = \frac{\Delta H_{bp}^{\circ}}{T_{bp}} = 88 \text{ J mol}^{-1} \text{ K}^{-1} \quad [2.3.1]$$

where:

ΔS_{bp}°	molar change of enthalpy
ΔH_{bp}°	molar change of entropy
T_{bp}	boiling point

If the enthalpy change is high it suggests that the solvent has a strong tendency to form associations.

Boiling point depends on molecular weight but also on structure. It is generally lower for branched and cyclic solvents. Boiling and freezing points are important considerations for solvent storage. Solvents are frequently stored under nitrogen blanket and they contribute to substantial emissions during storage. Freezing point of some solvents is above temperatures encountered in temperate climatic conditions. Although, solvents are usually very stable in their undercooled state, they rapidly crystallize when subjected to any mechanical or sonar impact.

Figures 2.3.2 to 2.3.6 illustrate how the boiling points of individual solvents in a group are related to other properties. Figure 2.3.2 shows that chemical structure of a solvent affects the relationship between its viscosity and the boiling point. Alcohols, in particular, show a much larger change in viscosity relative to boiling point than do aromatic hydrocarbons, esters and ketones. This is caused by strong associations between molecules of alcohols, which contain hydroxyl groups. Figure 2.3.3 shows that alcohols are also less volatile

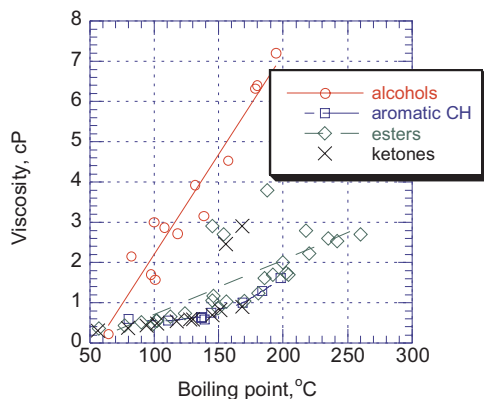


Figure 2.3.2. Effect of boiling point on solvent viscosity.

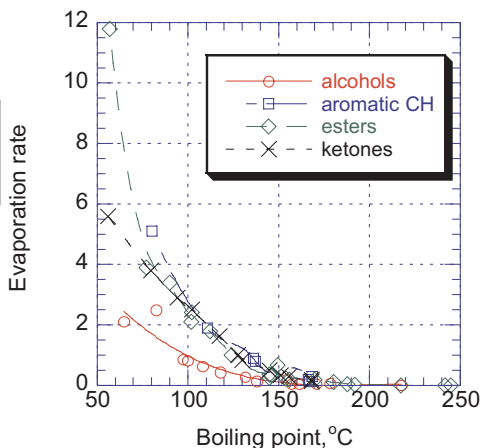


Figure 2.3.3. Effect of boiling point on solvent evaporation rate (relative to butyl acetate = 1).

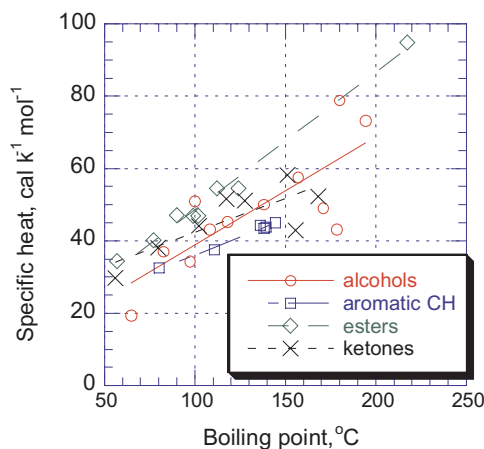


Figure 2.3.4. Specific heat of solvents vs. their boiling point.

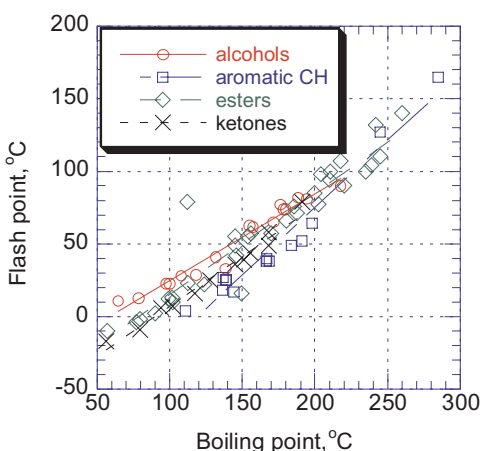


Figure 2.3.5. Flash point of solvents vs. their boiling point.

than other three groups of solvents and for the same reason. Viscosity and evaporation rate of aromatic hydrocarbons, esters, and ketones follow single relationship for all three groups of solvents, meaning that the boiling point has strong influence on these two properties. There are individual points on this set of graphs which do not fall close to the fitted curves. These discrepancies illustrate that chemical interactions influence viscosity and evaporation rate. However, for most members of the four groups of solvents, properties correlate most strongly with boiling point.

All linear relationships in Figure 2.3.4 indicate that specific heat is strongly related to the boiling point which is in agreement with the fact that boiling point is influenced by molecular weight. However, there are substantial differences in the relationships between dif-

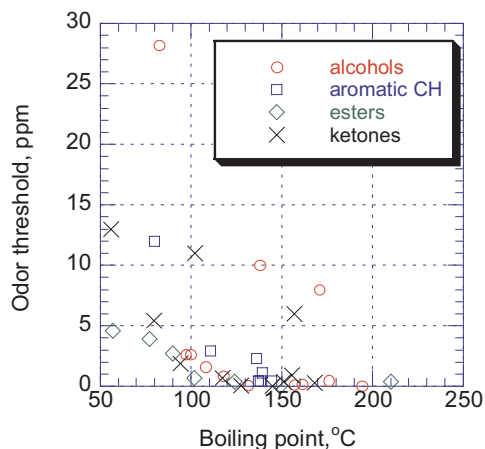


Figure 2.3.6. Odor threshold of solvent vs. its boiling point.

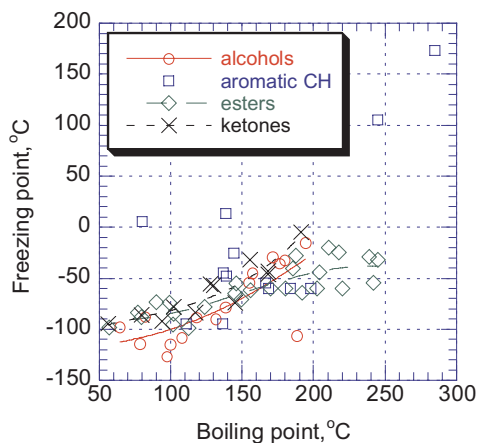


Figure 2.3.7. Relationship between boiling and freezing points of solvents.

ferent groups of solvents and many experimental points are scattered. Figure 2.3.5 verifies the origin of flash point which has strong correlation with boiling point. Here, all four chemical groups of solvents have the same relationship.

Odor threshold is an approximate but quite unreliable method of detection of solvent vapors. As the boiling point increases, the odor threshold (concentration in air when odor becomes detectable) decreases (Figure 2.3.6). This may suggest that slower evaporating solvents have longer residence time close to the source of contamination.

