

*“Agite, Auditores ornatissimi, transeamus alacres ad aliud negotiū! quum enim sic satis excusserimus ea quatuor Instrumenta artis, et naturae, quae modo relinquimus, videamus quintum genus horum, quod ipsi Chemiae fere proprium censetur, cui certe Chemistae principem locum prae omnibus assignant, in quo se jactant, serioque triumphant, cui artis suae, prae aliis omnibus effectus mirificos adscribunt. Atque illud quidem Menstruum vocaverunt.”**)

Hermannus Boerhaave (1668–1738)
De menstruīs dictis in chemia, in:
Elementa Chemiae (1733) [1, 2].

1 Introduction

The development of our knowledge of solutions reflects to some extent the development of chemistry itself [3]. Of all known substances, water was the first to be considered as a solvent. As far back as the time of the Greek philosophers there was speculation about the nature of solution and dissolution. The Greek alchemists considered all chemically active liquids under the name “Divine water”. In this context the word “water” was used to designate everything liquid or dissolved. The Greek philosopher Thales of Miletus (*ca.* 640–546 BC) asserted that water is the origin out of which everything arose and into everything resolved itself.

From these ancient times, a familiar and today often cited quotation of the famous Greek philosopher Aristotle (384–322 BC) was handed down, which reads in Latin *Corpora non agunt nisi fluida (or liquida) seu soluta*, and was translated into English as “Compounds do not react unless fluid or if dissolved” [43]. However, according to Hedvall [44], this seems to be a misinterpretation of the original text given in Greek as *Τά ὑγρά μικτά μάλιστα τῶν σωμάτων* (Ta hygra mikta malista ton somaton), which is probably taken from Aristotle’s work *De Generatione et Corruptione* [45]. According to Hedvall, this statement should be better read as „... it is chiefly the liquid substances which react” [44] or „... for instance liquids are the type of bodies most liable to mixing” [45c]. In this somewhat softened version, Aristotle’s statement is obviously less distinct and didactic. With respect of the many solid/solid reactions known today, it is quite understandable that solid-state chemists were not very happy with the common first version of Aristotle’s statement [43, 44].

The alchemist’s search for a universal solvent, the so-called “Alkahest” or “Menstruum universale”, as it was called by Paracelsus (1493–1541), indicates the importance given to solvents and the process of dissolution. Although the eager search of

* “Well then, my dear listeners, let us proceed with fervor to another problem! Having sufficiently analyzed in this manner the four resources of science and nature, which we are about to leave (*i.e.* fire, water, air, and earth) we must consider a fifth element which can almost be considered the most essential part of chemistry itself, which chemists boastfully, no doubt with reason, prefer above all others, and because of which they triumphantly celebrate, and to which they attribute above all others the marvellous effects of their science. And this they call the solvent (menstruum).”

the chemists of the 15th to 18th centuries did not in fact lead to the discovery of any “Alkahest”, the numerous experiments performed led to the uncovering of new solvents, new reactions, and new compounds*). From these experiences arose the earliest chemical rule that “like dissolves like” (*similia similibus solvuntur*). However, at that time, the words solution and dissolution comprised all operations leading to a liquid product and it was still a long way to the conceptual distinction between the physical dissolution of a salt or of sugar in water, and the chemical change of a substrate by dissolution, for example, of a metal in an acid. Thus, in the so-called chemiatry period (iatrochemistry period), it was believed that the nature of a substance was fundamentally lost upon dissolution. Van Helmont (1577–1644) was the first to strongly oppose this contention. He claimed that the dissolved substance had not disappeared, but was present in the solution, although in aqueous form, and could be recovered [4]. Nevertheless, the dissolution of a substance in a solvent remained a rather mysterious process. The famous Russian polymath Lomonosov (1711–1765) wrote in 1747: “Talking about the process of dissolution, it is generally said that all solvents penetrate into the pores of the body to be dissolved and gradually remove its particles. However, concerning the question of what forces cause this process of removal, there does not exist any somehow reasonable explanation, unless one arbitrarily attributes to the solvents sharp wedges, hooks or, who knows, any other kind of tools” [27].

The further development of modern solution theory is connected with three persons, namely the French researcher Raoult (1830–1901) [28], the Dutch physical chemist van’t Hoff (1852–1911) [5], and the Swedish scientist Arrhenius (1859–1927) [6]. Raoult systematically studied the effects of dissolved nonionic substances on the freezing and boiling point of liquids and noticed in 1886 that changing the solute/solvent ratio produces precise proportional changes in the physical properties of solutions. The observation that the vapour pressure of solvent above a solution is proportional to the mole fraction of solvent in the solution is today known as Raoult’s law [28].

