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Organic Sonochemistry

Challenges and Perspectives for the 21st Century

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Contents

Chapter 1
Cavitation and Chemical Reactivity

Abstract The sound is a mechanical vibration which propagates by elasticity through matter whatever its physical state. On liquid state, an interesting and unique physical phenomenon was identified at the end of nineteenth century and designated as cavitation, which is the birth, growth and collapse of tiny gas bubbles. The intensity of bubbles occurrence and of collapse violence is very dependent on the sound frequency. The most energetic cavitation activity occurs when using ultrasound frequencies, i.e. above the upper limit of human hearing (18 kHz). The incident irradiative frequency is therefore of crucial importance leading to effects on chemical systems of physical and/or chemical nature. Several other operational parameters do also greatly influence the cavitation process and are here described as well as most frequent types of ultrasonic devices working either on direct or indirect mode. 'Hotspot' theory and generally admitted reacting zones establishing rules of sonochemistry are also examined. Finally, some guidelines for good experimental use of ultrasonic devices are tentatively established by authors based on their own experience.

1.1 Introduction

To ease the reading of this Brief, necessary rudimental terms and fundamental knowledge on the origin and the nature of effects brought up by ultrasound on chemical systems will be introduced. Some of the most common ultrasonic devices will be also introduced. Factors impacting greatly sonochemical activity cannot be omitted, the balance between them allow to reach a maximal acoustic activity ensuring an optimum cavitation efficiency. These are incident irradiative frequency, working temperature, amplitude of the acoustic wave, physicochemical characteristics of the solvent, type of dissolved gases, etc. Some good rules of use, rather based on practical experience than on theoretical rules, will be also tentatively given. Indeed, an experimental misconduct can lead to false or even anomalous absence or overestimation of a spotted sonochemical activity. Finally, it is necessary to quantify the impact of ultrasound on studied chemical systems while getting rid of technological

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aspects. Several chemical or physical ‘dosimeters’ have been subsequently designed in order to rationalize these effects but also to authorize absolute comparison of results obtained with different equipment.

1.2 The Sound

The sound range is very large, from 20 Hz to more than 100 GHz. Commonly accepted subcategories are infrasound (below 20 Hz), audible sound (from 20 to 20 kHz), ultrasound (from 20 kHz to 100 MHz) and hypersound above (>100 MHz). The sound is a mechanical vibrating wave transmitted by elasticity of the considered medium as a longitudinal wave. The periodical succession of compressive and tensile stresses induces fluctuating pressures alongside the direction of the wave propagation. The variation of the acoustic pressure with time can be expressed as follows:

$$P_{\mathrm{A}} = P_{\mathrm{max}} \sin 2\pi f t \tag{1.1}$$

where P_{max} is the maximum pressure amplitude and f the frequency of the sound waves.

The physical state of the considered medium is of key importance as it is closely related to its couple elasticity/attenuation propagating waves. Wave attenuation depends on the absorption coefficient of the medium and of the distance from the source. Thus, the attenuation is stronger in gases than in liquids and smaller in solids than in liquids. As a representative example, the speed of sound is around 343 $\mathrm{m\ s^{-1}}$ in air and around 1480 $\mathrm{m\ s^{-1}}$ in water, and reaches values as high as 3850–5130 $\mathrm{m\ s^{-1}}$ in an iron matrix.

The sonochemistry is the science of using sound waves for operating chemical/physical changes induced on matter by mechanical and chemical actions at any frequency (Suslick 1988; Leighton 1994). However, among all usable sound frequencies, ultrasound offers the best possible combination in between sufficient energy to enable subsequent effects on chemical systems, ease of generation with piezoelectricity. In addition, users do not suffer any noticeable discomfort since ultrasound is inaudible for humans (Lepoint and Lepoint-Mullié 1998) (Fig. 1.1).

Two defined windows of frequency are of particular interest for sonochemists: low-frequency ultrasound known as ‘power’ ultrasound (ca. 20–100 kHz), where effects of physical nature are predominate; high-frequency ultrasound ranging from 200 to 2000 kHz, where effects of chemical nature are predominate, highlighting the crucial choice of the incident ultrasonic frequency (Mason and Lorimer 2002) (Fig. 1.2).

In any case, ultrasound cannot directly interact with vibrational/rotational frequencies of chemical bonds. Ultrasonic irradiation causes enhanced molecular motion creating an indirect phenomenon responsible for the consequential and unusual reactivity which is called *cavitation*.

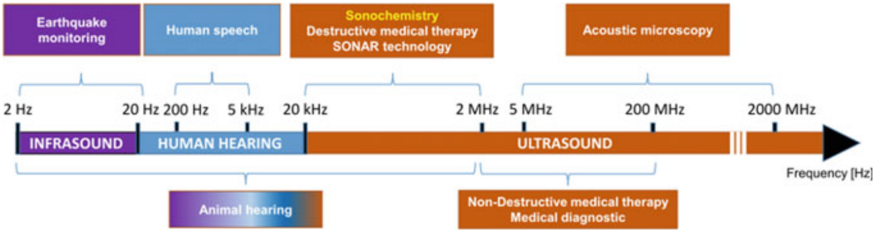
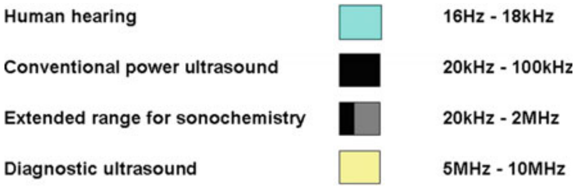


Fig. 1.1 Sound range



Human hearing	🟦	**16Hz - 18kHz**
Conventional power ultrasound	■	**20kHz - 100kHz**
Extended range for sonochemistry	◧	**20kHz - 2MHz**
Diagnostic ultrasound	🟨	**5MHz - 10MHz**

Fig. 1.2 The special ultrasonic classes. Reproduced with permission from T. Mason (www.sonochemistry.info/introdution.htm)

1.3 Cavitation and Origin of Ultrasonic Effects

The phenomenon of cavitation has been observed for the first time in 1893 by J. Thornycroft and S. Barnaby. The tests phase of the high-speed HMS warship ‘Daring’ revealed the existence of incipient microbubbles and major vibrations on propeller blades avoiding full speed and long-time motion. In 1895, Parsons established a direct relationship between these bubbles and the damages caused to the propeller. Lord Rayleigh circumvented later on the phenomenon by establishing laws governing hydrodynamic turbulences created by the high motion of the propeller responsible for the birth of cavitation microbubbles. His pioneering work has laid the foundations of modern bubble dynamics and is still quite useful today. The cavitation phenomenon corresponds thus to the birth and dynamic of microbubbles in a liquid medium under turbulent regime, and it can be of hydrodynamic or acoustic origin. Hydrodynamic cavitation is the birth of vapour bubbles consecutive of a brutal acceleration of a liquid, for example, when passing through an orifice or through a narrowing of its passage section (Gogate and Pandit 2005). Once the obstacle has passed, the fluid returns to its initial pressure conditions, and the vapour bubbles implode causing damages. Ultrasonic cavitation is similar in terms of birth, growth and collapse of microbubbles but under an acoustic field, which must reach a certain level of power to allow this phenomenon. A simple calculation using Eq. (1.1) reveals that applying frequencies of a few kHz to a liquid leads to pressure fluctuations up to a few atmospheres. If negative pressures over saturating vapour pressure insuring the intermolecular cohesion of a liquid are reached, the liquid literally tears and interstitial voids do create. These voids are then straightforwardly occupied by gases, originally dissolved in the bulk liquid medium, creating gaseous microbubbles. These latter do first pulsate on either non-linear or linear mode, according to the characteristics of the acoustic wave, and expand gradually during the alternation of compressive and tensile stresses. At one stage, they do violently and adiabatically collapse leading to very intense effects with localized liberation of high amounts of energy on the form of high temperature and pressure accompanied by violent mechanical effects. Cavitation can be initiated in many types of liquids (water, organic solvents, liquefied gases, molten organic and inorganic salts, supercritical fluids, etc.) over a wide range of experimental conditions. This complex dynamic behaviour strongly relies on properties of the liquid (surface tension, density, viscosity), on the acoustic field (intensity and frequency) and on the bubbles themselves (gas content, diameter). The minimum required acoustic pressure to enable cavitation is named ‘cavitation threshold’ (Lepoint and Lepoint-Mullié 1998). Typically, whereas the theoretical strength of water is around 1000 bar, only 1 bar appears to be necessary in practice to initiate cavitation. This is likely due to the presence of inhomogeneity acting as ‘structural defects’ in the irradiated material by weakening the intermolecular bonding network insuring cohesion of the liquid. Indeed, the presence of dissolved gas or even small size suspended dust particles do act as nucleating sites to trigger cavitation activity. In addition, it is worth mentioning that only a certain percentage of incipient microbubbles do reach the collapsing stage. Indeed, some do coalesce with neighbouring bubbles prior to eventually float and to release out from the liquid surface. Some others undergo collapse phase during the positive cycle of the ultrasonic pressure to initiate characteristic physical and chemical effects of ultrasound. Moreover, some have probably an unknown or random behaviour, revealing the complexity of cavitation phenomenon intimately linked to the bubbles dynamic.

1.4 Stable and Transient Cavitation Modes

In terms of collapse intensity, two different cavitating modes, referred as ‘stable’ and ‘transient’, can be defined with separate effects although a distinct frontier between the two states is not that obvious (Yasui 2011). In the case of the former, the cavitating gas bubbles, when submitted to a low amplitude ultrasonic wave, enter into resonance with the incident wave during a few hundreds to thousands of acoustic cycles. These small amplitude vibrations induce linear low-scale variations in the bubble’s size with small pressure variations, preventing violent collapse. It is usually admitted that this type of cavitation is responsible for enhanced mechanical effects in the bulk solution. On the contrary, a high amplitude ultrasonic wave will promote the rapid increase of the bubble’s diameter from a few to few hundreds μm diameter within a very small number of acoustic cycles resulting in a swift and violent collapsing step in a few μs, that is, transient cavitation. This phenomenon is responsible for sonoluminescence which is the emission of a diffuse light, observed as early as 1933, originating from the centre of the collapsing bubble (Suslick and Flannigan 2008). High-frequency ultrasound (>200 kHz) do favour the occurrence of this regime of cavitation, and consequently, the physical effects brought up by ultrasound vanish and chemical ones become predominant. However, this renders burdensome to operate this range of frequency in heterogeneous conditions unless adequate stirring is enabled with the possible risk of altering ultrasonic field and bubbles' dynamic.

1.5 'Hotspots' Theory and Reacting Zones

Several theories aiming at identifying and modelling direct and indirect effects brought up by collapsing bubbles on chemical systems, namely, plasma discharge, electrical, supercritical and hotspot theories, have been explored and critically confronted during the 1990s and 2000s. The 'hotspot' theory remains nowadays the generally admitted theory but it is of probable sight that the truth lies in the middle of these three theories (Chatel 2016). Each collapsing bubble is considered as a single microreactor, i.e. a local 'hotspot', where chemical and physical modifications do take origin. Numerous experimental and theoretical calculations have been conducted to estimate the temperature and pressure reached during the collapsing phases and values as high as 10^3 to 2×10^3 bar and 5×10^3 to 6×10^3 K, respectively, have been found. A considerable amount of work has been done to support this theory, and it is now conceded that reactions take place in all likelihood in three distinct zones of the hotspots:

- The centre of the cavitation bubble, where the highest temperature and pressure are reached. Trapped gaseous materials (solvents vapours, volatile organic molecules, etc.) in the collapsing bubbles undergo homolytic cleavage to afford free radical species. These then react with molecules located within the vicinity of the liquid/gas interface of the bubble.
- The interfacial zone between the bubble shell and the bulk solution, where the temperature reaches up to 2000 K after collapsing step. The physical state of this interface is still the cradle of nourished discussions notably how is dissipated/transformed the high amount of energy released during the adiabatic collapsing phase. In that region are localized most of chemical reactions involving radical species as their lifetime is generally too short to reach the bulk solution region in their native state. These radicals may either recombine or react with non-volatile molecules unable to fill the bubbles which may accumulate in that zone.
- Unreacted radicals formed in the cavities of the bubbles or at the interfacial zone recombine to form in situ stable molecules able then to react in the bulk solution region. Mechanical effects such as acoustic streaming, micro-jets, shock wave and shear forces do occur, leading to subsequent physical changes on solid materials or to emulsification in the case of a liquid/liquid system.

1.6 Parameters Influencing the Sonochemical Activity

It is generally accepted that the number of parameters exerting a possible influence on the fate of cavitation is relatively important. However, it is also commonly agreed that only a few of them exert a quantifiable impact, whose are summarized hereafter.

1.6.1 Ultrasonic Frequency

Frequency and intensity of the ultrasonic wave are obviously the two essential components of an ultrasonic wave. The frequency (f) of a sound wave is defined as c/λ where c is the celerity of sound (m/s) and λ the wavelength (m). Whereas a 20 kHz frequency displays a wavelength of 74 mm in water, this value is around 3 mm at 500 kHz. This difference in acoustic cycles numbers within the same period in between these two frequencies leads to a different dynamic behaviour of cavitation bubbles and certainly issue of whether transient or stable cavitation.

1.6.2 Acoustic Intensity

The intensity of a sound wave can be defined as the power carried per surface and can be expressed as follows:

$$I = P_{\mathrm{A}}^2 \big/ 2\rho c \tag{1.2}$$

where P_{A} is the acoustic pressure amplitude of the sound wave, ρ is the density of the medium and c is the celerity of sound in the medium.

However, this formula remains valid only for planar or spherical progressive waves with low-pressure variations. In the case of low-frequency ultrasound, variations of acoustic pressure may reach up to a few bars leading to a complex and non-linear acoustic system (Lepoint and Lepoint-Mullié 1998). When speaking about intensity, sonochemists do refer preferentially to the acoustic power delivered to the liquid medium by the ultrasonic device.

1.6.3 Temperature

Unsurprisingly, temperature exerts a great importance in sonochemistry. Regardless of the ultrasonic wave itself, the maximum cavitation efficiency will rely mainly on a good balance of several solvent's properties like viscosity, volatility and density. Thus, the bubbles' dynamic will be inherently affected by the changes induced on the medium properties by temperature variations. Each liquid possesses its optimum range of cavitation intensity such as water with a 20–50 °C range or ethanol around 15–27 °C (Niemczewski 1980). Monitoring/controlling of the working temperature actively prevents ‘false sonochemistry’ examples where beneficial effects are wrongly attributed to an ultrasonic consequence but due in fact to temperature rise. Low-frequency ultrasonic irradiation, through induced physical effects, creates an important macroscopic rise of temperature making necessary thermostatic control of the medium. At high frequency, the rise of temperature is greatly diminished in reason of the quasi-absence of mechanical effects resulting in a residual increase in temperature of a very few degrees easily controllable. Working at temperatures nearby boiling point may also appear inappropriate unless purposely intended. In these conditions, vaporization bubbles, displaying much bigger diameters than cavitation ones, coalesce with the latter suppressing greatly cavitation powerness. This phenomenon is usually referred as ‘vaporous’ cavitation. A liquid/gas emulsion may also take place acting as an ‘acoustic cushioning’ by reflecting sound waves since a gas phase has a higher attenuation factor than a liquid one.

1.6.4 Solvent Properties

A certain number of solvent properties can influence acoustic cavitation above all when considering the variety of potential liquid media (water, organic solvents, liquefied gases, molten organic and inorganic salts, etc.). In any case, the weaker the intermolecular forces insuring the cohesion of a liquid, the easier will be reached the cavitation threshold but also the less energetic it will be. Thus, liquids with high viscosities and surface tensions display higher cavitation threshold but also harsher collapsing conditions as higher acoustic pressures are necessary to tear apart molecules of the liquid. In addition, very volatile solvents are usually not recommended under low-frequency ultrasound since they may smooth acoustic activity by making a too dense bubbles cloud creating detrimental bubbles coalescence and sound wave reflection/attenuation.

1.6.5 Dissolved Gas

The first action of ultrasound on a liquid is degassing, such as when using an ultrasonic bath to degas solvents prior to HPLC use. Thus, cavitation may occur greatly at early stages followed by a less intensive period in reason of the degassing phase. For that reason, entrain gas is often added in order to sustain or even to promote cavitation activity. Interestingly, the nature of this gas is of crucial aspect since the ratio of specific heat (or polytropic ratio) of the ambient gas (C_p/C_v) exerts a great influence on temperature and pressure reached during the collapsing phase (Rooze et al. 2013). Typically, collapsing temperature and pressure reached in the presence of Argon (with a 1.66 Cp/Cv ratio) will be much higher than in the presence of nitrogen (with a 1.40 Cp/Cv ratio). Argon is a commonly added gas in sonochemistry's world to maximize cavitation powerness. Some dissolved entrain gases that present in solution such as H_2, O_2 or CO_2 undergo homolytic scission to afford radical species able then to participate or to trigger a variety of reactions including redox ones. Mixtures of some of these gases are also used to maximize specific desired effects.

1.7 Generation of Ultrasonic Waves and Subsequent Equipment

The conversion of alternative electrical energy into a mechanical vibration can be ensured either by magnetostriction (Briquard 1983; i.e. an induced magnetic field able to contract metals such as zinc or iron) or by piezoelectric properties of some inorganic materials. There is an obvious preference in the world of sonochemistry for the latter as the former are limited in terms of emitted frequency range with a maximum at 50 kHz. The direct piezoelectric phenomenon was discovered by P. and J. Curie in 1880 when they subjected quartz to an electric field which then emitted mechanical stresses. At early twentieth century, Lewis Richarson stipulated the possibility to probe the underwater obstacles by an experiment of the ultrasonic waves emission/recovery. Later on, Paul Langevin and Constantin Chilowski postulated that the use of high-frequency electrical oscillations may synchronously excite all the points of a large surface, which they named 'singing capacitor'. Thus, in 1917, they created the first transducer that was successfully put into action in the laboratory sink, the 'Langevin Triplet', able to enhance oscillations for underwater detection purpose (S.O.N.A.R). Historically, this is considered as the first technological breakthrough in ultrasonic technology. The frequency tuning of the triplet is obtained when the power consumption is minimal with a maximum displacement of the masses set in motion. Most common today's materials (ceramics) are made of barium titanate, lithium niobate or titanozirconate of lead (known as PZT), which display good piezoelectric activity together with ease of handling and shaping. Whatever the used material, a drilled or undrilled flat surface (disc, plate, etc.) is shaped with electrodes on both faces to electrically constraint the material (Fig. 1.3).