Figure 2.3.7 shows the relationship between boiling and freezing points. A general rule is that the difference between boiling and freezing points for analyzed solvents is $190 \pm 30^\circ\text{C}$. Relatively small fraction of solvents does not follow this rule. Natural solvent mixtures such as aromatic or aliphatic hydrocarbons deviate from the rule (note that hydrocarbons in Figure 2.3.7 depart from the general relationship). If more groups of solvents is investigated, it will be seen that CFCs, amines, and acids tend to have a lower temperature difference between boiling and freezing points whereas some aliphatic hydrocarbons and glycol ethers have a tendency towards a larger difference.

2.3.3 SPECIFIC GRAVITY

The specific gravity of most solvents is lower than that of water. When solvent is selected for extraction it is generally easy to find one which will float on the surface of water. Two groups of solvents: halogenated solvents and polyhydric alcohols have specific gravity greater than that of water. The specific gravity of alcohols and ketones increases with increasing molecular weight whereas the specific gravity of esters and glycol ethers decreases as their molecular weight decreases.

The specific gravity of solvents affects their industrial use in several ways. Solvents with a lower density are more economical to use because solvents are purchased by weight but many final products are sold by volume. The specific gravity of solvent should be considered in the designs for storage systems and packaging. When switching the solvent types in storage tanks one must determine the weight of new solvent which can be accommodated in the tank. A container of CFC with a specific gravity twice that of most solvents, may be

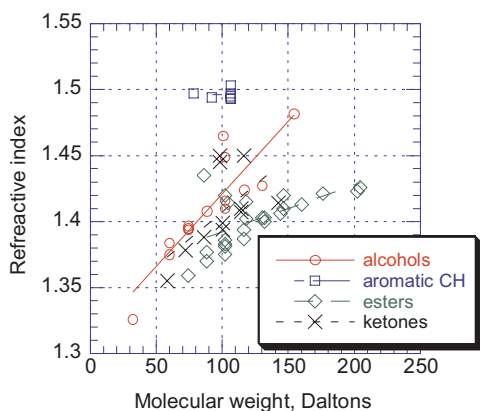


Figure 2.3.8. Refractive index for four groups of solvents as the function of their molecular weight.

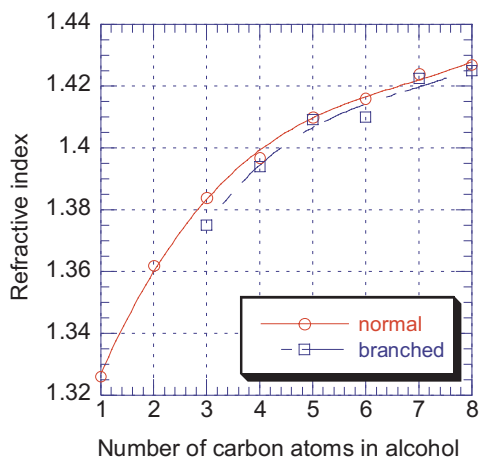


Figure 2.3.9. Refractive index of normal and branched alcohols as the function of number of carbon atoms in alcohol.

too heavy to handle. When metering by volume, temperature correction should always be used because solvent specific gravity changes substantially with temperature.

2.3.4 REFRACTIVE INDEX

Refractive index is the ratio of the velocity of light of a specified wavelength in air to its velocity in the examined substance. When the principle of measurement is used it may be defined as the sine of the angle of incidence divided by the sine of the angle of refraction. The absolute angle of refraction (relative to vacuum) is obtained by dividing the refractive index relative to air by a factor of 1.00027 which is the absolute refractive index of air. The ratio of the sines of the incident and refractive angles of light in the tested liquid is equal to the ratio of light velocity to the velocity of light in vacuum (that is why both definitions are correct). This equality is also referred to as Snell's law.

Figures 2.3.8 and 2.3.9 show the relationship between the molecular weight of a solvent and its refractive index. Figure 2.3.8 shows that there is a general tendency for the refractive index to increase as the molecular weight of the solvent increases. The data also indicates that there must be an additional factor governing refractive index. The chemical structure of the molecule also influences refractive index (Figure 2.3.9). Normal alcohols have a slightly higher refractive index than do branched alcohols. Cyclic alcohols have higher refractive indices than the linear and branched alcohols. For example, 1-hexanol has refractive index of 1.416, 4-methyl-2-pentanol 1.41, and cyclohexanol 1.465. Aromatic hydrocarbons are not dependent on molecular weight but rather on the position of substituent in the benzene ring (e.g., m-xylene has refractive index of 1.495, o-xylene 1.503, and p-xylene 1.493).

The data also show that the differences in refractive indices are rather small. This imposes restrictions on the precision of their determination. Major errors stem from poor instrument preparation and calibration and inadequate temperature control. The refractive index may change on average by $0.0005/^{\circ}\text{C}$. Refractive index is useful tool for determination of solvent purity but the precision of this estimation depends on relative difference be-

tween the solvent and the impurity. If this difference is small, the impurities, present in small quantities, will have little influence on the reading.

2.3.5 VAPOR DENSITY AND PRESSURE

The relative vapor density of solvents is given by the following equation:

$$d_{vp} = \frac{M_s}{M_{air}} \quad [2.3.2]$$

where:

M_s the molecular mass of solvents
 M_{air} the molecular mass of air (28.95 Daltons)

Figure 2.3.10 shows that the vapor density has linear correlation with molecular mass and that for both alcohols and ketones (as well as the other solvents) the relationship is similar. The data also show that solvent vapor densities are higher than air density. This makes ventilation a key factor in the removal of these vapors in the case of spill or emissions from equipment. Otherwise, the heavier than air vapors will flow along floors and depressions filling pits and subfloor rooms and leading to toxic exposure and/or risk of ignition and subsequent explosions.

The Clausius-Clapeyron equation gives the relationship between molecular weight of solvent and its vapor pressure:

$$\frac{d \ln p}{dT} = \frac{M\Delta}{RT^2} \quad [2.3.3]$$

where:

p vapor pressure
 T temperature
 M molecular mass of solvent
 Δ heat of vaporization
 R gas constant

Figure 2.3.11 shows that the vapor pressure of alcohols increases as the number of carbon atoms in the molecules and the molecular mass increases. A small increase in vapor pressure is produced when branched alcohols replace normal alcohols.

Vapor pressure at any given temperature can be estimated by the use of Antoine (eq. [2.3.4]) or Cox (eq. [2.3.5]) equation (or chart). Both equations are derived from Clausius-Clapeyron equation:

$$\log p = A - \frac{B}{C + T} \quad [2.3.4]$$

$$\log p = A - \frac{B}{T + 230} \quad [2.3.5]$$

where:

A, B, C constants. The constants A and B are different in each equation. The equations coincide when $C = 230$ in the Antoine equation.

From the above equations it is obvious that vapor pressure increases with temperature.

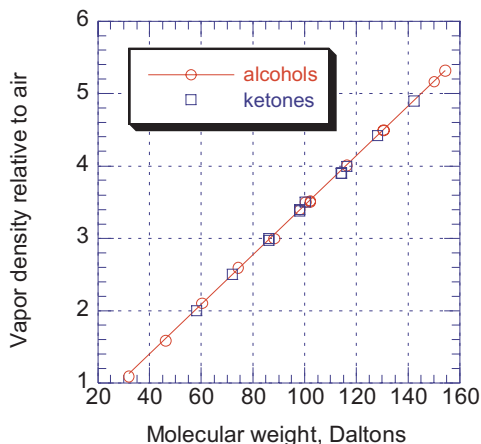


Figure 2.3.10. Vapor density relative to air of alcohols and ketones vs. their molecular weight.