The difficulty in explaining the effects of inorganic solutes on the physical properties of solutions led in 1884 to Arrhenius’ theory of incomplete and complete dissociation of ionic solutes (electrolytes, ionophores) into cations and anions in solution, which was only very reluctantly accepted by his contemporaries. Arrhenius derived his dissociation theory from comparison of the results obtained by measurements of electroconductivity and osmotic pressure of dilute electrolyte solutions [6].

The application of laws holding for gases to solutions by replacing pressure by osmotic pressure was extensively studied by van’t Hoff, who made osmotic pressure measurements another important physicochemical method in studies of solutions [5].

The integration of these three basic developments established the foundations of modern solution theory and the first Nobel prizes in chemistry were awarded to van’t Hoff (in 1901) and Arrhenius (in 1903) for their work on the osmotic pressure and the theory of electrolytic dissociation in dilute solutions, respectively.

The further development of solution chemistry is connected with the pioneering work of Ostwald (1853–1932), Nernst (1864–1941), Lewis (1875–1946), Debye (1884–

* Even if the once famous scholar J. B. Van Helmont (1577–1644) claimed to have prepared this “Alkahest” in a phial, together with the adherents of the alkahest theory he was ridiculed by his contemporaries who asked in which vessel he has stored this universal solvent.

1966), E. Hückel (1896–1980), and Bjerrum (1879–1958). More detailed reviews on the development of modern solution chemistry can be found in references [29, 30].

The influence of solvents on the rates of chemical reactions [7, 8] was first noted by Berthelot and Péan de Saint-Gilles in 1862 in connection with their studies on the esterification of acetic acid with ethanol: “... l'éthérisation est entravée et ralentie par l'emploi des dissolvants neutres étrangers à la réaction” [9]*). After thorough studies on the reaction of trialkylamines with haloalkanes, Menshutkin in 1890 concluded that a reaction cannot be separated from the medium in which it is performed [10]. In a letter to Prof. Louis Henry he wrote in 1890: “Or, l'expérience montre que ces dissolvants exercent sur la vitesse de combinaison une influence considérable. Si nous représentons par 1 la constante de vitesse de la réaction précitée dans l'hexane C_6H_{14} , cette constante pour la même combinaison dans $CH_3-CO-C_6H_5$, toutes choses égales d'ailleurs sera 847.7. La différence est énorme, mais, dans ce cas, elle n'atteint pas encore le maximum... Vous voyez que les dissolvants, soi-disant indifférents ne sont pas inertes; ils modifient profondément l'acte de la combinaison chimique. Cet énoncé est riche en conséquences pour la théorie chimique des dissolutions” [26]**). Menshutkin also discovered that, in reactions between liquids, one of the reaction partners may constitute an unfavourable solvent. Thus, in the preparation of acetanilide, it is not without importance whether aniline is added to an excess of acetic acid, or *vice versa*, since aniline in this case is an unfavourable reaction medium. Menshutkin related the influence of solvents primarily to their chemical, not their physical properties.

The influence of solvents on chemical equilibria was discovered in 1896, simultaneously with the discovery of keto-enol tautomerism***) in 1,3-dicarbonyl compounds (Claisen [14]: acetyl-dibenzoylmethane and tribenzoylmethane; Wislicenus [15]: methyl and ethyl formylphenylacetate; Knorr [16]: ethyl dibenzoylsuccinate and ethyl diacetylsuccinate) and the nitro-isonitro tautomerism of primary and secondary nitro compounds (Hantzsch [17]: phenyl-nitromethane). Thus, Claisen wrote: “Es gibt

Verbindungen, welche sowohl in der Form $\begin{array}{c} | \\ -C(OH)=C-CO- \\ | \\ -CO-CH-CO- \end{array}$ wie in der Form $\begin{array}{c} | \\ -CO-CH-CO- \\ | \end{array}$ zu bestehen vermögen; von der Natur der angelagerten Reste, von

* “... the esterification is disturbed and decelerated on addition of neutral solvents not belonging to the reaction” [9].

** “Now, experience shows that solvents exert considerable influence on reaction rates. If we represent the rate constant of the reaction to be studied in hexane C_6H_{14} by 1, then, all else being equal, this constant for the same reaction in $CH_3-CO-C_6H_5$ will be 847.7. The increase is enormous, but in this case it has not even reached its maximum... So you see that solvents, in spite of appearing at first to be indifferent, are by no means inert; they can greatly influence the course of chemical reactions. This statement is full of consequences for the chemical theory of dissolutions” [26].