Fig. 1.3 Various shapes and designs of PZT ceramics (© CeramTec)

Noteworthy, piezoelectric ceramics do resonate at some specific frequencies depending on their initial shape (thickness, diameter, etc.). The ceramic is then incorporated in different set-ups, called transducers to enable ultrasonic waves emissions. These latter can be then mounted on several types of equipment with or without contact (direct or indirect modes) between the ultrasonic emitting zone and the reaction medium. Many types of ultrasonic apparatuses are now commercially available from the simplest to the most complex architecture and for small to big volumes. However, availability of high-frequency devices remains still nowadays anecdotic as compared to low-frequency ones. This comes probably from a set of reasons as compared to low-frequency devices. Typically, the thinness of high-frequency ceramics renders them more fragile and more delicate to shape. The poor conversion ratio of electrical energy and the quasi-absence of physical effects of ultrasound make high-frequency ultrasound hardly adequate for heterogeneous chemical systems.

1.7.1 Ultrasonic Bath

This apparatus is the most available, cheapest and the most known ultrasonic device, historically designed for cleaning and analytical grade solvent degassing. Transducers are usually glued at the bottom and/or on the sides of a water-containing tank. The reaction vessel is generally plunged into the tank enabling only an indirect irradiation mode. Most of the pioneering works in the 80s/90s have been accomplished with this equipment at the dawn of sonochemistry field. However, it exhibits also some important drawbacks owing to its extremely basic conception. First, this conception prevents the formation of a homogeneous acoustic field highlighting the importance of the position of the reaction vessel. Then, chemical effects cannot be expected at both such a low ultrasonic frequency and amplitude. Mechanical effects predominate making this system adequate for heterogeneous chemical systems for several purposes among extraction, analyses or organic synthetic chemistry.

1.7.2 Ultrasonic Horn System

It is the most powerful available ultrasonic device. Contrary to the ultrasonic bath, a horn (or probe) enables a direct irradiation mode with the emitting tip plunging into the reaction medium (such a system is inherited from biological cell disruptors). A commonly designed ‘ultrasonic probe’ is in fact constituted of four main parts with a generator, a piezoelectric transducer, an amplifying part (or booster) and the horn itself. The booster and horn parts must be made of very hard materials not only to stand with relatively high mechanical stresses but also to resist to cavitation erosion. Thus, they are usually made of titanium alloys or stainless steel. Ultrasonic probes are all low-frequency ultrasonic devices from 20 to 100 kHz. Since high-intensity ultrasonic waves are emitted directly into the reaction vessel, the thermal release is very important and reactions must be thermostatically controlled. Although made of hard materials, the emitting zone of the dipped probe undergoes deep damage with time. Badly eroded parts should be changed or eventually sanded notably because tiny metallic particles may be dispersed into the liquid medium and eventually interfere on the course of the reaction (poisoning, catalytic side reactions, metallic inclusions in frameworks, etc.).

1.7.3 'Cup-Horn' Systems

This set-up is at midway between a horn and a cleaning bath system but remains of more confidential use than the two previously described ones. It is comparable to a high-intensity ultrasonic bath with irradiation from bottom to top with an inverted probe placed in a glass- or metal-made vessel or 'cup'. This system can be used in both indirect and direct mode. The reaction vessel can be placed in the water filling the ultrasonic reactor or chemicals can also be poured directly into the ultrasonic reactor. This set-up enables much higher acoustic intensities than common ultrasonic baths making necessary to use a double-jacketed reactor to enable thermostatic control of the reaction medium.

For high-frequency systems, it is compulsory to adopt a 'bottom to top' irradiation mode in reason of the technological aspects of piezoceramic materials. Indirect irradiation mode should be avoided since these systems are poorly energetic and the presence of the walls of a glass reactor will enhance reflection of sound waves. However, in the case of aggressive liquid media, these fragile ceramics can be efficiently protected by tightly glued glass windows bearing a multiple of $n/4\lambda$ thickness (with $n = 1$–3), ensuring a sound 'transparency' of the glass window. Except for piezoceramics, the commercial availability of 'ready to use' high-frequency devices is very scarce as compared to low-frequency set-ups. This is the consequence of finding in literature almost solely high-frequency purpose-made irradiant systems.

1.8 Guidelines for Adequate Use of Ultrasonic Devices

Some rules of good use are hereafter given based on the own practical experience of the authors with respect to important precepts in sonochemistry according to the type of ultrasonic devices.

Precepts for bath systems:

- Fill the bath to the level preconized by the supplier.
- Never let an ultrasonic bath running out of liquid.
- Try to locate the most powerful cavitation zones (can be done by dipping a sheet of alumina foil into the bath to map colonies of drilled spots on the foil).
- Always place the reaction vessel on the same X-Y-Z position for reproducibility.

- Never place a reaction vessel directly in contact with the bottom emitting wall of the water tank but tightly and adequately suspended in the tank.
- Better to use a flat-bottom vessel than a round-bottom one to maximize surface exposure of the vessel to ultrasonic waves.
- The level of the liquid inside the reaction vessel should be more or less at the same height than the level of water filling the cleaning bath to maximize surfacing mechanical effects.

Precepts for horn systems:

- Check the integrity of the horn tip immersed into the reaction vessel. If the tip is badly damaged, it must be changed to avoid metal contamination and loss of acoustical power.
- A damaged tip can be sanded and polished but with possible risk of probe detuning and lower deliverable cavitation intensity.
- Reaction vessel must be thermostatically controlled prior (to avoid unwished side effects due to the sudden rise in temperature such vaporous cavitation, enhanced degassing effect, overheating, etc.) and during the experiment.
- Position the emitting horn not too close from the bottom of the vessel to avoid reflection which may dramatically damage the ultrasonic horn and not too close from the liquid level to avoid cushioning effects with ambient gas and to minimize dead zones.
- Homogenize a solid/liquid heterogeneous solution by adding gradually the solid and a liquid/liquid solution by placing the horn just above the liquid/liquid interface to literally ‘push’ one liquid into another one.
- A round-bottom flask is preferred than a flat one for a better dispersion of ultrasonic waves throughout the vessel and to prevent reflection of the sound waves leading to the overheating of the probe.
- Pressurized reactions with horn systems are possible but be sure that the horn and the set-up are connected at the null (or nodal) point of the probe to avoid probe damages and overheating.

Precepts for ‘cup-horn’ systems at high frequency:

- The height of the liquid column submitted to ultrasonic waves is of importance (de La Rochebrochard et al. 2012). This parameter, which is often obscured because it is difficult to apprehend, is nevertheless crucial for a maximum and homogeneous distribution of the acoustic energy across the ultrasonic reactor. This optimization can be achieved with adequate chemical dosimeters introduced in the next paragraph.
- Heavily heterogeneous systems must not be submitted to high-frequency ‘cup-horn’ systems as solids will depose at the bottom of the reactor where is located the ceramic resulting in high reflection of ultrasonic waves and breakage of the ceramic.
- Pressurized reactions are barely possible with high-frequency ‘cup-horn’ systems notably in reason of the fragility of the ceramics and reached weak power levels of ultrasound.

The design of the ultrasonic reactor plays also a crucial role in the distribution of the acoustic energy. Usually, reaction vessels incorporating curves lines are more adequate for ultrasound than the ones bearing right angles as opened angles help to scatter acoustic waves throughout the liquid medium. In addition, to further expand towards sustainable development, the energetic consumption remains of high concern in the world of sonochemistry with more or less optimized commercially available or lab-made equipment. One way to reduce the energetic bill is to use pulsed ultrasound instead of continuous one. The obvious output will be a decrease in the overall energetic consumption of the reaction but also may reduce the cushioning effects of the ineffective bubbles clouds. Silent periods can help to dissolve or to disperse out these ineffective bubbles close to the irradiation source which leads to less energy scattered by the bubbles. It is also important to endeavour a comparison between ultrasonic-assisted and silent reactions with strictly same experimental conditions apart from the activation method prior to claim any substantial effect of ultrasound. Then, further investigation can be eventually undertaken to reveal the nature of and to quantify the effects of ultrasound, i.e. physical and/or chemical origin. For that, several chemical and physical methodologies or technologies have been designed.

1.9 Physical and Chemical Dosimetry Methods to Quantify/Qualify Cavitation Activity

To elucidate a mechanism occurring under ultrasonic irradiation, a full characterization of the acoustic field is necessary. The determination of the ultrasonic energy distribution throughout a reaction vessel is also of high interest for scalability to determine optimum operating parameters. Moreover, ultrasonic effects can be of either physical or chemical nature emphasizing the complexity of measurements and above all about their real significance. Physical and chemical effects can predominate or coexist according to the incident ultrasonic frequency and the other aforementioned operating parameters, making difficult the development of a single method. Several chemical and physical dosimetry methods have been therefore designed to confront critically results collected with different set-ups with standardized methodologies. The most known and used are hereafter introduced with respective easiness to be implemented.

1.9.1 Physical Methods

The acoustic pressure can be measured by calorimetry as the propagation of the ultrasonic waves throughout the liquid medium provokes measurable heating phenomena (Kimura et al. 1996). The reaction vessel is here assimilated as a calorimeter containing the mass of liquid (m) submitted to ultrasound. The rise of temperature is monitored and plotted as a function of time over a short period (2–3 min) without thermostatic control. The deduced slope $\Delta T/\Delta t$ is then set into the next equation to determine the calorimetric power of an incident ultrasonic wave:

$$\mathrm{Pcal}(W) = m.\mathrm{Cp}.\Delta T \big/ \Delta t \tag{1.3}$$

where Cp is the isobaric thermal capacity.

In reason of the non-linear behaviour of acoustic waves and subsequent cavitation bubbles at high amplitude, the bulk temperature might not be spatially homogeneous. Different measurements location within the same reactor may thus present some noticeable variations (Al-Juboori et al. 2014).

Another way to measure the acoustic pressure is the radiometric method which is the measurement of the force exerted by a sound beam on any partially reflecting surface (Lepoint and Lepoint-Mullié 1998). The spatial distribution of the ultrasonic pressure intensity can be undertaken by mean of a hydrophone but their high sensitivity together with fragility are limiting parameters for non-linear high intensities sound fields. The latest development in the physical characterization of the acoustic cavitation has been recently enabled with the design of cavitometers. These latter allow to study the cavitation noise spectra to analyse the dynamic process of cavitation by measuring acoustic pressures at particular frequencies but this equipment is still on lab-stage development (Dezhkunov et al. 2013).

1.9.2 Chemical Methods

Previously described methods do macroscopically measure the acoustic pressure through the effects produced in the propagation liquid, namely, heating and exerted forces on a surface. However, they do not allow to determine the radical production consecutive of collapsing bubbles, that is, the chemical component of ultrasonic effects (Lida et al. 2005). Several reactions bearing a radical pathway have been designed to qualify/quantify the production of radicals, in particular in water with the production of OH° by help of spectrophotometric reactions (Koda et al. 2003; Kimura et al. 1996), para-chlorobenzoic acid degradation (Neppolian et al. 2004) or fluorimetric methodologies (Hirano and Kobayashi 2016), terephthalate oxidation (Mason et al. 1994) and luminol sonochemiluminescence (Pétrier et al. 1994; Hatanaka et al. 2000). Fricke and Weissler reactions being the most studied and used chemical dosimetry methods, a quick insight is given here below:

- Fricke reaction: A Fe^{2+} solution of $FeSO_4$ in the presence of H_2SO_4 and NaCl is submitted to ultrasound and the production of OH° can be estimated through the oxidative conversion of Fe^{2+} ions into Fe^{3+} ions where the number of OH° is approximatively equal to one-quarter the amount of produced Fe^{3+}.

- Weissler reaction: A KI solution is submitted to ultrasonic irradiation and the oxidative production of iodine I_3^- is monitored by UV spectroscopy at around 350 nm.
- p-CBA probe reaction: The oxidative disappearance of para-chlorobenzoic acid is monitored throughout time by UV detection at 234 nm.

Weissler reaction appears nowadays as the most implemented because it is the easiest and most reliable chemical way to quantify OH° formation.

1.10 The Three Types of Sonochemical Reactions

The dynamic behaviour of the cavitation bubbles in homogeneous or heterogeneous medium presents noticeable differences. Whereas they are rather spherical in homogeneous solutions, they appear to be deformed in heterogeneous conditions notably in the presence of solid particles where they can be absorbed or even trapped within the crevices of the solid network. In that case, collapsing bubble develops hot jet of liquid directed towards the solid, eroding its surface together with secondary mechanical effects such as microstreaming, shock waves and micro-jets greatly impacting kinetics and yields (Suslick 1988; Lepoint and Lepoint-Mullié 1998). This aspect represents a large part of the literature related to *heterogeneous* organic environmental sonochemistry. On the other hand, in homogeneous conditions, mechanical effects vanish and chemical effects predominate with more energetically violent collapses. Cavitation originating from dissolved gas/volatilized molecules in a homogeneous solution is usually referred as homogeneous cavitation and focuses on the creation and subsequent faith of formed in situ radical species. Synthetic organic reactions can be theoretically designed with reactants and solvents with adequate volatility, affinity, miscibility and reactivity to draw up a synthetic route. An organic synthetic reaction occurring in heterogeneous conditions can be conjointly promoted by both physical and chemical effects of ultrasound whereas the one occurring in homogeneous conditions can be barely promoted by physical effects. Three classes of sonochemical reactions have been established as early as 1993 by the late J. L. Luche, leading pioneer in the field of organic synthetic sonochemistry. Indeed, he published his first article about Barbier reaction with organolithium compounds in a cleaning bath announcing the renewal of the discipline after almost 70 years of silence following the first ever published paper in 1927 by A. Loomis.

- Type I: *Sonochemical reactions occurring in homogeneous phase, also called 'true' sonochemistry that is driven by a radical pathway, in particular S.E.T (single electron transfer) mechanisms*. The formation of highly reactive intermediates radical species able to initiate different mechanistic paths than under classical conditions is enabled. The use of radical scavengers can reveal the radical nature of the mechanism by quenching the reaction.
- Type II: *Sonochemical reactions occurring in heterogeneous phase, also called 'false' chemistry*. Physical effects arisen from collapsing bubbles generate reduc-

tion of particles sizes, enhanced mass transfer, emulsification, harsh mixing, etc. responsible for enhanced kinetics without changing the nature of the mechanistic pathway.

- Type III: *Sonochemical reactions occurring in heterogeneous phase but able also to follow an S.E.T mechanism.* These reactions possess an ambivalent character as chemical and physical effects of ultrasound may jointly impact favourably the issue of a reaction. It is usually very troublesome to determine which effect is in particular responsible and why. The most striking example is probably the first known example of 'sonochemical switching' found in 1984 by T. Ando et al. In that chemical system, resulting products obtained under mechanical stirring and ultrasonic irradiation are different. The authors stated that the use of 'ultrasound completely switched the reaction pathway from electrophilic aromatic substitution to an aliphatic nucleophilic substitution'.

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Chapter 2
Efficient Organic Synthesis: What Ultrasound Makes Easier

Abstract The application of ultrasound waves to induce and enhance chemical reactivity dates back to the pioneering studies by Richards and Loomis in the late 1920s. The long journey, now entering the twenty-first century, has been accompanied by decades of low and high research activity. But arguably, the marriage between synthesis, organic synthesis in particular, and sonochemistry has been especially fruitful from the 1980s onwards. We now realize the pluses conveyed by sonication, in terms of efficiency, acceleration and selectivity. Mechanistic switching and/or different product distribution relative to non-irradiated conditions also represent salient features observed frequently in sonochemical reactions. This chapter summarizes a series of fundamental ideas in organic sonochemistry and introduces the subject within the framework of green chemistry and sustainability. Representative examples gathered in recent literature help to appreciate the added value of sonochemistry as tool.

2.1 Sonochemistry for Sustainability. General Remarks

The concepts of green chemistry, according to its 12 principles, and green engineering have now become dominant and essential considerations for all chemists across the whole range of chemical disciplines. If one may say so, green chemistry is often invoked as *magic touch*, in the hope such words will promote our own research still further. Inevitably, this has generated both misuse and abuse (*vide infra*), although we should nevertheless be strongly committed to building a green chemistry toolbox that can deliver sustainability throughout processes, from their first design basis, and thus reduce anthropogenic impact on human health and the environment.

Sonochemistry focuses primarily on processes and transformations that are aided by acoustic cavitation. In line with other enabling technologies, such as electrochemistry and photochemistry, sonochemistry (effects caused by the propagation of pressure waves in liquids) has the potential to dramatically influence a wide variety of chemical reactions by reducing their reaction times, increasing yields and halting the formation of unwanted by-products and competing pathways. It is not an exag-

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geration to say that the broad scope of power ultrasonics today—it is used in such widely varied disciplines as polymer science, food technology, materials science and the treatment of wastewater—has been significantly boosted by the expertise gained from the field of sonosynthesis over the more than 90 years of its study (Chen et al. 2011; Gallego-Juárez and Graff 2015; Chatel 2017). The benefits offered lead to (i) the acceleration of chemical reactions; (ii) the use of less forcing conditions; (iii) more economical processes via the use of cruder reagents; (iv) reductions in the number of reaction steps required; (v) the initiation of stubborn reactions; (vi) reductions in induction periods; (vii) enhancements in catalytic activity and/or efficiency; and (viii) enhancements in radical reactions. Such effects are especially noticeable in heterogeneous sonochemistry, i.e. reactions on and in the vicinity of solid surfaces where, in addition to the enhanced mass and heat transfer caused by ultrasonic agitation, species released by cavitation into the bulk liquid will also interact with adsorbed reagents and the catalytic sites of a solid.