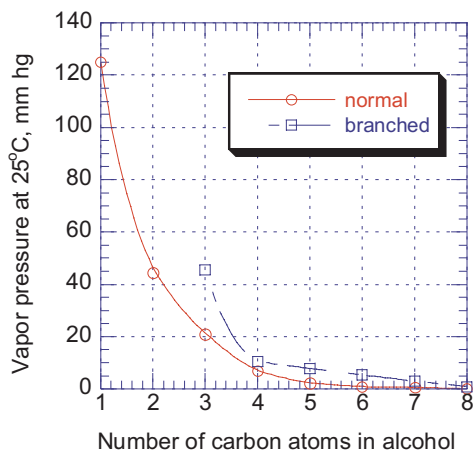


Figure 2.3.11. Vapor pressure at 25°C of normal and branched alcohols vs. number of carbon atoms in their molecule.

The vapor pressure at the boiling point of a pure solvent is equal to atmospheric pressure. When solvents are used in mixtures or solutions, the vapor pressure is affected by other components present in the mixture. For example, if a solvent is hydrophilic, the addition of a hydrophilic solute decreases the vapor pressure. The addition of a hydrophobic solute to a hydrophilic solvent increases the vapor pressure. Alcohols have hydrophobic chains, therefore addition of small quantities of alcohol to water increases vapor pressure of resulting solution. Because of these phenomena and other types of associations between solvents in their mixtures, theory cannot be used to accurately predict the resulting vapor pressure.

Raoult's Law has limited prediction capability of the vapor pressure of two miscible solvents:

$$p_{12} = m_1 p_1 + (1 - m_1) p_2 \quad [2.3.6]$$

where:

p_{12}	vapor pressure of the mixture
m_1	molar fraction of the first component
p_1, p_2	vapor pressures of the components

If associations exist between molecules in the mixture, the vapor pressure of the mixture is lower than that predicted by the law.

2.3.6 SOLVENT VOLATILITY

The evaporation rate of solvents is important in many applications. This has resulted in attempts to model and predict solvent volatility. The evaporation rate of a solvent depends on its vapor pressure at the processing temperature, the boiling point, specific heat, enthalpy and heat of vaporization of the solvent, the rate of heat supply, the degree of association between solvent molecules and between solvent and solute molecules, the surface tension of the liquid, the rate of air movement above the liquid surface, and humidity of air surrounding the liquid surface.

The vapor pressure of solvent was found in the previous section to depend on its molecular weight and temperature. Figure 2.3.3 shows that the evaporation rate of a solvent may be predicted based on knowledge of its boiling point and Figure 2.3.4 shows that the specific heat of solvent also relates to its boiling point. The boiling point of solvent also depends on its molecular weight as does enthalpy and heat of vaporization. But there is not a high degree of correlation among these quantities because molecular associations exist which cannot be expressed by universal relationship. For this reason experimental values are used to compare properties of different solvents. The two most frequently used reference solvents are: diethyl ether (Europe) and butyl acetate (USA). The evaporation rate of other solvents is determined under identical conditions and the solvents are ranked accordingly. If diethyl ether is used as a reference point, solvents are grouped into four groups: high volatility < 10, moderate volatility 10-35, low volatility 35-50, and very low volatility > 50. If butyl acetate is used as the reference solvent, the solvents are grouped into three classes: rapid evaporation solvents > 3, moderate 0.8-3, and slow evaporating solvents < 0.8.

In some applications such as coatings, casting, etc., evaporation rate is not the only important parameter. The composition must be adjusted to control rheological properties, prevent shrinkage, precipitation, formation of haze, and to provide the required morphology. Solvents with different evaporation rates can address all existing requirements.

Both the surface tension of mixture and solvent diffusion affect the evaporation rate. This becomes a complex function dependent not only on the solvents present but also on influence of solutes on both surface tension and diffusion. These relationships affect the real evaporation rates of solvents from the complicated mixtures in the final products. In addition, solvent evaporation also depends on relative humidity and air movement.

2.3.7 FLASH POINT

Flash point is the lowest temperature, corrected to normal atmospheric pressure (101.3 kPa), at which the application of an ignition source causes the vapors of a specimen to ignite under the specific conditions of the test. Flash point determination methods are designed to be applied to a pure liquid but, in practice, mixtures are also evaluated. It is important to understand limitations of such data. The flash point of a solvent mixture can be changed by adding various quantities of other solvents. For example, the addition of water or halogenated hydrocarbons will generally increase the flash point temperature of mixture. The flash point can also be changed by forming an azeotropic mixture of solvents or by increasing the interaction between solvents. At the same time, the flash point of single component within the mixture is not changed. If conditions during production, application, or in a spill allow the separation or removal of a material added to increase the flash point, then the flash point will revert to that of the lowest boiling flammable component.

An approximate flash point can be estimated from the boiling point of solvent using the following equation:

$$\text{Flash point} = 0.74T_b \quad [2.3.7]$$

Figure 2.3.5 shows that there is often good correlation between the two but there are instances where the relationship does not hold. The correlation for different groups of solvents varies between 0.89 to 0.96.

Flash point can also be estimated from vapor pressure using the following equation:

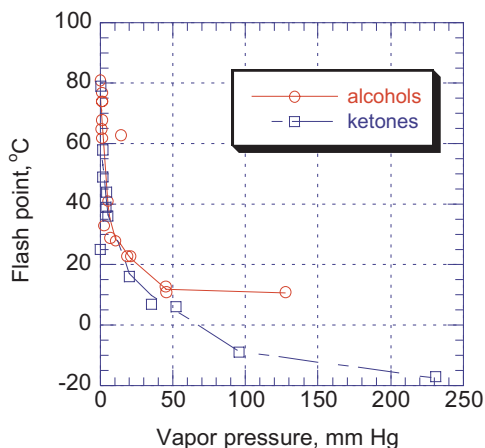


Figure 2.3.12. Flash point vs. vapor pressure of solvent.

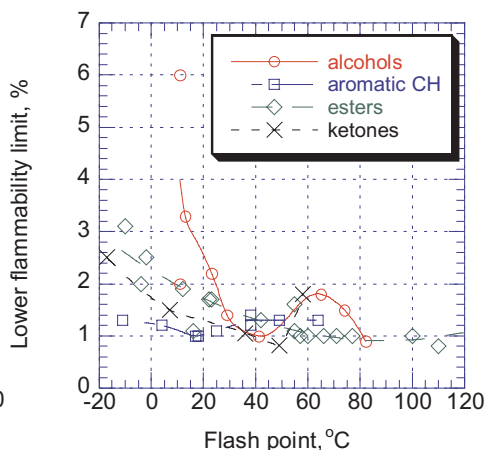


Figure 2.3.13. Lower flammability limit of solvents vs their flash points.

$$\text{Flash point} = a \log p + b$$

[2.3.8]

The constants a and b are specific to each group of solvents. Figure 2.3.12 shows that estimation of flash point from vapor pressure of solvent is less accurate than its estimation from boiling point.