*** The first observation of a tautomeric equilibrium was made in 1884 by Zincke at Marburg [11]. He observed that, surprisingly, the reaction of 1,4-naphthoquinone with phenylhydrazine gives the same product as that obtained from the coupling reaction of 1-naphthol with benzenediazonium salts. This phenomenon, that the substrate can react either as phenylhydrazone or as a hydroxyazo compound, depending on the reaction circumstances, was called *Ortsisomerie* by Zincke [11]. Later on, the name *tautomerism*, with a different meaning however from that accepted today, was introduced by Laar [12]. For a description of the development of the concept of tautomerism, see Ingold [13].

der Temperatur, bei den gelösten Substanzen auch von der Art des Lösungsmittels hängt es ab, welche von den beiden Formen die beständigere ist" [14]*). The study of the keto-enol equilibrium of ethyl formylphenylacetate in eight solvents led Wislicenus to the conclusion that the keto form predominates in alcoholic solution, the enol form in trichloromethane or benzene. He stated that the final ratio in which the two tautomeric forms coexist must depend on the nature of the solvent and on its dissociating power, whereby he suggested that the dielectric constants were a possible measure of this "power". Stobbe was the first to review these results [18]. He divided the solvents into two groups according to their ability to isomerize tautomeric compounds. His classification reflects, to some extent, the modern division into protic and aprotic solvents. The effect of solvent on constitutional and tautomeric isomerization equilibria was later studied in detail by Dimroth [19] (using triazole derivatives, *e.g.* 5-amino-4-methoxycarbonyl-1-phenyl-1,2,3-triazole) and Meyer [20] (using ethyl acetoacetate).

It has long been known that UV/Vis absorption spectra may be influenced by the phase (gas or liquid) and that the solvent can bring about a change in the position, intensity, and shape of the absorption band**). Hantzsch later termed this phenomenon *solvatochromism****) [22]. The search for a relationship between solvent effect and solvent property led Kundt in 1878 to propose the rule, later named after him, that increasing dispersion (*i.e.* increasing index of refraction) is related to a shift of the absorption maximum towards longer wavelength [23]. This he established on the basis of UV/Vis absorption spectra of six dyestuffs, namely chlorophyll, fuchsin, aniline green, cyanine, quinizarin, and egg yolk in twelve different solvents. The – albeit limited – validity of Kundt's rule, *e.g.* found in the cases of 4-hydroxyazobenzene [24] and acetone [25], led to the realization that the effect of solvent on dissolved molecules is a result of electrical fields. These fields in turn originate from the dipolar properties of the molecules in question [25]. The similarities in the relationships between solvent effects on reaction rate, equilibrium position, and absorption spectra has been related to the general solvating ability of the solvent in a fundamental paper by Scheibe *et al.* [25].

More recently, research on solvents and solutions has again become a topic of interest because many of the solvents commonly used in laboratories and in the chemical industry are considered as unsafe for reasons of environmental protection. On the list of damaging chemicals, solvents rank highly because they are often used in huge amounts and because they are volatile liquids that are difficult to contain. Therefore, the introduction of cleaner technologies has become a major concern throughout both academia and industry [31–34]. This includes the development of environmentally benign new solvents, sometimes called *neoteric solvents* (neoteric = recent, new, modern), constituting a class of novel solvents with desirable, less hazardous, new properties [35, 36]. The

* "There are compounds capable of existence in the form —C(OH)=C—CO— as well as in the form —CO—CH—CO— ; it depends on the nature of the substituents, the temperature, and for dissolved compounds, also on the nature of the solvent, which of the two forms will be the more stable" [14].

** A survey of older works of solvent effects on UV/Vis absorption spectra has been given by Sheppard [21].

*** It should be noted that the now generally accepted meaning of the term *solvatochromism* differs from that introduced by Hantzsch (*cf.* Section 6.2).

term *neoteric solvents* covers supercritical fluids, ionic liquids, and also perfluorohydrocarbons (as used in fluoruous biphasic systems). In addition, water, often considered incompatible with organic synthesis, in recent decades has attracted increasing interest as an environmentally benign and cheap solvent for a multitude of organic reactions [46]. Table A-14 in Chapter A.10 (Appendix) collects some recommendations for the substitution of hazardous solvents, together with the relevant literature references; see also Chapter 8.

For the development of a sustainable chemistry based on clean technologies, the best solvent would be no solvent at all. For this reason, considerable efforts have recently been made to design reactions that proceed under solvent-free conditions, using modern techniques such as reactions on solid mineral supports (alumina, silica, clays), solid-state reactions without any solvent, support, or catalyst between neat reactants, solid-liquid phase-transfer catalysed and microwave-activated reactions, as well as gas-phase reactions [37–42]. A representative recent example of a highly efficient solvent-free organic synthesis is the (*S*)-proline-catalysed stereoselective aldol reaction between cyclohexanone and 4-nitrobenzaldehyde, applying a very simple mechano-chemical technique such as ball milling [42].

However, not all organic reactions can be carried out in the absence of a solvent; some organic reactions even proceed explosively in the solid state! Therefore, solvents will still be useful in mediating and moderating chemical reactions and this book on solvent effects will certainly not become superfluous in the foreseeable future.