2.2 The Need for Metrics

A comparative analysis of the green chemistry credentials of reactions—the use of non-toxic reagents and solvents, non-hazardous protocols and operational conditions—shows that many syntheses that claim to be green are actually far from being so. A series of chemistry metrics that assess yield, selectivity, waste, reaction efficiency and mass productivity, among others, has been introduced. Moreover, process metrics include a number of other categories, such as reactor design, type of mixing, throughput, inherent hazards, renewability, recyclability, product quality and cost (Jiménez-González and Constable 2011). They are all useful in making meaningful comparisons between methods and process options. It is always helpful to remember that any given reaction can be activated by different methods, which can produce similar or completely different results (Bruckmann et al. 2008; Tabasso et al. 2015). The choice of which method to use depends on operation conditions: controllability, scalability, ease of cleaning and maintenance as well as energy costs.

What can be misleading is the lack of critical appraisal that occurs when syntheses are carried out under the so-called green conditions (such as solvent-free reactions and reactions in water), while the amount of volatile solvents required for product isolation and purification can be overlooked and the fate of waste ignored (Fegade and Tremblay 2017; Cintas 2016). The systematic use of metrics is thus mandatory, although it is rarely employed by sonochemists. Percentages for atom economy or carbon efficiency (for organic reactions), and mass intensity, an adimensional parameter which relates the total mass in the reaction vessel to the product mass, serve as useful indications of efficiency (Constable et al. 2002; Jiménez-González et al. 2012). Even the use of water, which is usually excluded from mass metrics as it does not constitute an environmental impact *per se*, could be a major concern in the future. In many parts of the world, competition for potable (drinking) water has become a significant issue, meaning that running reactions in water and the impact of both the chemicals and equipment required to purify it are fast becoming non-innocuous issues (Jiménez-González and Constable 2011).

Energy reduction via process intensification and modification are pursued by large industries, including the petrochemical and pharmaceutical sectors. This key point is largely overlooked in bench chemistry. Energy metrics are usually similar to those for mass, accounting for the energy required to produce starting materials and products, the recycling of materials and solvents and waste treatment. Accordingly, energy valorization should look to reduce the energy used by an entire protocol, rather than just the energy used to heat or cool the reaction vessel (Jiménez-González and Constable 2011). The best way to do this is to measure energy consumption using some kind of electricity metre linked in series with whatever apparatus is being used in a reaction's operation. In fact, *ca* 80% energy reduction, relative to heating in an oil bath, has been reported for a Suzuki coupling performed under MW (microwave), irradiation (Gronnow et al. 2005), using this method. This kind of energy measurement can be easily accomplished in ultrasound-assisted reactions (Cintas 2016) and extrapolated to sequential designs where both mass and energy consumption are evaluated (Andraos 2016).

2.3 Reactivity in Ultrasonic Fields

It is now well accepted that the chemical effects of sonication arise from cavitation, as acoustic radiation does not interact with matter at the atomic or molecular levels. Bubble collapse leads to quasi-adiabatic heating of the vapour inside the bubble, giving rise to local hot spots in the fluid. Overall, cavitation transforms the low-energy-density sound field into high kinetic energy which is released in very short bursts. The immediate consequence of the presence of pyrolyzed vapour is the potential formation of high-energy excited species, such as hydrogen radicals (H), and hydroxyl radicals (HO), which can then participate in reactions in the bulk liquid at room temperature. The most innovative aspect of sonochemistry lies in *reaction switching*, which is the formation of products that are not usually produced in regular thermal reactions and/or the alteration of their distribution.

The rationalization of sonochemical reactivity, i.e. an understanding of what kind of chemical reactions will be particularly sensitive to sonication and to what extent, is a matter of empiricism. As formulated by Luche in the early 1990s, a tentative classification of reaction types often means considering their mechanisms (Luche 1993). While we will not go into too much detail here, Fig. 2.1, which shows the possible mechanisms that can take place under sonication using conventional organic synthesis nomenclature, provides a sufficient overview.

In a *convergent process,* the substrates can react by means of either a radical or a polar pathway and furnish identical products. Some organometallic reactions (Barbier-like, for instance), may be classified in this way as radical ions stemming from a radical mechanism will be preferentially generated by ultrasound and yet produce the same organometallic reagent as derived from a polar route. By con-

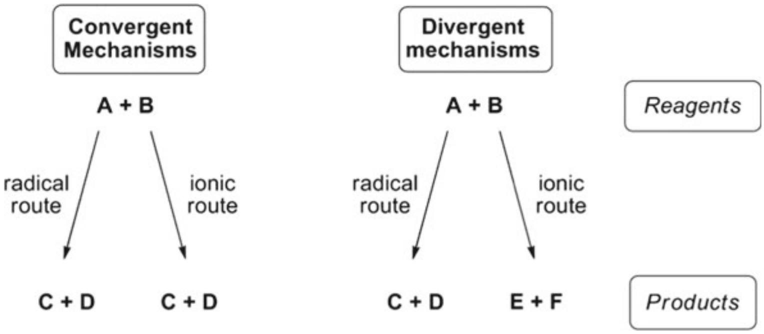

Fig. 2.1 Convergent versus divergent mechanisms in organic synthesis

trast, *divergent processes* involve competing ionic and radical mechanisms that lead to different products and selectivities; *the scenario in which sonochemical switching occurs*. The improved mechanical effects caused by cavitation, especially in enhancing mass transfer, mean that ultrasound-promoted reactions produce the common pluses that are observed experimentally and that lead to increased rates and yields under milder conditions (numerous reactions can be successfully carried out at ambient temperature). This *false sonochemistry* (Luche 1993), in which neither cavitation-generated intermediates nor mechanistic switching is involved, is relevant in and of itself and is frequently sufficient to make certain synthetic transformations possible, in the same way as other activation methods (e.g. ball milling and MW irradiation).

It is worth saying, however, that the lure of sonochemistry in recent years has also resulted in repetitive research that reports no more than well-established organic transformations re-elaborated for the ultrasonic field, with little or no characterization of cavitational parameters and, in general, without an assessment of green metrics. The absence of sonochemical parameters makes it difficult to reproduce some of these experiments; once again we stress the importance of addressing this concern in contemporary sonochemistry (Wood et al. 2017).

2.4 Sonochemical Approaches in Organic Synthesis

A SciFinder® search covering the period from 2007 to mid-2017 identifies nearly 6400 publications that contain both the concepts ‘ultrasound’ and ‘organic synthesis’, and approximately 3500 citations that contain both ‘sonochemistry’ and ‘synthesis’; 154 were review articles.

Green chemistry experts agree that an exploration of new chemical transformations is required if the challenges of sustainability are to be met. These challenges include the following: (1) ways to dramatically shorten synthetic steps and/or simplify the use of auxiliary reagents and protecting groups; (2) the development of strategies for difficult reactions (e.g. C–H activation, cross-dehydrogenative couplings in aqueous media); (3) cross-couplings of unactivated partners in water, where the H_2O molecule is a competing nucleophile; and (4) direct transformations of renewable biomass (especially lignins for the production of fuels and aromatic compounds), and abundant feedstocks (CO_2 and CH_4), into high-value chemicals (Li et al. 2015; Li 2017). These processes can be appropriately managed using enabling and intrinsically sustainable methods, such as microwaves, ultrasound, electrocells and photoreactors. The future of chemical synthesis—*even synthesis on demand*—will depend on machines (or micromachines) in continuous flow, which can reduce the risk of hazards and allow multistep and complex settings to be realized (Fitzpatrick et al. 2016).

As expected, the field of sonochemistry has already focused its attention on the above-mentioned targets and interested readers are referred to a number of comprehensive works that deal with the subject in detail (Luche 1998; Cella and Stefani 2009; Cintas et al. 2011; Mojtahedi and Abaee 2011; Shingare and Shingate 2011; Chatel and MacFarlane 2014; Tagliapietra et al. 2015; Chatel 2017; Domini et al. 2017; Lupacchini et al. 2017). This volume will look at two specific synthetic applications, namely reactivity in neoteric media, ionic liquids in particular (Chap. 3), and biomass valorization (Chap. 4), in later chapters, although some overlap with this chapter is inevitable. We shall now concentrate on some synthetic situations where sonication shows distinctive or improved results over the non-irradiated procedure. Illustrative examples have been restricted to coupling reactions that lead to carbon–carbon and carbon–heteroatom bond formation and include heterocyclic assembly via one-pot and multicomponent reactions, as well as oxidations and reductions, which all show high levels of atom economy and mass efficiency, making them suitable for combinatorial and parallel syntheses in the pharmaceutical industry. Transformations in aqueous media are noticeable as sonication has proven to be advantageous by favouring mixing and influencing hydrophobic interactions. Finally, before concluding, a short section will be devoted to sono-electro-organic synthesis. Sono-electrochemistry was actually one of the first combinations with ultrasound leading to various successful applications (Pollet and Hihn 2011). This subdiscipline deserves a monograph on its own and, obviously, it cannot be treated here in detail. We shall highlight a few references that illustrate various synthetic applications of current interest.

2.4.1 Catalytic and Non-catalytic Couplings

The rapid micromixing and thermal conditions caused by sonication-pulse-driven bubble collapse are sufficient to promote numerous catalyst-free organic reactions (Banerjee 2017a). In fact, ultrasound alone can replace the action of phase-transfer catalysts by efficiently disrupting the organic–water interface in two-phase reactions.

A sonochemical variation of ring-closing metathesis (RCM), a powerful strategy in synthetic chemistry, can be advantageously performed in water at ambient temperature without surfactants and organic co-solvents (Gułajski et al. 2008). The

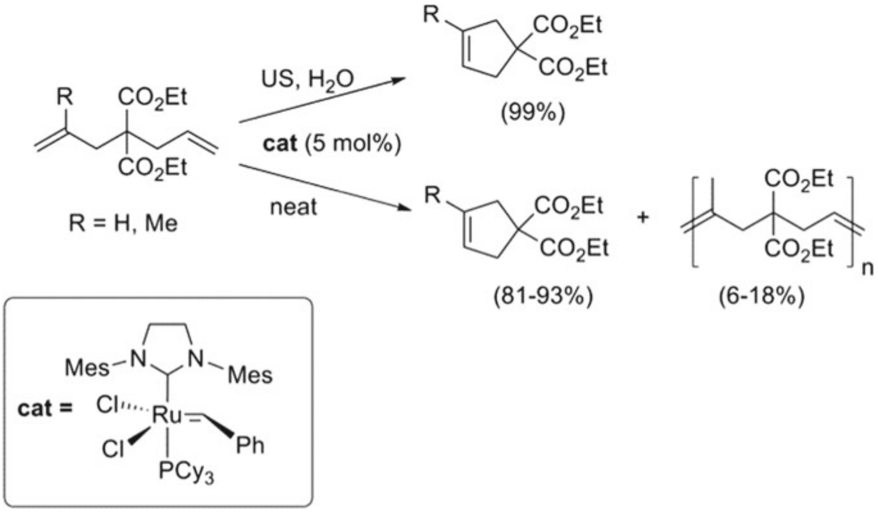

Fig. 2.2 Olefin metathesis in aqueous medium using acoustic emulsification

metathesis reaction took place inside the water-insoluble droplets of the diene, giving the carbocyclic product in an almost quantitative yield (Fig. 2.2). It is worth pointing out that, under neat conditions, the metathesis proceeded in good yields, although by-products, generated from diene oligomerization, were observed. The side reaction did not occur under micellar conditions.

An ultrasound-assisted cross metathesis, run in an organic solvent (CH_2Cl_2) at 55 °C, has produced alkenyl phosphonates, including nucleoside derivatives, in moderate to good yields (49–92%). The process was catalysed by a variety of second-generation ruthenium catalysts with low catalyst loads (3–15 mol%). Sonication was vastly superior to classical heating, which led to low yields and favoured the formation of homodimeric side products (Sari et al. 2013). MW irradiation (at 100 °C), also provided disappointing results, probably due to the thermal decomposition of the Ru catalyst. It is believed that ultrasound played a threefold role: (a) mechanically forcing the ligand dissociation of the latent precatalyst to generate the active species; (b) removing the ethylene gas, thanks to the degassing effect of ultrasound, that was generated during the reaction, and (c) permitting the less reactive homodimer to react, leading to the formation of the desired olefin (Fig. 2.3).

An interesting dynamic disulfide metathesis induced by sonication has been reported recently and provides clean equilibrium mixtures of disulfides in less than 24 h, depending on the ultrasound source (Fritze and von Delius 2016). The solvent plays a crucial role as the source of the radical species, although reaction rates were not particularly affected by argon or air atmospheres. Pulsed irradiation with a 20-kHz sonotrode afforded equilibrating mixtures in 1 h, whereas an ultrasonic bath took longer (*ca*. 24 h), to furnish equilibration. Poorer results were obtained using UV light and MW irradiation. Moreover, the reversible metathesis of disulfide bonds

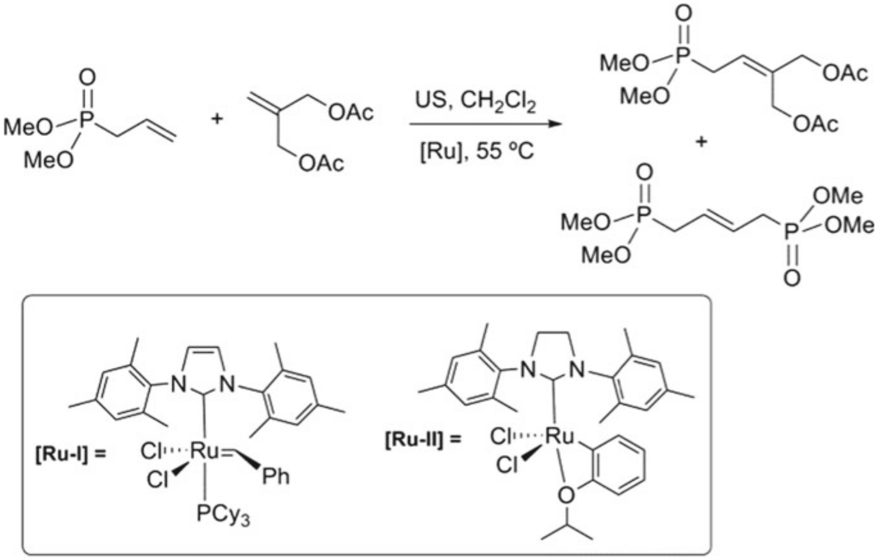

Fig. 2.3 Formation of alkenyl phosphonates via sonochemical metathesis

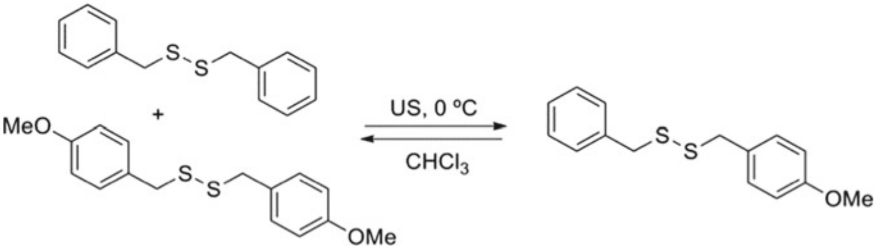

Fig. 2.4 Disulfide metathesis induced by sonication

is usually induced by a combination of a reducing agent and base, which were not necessary for the sonochemically activated reaction (Fig. 2.4).

As noted above, the drawbacks associated with insoluble organic substrates in water can be overcome by sonication, which enhances mass transfer and hydrophobic interactions. The so-called on water concept, even though the actual mechanism is not completely understood, has found wide applicability in organic synthesis, often tolerating functional groups which would otherwise be cleaved under other conditions. The facile and straightforward synthesis of 2-oxo-benzo[1,4]oxazines, in water under ultrasound, has thus been recently reported (Jaiswal et al. 2017). Given the aqueous insolubility of the starting materials, the protocol constitutes an example of an ‘on water’ reaction where sonication greatly contributes to interfacial contact. The target heterocycles are obtained in high yields and virtually no side products are produced, while chromatographic purification is avoided in most cases. The proce-

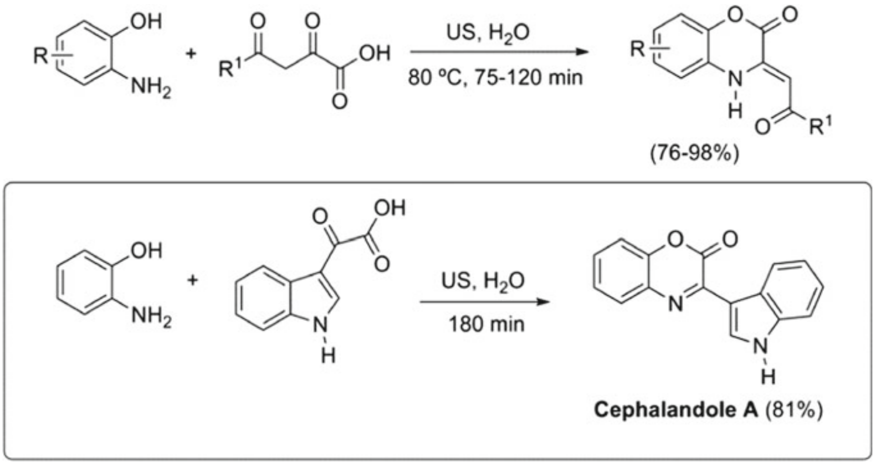

Fig. 2.5 Sonochemical aqueous synthesis of benzo[1,4]oxazines, exemplified by a short route to Cephalandole A

dure compares favourably with previous reports that involve either metal-catalysed or metal-free syntheses under phase-transfer catalysis. The fused bicyclic system is present in some natural products, and the method was applied to a one-pot synthesis of the antitumour indole alkaloid Cephalandole A (Fig. 2.5). A related coupling, using a chiral diamino derivative as the catalyst, namely, (*S*,*S*)-diphenylethylenediamine, led to an expeditious synthesis of the anticoagulant warfarin in its optically pure form and was conducted in aqueous solution under ultrasound (Rogozinska et al. 2011).