2.3.8 FLAMMABILITY LIMITS

Two limits of solvent flammability exist. The lower flammability limit is the minimum concentration of solvent vapor in oxidizing gas (air) that is capable of propagating a flame through a homogeneous mixture of the oxidizer and the solvent vapor. Below the lower flammability limit the mixture is too lean to burn or explode. The upper flammability limit is the maximum concentration of solvent vapor in an oxidizing gas (air) above which propagation of flame does not occur. Mixtures with solvent vapor concentrations above the upper flammability limit are too rich in solvent or too lean in oxidizer to burn or explode.

The flammable limits depend on oxygen concentration, concentration of gases other than oxygen, the inert gas type and concentration, the size of the equipment, the direction of flame propagation, and the pressure, temperature, turbulence and composition of the mixture. The addition of inert gases to the atmosphere containing solvent is frequently used to reduce the probability of an explosion. It is generally assumed that if the concentration of oxygen is below 3%, no ignition will occur. The type of inert gas is also important. Carbon dioxide is more efficient inert gas than nitrogen. The size of equipment matters because of the uniformity of vapor concentration. A larger head space tends to increase the risk of inhomogeneity. The cooling effect of the equipment walls influences the evaporation rate and the vapor temperature and should be used in risk assessment.

The flash point is not the temperature at which the vapor pressure in air equals the lower flammable limit. Although both parameters have some correspondence there are large differences between groups of solvents. There is a general tendency for solvents with a lower flammability limit to have a lower flash point. The flash point determination uses a

downward and horizontal propagation of flame. Flame propagation in these directions generally requires a higher vapor concentration than it is required for the upward flame propagation used to determine flammability limits. The flame in flash point determination is at some distance from the surface where the vapor concentration is at its highest (because vapors have higher density than air) than exists on the liquid surface thus flash analysis underestimates concentration of vapor.

An increased vapor pressure typically increases the upper limit of flammability and reduces the lower limit of flammability. Pressures below atmospheric have little influence on flammability limits. An increase in temperature increases the evaporation rate and thus decreases the lower limit of flammability.

There are a few general rules which help in the estimation of flammability limits. In the case of hydrocarbons, the lower limit can be estimated from simple formula: 6/number of carbon atoms in molecule; for benzene and its derivatives the formula changes to: 8/number of carbon atoms. To calculate the upper limits, the number of hydrogen and carbon atoms is used in calculation.

The lower flammability limit of a mixture can be estimated from Le Chatelier's Law:

$$LFL_{mix} = \frac{100}{\frac{\phi_1}{LFL_1} + \frac{\phi_2}{LFL_2} + \dots + \frac{\phi_n}{LFL_n}} \quad [2.3.9]$$

where:

ϕ_i fraction of components 1, 2, ..., n
 LFL_i lower flammability limit of component 1, 2, ..., n

2.3.9 SOURCES OF IGNITION AND AUTOIGNITION TEMPERATURE

Sources of ignition can be divided to mechanical sources (impact, abrasive friction, bearings, misaligned machine parts, choking or jamming of material, drilling and other maintenance operations, etc), electrical (broken light, cable break, electric motor, switch gear, liquid velocity, surface or personal charge, rubbing of different materials, liquid spraying or jetting, lightning, stray currents, radio frequency), thermal (hot surface, smoking, hot transfer lines, electric lamps, metal welding, oxidation and chemical reactions, pilot light, arson, change of pressure, etc.), and chemical (peroxides, polymerization, catalysts, lack of inhibitor, heat of crystallization, thermite reaction, unstable substances, decomposition reactions). This long list shows that when making efforts to eliminate ignition sources, it is also essential to operate at safe concentrations of volatile, flammable materials because of numerous and highly varied sources of ignition.

The energy required for ignition is determined by the chemical structure of the solvent, the composition of the flammable mixture, and temperature. The energy of ignition of hydrocarbons decreases in the order alkanes > alkenes > alkynes (the presence of double or triple bond decreases the energy energy required for ignition). The energy requirement increases with an increase in molecular mass and an increase branching. Conjugated structure generally requires less ignition energy. Substituents increase the required ignition energy in the following order: mercaptan < hydroxyl < chloride < amine. Ethers and ketones require higher ignition energy but an aromatic group has little influence. Peroxides require extremely little energy to ignite.

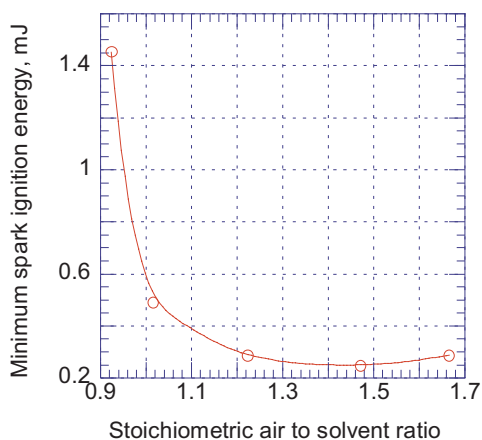


Figure 2.3.14. Minimum ignition energy vs. stoichiometric ratio of air to methyl ethyl ketone. [Data from H F Calcote, C A Gregory, C M Barnett, R B Gilmer, *Ind. Eng. Chem.*, **44**, 2656 (1952)].

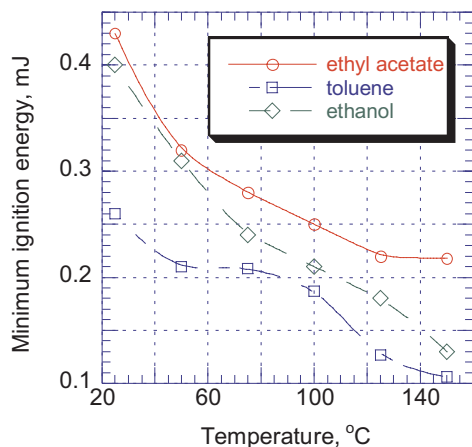


Figure 2.3.15. Minimum ignition energy vs. temperature for selected solvents. [Data from V S Kravchenko, V A Bondar, *Explosion Safety of electrical Discharges and Frictional Sparks*, *Khimia*, Moscow, 1976].

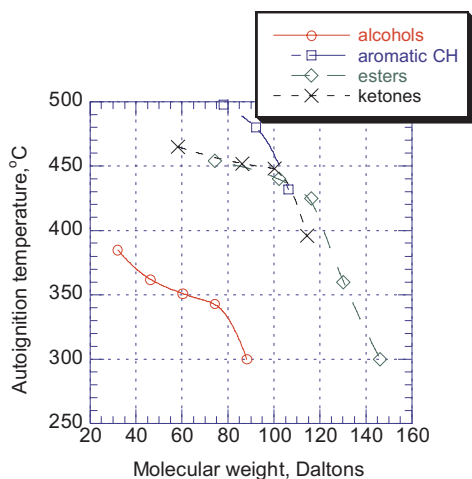


Figure 2.3.16. Autoignition temperature of selected solvents vs. their molecular weight.

the composition of the vapor/ air mixture, the oxygen concentration, the shape and size of the combustion chamber, the rate and duration of heating, and on catalytic effects. Figure 2.3.16 shows the effect of chemical structure on autoignition temperature. The general trend for all groups of solvents is that the autoignition temperature decreases as molecular weight increases. Esters and ketones behave almost identically in this respect and aromatic hydrocarbons are very similar. The presence of a hydroxyl group substantially reduces autoignition temperature.

Figure 2.3.14 shows the effect of changing the ratio of air to methyl ethyl ketone on the minimum spark ignition energy. The ignition energy decreases within the studied range as the amount of air increases (less flammable content). Figure 2.3.15 shows the effect of temperature on the minimum ignition energy of selected solvents. There are differences between solvents resulting from differences in chemical structure as discussed above but the trend is consistent – a decrease of required energy as temperature increases.

The autoignition temperature is the minimum temperature required to initiate combustion in the absence of a spark or flame. The autoignition temperature depends on the chemical structure of solvent,

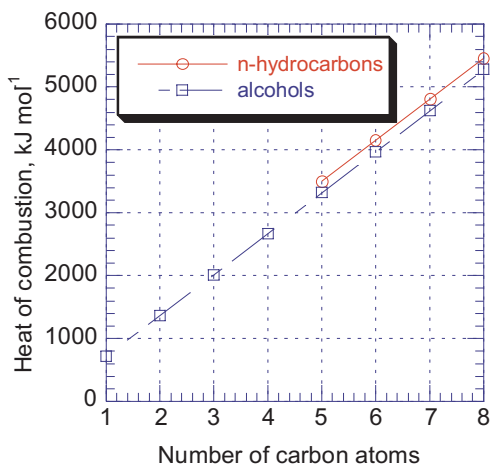


Figure 2.3.17. Heat of combustion vs. number of carbon atoms in molecule.

Heat of combustion, also known as calorific value, is the quantity of energy per mole released during combustion. It coincides with the heat of reaction. Solvents have higher heats of combustion than typical fuels such as natural gas, propane or butane. They can be very good source of energy in plants which process solutions. In addition to supplying energy, the combustion of solvents can be developed to be one of the cleanest method of processing from solutions. Two approaches are commonly used: solvent vapors are directed to a combustion chamber or spent solvents are burned in furnaces. The heat of combustion of a liquid solvent is less than 1% lower than the heat of combustion of a vapor.

Figure 2.3.17 shows the relationship between the heat of combustion and the number number of carbon atoms in the molecule. The heat of combustion increases as molecular weight increases and decreases when functional groups are present.

2.3.11 HEAT OF FUSION

Heat of fusion is the amount of heat to melt the frozen solvent. It can be used to determine the freezing point depression of solute.

2.3.12 ELECTRIC CONDUCTIVITY

Electric conductivity is the reciprocal of specific resistance. The units typically used are either $\text{ohm}^{-1} \text{m}^{-1}$ or, because the conductivities of solvents are very small picosiemens per meter which is equivalent to $10^{-12} \text{ohm}^{-1} \text{m}^{-1}$. The electric conductivity of solvents is very low (typically between $10^{-3} - 10^{-9} \text{ohm}^{-1} \text{m}^{-1}$). The presence of acids, bases, salts, and dissolved carbon dioxide might contribute to increased conductivity. Free ions are solely responsible for the electric conductivity of solution. This can be conveniently determined by measuring the conductivity of the solvent or the conductivity of the water extract of solvent impurities. The electronic industry and aviation industry have the major interest in these determinations.

2.3.13 DIELECTRIC CONSTANT (RELATIVE PERMITTIVITY)

The dielectric constant (or relative permittivity) of a solvent reflects its molecular symmetry. The value of the dielectric constant is established from a measurement relative to vacuum. The effect is produced by the orientation of dipoles along an externally applied

The effect of the air to solvent ratio on autoignition temperature is similar to that on ignition energy (see Figure 2.3.14). As the oxygen concentration increases within the range of the flammability limits, the autoignition temperature increases. The autoignition temperature increases when the size of combustion chamber decreases. Rapid heating reduces the autoignition temperature and catalytic substance may drastically reduce it.

2.3.10 HEAT OF COMBUSTION (CALORIFIC VALUE)

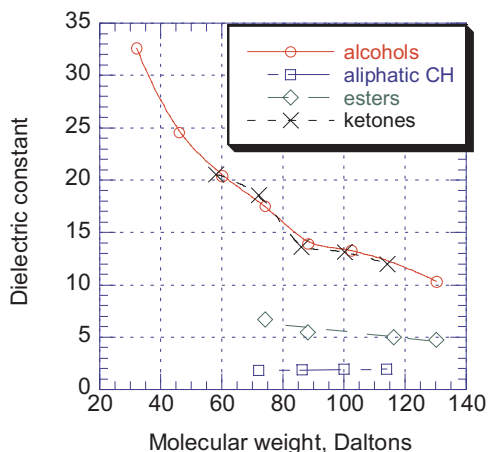


Figure 2.3.18. Dielectric constant vs. molecular weight of selected solvents.

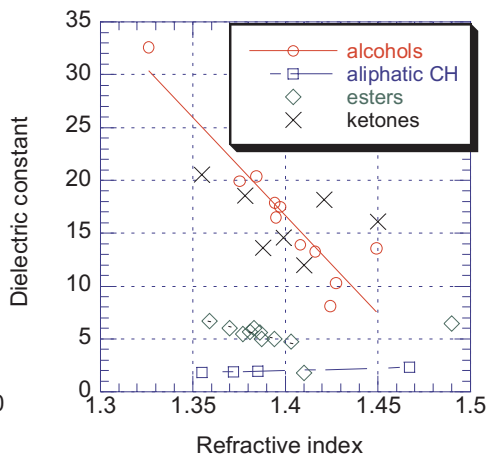


Figure 2.3.19. Dielectric constant of selected solvents vs. their refractive index.

electric field and from the separation of charges in apolar molecules. This orientation causes polarization of the molecules and a drop in electric field strength. Dielectric constant data may be used in many ways. In particular, it is the factor which permits the evaluation of electrostatic hazards. The rate of charge decay is a product of dielectric constant and resistivity.

In solvent research, dielectric constant has a special place as a parameter characteristic of solvent polarity. The dielectric constant, ϵ , is used to calculate dipole moment, μ :

$$\mu = \frac{\epsilon - 1}{\epsilon - 2} V_M \quad [2.3.10]$$

where:

V_M molar volume

The product of dipole moment and dielectric constant is called the electrostatic factor and it is a means of classifying solvents according to their polarity.

Figure 2.3.18 shows that the dielectric constant correlates with molecular weight. It is only with aliphatic hydrocarbons that the dielectric constant increases slightly as the molecular weight increases. The dielectric constant of alcohols, esters, and ketones decreases as their molecular weight increases, but only alcohols and ketones have the same relationship. The dielectric constants of esters are well below those of alcohols and ketones.

The dielectric constant also correlates with refractive index. In the case of aliphatic hydrocarbons, the dielectric constant increases slightly as refractive index increases. Both aromatic and aliphatic hydrocarbons have dielectric constants which follow the relationship: $\epsilon \approx n_D^2$. The dielectric constants of alcohols, esters and ketones decrease as the refractive constants increase but only alcohols and ketones form a similar relationship. The dielectric constants of ketones poorly correlate with their refractive indices.

2.3.14 OCCUPATIONAL EXPOSURE INDICATORS

The measurement of solvent concentration in the workplace place is required by national regulations. These regulations specify, for individual solvents, at least three different concentrations points: the maximum allowable concentration for an 8 hour day exposure, the maximum concentration for short exposure (either 15 or 30 min), and concentration which must not be exceeded at any time. These are listed in the regulations for solvents. The listing is frequently reviewed and updated by the authorities based on the most currently available information.