A cationic surfactant, cetyltrimethylammonium hydroxide (CTAOH), has been used to increase the solubility of organic substrates, isatin and aryl/heteroaryl ketones, whose condensation produces quinolines (Fig. 2.6). The conventional protocol uses strong bases (NaOH or KOH), in hydroalcoholic media and creates toxic wastewater. Sonication (22 kHz, 40% amplitude), at room temperature and in the presence of CTAOH in a substoichiometric amount, significantly decreased the reaction time (by *ca*. threefold), as compared to the same procedure under silent conditions, and afforded the corresponding quinolines in 75–95% yields (More and Shankarling 2017). The catalyst was recycled and the yield was only found to decrease by 10% after the fourth cycle. In terms of energy savings (energy supplied in kJ per mass of product), sonication saved more than 78% energy compared to the non-irradiated reaction.

Orthogonal couplings, which are especially suitable for in vivo labelling and monitoring as the functional groups involved do not interfere with biochemical machinery, are illustrated by a number of metal-catalysed and metal-free (cyclo)additions, with Cu-catalysed alkyne-azide cycloadditions (CuAAC), being the classic example of such orthogonal click reactions. Both the in situ generation of the active Cu(I) species and the subsequent removal of copper-salt by-products are very often limitations. The use of metallic copper under ultrasound improves the click reaction

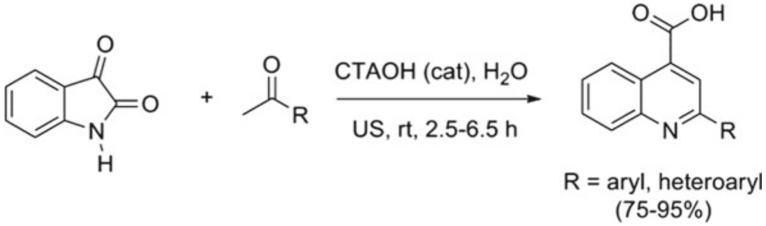

Fig. 2.6 Surfactant-catalysed coupling of isatin and aromatic ketones under sonication

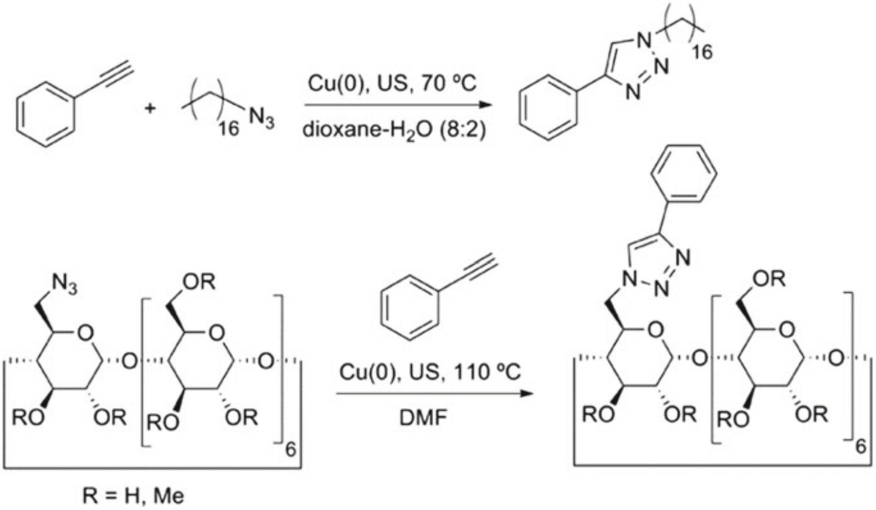

Fig. 2.7 Alkyne-azide click reactions catalysed by metallic copper under ultrasound

further in terms of yields and shorter reaction times, and does not require additional ligands (Cintas et al. 2010). Sonication enhances both mass and electron transfer to the organic acceptor, while also reducing copper passivation. The protocol was applied to azides derived from hydrocarbons and cyclodextrins in aqueous media and the more polar, though toxic, dimethylformamide (DMF), which allows for higher reaction temperatures. 1,4-disubstituted triazoles were obtained in 2–4 h, with faster transformations, through the combined use of sonication and microwave irradiation (Fig. 2.7).

Improved results can be attained by employing micro- or nanostructured metal catalysts (Domini et al. 2017). Hybrid ZnO–CuO core-branch nanoparticles (NPs) have active facets and defects along with a large surface area, characteristics that make them suitable for ultrasound-enhanced heterogeneous catalysis (Park et al. 2012). The optimal conditions for CuAAC couplings were 3 mol% of ZnO–CuO catalyst at room temperature for 10 min, which afforded the triazole product in nearly quantitative yields (Fig. 2.8). Either no reaction or sluggish results were obtained with ZnO and

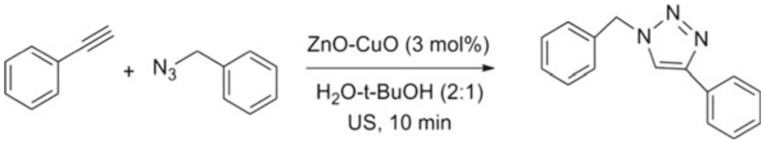

Fig. 2.8 Alkyne-azide cycloaddition using ZnO–CuO NPs under sonication

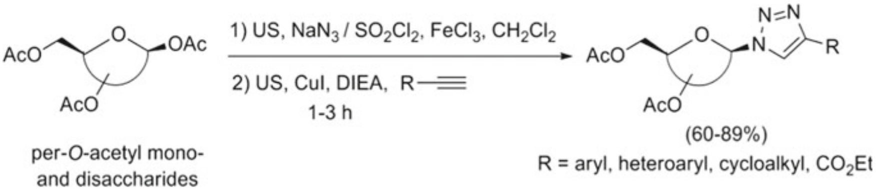

Fig. 2.9 Anomeric azidation and formation of nucleosidic triazoles from per-*O*-acetyl mono- and disaccharides under ultrasound

CuO, each used alone. The catalyst was reused repeatedly without significant loss of activity (76% yield after the sixth cycle). Ultrasound favoured the conversion of the Cu(II) precursor into the Cu(I) species. Cycloaddition was inhibited via the addition of a radical scavenger (TEMPO), which indicates that the reaction intermediate was probably a radical species.

The anomeric azidation of protected sugars has also been conducted and made use of a cheap $FeCl_3$ and CuI catalyst combination (Marzag et al. 2015). The one-pot protocol involves the sequential formation of a soluble organic azide, $SO_2(N_3)_2$, generated in situ from sodium azide and sulfuryl chloride under sonication (bath, *ca.* 40 kHz), followed by the cycloaddition of the resulting azido derivatives with terminal alkynes, run under sonication at room temperature. This second step requires the use of diisopropylethylamine (DIEA), as an additive and the overall transformation remarkably retains the anomeric configuration (Fig. 2.9).

A structurally related orthogonal cycloaddition has been reported to produce dense nitrogen-containing rings (tetrazoles) and involves the coupling of nitriles and azides. This click variation uses zinc as the catalyst in aqueous solution, although a tedious and time-consuming workup is required to remove zinc salts. An alternative to this protocol uses clays, as environmentally benign catalysts, that can be filtered off and reused. This can be done under conventional heating or ultrasonic irradiation, but the latter reduces reaction times and enhances yields. The cycloaddition can be conducted in either water or DMF and was faster with aryl nitriles bearing electron-withdrawing groups (Chermahini et al. 2010).

A thiol-ene click-type coupling has also been described as occurring under sonication (Skinner et al. 2012). The method works for a range of primary alkenes in both toluene and water, and is found to be suitable for aqueous reactions in the presence of air. Even if thermal reactions are slightly faster, the sonochemical variation does not require an initiator and takes advantage of the production of OH radicals upon water sonolysis. Thiol-ene additions are also behind a convenient sonochemical synthesis of environmentally friendly thermoplastic polyurethanes (González-Paz et al. 2011). Unsaturated oleate and 10-undecenoate derivatives were reacted with 2-hydroxyethanethiol to give the corresponding monomers, which were then polymerized in DMF solution with 4,4′-methylenebis(phenylisocyanate) using a tin(II) catalyst under sonication. This resulted in high-yielding polymers (80–99%), with narrow molecular weight averages (Fig. 2.10).

A further example, which is also linked to natural product valorization and illustrates the application of ultrasound to raw materials devoid of protecting groups, is the one-step direct glycosylation of unprotected sugars (D-glucose, D-galactose, D-mannose and L-rhamnose) with flavanones (Santos et al. 2013). The transformation was accomplished with complete regio- and stereoselectivity, and yielded 8-*C*-monoglycosides with the aglycon moiety in the equatorial position (i.e. α-anomers), under both refluxing conditions and ultrasound irradiation (45 kHz, 80 W, 80 °C) in a 2:1 $CH_3CN–H_2O$ solvent mixture. The rare earth-based catalyst praseodymium triflate was found to be the most efficient coupling agent and afforded the corresponding glycosides in moderate yields (32–38%). Sonication caused a *ca.* threefold decrease in reaction times with respect to conventional heating (Fig. 2.11). Extensions to disaccharides gave better results (up to 56% yield and a fourfold time decrease under ultrasound).

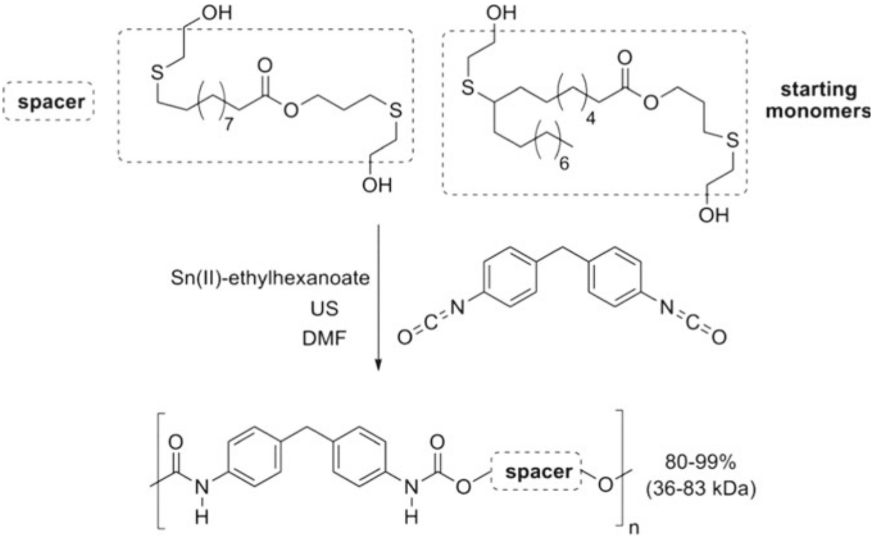

Fig. 2.10 Preparation of thermoplastic polyurethanes by thiol-ene addition and Sn(II)-catalysed sonochemical polymerization

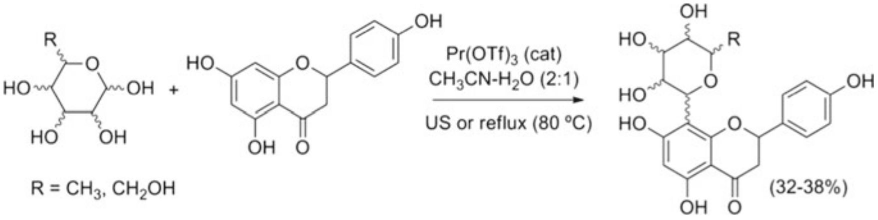

Fig. 2.11 Regioselective catalytic glycosidation of unprotected sugars with flavanones

2.4.2 Multicomponent Reactions and Parallel Syntheses

The term multicomponent reaction (often abbreviated MCR) generally refers to the coupling of three or more reaction partners in sequential fashion and represents one of the most elegant and atom-economic protocols for the rapid assembly of carbo- and heterocyclic units to give complex and functionalized molecules. These transformations can be conducted in aqueous mixtures or organic solvents and are usually assisted by a catalyst or promoter. Ultrasound exerts a significant mechanical homogenizing effect that enables water or water–organic co-solvent mixtures to be used under milder conditions than those found in silent reactions (Banerjee 2017b).

In some cases, water-soluble organic solvents that enhance interfacial contact with insoluble substrates and increase their aqueous solubility (up to 200 times)—called *hydrotropes*—also provide extra benefits to cavitation in a way similar to that of a surfactant. The term hydrotrope indicates non-micelle forming substances, i.e. substances that do not have a critical concentration above which self-aggregation occurs and that lead to increased solubility in hydrophobic compounds. A combination of low vapour pressure and the increased viscosity of the aqueous hydrotropic solution, relative to pure water, means that stronger cavitational collapse provides greater reactant heating during compressional cycles and therefore faster reactions. In fact, the use of a hydrotropic solution has provided good results in an MCR of acetophenones, aniline and aryl aldehydes in an aqueous solution containing sodium *p*-toluenesulfonate at a concentration (50% w/v), that facilitated the maximum solubilization of the organic compounds (Fig. 2.12). The hydrotropic solution was reused after product separation (Kamble et al. 2012).

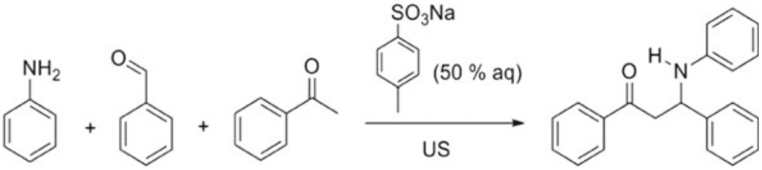

Fig. 2.12 A three-component reaction in a hydrotropic solution, stimulated by sonication, that yields β-amino carbonyl compounds

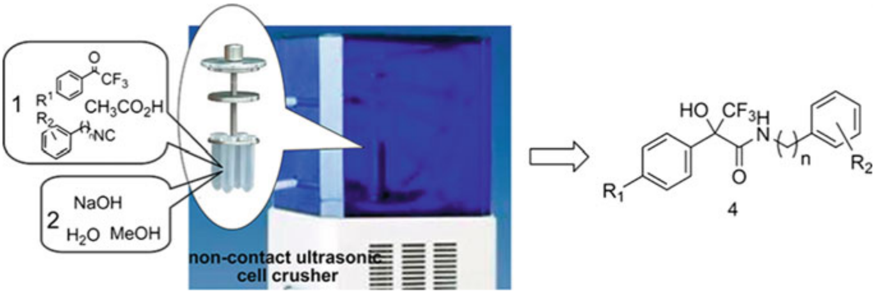

Fig. 2.13 Combinatorial synthesis involving sequential Passerini/hydrolysis reactions using a non-contact ultrasonic cell. Reproduced with permission. Copyright 2014 The American Chemical Society

The application of ultrasound to MCRs is well documented (Banerjee 2017b), and numerous examples of both catalytic and non-catalytic strategies exist (Datta and Pasha 2012; Ablajan et al. 2012). Nevertheless, the advantages are even more noticeable when sonication simplifies and/or improves the design of large compound libraries that are suitable for biological screening. A sonochemical one-pot Passerini/hydrolysis sequential reaction has been developed for the synthesis of a library of trifluoro-substituted lactamide derivatives (47 compounds), which were evaluated for use as fungicidal agents (Yu et al. 2014). However, the physical activation of combinatorial sequential processes can be technically problematic. To overcome this hurdle, the authors performed the syntheses in inexpensive centrifuge tubes using a non-contact ultrasonic cell crusher for ultrasonic irradiation. The apparatus can accommodate both 0.5 and 10-mL sealed centrifuge tubes, thus allowing for simultaneous reactions (Fig. 2.13). The non-contact sonic horn also removes the possibility of cross-contamination. Yields were similar to those of the two-step process, which uses contact sonication for the Passerini reaction. The ultrasound-assisted transformation was approximately eight times faster than the silent reaction.

More complex structures, spirooxindole–pyrrolidine or pyrrolo[1,2-*c*]thiazole fused to a coumarin core (30 examples in 80–96% yield), have been obtained in a one-pot sequential four-component reaction involving 2,2-dimethyl-1-3-dioxane-4,6-dione, substituted salicylaldehydes, isatins and cyclic α-amino acids (Kanchithalaivan et al. 2014). The whole ultrasonic process ran in aqueous methanol at 50 °C, took less than 2 h and provided yields that were higher (*ca*. 30% increase) than those obtained under thermal conditions (Fig. 2.14).

The use of ultrasound in combinatorial strategies not only provides access to products in greater conversions and without unwanted products, but also simplifies workup, especially under solvent-free conditions. While not an MCR in itself, a parallel chromatographic-free synthesis of 3-arylcoumarins involves a one-pot acylation/cyclization between *N*-acylbenzotriazoles and 2-hydroxybenzaldehydes. The condensation requires the presence of triethylamine and is essentially complete after 5 min at room temperature (Wet-Osot et al. 2016).

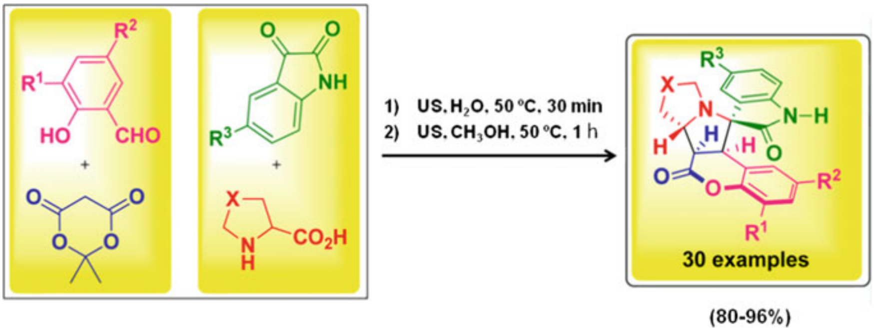

Fig. 2.14 A sequential four-component reaction yielding highly functionalized heterocycles that was improved under sonication. Reproduced (in part) with permission. Copyright 2014 The American Chemical Society

2.4.3 *Reduction and Oxidation*

Hydrogenation and oxidation have long been explored by sonochemists in their search for straightforward, mild transformations. Redox reactions are a must in organic synthesis and generally proceed with high levels of atom economy (Jiménez-González and Constable 2011). They usually involve concerted or polar mechanisms (although radical pathways can be induced as well), and acceleration in heterogeneous catalysis is most likely due to enhanced mechanical effects. As is the case with other examples of *false sonochemistry*, the ultrasonic effect may be overemphasized as stirring and increases in bulk temperature play synergetic roles.