In the USA, the threshold limit value, time-weighted average concentration, TLV-TWA, is specified by several bodies, including the American Conference of Governmental Industrial Hygienists, ACGIH, the National Institute of Safety and Health, NIOSH, and the Occupational Safety and Health Administration, OSHA. The values for individual solvents stated on these three lists are very similar. Usually the NIOSH TLV-TWA are lower than on the other two lists. Similar specifications are available in other countries (for example, OES in UK, or MAK in Germany). The values for individual solvents are selected based on the presumption that the maximum allowable concentration should not cause injury to a person working under these conditions for 8 hours a day.

For solvent mixtures, the following equation is used in Germany to calculate allowable limit:

$$I_{MAK} = \sum_{i=1}^{i=n} \frac{c_i}{MAK_i} \quad [2.3.11]$$

where:

I_{MAK}	evaluation index
c	concentrations of components 1, 2, ..., n
MAK	maximum permissible concentrations for components 1, 2, ..., n

The maximum concentrations for short exposure is the most frequently limit specified for an exposure of 15 min with a maximum of 4 such occurrences per day each occurring at least 60 min apart from each other. These values are 0-4 times larger than TLVs. They are selected based on the risks associated with an individual solvent.

Solvent concentrations which should not be exceeded at any time are seldom specified in regulations but, if they are, the values stated as limits are similar to those on the three lists.

In addition, to maintaining concentration below limiting values, adequate protection should be used to prevent the inhalation of vapors and contact with the skin (see Chapter 24).

2.3.15 ODOR THRESHOLD

The principal for odor threshold was developed to relate the human sense of smell to the concentration of the offending substances. If the substance is toxic, its detection may provide early warning to the danger. However, if the odor threshold is higher than the concentration at which harm may be caused it is not an effective warning system. Toxic substances may have very little or no odor (e.g., carbon monoxide) and an individual's sense of smell may vary widely in its detection capabilities. A knowledge of odor threshold is most useful in determining the relative nuisance factor for an air pollutant when designing a control system to avoid complaints from neighboring people surrounding a facility. Regulations often state (as they do for example in Ontario, Canada) that, even when the established concentra-

tion limits for air pollutants are met, if neighbors complain, penalties will be applied. Figure 2.3.6 shows that odor threshold is related to the boiling point (although odor threshold decreases with boiling point increasing). It is known from comparisons of TLV and odor detection that odor detection is not a reliable factor.

2.3.16 TOXICITY INDICATORS

Lethal dose, LD50, and lethal concentration, LC50, are commonly used indicators of substance toxicity. LD50 is reported in milligrams of substance per kilogram of body weight to cause death in 50% of tested animals (exception is LC50 which is given in ppm over usually the period of 4 hours to produce the same effect). It is customary to use three values: LD50-oral, LD50-dermal, and LC50-inhalation which determine the effect of a chemical substance on ingestion, contact with the skin and inhalation. The preferred test animal for LD50-oral and LC50-inhalation is the rat. The rabbit is commonly used for LD50-dermal determination but other test animals are also used.

There is no official guideline on how to use this data but the Hodge-Sterner table is frequently referred to in order to assign a particular substance to a group which falls within certain limits of toxicity. According to this table, dangerously toxic substances are those which have $LD50 < 1$ mg/kg, seriously toxic - 1-50, highly toxic - 50-500, moderately toxic - 500-5,000, slightly toxic - 5,000-15,000, and extremely low toxic - $>15,000$ mg/kg. Using this classification one may assess the degree of toxicity of solvents based on a lethal dose scale. No solvent is classified as a dangerously toxic material. Ethylenediaminetetraacetic acid and furfural are seriously toxic materials. Butoxyethanol, ethylene oxide, formaldehyde, metasulfonic acid, 3-methyl-2-butanone, N-nitrosodimethylamine, and triethylamine are classified as highly toxic material. The remaining solvents fall into the moderately, slightly, and extremely low toxic material classes.

The LD50-oral is usually assigned a lower value than LD50-dermal but there are many cases where the opposite applies. Toxicity information is usually further expanded by adding more details regarding test animals and target organs.

In addition to estimates of toxicity for individual solvents, there are lists which designate individual solvents as carcinogenic, mutagenic, and reproductively toxic. These lists contain the name of solvent with yes or no remark (or similar). If a solvent is not present on the list that does not endorse its benign nature because only materials that have been tested are included in the lists. To further elaborate, materials are usually divided into three categories: substance known to cause effect on humans, substance which has caused responses in animal testing and given reasons to believe that similar reactions can be expected with human exposures, and substance which is suspected to cause responses based on experimental evidence.

In the USA, four agencies generate lists of carcinogens. These are: the Environmental Protection Agency, EPA, the International Agency for Research on Cancer, IRAC, the National Toxicology Program, NTP, and the Occupational Safety and Health Administration, OSHA. Although, there is a good agreement between all four lists, each assessment differs in some respects. The following solvents made at least one of the lists (no distinction is given here to the category assignment but any known or suspected carcinogen found on any list is given (for more details see Chapter 3)): acetone, acrolein, benzene, carbon tetrachloride, dichloromethane, 1,4-dioxane, ethylene oxide, formaldehyde, furfural, d-limonene, N-nitrosodimethyl amine, propylene oxide, tetrachloroethylene, 2,4-toluenediisocyanate, 1,1,2-trichloroethylene, and trichloromethane.

Mutagenic substances have the ability to induce genetic changes in DNA. The mutagenicity list maintained in the USA includes the following solvents: all solvents listed above for carcinogenic properties with exception of dichloromethane, d-limonene, and tetrachloroethylene. In addition, the following long list solvents: 1-butanol, 2-butanol, γ -butyrolactone, 2-(2-n-butoxyethoxy)ethanol, chlororodifluoromethane, chloromethane, diacetone alcohol, dichloromethane, diethyl ether, dimethyl amine, dimethylene glycol dimethyl ether, dimethyl sulfoxide, ethanol, 2-ethoxyethanol, 2-ethoxyethanol acetate, ethyl acetate, ethyl propionate, ethylbenzene, ethylene glycol diethyl ether, ethylene glycol methyl ether acetate, ethylene glycol monophenyl ether, ethylenediaminetetraacetic acid, formic acid, furfuryl alcohol, heptane, hexane, methyl acetate, 3-methyl-2-butanol, methyl ester of butyric acid, methyl propionate, N-methylpyrrolidone, monomethylamine, 1-octanol, 1-pentanol, 1-propanol, propyl acetate, sulfolane, 1,1,1-trichloroethane, triethylene glycol, triethylene glycol dimethyl ether, trifluoromethane, trimethylene glycol, and xylene (mixture only). It is apparent that this much longer list includes commonly used solvents from the groups of alcohols, halogenated solvents, hydrocarbons, glycols, and esters.

The following solvents are reported to impair fertility: chloroform, ethylene glycol and its acetate, 2-methoxypropanol, 2-methoxypropyl acetate, dichloromethane, methylene glycol and its acetate, and N,N-dimethylformamide.

2.3.17 OZONE - DEPLETION AND CREATION POTENTIAL

Ozone depletion potential is measured relative to CFC-11 and it represents the amount of ozone destroyed by emission of a vapor over its entire atmospheric lifetime relative to that caused by the emission of the same mass of CFC-11.

Urban ozone formation potential is expressed relative to ethene. It represents the potential of an organic solvents vapor to form ozone relative to that of ethene ($(\text{g O}_3/\text{g solvent})/(\text{g O}_3/\text{g ethene})$). Several groups of solvents, including alcohols, aldehydes, amines, aliphatic and aromatic hydrocarbons, esters, ethers, and ketones are active in ozone formation. Aldehydes, xylenes, some unsaturated compounds, and some terpenes are the most active among those.

2.3.18 OXYGEN DEMAND

There are several indicators of solvent biodegradation. Most solvents have a biodegradation half-life of days to weeks and some biodegrade even faster.

The amount of oxygen required for its biodegradation is a measure of a solvent's impact on natural resources. Several factors are used to estimate this, such as biological oxygen demand, BOD, after 5-day and 20-day aerobic tests, chemical oxygen demand, COD, and theoretical oxygen demand, TOD. All results are given in grams of oxygen per gram of solvent. COD is the amount of oxygen removed during oxidation in the presence of permanganate or dichromate. TOD is the theoretically calculated amount of oxygen required to oxidize solvent to CO_2 and H_2O . Most alcohols and aromatic hydrocarbons have a highest BOD5. They consume twice their own weight in oxygen.

2.3.19 SOLUBILITY

The prediction of solubility of various solutes in various solvents is a major focus of research. An early theory has been that "like dissolves like". Regardless of the apparent merits of this theory it is not sufficiently rigorous and is overly simple.

A universal approach was developed by Hildebrand who assumed that the mutual solubility of components depends on the cohesive pressure, c . The square root of cohesive pressure is the Hildebrand's solubility parameter, δ

$$\delta = \sqrt{c} = \sqrt{\frac{\Delta H_v - RT}{V_m}} \quad [2.3.12]$$

where:

ΔH_v	heat of vaporization
R	gas constant
T	temperature
V_m	molar volume of solvent = M/d
M	molecular mass of solvent
d	density of solvent

Frequently, the term RT is neglected because it accounts for only 5-10% of the heat of vaporization. This equation explains the reasons for the correlation between the Hildebrand solubility parameter and heat of vaporization as given in Figure 2.3.1.

The Hildebrand model takes into account only the dimensions of molecules or of the molecular segments participating in the process of solvation and dispersion interactions. The model is useful, therefore, in predicting the solubility of non-polar substrates. The solubility parameters of solvents and solutes are compared and if they are similar there is high probability (exceptions exist) that the solvents are miscible that a solute is soluble in a solvent. Two solvents having the same solubility parameters should have the same dissolving capabilities. If one solvent has solubility parameter slightly below the solubility parameter of solute and the second solvent has solubility parameter above the solute, the mixture of both solvents should give better results than either solvent alone. This model is an experimental and mathematical development of the simple rule of "like dissolves like".

Solvents and solutes also interact by donor-acceptor, electron pair, and hydrogen bonding interactions. It can be predicted that the above concept is not fully universal, especially in the case of solutes and solvents which may apply these interactions in their solubilizing action. Hansen developed a three-dimensional scale with parameters to expand theory in order to include these interactions. Hansen defined solubility parameter by the following equation:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad [2.3.13]$$

where:

δ_d	dispersion contribution to solubility parameter
δ_p	polar contribution to solubility parameter
δ_h	hydrogen bonding contribution to solubility parameter

Hansen defined solvent as a point in three-dimensional space and solutes as volumes (or spheres of solubility). If a solvent point is within the boundaries of a solute volume space then the solute can be dissolved by the solvent. If the point characterizing the solvent is outside the volume space of a solute (or resin) such a solvent does not dissolve the solute. The solubility model based on this concept is broadly applied today by modern computer techniques using data obtained for solvents (the three components of solubility parameters) and solutes (characteristic volumes). A triangular graph can be used to outline the limits of

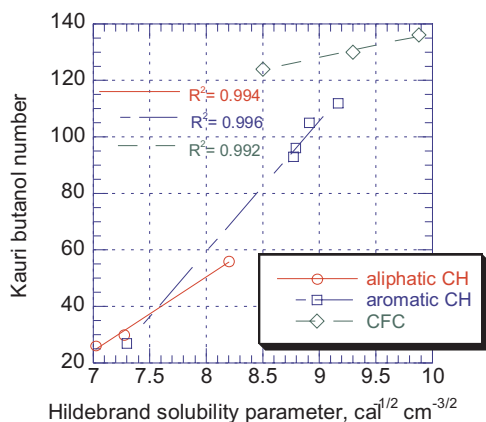


Figure 2.3.20. Kauri butanol number vs. Hildebrand solubility parameter.

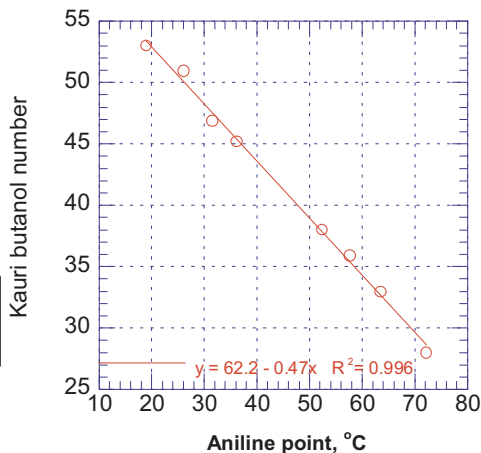


Figure 2.3.21. Kauri butanol number vs. aniline point.

solubility and place different solvents within the matrix to determine their potential dissolving capability for a particular resin.

Simpler methods are also used. In the paint industry, Kauri butanol values are determined by establishing the tolerance of a standard solution of Kauri resin in n-butanol to the addition of diluents. This method is applicable to hydrocarbons (both aromatic and aliphatic) and CFCs. Figure 2.3.20 shows that there is a good correlation between the Kauri butanol number and the Hildebrand solubility parameter. The Kauri butanol number can be as high as 1000 (amyl ester of lactic acid) or 500 (Freon solvent M-162).

The aniline point determination is another method of establishing the solubilizing power of a solvent by simple means. Here, the temperature is measured at which a solution just becomes cloudy. Figure 2.3.21 shows that there is a good correlation between the Kauri number and the aniline point. Also dilution ratio of cellulose solution is measured by standardized methods (see Chapter 15).

2.3.20 OTHER TYPICAL SOLVENT PROPERTIES AND INDICATORS

There are many other solvent properties and indices which assist in solvent identification and selection and help us to understand the performance characteristics of solvents. Most data characterizing the most important properties were discussed in the sections above. The solvent properties and classification indicators, which are discussed below, are included in the Solvent Database available on CD-ROM from ChemTec Publishing.

Name. A solvent may have several names such as common name, Chemical Abstracts name, and name according to IUPAC systematic nomenclature. Common names have been used throughout this book and in the CD-ROM database because they are well understood by potential users. Also, CAS numbers are given in the database to allow user of the database to use the information with Chemical Abstract searches. In the case of commercial solvents which are proprietary mixtures, the commercial name is used.

The molecular formula for each solvent is given in the database, followed by the molecular formula in Hills notation, and the molecular mass (if solvent is not a mixture).