While sonochemical hydrogenations depend strongly on catalyst choice, changes in selectivity are rare (Disselkamp et al. 2004), and ultrasound generally only moderately increases reaction rates (Domini et al. 2017). The influence of frequency, which is often overlooked, shows how better results are obtained at low frequency (40 kHz), which is to be expected because the mass transfer is considerably reduced above 380 kHz (more intensity is required to cavitate a liquid as frequency increases). Additional mechanical stirring and sonication provide similar results at higher frequencies (Tripathi et al. 2015). Technical improvements and catalyst modification appear to be the future of sonochemical hydrogenations. We herein present two modifications that serve to illustrate the point. A home-made reactor developed by Cravotto's group, in collaboration with an industrial partner, can carry out ultrasonic hydrogenation at relatively low pressures of up to 7 bars (Hessel et al. 2013). In another interesting modification, a sonic horn has been connected to a pressurized autoclave that can tolerate pressures of up to 50-bar and perform hydrogenations at a variety of temperatures (Toukoniitty et al. 2005). This device was employed for the hydrogenation of D-fructose into D-mannitol using a range of cheap metal catalysts (Raney-Ni, Cu/SiO_2 and $Cu/ZnO/Al_2O_3$), the first of which provided higher conversions (Fig. 2.15).

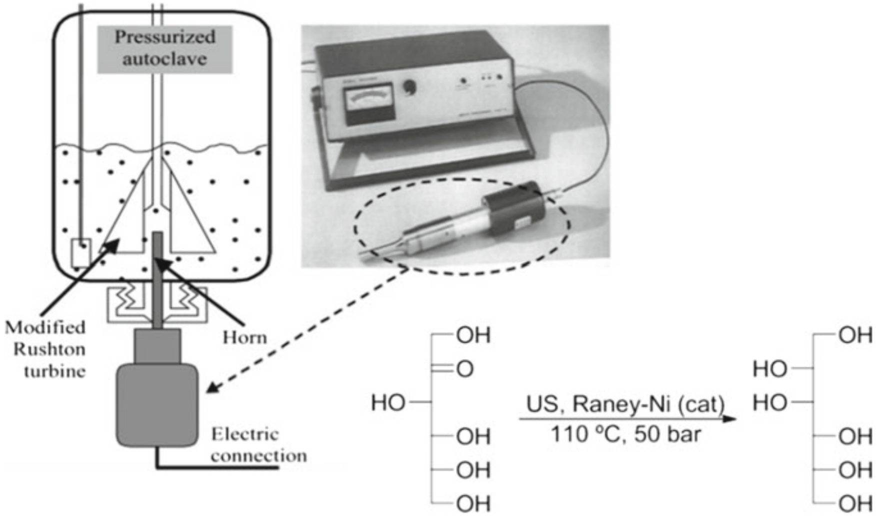

Fig. 2.15 A hydrogenation reactor which combines ultrasonic irradiation and a pressurized autoclave that was used to reduce sugars to their corresponding polyols. Reproduced (in part) with permission. Copyright 2005 The American Chemical Society

Functional group oxidations are more challenging as most reagents are not particularly green and often produce metal-containing wastes. The use of molecular oxygen is potentially hazardous, on multigram scales in particular, unless a continuous flow system is incorporated (Gemoets et al. 2016). Numerous oxidations have been conducted under sonication and, once again, enhanced mass transfer, ambient conditions and low catalytic loadings are the key advantages. In a few cases (e.g. alkene epoxidation), sonication can bypass the multiple steps, which would ensue under conventional conditions, of a reaction making it a direct, simplified protocol. In fact, the cross-coupling of acetophenones and aryl aldehydes can be achieved in a one-pot procedure with H_2O_2 and a base (Fig. 2.16), directly leading to the epoxide derivatives (Li et al. 2010). The direct sonication of H_2O_2 and nitriles (RCN), in the presence of cyclohexene, gives rise to cyclohexene oxide. It is thought that the in situ generation of peroxycarboximidic acids [RC(=NH)OOH] produces the actual epoxidation reagent (Braghiroli et al. 2006). Cyclohexene oxide has been obtained, on an industrial level, in a loop reactor under ultrasound at ambient temperature using a mixture of oxygen and isobutyraldehyde (Zhang et al. 2007).

A remarkable example of mechanistic switching, which occurred by simply using a combination of ultrasound and a hydrophobic ionic liquid as the solvent instead of silent conditions in acetonitrile (cf. Chap. 3), has been observed during the epoxidation of various alkenes with $H_2O_2/NaHCO_3$ and a manganese-porphyrin catalyst (Chatel et al. 2012). Whereas the bleaching of the catalyst in CH_3CN meant the epoxidation followed a route in which peroxycarbonate was the oxidant ($NaHCO_4$), the use of an ionic liquid protected the catalyst from degradation and sonication

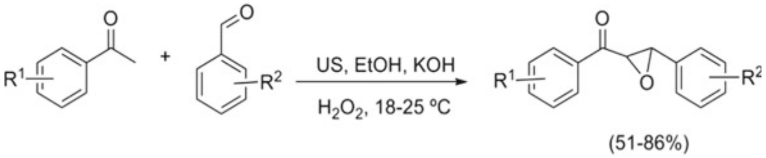

Fig. 2.16 Direct sonochemical epoxidation from aromatic carbonyl compounds without the isolation of alkene intermediates

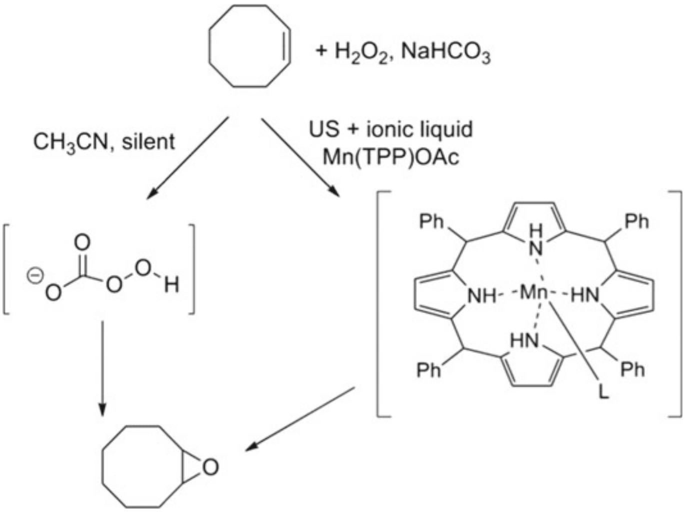

Fig. 2.17 Oxidative switching under sonication in an ionic liquid using a Mn-porphyrin-based catalyst

kinetically favoured the formation of a high-valent oxo–Mn-porphyrin as the actual oxidant (Fig. 2.17). The authors were able to demonstrate the distinctive mechanisms using a chiral porphyrin as the catalyst. While enantioenriched epoxides were obtained in the ionic liquid, a racemic derivative was formed in CH_3CN without sonication, thus confirming the decomposition of the metalloporphyrin catalyst.

Recent years have seen sonochemists pay attention to the chemical manipulation of natural feedstocks in the production of fine chemicals. Mild operational conditions are required for sensitive natural products to remain unaffected and for regioselective transformations to be induced. Carbohydrates are a perfect illustration of the ongoing activity in the field of biomass valorisation, which is in need of protocols that can alter lignocellulosic skeletons at will (Chatel et al. 2014; Li et al. 2015; Tabasso et al. 2015; Chatel 2017). For example, a regioselective oxidation of sucrose (at primary hydroxyl groups), which dates back to the early 2000s, highlighted the potential of the homogeneous combination of NaOCl and TEMPO (a stable nitroxyl radical), as an oxidizing agent in aqueous solution (Brochette-Lemoine et al. 2000). The authors stressed the importance of the ultrasonic treatment of the oxidizing mix-

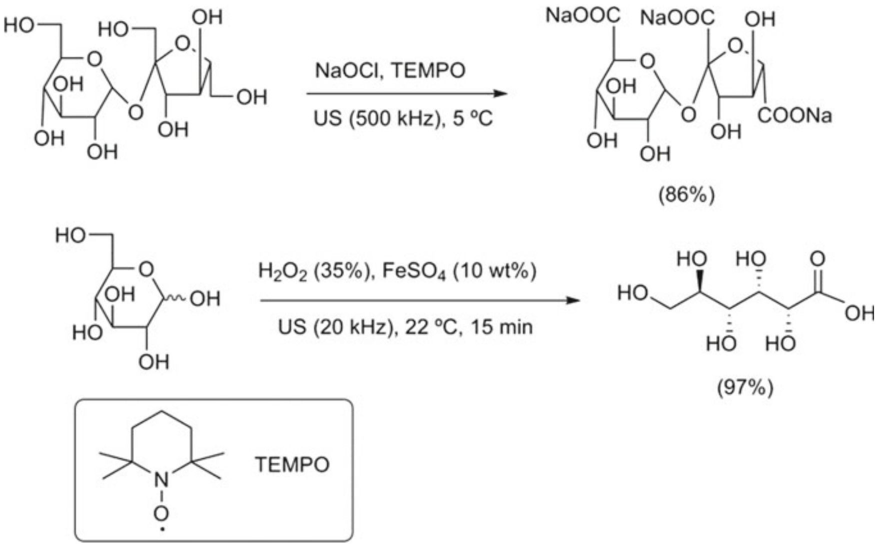

Fig. 2.18 Selective oxidations of carbohydrate derivatives under ultrasonic activation

ture prior to the addition of sucrose. Moreover, the results were dependent on the chosen frequency and output power (Fig. 2.18). This paper also reported the heterogeneous oligomerization of glucose with hydrophobic alcohols, whose acceleration was attributed to enhanced sonomixing. The same group underlined the role that frequency effects play during the oxidation of other glucosides using TEMPO-mediated oxidation in the presence of NaOCl/NaBr (Brochette-Lemoine et al. 1999). The catalytic cycle under ultrasound produces the nitrosonium ion as the active oxidizing species, making the presence of a stoichiometric amount of NaBr unnecessary, and thus reducing toxicity. More recently, a selective oxidation of D-glucose to gluconic acid under mild and economic conditions (H_2O_2, $FeSO_4$, room temperature), with ultrasound (20 kHz, 0.25 W/mL), has been reported (Rinsant et al. 2014). Almost quantitative yields were obtained in 15 min at 25 °C. This transformation is a case of a sono-Fenton reaction, where ultrasound favours the in situ generation of hydroxyl radicals (HO), via reaction between H_2O_2 and Fe(II) ions. As proof of the mechanism, a radical scavenger (*t*-butyl alcohol), was used to quench the reaction, which then yielded less than 1% of gluconic acid.

The above-mentioned oxidations are usually performed with sonic horns, which can deliver energy at known frequencies and high power intensities. These aspects and their reproducibility may be problematic when using ultrasonic baths (regrettably some past papers on carbohydrate sonochemistry do not mention the working frequency of the baths). Nevertheless, the relatively low acoustic energy of ultrasonic baths is not necessarily a major drawback in many syntheses and often allows sensitive reagents and enzymes to be used. Unsuccessful protocols should however be redesigned for use with probes. An example of the benefits of ultrasonic baths can be found in the selective and reproducible room-temperature oxidation of glucose to gluconic acid (100% conversion in 15 min), in which the low acoustic energy protects the active gold catalyst (Au/SiO_2), and substrates from decomposition. This same catalytic system, when applied to cyclohexene oxidation, leads to the corresponding alcohol in 55% conversion at room temperature, and 68% conversion at 80 °C (Bujak et al. 2012).

2.4.4 Sono-Electro-Organic Syntheses

In recent years the old field of electrochemistry, dating back to pioneering studies in physical chemistry at the dawn of the twentieth century, has received considerable attention as a mild, versatile and sustainable technique in organic synthesis with a focus on the preparation of fine chemicals and drugs (Yan et al. 2017; Atobe et al. 2018; Mitsudo et al. 2018; Moeller 2018). Both anodic oxidations and cathodic reductions involve single electron transfer (SET) reactions, which in line with the rules of true sonochemistry, could be further enhanced by ultrasonic irradiation. Very often, however, this important point is not evaluated by mechanistic studies. In fact, most effects should be ascribed to improved mass transfer from solution to electrodes caused by the more efficient ultrasonic stirring (Pollet and Hihn 2011).

Perhaps the most known electrochemical transformation is the Kolbe reaction, where the anodic oxidation of alkyl carboxylates releases alkyl radicals that then dimerize to form a new carbon–carbon bond. In the classical Kolbe electrolysis, a base is added to generate carboxylate salts serving as substrates and electrolytes. The aqueous medium complicates the transformation of poorly soluble organic compounds as well as the subsequent workup and product isolation. Compton and his group developed an aqueous protocol for water-immiscible aliphatic acids through sonication and emulsion formation (Wadhawan et al. 2001). Unlike homogeneous reactions, yields in this biphasic system were independent of the electrode material.

The positive role of sonication via emulsification reactions is also evidenced in a useful allylation reaction performed in an ionic liquid (1-ethyl-3-methylimidazolium BF_4). The nucleophile (allyl trimethylsilane) is scarcely soluble in that medium, but acoustic emulsification favours its condensation with an iminium electrophile generated anodically (Asami et al. 2008). It should be noted that mechanical stirring (1500 rpm) was unable to generate a stable emulsion due to the high viscosity of the ionic liquid, while ultrasonication (20 kHz, 150 W/cm^2) triggered an efficient coupling. A sono-electrochemical reaction using Et_3N-3HF ionic liquid was successfully applied to a Pummerer-type fluorination of organosulfur compounds having electron-withdrawing groups at the α-carbon in moderate to good yields (Sunaga et al. 2009). Again, sonication improved both yields and selectivity (mono- vs. di-fluorination) relative to mechanical stirring (Fig. 2.19). The best selectivity (quantitative monofluorination) was achieved at lower current density (2.5 mA/cm^2), although high current density (50 mA/cm^2) still afforded good selection and overall yields.

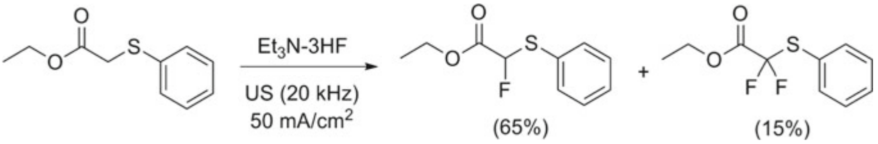

Fig. 2.19 Efficient sono-electrochemical fluorination of organosulfur compounds in ionic liquids under emulsification conditions

Electropolymerization of pyrrole and thiophene derivatives has been conducted in the presence of high-frequency ultrasonic fields (500 kHz), which leads to valuable conducting polymers (Et Taouil et al. 2010, 2011). As expected, sonication favours greatly electrodeposition, although the benefits of ultrasonic irradiation are not only a better mass transfer, because it also affects the thickness and texture of the electrodeposited films as unveiled by SEM studies. These transformations are also influenced by the nature of the organic salts employed as electrolytes and the metallic electrode.

2.5 Conclusions and the Future

Sonochemistry has now become a mature discipline that can boast of a rich and fertile history, which interlinks physics and chemistry. The road to reproducibility, accurate control and enabling strategies still requires further understanding and sound rationale to be used in the examination of cavitational effects. Although an in-depth analysis of cavitation, in terms of physics or mathematics, is not usually needed, practitioners should bear in mind the importance of measurable acoustic parameters and the influence of reactor design on experimental results. Furthermore, estimations of metrics should be carried out if comparative analyses are to be carried out.

The real potential of ultrasound lies in the true sonochemical effects that it provides and that are capable of switching reaction outcomes to unexpected products and selectivities, and open the way for non-anticipated mechanistic routes. Even their purely physical effects mean that ultrasonic waves can dramatically enhance chemical transformations and give improved results and higher efficiencies. Sonochemistry will undoubtedly continue to help chemists to overcome synthetic limitations and broaden its range of applications. Ultrasound-assisted protocols can be successfully combined with other methods and techniques, thus broadening their scope and allowing for their use on new targets, as documented briefly in other chapters. Synthesis is invariably the core of organic sonochemistry and numerous applications are often dependent on synthetic elaboration and available products. It is hoped that these pursuits will be a valuable research domain for years to come.

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Chapter 3
Sonication in Neoteric Solvents. A Further Look at Synthetic Plans

Abstract The use of neoteric solvents to substitute organic molecular solvents offers new opportunities to develop more environmentally friendly synthetic organic chemistry to access to new molecules, materials or processes. Most known and investigated neoteric solvents (NS) remain nowadays supercritical fluids (SCF), room temperature ionic liquids (RTILS) and deep eutectic solvents (DES). Each of them offers several advantages over organic molecular solvents but also display inherent drawbacks. In order to tackle the latter moving forward to safer and faster processes, ultrasound technology was recently coupled synergistically with these new media. These three categories of NS are hereafter briefly introduced together with their own remarkable properties permitting their use as alternative benign solvents. Insights of striking developed applications with ultrasound will be then given in order to unleash the promising potential of coupling ultrasound technology with neoteric solvents.

3.1 Introduction

In one and half century of history, the notoriety of organic synthetic chemistry changed from beneficial to detrimental to humankind with strong environmental and safety concerns in all compartments of our living environment. Green chemistry concept through 12 main principles incites R&D community to adopt more sustainable ways to achieve chemical transformations with an enhanced green environmental fingerprint. The spirit is to tackle at source all harmful parameters among toxicity, safety and environmental impact together with associated costs. One of the core problems remains the use of common organic molecular solvents whose are unsafe, toxic, flammable and volatile for most of them. Indeed, on the list of damaging chemicals, solvents rank at the highest place. They are indeed the main constituents of a chemical reaction, leading to huge amounts of wastes to be treated off/disposed, and they are also largely responsible for VOCs worldwide emissions. Water may appear as the most natural alternative being itself the most environmentally possible benign solvent associated with cheapness and availability. However, its poor solubility or on the contrary its exacerbated reactivity with some organic

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molecules remain as insuperable obstacles. In addition, its recycling is a highly energy process. In parallel, the birth of Green Chemistry concept has allowed the emergence of new types of eco-friendly solvents. This new generation of solvents is often called neoteric solvents (neoteric comes from Greek 'neōterikos' for newer). These latter, also named as second-generation solvents, can possibly offer flexible physical–chemical properties to chemists and engineers to develop specific reaction processes with optimized conditions. The simultaneous existence of several classes of neoteric solvents underlines that there cannot be a single alternative to replace so many organic molecular solvents. Indeed, these latter display different physical—chemical properties in so many cases of different organic synthetic reactivity, and the solution lies rather in a set of flexible alternatives.

As, for example, ionic liquids and DES exhibit some remarkable physical–chemical properties originating their success. However, both also display much higher viscosity as compared to molecular organic solvents which can be a major obstacle for R&D development since viscosity is a brake for chemical reactivity, molecular diffusion, kinetics, etc. To overcome this, ultrasound, in particular low-frequency one with enhanced mechanical effects, has been quickly approached to be coupled with the use of these NS. The addition of a co-solvent to decrease viscosity values has been approached but subsequent changes in the intrinsic properties of the resulting medium lead to inevitable differences in chemical behaviour. Similarly, SCF possess some remarkable intrinsic properties and are subsequently highly investigated notably in the field of extraction. However, the absence of any kinds of mechanical effects rises several problems when target compounds are trapped in a complex matrix. The usage of ultrasound helps to improve greatly extraction efficiency notably through the harsh mechanical effects generated by low-frequency ultrasound. In truth and in practical, NS have become interdisciplinary fields utilized by chemists, chemical engineers, physicists and specialized scientists (food, agronomy, biotechnologies, etc.), and it is certain that the use of these new media will be intensified in a near future in both science and engineering laboratories.

3.2 The Three Most Promising Classes of Neoteric Solvents

3.2.1 Supercritical Fluids (SCF)

Supercritical fluids (SCF) are considered as the 'fourth' state of the matter without having a definite phase. A French Scientist, Baron Charles Cagniard de la Tour, has discovered this state in 1822 but the term of SCF is from Thomas Andrew, an Irish chemist. The first ever experiment with SCF was performed in 1879 when Hannay and Hogarth studied the solubility of several halide-based metallic salts ($CoCl_3$, $FeCl_3$, KBr, etc.) in SC ethanol to probe solvating ability of these fluids. The state of supercritical is reached when a fluid is heated and compressed above his critical point. SCF have a particular behaviour at midway from the liquid and gas states

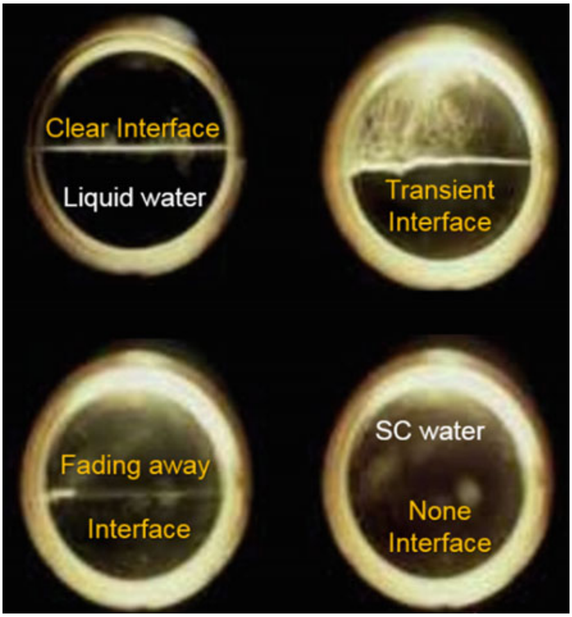

Fig. 3.1 The formation of supercritical water

with some particular properties among weak viscosity (such as gases), high density (such as liquids) or an intermediate diffusivity coefficient (between gas and liquid phases). In addition, SCF have no surface tension because they are not subject to the vapour–liquid boundary. In 1970, after almost one century of unconcern, a significant development happened with the green extraction of caffeine from coffee beans with SC CO_2 leading to numerous important patents with scaling-up (Fig. 3.1).

Since then, the craze has never faded acknowledged by the ever increasing number of applications dealing with SCF. CO_2 and water remain currently the most used fluids. Other compounds such as ethane, ethanol, methanol, ammonia, nitrogen, etc. are also used with possible blending (such as SCF CO_2 with methanol) to tune some of the properties of the fluids to reach desired conditions. Up to date, SCF fluids are investigated in:

→ Cleaning and degreasing,
→ Nucleation and particle size regulation,
→ Remediation of soils (poisoned by organic moieties),
→ Synthesis of polymers and organic molecules,
→ Impregnation and in situ deposition of chemicals,
→ Microbial inactivation and
→ Extraction of valuable biomolecules (cosmetic, pharmaceutics, food, etc.).

Equipment coupling ultrasound and SCF technologies are currently not commercially available and of small scale. However, in view of the potential revealed by the literature in many domains, it is a safe bet that this gives a glimpse of a bright future for this coupled technology.

3.2.2 Ionic Liquids (ILs)

Ionic liquids are organic salts made of poorly coordinated cations/anions combinations ensuring a law lattice energy enabling a liquid state at room temperature or at least below 100 °C. The cationic part must be of organic nature whereas the anion can be or organic or inorganic origin. At least one of the constituting moieties of this ionic pair must present delocalized charge(s) to prevent the formation of a stable crystal lattice. Organic cations are usually large ones and are derived from molecules bearing a heteroatom with an available lone pair such as nitrogen, sulphur or phosphorus (Fig. 3.2).

The success met by this family of compounds towards R&D community arises from some of their remarkable physical–chemical properties. The virtual absence of vapour pressure enabling recyclability, their inflammability, their thermal and chemical stability and large range of liquid phase makes them adequate for very different experimental conditions, solvation properties, high conductivity, etc. In addition, some of their properties among density or viscosity can be tuned to reach desired values. Otherwise, the tank of possible ILs' structures is quasi-endless with theoretically up to 10^{18} possibilities but must be weighted by help of a computational screening. Several generations of ILs have been discovered and the number of applications where ILs were found to be beneficial as catalyst, solvent, additive, polymer, etc. is impressive among:

→ Organic and inorganic synthetic chemistry,
→ Polymer chemistry and material sciences,
→ Catalysis,
→ Electrochemistry,

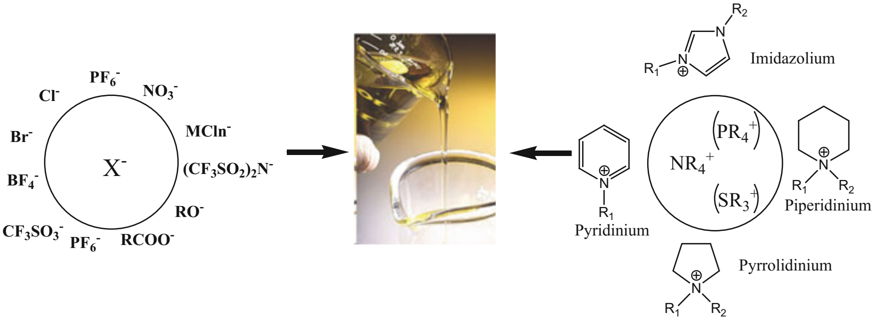

Fig. 3.2 The structure of ionic liquids

→ Energy storage and conversion,
→ Extraction, segregation and separation processes, and
→ Biomass valorization and biotechnologies.

This is testified by the current high rate of publication lasting for more than 10 years. However, enthusiasm seems to attenuate with time notably as an increasing number of studies on these moieties reported that they were not totally inert under several explored reaction conditions. In addition, ILs compounds show major drawbacks such as non-negligible toxicity, high cost and a poor biodegradability. An alternative approach was to develop ILs based on bio-based components enabling biodegradability properties and low toxicity. Numerous ILs based on amino acids, carboxylic acids, quaternary ammonium, phosphonium, etc. have recently emerged. As a striking example, cholinium-based ionic liquids combined with amino acid anions ([Ch][AA] ILs) have been reported to have very promising properties (Dominguez de Maria 2013) including adequate toxicity and biodegradability for large-scale implementation (Petkovic et al. 2010), reviving the initial craze of this family of compounds.

3.2.3 *Deep Eutectic Solvents (DES)*

DES, also named as NADES for natural deep eutectic solvents, are among the latest breakthroughs in the world of green solvents. Whereas ILs are considered as ionic compounds, DES can be said to be ionic mixtures obtained from the mixing of two or more cheaper and non-toxic molecular components, i.e. an HBA (for hydrogen bond acceptor) and an HBD (hydrogen bond donor). Both components do dynamically exchange a hydrogen bond leading to a eutectic combination (Smith et al. 2014). In many reports, DES are typically prepared from choline chloride as HBA with diverse HBD such as urea, carboxylic acids or polyols although several sub-classes of DES do exist (Fig. 3.3).

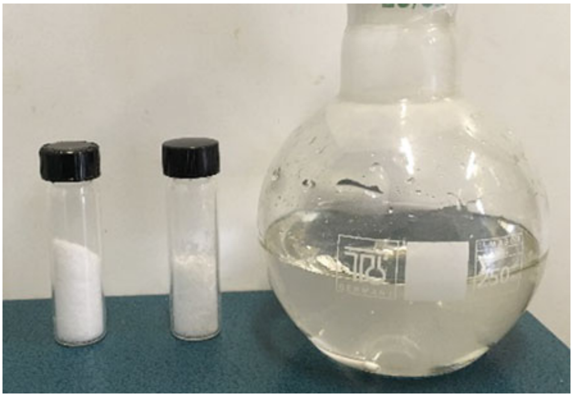

Fig. 3.3 Typical natural eutectic solvents. From the left to right: choline chloride, urea and choline chloride–urea (1:2, mole/mole)

DES can be considered as cousins of ILs as they share several remarkable properties such as negligible vapour pressure, non-flammability, good solubility with organic and inorganic compounds, etc. Similarly to ILs, some of their intrinsic properties can also be finely tuned by changing the HBA/HBD ratio. Owing to this dynamic H exchange, DES are generally hydrophilic moieties. This may be a brake to their development notably in the field of separation and analysis but the R&D community is just beginning to take hold of the subject, and progresses are soon to be expected. In addition, they are said to be non-toxic, biodegradable and biocompatible. They have subsequently gained high interest in many different fields including:

→ Organic synthetic chemistry,
→ Catalysis,
→ Material chemistry,
→ Gas absorption and segregation,
→ Nanotechnology,
→ Biomass valorization and
→ Extraction, segregation and separation processes.

Owing to their natural constitution, DES are adequate for foods, pharmaceuticals and cosmetics industries and may replace efficiently conventional molecular solvents as well as ILs where biocompatibility and non-toxicity are critical.

3.3 Why Coupling Ultrasound to Neoteric Solvents

The rapid global awareness of the scientific community of the need to preserve our environment at the end of the twentieth century prompted it to renew ways of thinking and doing synthetic chemistry. This pivotal period between the twentieth and twenty-first centuries coincides with the emergence of several technologies, ‘physical’ ones such as microwave or ultrasound and ‘chemical’ ones such as NS media. All were investigated singly or conjointly in different areas of chemical sciences but all with the unique aim of improving all that could be improved in a reaction process: time, yield, selectivity, recycling, toxicity, etc. Developing new synthetic pathways that are not only efficient but also by-product free with high yields while being eco-compatible is pressing but necessary nowadays challenge for organic chemists. Apart from the environmental considerations set out above, the combination of neoteric solvents and ultrasonic irradiation is therefore expected either in a synergistic effect or where this coupling may overcome severe technical hurdles or open new fields of investigation. First literature examples of NS/US coupling were released out the same year (2001) with the study of a Heck system in an IL/US system (Deshmukh et al. 2001) and the enhanced dissolution of uranium oxides in SC CO_2/US (Trofimov et al. 2001). Since then, success never faded and the number of publications combining US and NS is exponentially increasing in particular with ILs (Chatel and MacFarlane 2014; Khaw et al. 2017).

3.4 Applications of Ultrasound and Neoteric Solvents

Ultrasound remains a very attractive technology in reason of its simplicity and easiness to be implemented together with milder conditions as compared to classical silent conditions, i.e. absence of ultrasonic irradiation. Regardless of the incident working ultrasonic frequency, effects arising from cavitation phenomenon are intimately dependent on the contents of the cavitation bubbles. In the world of sonochemistry, low vapour pressure solvents are generally preferred to exalt consecutive direct and indirect effects of both physical and chemical origin arising from optimized collapsing conditions. ILs and DESs possessing virtually none vapour pressure might appear as ideal liquid media for ultrasound. Similarly, an SCF phase is reached under moderate to high pressure (and temperature) according to the fluid, making more difficult the occurrence of cavitation but when the cavitation threshold is reached, more pronounced subsequent effects do occur. However, the optimized operating conditions rely on a judicious balance between physicochemical properties of the NS, operating conditions of the ultrasonic system (frequency, output power, design of reactor) and experimental conditions (temperature, pressure, surrounding gas, etc.). If such a compromise is not found, lack of obvious effect or even decomposition of the considered medium may occur as for ILs (Oxley et al. 2003). Regardless of the class of NS, biomass processing (cf. Chap. 4), extraction/separation processes, materials preparation (not discussed in this monograph) and synthetic organic synthesis (cf. Chap. 2) are nowadays the four main domains where coupling methodologies with US are prominent.

3.4.1 *Synthesis in Neoteric Solvents under Ultrasound*

It is nowadays recognized that the substitution of environmentally unfriendly molecular solvents can reduce the negative impact of environment (Adams et al. 2004). Among the aforementioned NS, ILs remain nowadays the most investigated in synthetic chemistry owing to their remarkable properties, seniority with respect to DES and liquid phase at atmospheric pressure with respect to SCF. Numerous well-known named, unnamed and derivatives organic reactions among Sonogashira, Knoevenagel, Suzuki, Michael and Baylis–Hillman additions, Friedel–Craft, Diels–Alder, Mannich, Morita–Baylis–Hillman, etc. were thoroughly investigated in ILs/US systems. Invariably, improvements in terms of time, yield, selectivity, amount of catalyst and other possible green advantages such as recycling, decreased energetic consumption and of waste production were reported as compared to silent conditions (Chatel and MacFarlane 2014). Noteworthy, the general synthesis of ILs themselves has been greatly improved by using ultrasound in a neat manner as early as 2002 (Leveque et al. 2002; Namboodiri and Varma 2002). Although all these striking examples are as many ideal boosters advocating for scale-up, pilot or industrial-scale applications combining both US and ILs technologies are not of actuality and may even never

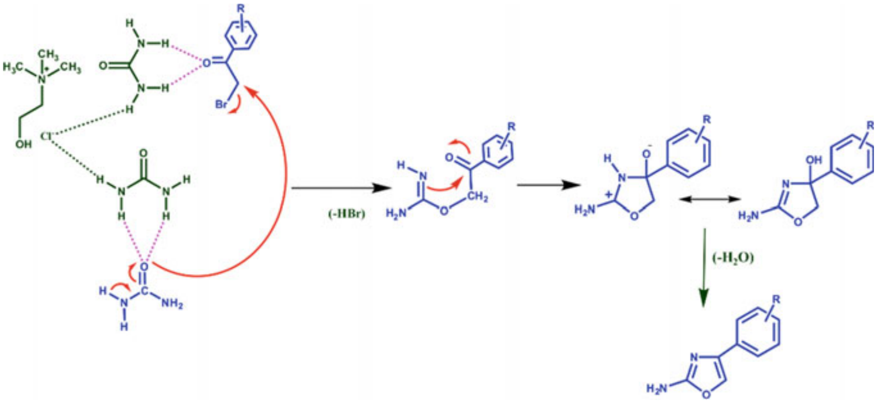

Fig. 3.4 Plausible mechanism for synthesis of oxazole derivatives from Singh

come out. Indeed, since 2014, the number of yearly published articles related to the use of ILs in synthesis, with and without ultrasound, undergoes a real and constant decline. Although an effect of 'déjà vu' may explain partially this as the potential is no more to be demonstrated, this can originate also from a better knowledge of IL. Their toxicity can no longer be neglected, still with remaining hurdles such as significant viscosity and density but above all persistent production costs. This decline chronologically coincides with the recent and swift emergence of the latest known class of NS, DES. Today, there are very still few studies exploring the combined use of sonochemistry with DES as a reaction medium. Indeed, the combination of US with DES applied to organic synthesis was implemented for the first time for the synthesis of new oxazole derivatives (Singh et al. 2013). In this work, the authors propose an inter-comparison between a conventional thermal method with usual organic solvents and a sonochemical synthesis with or without DES. For this, they used a horn type transducer at a frequency of 22 kHz and different DES and then compared the results of the combined synthesis with the thermal method. It is shown that the synthesis by US/DES gives excellent reaction yields with times ranging from 3 to 5 h in the thermal method to 8–20 min in ultrasound especially with the use of choline chloride (ChCl): urea (1:2). In addition, the energy expenditure calculation shows a gain of about 85% in the combined method US/DES and it is shown that the DES could be recycled and reused very efficiently. The proposed mechanism is that of a stabilization of the carbonyl group of the phenacyl derivative by the DES via a hydrogen bond promoting cyclization. The authors also state that ultrasound, due to the extreme conditions of cavitation bubbles, favours the dehydration step, which doubly accelerates the reaction (Fig. 3.4).