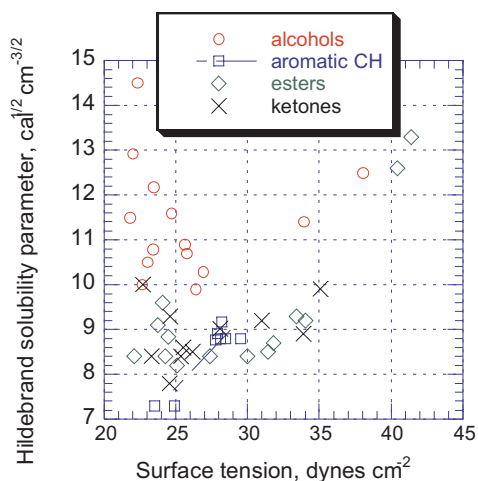


Figure 2.3.22. Hildebrand solubility parameter vs. surface tension for four groups of solvents.

gram of solvent or in a generic statement (e.g. miscible, slight). Many solvents are hygroscopic, especially those which contain hydroxyl groups. These solvents will absorb water from their surrounding until equilibrium is reached. The equilibrium concentration depends on the relative humidity of air and the temperature. If solvents must maintain a low concentration of water, vents of storage tanks should be fitted with silica gel or molecular sieves cartridges or tanks should be sealed and equipped with pressure and vacuum relief vents which open only to relieve pressure or to admit a dry inert gas to replace the volume pumped out. Preferably prevention of water from contacting solvents or the selection of solvents with a low water content is more economical than the expensive operation of drying a wet solvent.

Surface tension and solubility parameter have been related in the following equation:

$$\delta = 2.1K \left[\frac{\gamma}{V^{1/3}} \right]^a \quad [2.3.14]$$

where:

δ	Hildebrand solubility parameter
K, a	constants
γ	surface tension
V	molar volume of the solvent

However, Figure 2.3.22 shows that the parameters correlate only for aromatic hydrocarbons. For three other groups the points are scattered. The equation has a very limited predictive value.

Viscosity. Figure 2.3.2 shows that viscosity of solvents correlates with their boiling point. There are substantial differences in the viscosity - boiling point relationship among alcohols and other groups of solvents. These are due to the influence of hydrogen bonding on the viscosity of alcohols.

The CAS number identifies the chemical compound or composition without ambiguity.

RTECS number is the symbol given by Registry of Toxic Effects of Chemical Substances (e.g. AH4025000) to identify toxic substances.

Composition is given for solvents which are manufactured under trade name and have a proprietary composition (if such information is available).

Solvent purity (impurities) is given as a percent and known impurities and their concentrations are provided.

Hygroscopicity and water solubility of solvents is an important characteristic in many applications. The data are given in the database either in mg of water per kilo-

Thermal conductivity of solvents is an important property which determines the heat transfer in a solvent or solution and influences the evaporation rate of solvents as a solution is being dried.

Activity coefficients may be applied to different processes. In one application, the activity coefficient is a measure of the escaping tendency from liquid to another liquid or a gaseous phase (in the liquid to gas phase they can be quantified using Henry's Law coefficient). These activity coefficients are derived from distillation data at temperatures near the boiling point or from liquid-liquid extraction calculations. In another application as defined by Hildebrand and Scratchard solvent activity to dissolve a non-electrolyte solute is given by equation:

$$\ln f = \frac{V_m (\delta_{\text{solute}} - \delta_{\text{solvent}})^2}{RT} \quad [2.3.15]$$

where:

f	activity coefficient
V_m	molar volume of solute
δ_{solute}	solubility parameter of solute
δ_{solvent}	solubility parameter of solvent
RT	gas constant x temperature

This coefficient is used to express rate constants of bimolecular reactions.

Azeotropes. One solvent may form azeotropes with another solvent due to molecular association. This physical principle can be exploited in several ways. The most important in solvent applications is the possibility of reducing the boiling temperature (some azeotropes have lower boiling point) therefore an applied product such as a coating may lose its solvents and dry faster. The formation of such azeotrope also lowers flash point by which it increases hazards in product use. The formation of an azeotrope is frequently used to remove water from a material or a solvent. It affects the results of a distillation since azeotrope formation makes it difficult to obtain pure components from a mixture by distillation. Azeotrope formation can be suppressed by lowering the boiling point (distillation under vacuum). One benefit of azeotropic distillation is the reduction in the heat required to evaporate solvents.

Henry's constant is a measure of the escaping tendency of a solvent from a very dilute solution. It is given by a simple equation: Henry's constant = $p \times \phi$ where p is the pressure of pure solvent at the solution temperature and ϕ is the solvent concentration in the liquid phase. A high value of Henry's constant indicates that solvent can be easily stripped from dilute water solution. It can also be used to calculate TLV levels by knowing concentration of a solvent in a solution according to the equation: TLV (in ppm) = $[18 H (\text{concentration of solvent in water})] / \text{molecular weight of solvent}$.

pH and corrosivity. The pH of solvents is of limited value but it is sometimes useful if the solvent has strong basic or acidic properties which could cause corrosion problems.

The acid dissociation constant is the equilibrium constant for ionization of an acid and is expressed in negative log units.

The color of a solvent may influence the effect of solvent on the final product and allow the evaluation of solvent quality. The colorless solvents are most common but there are many examples of intrinsically colored solvents and solvents which are colored because of an admixture or inadequate storage conditions or too long storage.

Odor. Odor threshold (discussed above) is not a precise tool for estimation concentration of vapors. The description of odor has little relevance to the identification of solvent but description of odors in the database may be helpful in the selection of solvent to minimize odor or make it less intrusive.

UV absorption maxima for different solvents given in the database are useful to predict the potential effect of solvent on UV absorption from sun light. The collection of data is also useful for analytical purposes.

Solvent partition - activated carbon and between octanol and water. Solvents can be economically removed from dilute solutions by activated carbon or ion exchange resins. Activated carbon partition coefficient which helps to determine the amount of activated carbon needed to remove a contaminant can be obtained using the following equation:

$$m = \frac{w}{Pc} \quad [2.3.16]$$

where:

w	total weight of solvent in solution
P	partition coefficient
c	residual concentration of solvent remaining after treatment.

The octanol/water partition coefficient is the log of solubility of the solvent in water relative to that in octanol. This coefficient is used to estimate biological effects of solvents. It can also be used to estimate the potential usefulness of a solvent extraction from water by any third solvent.

Soil adsorption constant is a log of the amount of a solvent absorbed per unit weight of organic carbon in soil or sediment.

Atmospheric half-life of solvents due to reaction in the atmosphere with hydroxyl radicals and ozone is a measure of the persistence of particular solvent and its effect on atmospheric pollution.

Hydroxyl rate constant is the reaction rate constant of the solvent with hydroxyl radicals in the atmosphere.

Global warming potential of a well-mixed gas is defined as the time-integrated commitment to radiative forcing from the instantaneous release of 1 kg of trace gas expressed relative to that from the release of 1 kg of CO₂.

Biodegradation half-life determines persistence of the solvent in soil. Commercial proprietary solvents mixtures are classified as biodegradable and solvents having known chemical compositions are classified according to the time required for biodegradation to cut their initial mass to half.

Target organs most likely affected organs by exposure to solvents. The database contains a list of organs targeted by individual solvents.

Hazchem Code was developed in the UK for use by emergency services to determine appropriate actions when dealing with transportation emergencies. It is also a useful to apply as a label on storage tanks. It consists a number and one or two letters. The number informs about the firefighting medium to be used. The first letter gives information on explosion risk, personal protection and action. A second letter (E) may be added if evacuation is required.