The same team also demonstrated the superiority of the US/ChCl: urea (1:2) synergy over conventional solvents and various catalysts used in the thermal method for the synthesis of β-functionalized ketone derivatives (Yadav and Shankarling 2014) or tricyanovinylation of aromatic derivatives (Sanap and Shankarling 2014). Bakht et al. (2016) reach the same conclusions with the synthesis of isoxazoline derivatives using different ratio of a mixture of benzalkonium chloride and urea. These papers suggest that the increase in mass transfer combined with the chemical effects of cavitation bubbles causes an increase in reaction yields and a reduction in synthesis time.

The synthesis of metal–organic framework (MOF) was also investigated by using the combination US/ChCl: dimethylurea (Kim et al. 2011). The examination of results shows that Cu-benzotricarboxylate derivatives exhibit identical uptake capacities than materials obtained by conventional method in DMF but with a drastic reduction in reaction time (36 h for conv. vs. 30–120 min. for US, respectively).

Recently, a mixture of ChCl: urea was also used to perform the heterogeneous synthesis of nitroaromatic derivatives catalysed by silica-based magnetic composite by working at frequency of 40 kHz and at an output power of 250 W (Maleki and Agahie 2017). The authors concluded on the positive synergistic effects of ChCl: urea/US to promote selective ultrasonoxidations. All these examples, although yet very few, emphasize that reactions usually done in ILs in the presence of ultrasound might be also done in DES. The substation of ILs by DES may be even more beneficial considering that DES are made of cheap and natural products, thereby eliminating possible problems of environmental concern and drastically decreasing production and operating costs.

3.4.2 Ultrasound-Assisted-NES-Extraction (UA-NS-E)

Such as in the field of synthetic organic chemistry, the combined use of neoteric solvents and ultrasound in microextraction and extraction applications, particularly in the food industry, began in the same pivotal period of early 2000s. High-intensity and low-frequency ultrasonic cavitation allows obviously to enhance mass transfer processes and proves to be an effective tool in extraction processes. The solvation properties, high chemical and thermal stabilities, and tunability of ILs have been leveraged for increasing extraction yields in reduced times compared to conventional conditions. Extractions processes can be carried out on water, biological and food matrices in order to extract the active compounds (organic or inorganic), oil from seeds or to pre-concentrate organic pollutants for analytical purpose (Han and Row 2010; Passos et al. 2014). While the supercritical fluid extraction (SFE) is relatively implemented in agro-industry, the use at laboratory scale is reversely much lower than that of ionic liquids. Indeed, accessing to SFC technology is costlier than synthesizing organic molecules such as ILs or DES and to use them on classical or easily accessible conditions of temperature and pressure. Most of the ILs applications combined with ultrasound are generally implemented with cleaning bathes probably because of a higher commercial availability, lower price and easiness to use the latter as compared to probes equipment although greater mechanical effects are expected. Owing to their youngness, DES are not yet as highly investigated as ILs but as emphasized earlier their striking potential will certainly ensure a bright future for them. Indeed, the greater variety of deep eutectic solvents used for the improvement of the extraction techniques, compared to the organic synthesis, makes it possible to highlight the will of the experimenters to adapt the extraction agents with respect to the submitted matrices to the synergistic effect. Binary choline chloride associations can be made with urea, oxalic and lactic acids, glycerol, ethylene glycol or glycine associated to with different dilution factor in water. These mixtures present various hydrogen bonding abilities, electrostatic interactions and viscosities able to improve the extraction efficiency. Thus, the natural deep eutectic solvent (NADES) are particularly effective for the extraction of polyphenol derivatives in medicinal substances (Bakirtzi et al. 2016) or solubilization of proteins from gluten (Lores et al. 2017). Lately, two novel hydrophilic magnetic deep eutectic solvents, based on trinary mixtures of ChCl/phenol or ethylene glycol/$FeCl_3$, were efficiently used for the microextraction of thiophene proving that extraction is an important field of investigation for new DES (Khezeli and Daneshfar 2017).

3.5 Conclusion

The synergistic effect of the NS/ultrasound combination has been demonstrated many times in recent years. It manifests itself by an improvement of the reaction yields in drastically reduced times and sometimes selectively in milder conditions. Today, apart from SCF where yet domains of investigation and property tunability are lesser as compared to ILs and DES, the tunability of ILs and DES is an undeniable property for the development of innumerable applications. According to the operating parameters of ultrasonic devices, the neoteric solvents are particularly suitable to replace traditional solvents in a greener approach of chemistry whatever the topic. Up to date, DES seem more suitable due to the fact that they are little or non-toxic and biodegradable as compared to ILs although some bio-sourced ones have recently emerged. In addition, DES are economically more affordable and technically more accessible as they require a single synthetic step whereas most of ILs require several synthetic steps with long and fastidious workups. They are also easily reusable in a simple and effective way. However, hydrophobic ILs can be easily designed what can be hardly conceived with DES, what further gives yet an edge to the former on certain applications. Finally, both NS being highly viscous, local hot spots may occur leading to unexpected decomposition of the medium and a fine-tuning and control of operating conditions is required. The decomposition of ILs has been already spotted out in the case of harsh ultrasonic conditions but not yet in the case of DES owing to their youngness but being as well viscous, it is of probable sight that decomposition may occur in similar operating conditions.

From a purely ultrasonic point of view, the literature suffers from an excessive use of cleaning baths compared to sonotrodes and ultrasonic reactors. In this sense, we urge the community to investigate more with more sophisticated devices to further explore the tremendous possibilities of the NS/US combination.

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Chapter 4
Effective Biomass Valorization Procedures Using Ultrasound and Hydrodynamic Cavitation

Abstract The inherent chemical complexity of biomass renders it as a very attractive source to be recycled and converted into value-added chemicals representing perhaps the largest challenge facing the twenty-first century. To face this issue, over the last three decades, significant effort has been spent for the development of environmentally friendly protocols by means of non-conventional energy sources such as ultrasound (US) and hydrodynamic cavitation (HC) for biomass pretreatment and subsequent chemical transformations.

4.1 Introduction

The last few decades have been witness to increasing interest in renewable sources of chemicals, materials and energy, as commonly used fossil sources begin to run out. The use of biomass, in particular, has seen a growth spurt; a tendency that is bound to intensify as renewables continues to become mainstream. The term biomass commonly refers to animal- and vegetable-derived feedstocks, although most of the biomass on earth is in the form of lignocellulose representing the non-edible part of woody and herbaceous plants (Ahmad et al. 2017). In order to make best use of the lignocellulosic material, its biomass can also be used in a biorefinery as an alternative feedstock for the chemical industry (Amidon et al. 2008). However, some challenging limitations still remain, despite the concept's industrial potential being enormous. The complexity of lignocellulosic biomass chemistry and the variability in its structure are two significant drawbacks to its conversion. Moreover, its high oxygen content as well as the presence of impurities of differing nature, polyfunctionality and low accessibility for catalysts and biocatalysts make transposing current catalytic processes to the production of biomass rather difficult (Corma et al. 2007).

The conversion of lignocellulosic materials to get biofuels is made up of three key steps: (1) the material pretreatment, (2) the cellulose and hemicellulose conversion into fermentable sugars, and (3) the sugars fermentation into raw biofuels. Sugars can

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Silvia Tabasso and Emanuela Calcio Gaudino contributed to this chapter.

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also be converted into platform chemicals, such as ethanol, acetone, butanol, lactic acid, itaconic acid and amino acids, using microbiological processes. Several technological challenges arise dealing with the conversion of lignocellulosic biomass, in particular concerning the pretreatment step. The aim of pretreatment is to improve the enzymatic access to cellulose for the hydrolysis, enhancing the sugars yields. The hydrolysis of cellulose is limited by some factors, such as its degree of polymerization, crystallinity, available surface area, lignin and moisture contents. In the past, different pretreatment options have been explored: wet oxidation, organosolv, hydrothermal, acidic, alkaline, ammonia fibre explosion and, more recently, ionic liquid pretreatment (Kumar et al. 2009; Hendriks and Zeeman 2009; Kumar and Sharma 2017). Nevertheless, all of them appear as expensive, energy intensive and utilize chemicals that require special disposal.

The widespread use of lignocellulosic resources that has occurred over recent years has drawn considerable attention to the development of new but sustainable processes based on non-conventional technologies. These technologies are certainly capable of fractionating lignocellulosic biomass, depolymerising (hemi)cellulose and lignin, and converting carbohydrates into more highly value-added chemicals. However, their energy consumption has to be assessed before any subsequent application can be performed on an industrial level (Tabasso et al. 2015). Acoustic and hydrodynamic cavitation are able to provide severe physicochemical environment hardly reachable using other engineering methods (Cintas et al. 2015), especially in terms of energy efficiency, and to efficiently process recalcitrant lignocellulosic biomass affording high-value chemicals. Cavitation can increase pore sizes and accessible surface areas, while also decreasing the polymerization and crystallinity degrees of cellulose, and improving the biodegradability and enzymatic hydrolysis of biomass residues. Moreover, significant decreases in pretreatment time and temperature are the most attractive features of US-assisted biomass pretreatment. In fact, US induces faster structure damage through several mechanisms: fragmentation, erosion, sonocapillary effect, sonoporation and local shear stress.

The aim of this chapter is to highlight the impact that acoustic and hydrodynamic cavitation have on biomass valorization by investigating the role that the key parameters play in the sustainability of the overall processes.

4.2 Biomass Pretreatment

4.2.1 Acoustic Cavitation as Suitable Biomass Pretreatment

The structure of lignocellulosic materials makes pretreatment essential in order to obtain fermentable sugars in the hydrolysis step. One of the most important limiting factors to obstructing cellulose hydrolysis is the lignin content. Indeed, lignin, being a structural polymer, imparts strength to plant cell walls by covalently linking to (hemi)cellulose, thus preventing carbohydrate exposure for enzymatic attack

(Yuan et al. 2013). In addition, the cellulose hydrolysis depends greatly upon enzyme adsorption onto the substrate surface and lignin may irreversibly adsorb enzymes causing their inactivation. Based on these considerations, a pretreatment step is essential to achieve the effective enzymatic digestion of lignocellulosic biomass for the production of biofuels. In recent years, innumerable pretreatment processes have been developed to improve the lignocellulosic digestibility:

- Physical,
- Chemical [organosolv process; oxidative delignification; alkali pretreatment; acid pretreatment; ionic liquids (ILs) pretreatment],
- Chemical–physical [steam explosion; hydrothermal pretreatment; supercritical CO_2 (SC-CO_2) pretreatment; ammonia fibre explosion (AFEX)], and
- Biological pretreatment.

While each pretreatment process has its own specificity (Sun et al. 2016), chemical and physicochemical pretreatment types are the most promising ones for industrial applications.

However, a critical analysis of the literature highlights that pretreatment methods can be '*tailor-made*' for each individual biomass. Therefore, they should be meticulously selected and designed according to the specific properties of the biomass to be achieved. In fact, a suitable pretreatment should not only significantly improve the digestibility of biomass but also address the economical features of biofuel production (Taherzadeh and Karimi 2008). Furthermore, it can be stated that a single pretreatment method authorizing a complete biomass delignification in an economic and environmentally friendly manner has not yet been achieved (Iskalieva et al. 2012).

A number of researchers have recently exploited US for the intensification of biomass delignification under alkaline conditions. In fact, hydroxyl ions are responsible for delignification during alkali pretreatment, based on the fragmentation, the degradation and the dissolution of biomass lignin. Although a preliminary hypothesis being carried out, the exact physical mechanism of US-assisted delignification under alkali condition has not yet been established.

In this context, Singh et al. (2014) have attempted to give mechanistic insight into the US-assisted delignification of carrot grass (*Parthenium hysterophorus*) in the presence of NaOH. They observed that both the physical and chemical effects of transient cavitation contributed to the final delignification (90%), when the substrate was pretreated with US (20 kHz, 500 W) under alkali conditions with NaOH (1.5% w/v). This yield was double than that of the conventional pretreatment (mechanical stirring). Furthermore, the physical effect of shock waves leads to the lignin matrix depolymerization via the homolytic cleavage of phenyl ether α–O–4 and β–O–4 bonds. On the other hand, the chemical effect of radical generation promotes the hydroxylation/oxidation of the aromatic moieties and the side chain elimination. These peculiar mechanisms mean that US treatment provides effective delignification at ambient temperature, with low amounts of delignifying agents together with decristallisation of cellulose through partial depolymerization.

He et al. (2017) have also investigated the effects of US pretreatment on structural changes in biomass. In particular, eucalyptus wood (particle size 0.5 mm) was pretreated (0.5–1.5 h) under alkali condition (NaOH) using an US bath working at 28 kHz and 300 W. US pretreatment had a strong influence on the tissue structure of biomass, as it reduced its lignin content and increased its crystallinity (up to 35.5%), making it prone to subsequent enzymatic hydrolysis.

Since it is well known that biomass delignification under alkaline conditions can be improved by increasing pretreatment temperature, the heat produced under US irradiation may be a profitable way to save energy and time. Wu et al. (2017) have demonstrated that the heat dissipated from a horn-type sonicator, operating at 22 kHz and 300 W for 70 min, led to a reliable and effective methodology for rice straw alkali pretreatment. This protocol provided 3.5-fold higher concentrations of reducing sugars after 48 h of enzymatic saccharification (2.91 vs. 0.85 g L^{-1}) than in the absence of US. These results can be attributed to a higher cellulose content present in US pretreated samples and lower hemicellulose and lignin contents, together with higher surface area and porosity as compared to untreated samples. However, it should be noted that the porosity, surface area and cellulose content of pretreated straw samples increased with increasing alkali concentration (NaOH w/v: 0.4, 0.6, 0.8 and 1.0%,) with or without US.

Another effective US-assisted alkali pretreatment of chilli post-harvest residue has been reported by Sindhu et al. (2017). Biomass US pretreatment (80 kHz, 0–60 min) was performed in the presence of either KOH, NaOH, or $Ca(OH)_2$ and was followed by hydrothermal treatment in an autoclave (121 °C, 60 min) before enzymatic hydrolysis. The authors studied the interaction between sonication time and biomass loading on enzymatic hydrolysis. Maximum reducing sugar yield (0.44 g/g) was reported at high levels of sonication time (up to 60 min) and middle levels of lignocellulosic loading (11.0–15.0% w/w). This US pretreatment was able to effectively remove lignin and hemicelluloses from chilli post-harvest residue and improve the final sugar yield. Furthermore, an inhibitor analysis of the hydrolyzate revealed that furfural, 5-hydroxymethylfurfural and organic acids, such as citric acid, propionic acid and succinic acid, were not present. This means that fermentation could be carried out without the prior detoxification of the hydrolysate, yielding 1.94% ethanol with a fermentation efficiency of 70.08%.

Sugarcane bagasse was also investigated for the production of ethanol after pretreatment (Kandasamy et al. 2017). The raw biomass was first pretreated under acidic (H_2SO_4 2.5–3.5%), alkali (NaOH 22–25%) and US conditions (20 kHz, 100 W) used either alone or combined. Using SEM analyses, it was established that the complex bagasse structure was destroyed after combined acid/US pretreatment (Fig. 4.1). The pretreated bagasse was then used as substrate for fermentation to biofuels without prior enzymatic hydrolysis, yielding higher ethanol production as compared to the previous results reported in the literature. An ethanol concentration of 911 mg/L was achieved combining all the pretreatment types; the bagasse was treated with acid (3%) and US (50 or 109 W), and then with alkaline (23%) and US (50 or 109 W).

Another interesting application of US concerns the delignification of waste newspaper (Subhedar and Gogate 2014a). A ca. twofold increase in delignification (around

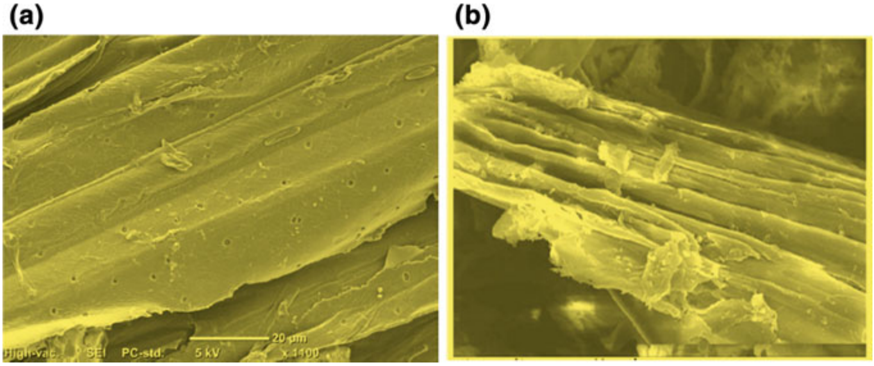
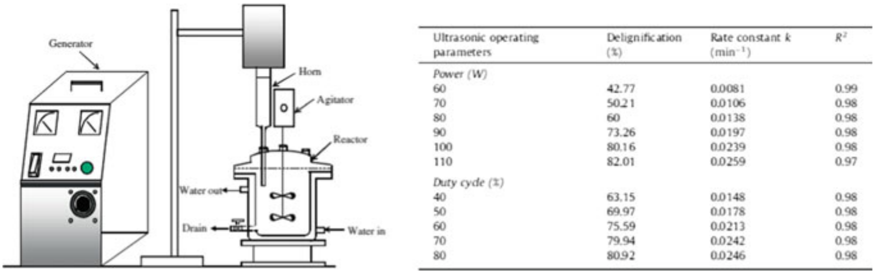


Fig. 4.1 Bagasse structure before (**a**) and after (**b**) acidic (3%) and US pretreatment. Reprinted from Kandasamy et al. (2017). Copyright (2017) with permission from MDPI

80%), compared to alkaline pretreatment alone, was achieved using US-assisted alkaline treatment (20 Hz, 100 W, 70 min) (Fig. 4.2). The so treated biomass was a superior substrate for enzymatic hydrolysis and ethanol fermentation, owing to its high cellulose content.

US-assisted lignocellulose fractionation generally improved the effectiveness of subsequent treatments as it affords resulting products in higher yields and selectivity. Garcia et al. (2011) reported similar results for *Olea europaea* biomass where US pretreatment (50 Hz, 420 W) led to higher delignification and less cellulose degradation. Moreover, no significant modifications in the structure and thermal behaviour of the recovered lignin were observed after sonication.

The US pretreatment was also evaluated on the acid hydrolysis of oil palm empty fruit bunch fibres (OPEFB) (Yunus et al. 2010), a biomass which shows a huge potential for bioethanol production. Indeed, the amount of fermentable sugars, xylose and glucose obtained from OPEFB was estimated to contain up to 70% of its principal components. An US probe working at 20 kHz and 2 kW power was used at 25 °C



Ultrasonic operating parameters	Delignification (%)	Rate constant *k* (min^{-1})	R^2
Power (W)			
60	42.77	0.0081	0.99
70	50.21	0.0106	0.98
80	60	0.0138	0.98
90	73.26	0.0197	0.98
100	80.16	0.0239	0.98
110	82.01	0.0259	0.97
Duty cycle (%)			
40	63.15	0.0148	0.98
50	69.97	0.0178	0.98
60	75.59	0.0213	0.98
70	79.94	0.0242	0.98
80	80.92	0.0246	0.98

Fig. 4.2 Experimental set-up for US-assisted alkaline pretreatment (left); effect of US operating conditions on delignification rate (right). Reprinted from Subhedar and Gogate (2014a), Copyright (2014), with permission from Elsevier (License Number: 4358680896216)

for 45 min, affording a maximum xylose yield of 58% after the hydrolytic tests, while untreated biomass afforded only 22% of xylose. This noticeable difference reveals that directly exposing OPEFB fibres to ultrasonication power at a variety of amplitudes has a marked effect on the efficiency of low-temperature acid hydrolysis. This was mainly due to the removal of silica bodies from the surface of the OPEFB fibres prior to acid hydrolysis.

In order to increase the enzymatic digestibility of rice straw (RS), Xiong et al. (2017) have recently reported the use of US-assisted pretreatment in the presence of Fenton's reagent and a horn-type US device working at 22 kHz and 200–600 W. They confirmed that the US-assisted Fenton process facilitated the reliable and effective pretreatment of RS for the next enzymatic hydrolysis step (Fig. 4.3). The RS that had been pretreated with US-assisted Fenton's reagent (U/F-RS) exhibited the largest specific surface area and the lowest degree of polymerization (DP) and led the highest enzymatic accessibility. Furthermore, the reducing sugar amount released from U/F-RS after 48 h of enzymatic saccharification was around fourfold higher than from raw RS and 1.5 times more from RS treated with Fenton's reagent (F-RS) in the absence of US. Since the hemicellulose and lignin contents in U/F-RS are similar to those in F-RS, the high enzymatic activity observed in U/F-RS can be attributed to the higher specific surface area and lower DP. Whereas the conventional Fenton's reagent process usually takes dozens of hours, the US-assisted Fenton protocol only takes 3 h to provide similar enzymatic saccharification yields.

US-assisted pretreatment in the presence of tetra-butylammonium hydroxide (TBAH) has recently been introduced (Zhong et al. 2017) to enhance the biodegradability of wheat straw biomass. The synergistic chemical and mechanical pretreatment was designed for both the external surface destruction and internal structure disruption of the lignocellulosic matrix (Fig. 4.4).

This process led to highly efficient lignin removal and obvious structural (crystallinity) transformation in pretreated straws. Process analysis indicated that treatment time, temperature and US power intensity were pivotal for the success of the tetra-butylammonium hydroxide pretreatment. A saccharification yield of approxi-

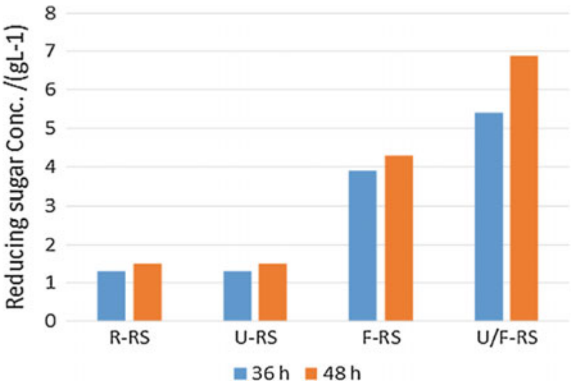


Fig. 4.3 Reducing sugars released from raw pretreated rice straw samples. [R-RS = (row RS); U-RS = (US pretreated RS at 400 W)]; F-RS = (conventional Fenton's reagent process); U/F-RS = (combined US/Fenton process)

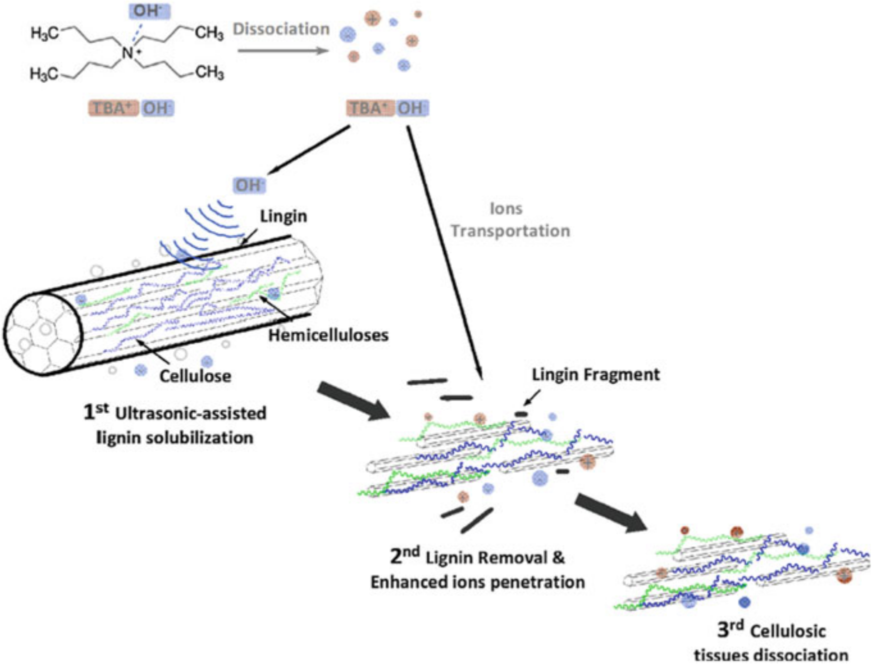


Fig. 4.4 Mechanism of US-assisted lignocellulose pretreatment with TBAH. Reprinted from Zhong et al. (2017), Copyright (2017), with permission from Elsevier (License Number: 4358690748819)

mately 90%, which was four times that acquired from untreated straw, was obtained from wheat straw pretreated at 50 °C for 0.5 h under 344 W/cm^2 of US power. All these results suggest that combined chemical and mechanical treatments can significantly improve the bio-accessibility of lignocelluloses, leading to enhanced utilization efficiency. Furthermore, TBAH could be recycled several times without a significant loss in activity.

US technology has also successfully been used, at different powers (60–540 W) and for a variety of times (10–30 min), by Ivetić et al. (2017) as a suitable pretreatment for sugar beet shred biomass (solid loading 2–4%).

In fact, under the reported conditions, US (22–25 kHz) caused up to 28% material solubilization, while cellulose recovery was around 90%. Furthermore, US provided sugar beet shreds that were more susceptible to cellulase adsorption (having 1.4–15 times higher maximum adsorption capability) and enzymatic hydrolysis than untreated ones. The highest cellulose enzymatic hydrolysis yield (around 780 mg/g cellulose) was 3.7 times higher than that obtained from the untreated biomass. This indicates that US may be a good choice for the pretreatment of sugar beet shreds before cellulose enzymatic hydrolysis.

4.2.1.1 Acoustic Cavitation in the Presence of Alternative Solvents

Lignin has been identified as one of the major obstacles to the efficient enzymatic hydrolysis. The use of ionic liquids (ILs) in biomass fractionation proved an effective mean of disrupting the intricate network of non-covalent interactions of lignin. It has been reported that the imidazolium cations of ILs may interact with the aromatic rings of lignin, via π–π interactions, to promote its dissolution. In particular, the relatively small 1-hexyl-3-methylimidazolium $[HMIM]^+$ cation was found efficient in fractionating lignocellulosic biomass. Moreover, ILs containing an anion with strong hydrogen-bond capability also shows good solubility for lignin (Mäki-Arvela et al. 2010).

In this regard, imidazolium-based ionic liquids displaying a large variety of anions (chloride, sulphate, acetate, phosphate, methanesulfonate, *p*-toluenesulfonate) have been investigated by Zhang et al. (2015). Corn stover was chosen as the starting material, due to its complex structure. Its fractionation into cellulose, hemicellulose and lignin was successfully performed in ILs at 70 °C after 3 h of US irradiation (400 W). Higher yields of lignin (S-G-H type) were isolated in the presence of [HMIM]OAc and [HMIM]Cl (60.48% of the original lignin). Achievements were imputed to both the hydrogen-bond capability and the acidity of the engaged ILs Moreover, the same study revealed that the use of a small anion was preferable as it was able to diffuse into the lignocellulosic matrix more quickly. The use of a chloride anion, a small-sized and strong hydrogen-bond acceptor, with a small-sized cation ($[HMIM]^+$) showed an effective pretreatment solvent for the dissolution of lignin. The enzymatic hydrolysis of recovered cellulose was performed, affording a high yield (97.77%) of reducing sugars. These ILs have shown a great potential for the preparation of biofuels.

Besides the ionic liquids commonly used for lignocellulosic biomass pretreatment, recent years have been witness to even greater interest in bio-based deep eutectic solvents (NaDES). In fact, these mixtures have been reported to be more biodegradable and bio-renewable than the even more expensive imidazolium ILs commonly used for pretreatment. In this context, Ninomiya et al. (2013) have reported, for the first time, that the US-assisted pretreatment of powdered bamboo biomass in the presence of choline acetate (ChOAc) was able to dramatically improve the subsequent saccharification yields. When thermally pretreated at 110 °C for 60 min in ChOAc, saccharification yield was approximatively 55%, whereas it reaches 92% after the US pretreatment (24 kHz and 35 W power) in the same solvent at 25 °C for 60 min. Moreover, the reported analyses showed that the cellulose crystallinity of pretreated bamboo powder was lower after ultrasonic pretreatment in ChOAc than after thermal pretreatment (Fig. 4.5).

In order to examine the capabilities of ChOAc in the pretreatment of different lignocellulosic materials, Ninomiya et al. (2015) used bagasse powder that was US pretreated in the presence of ChOAc for subsequent enzymatic hydrolysis. The mixture was sonicated for 60 min at 24 kHz and an emission power of 35 W using an ultrasonic sonotrode. After ChOAc pretreatment, cellulose and hemicellulose saccharification percentages were higher, with an enzymatic reaction time of 48 h,

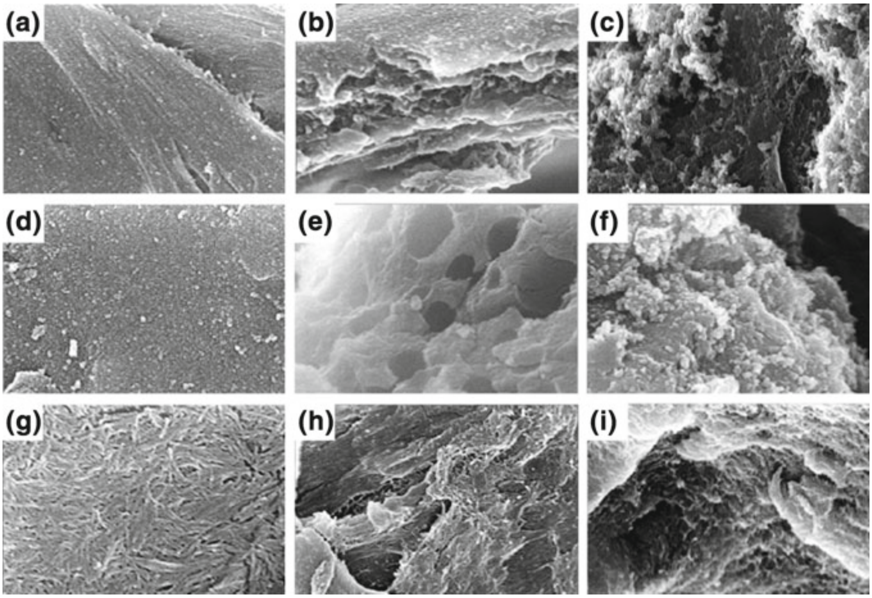


Fig. 4.5 Scanning electron micrographs of bamboo powder (**a**–**c**), alkali lignin (**d**–**f**) and microcrystalline cellulose (**g**–**i**). Original biomass without pretreatment (**a**, **d** and **g**); thermal pretreatment in ChOAc (**b**, **e** and **h**); and US pretreatment in ChCOAc (**c** and **e**). Pretreatment time was 60 min. Reprinted from Ninomiya et al. (2013), Copyright (2013), with permission from Elsevier (License Number: 4358700095389)

reaching 85 and 100% of the theoretical maximum. Another approach for the in situ enzymatic saccharification of cellulose in ionic liquids has been presented by Yang et al. (2010). For this purpose, the solubility of cellulose and corresponding cellulase activity (for saccharification) were tested using a variety of alkylphosphate ILs, while US pretreatment was used to prompt further conversion. 1,3-dimethylimidazolium dimethylphosphate ([MMIM]DMP), which gave favourable solubility and biocompatibility, was selected for the aqueous–IL system and the enzymatic in situ saccharification of cellulose.

In aqueous–ILs using ultrasonic pretreatment, the conversion of cellulose increased by 52.71%, compared to that of untreated cellulose. Moreover, higher conversions (95.48%) were obtained in aqueous-[Mmim]DMP by conducting US pretreatment (45 kHz, 100 W) for 30 min at 60 °C.

Indeed, the US pretreatment performed in aqueous–ILs decreased the cellulose polymerization and crystallization degrees, which may contribute to the increased rate of enzymatic hydrolysis.

[EMIM]OAc has been frequently reported as the most effective IL for cellulose dissolution and pretreatment of enzymatic hydrolysis (Brandt et al. 2013). Pretreatment with ChOAc enhanced cellulose saccharification to the same degree as with [EMIM]OAc, suggesting that the acetate anion plays an important role in the reduction of cellulose crystallinity. Anions generally act as hydrogen-bond acceptors and interact with the hydroxyl groups of cellulose weakening its crystalline structure, whereas cations interact with lignin through hydrogen bonding and π–π interactions. By contrast, the inhibitory effects of ChOAc on cellulose were significantly lower than those of [EMIM]OAc, because the cholinium cation was more biocompatible than the imidazolium one. It is therefore suggested that ChOAc is a promising alternative to [EMIM]OAc for pretreatment and for the in situ saccharification of lignocellulosic biomass.

4.2.1.2 Hydrodynamic Cavitation as Suitable Biomass Pretreatment

Phenolic hydroxyl groups in lignin dissociate under alkaline conditions forming a resonance stabilized phenoxy radical, which is the initiator of depolymerization reactions. An alkaline pretreatment carried out by HC promotes the formation of hydroxyl and hydroperoxy radicals required for the delignification reaction, thus intensifying the overall reactions rates. In addition, shock waves formed during HC are responsible for the breakage of some chemical bonds between lignin and cellulose in the biomass. The main advantage of HC is that the conditions of high temperature and pressure necessary for delignification are generated locally by the collapse of shock waves, while the overall process still remains at ambient conditions, thus avoiding the requirements for a heating device.

These features make HC a valuable tool for biomass pretreatment; a key step in the biochemical processes to biofuels. For example, HC has been applied in the alkaline pretreatment (3.0% NaOH) of reed, used as starting material for the production of bioethanol (Kim et al. 2015).

HC has also been used to improve the efficiency of the alkaline pretreatment of sugarcane bagasse (SCB) for ethanol production (Hilares et al. 2016, 2017). A lignin removal of 60.4% was achieved in only 30–45 min of HC treatment with 97.2% of enzymatic digestibility. This result was accompanied by the drastic change in biomass structure provoked by the immensely destructive cavitation.

Finally, the efficiency of the HC and US technologies, with regard to the polysaccharide degradation of corn stover in flow-through mode, has been compared (Nakashima et al. 2016). The US-SP pretreatment of corn stover led to lower digestibility than that provided by the HC-SP process, which was more efficient in terms of both glucose and xylose production. This difference can be ascribed to the 50% greater lignin removal obtained by the HC-SP system. The inhibitor furfural was not generated in any process, because the pretreatment was conducted under mild conditions at 30 °C. A comparison of the energy efficiency of the HC- and US-assisted pretreatment of SCB, reed and corn stover is summarized in Table 4.1.

The hydrodynamic delignification of wheat straw, used for the production of paper, provided some advantages, such as the reduction of treatment time, energy consumption (almost 50%) and temperature (ambient temperature). Furthermore,

Table 4.1 Comparison of energy efficiency during HC- and US-assisted processes

System	Pretreatment conditions	Biomass	Efficiency of pretreatment (*g* of glucose/J)
HC-NaOH	NaOH (1.9% w/v) 45 min	Sugarcane bagasse	6.43×10^{-5}
US-NaOH			2.61×10^{-5}
HC-NaOH	NaOH (3.0% w/v) 40 min	Reed	6.51×10^{-5}
US-NaOH			2.58×10^{-5}
HC-SP	$NaCO_3$ (0.4 mol/L) H_2O_2 (0.6 mol/L) 60 min	Corn stover	2.24×10^{-5}
US-SP			0.11×10^{-5}

the versatility of the process was higher, as it was possible to adjust a number of parameters (rotation speed of the rotor, consistency of the straw) according to the final properties required of the paper.

4.3 Ultrasound-Assisted Biomass Enzymatic Hydrolysis

Recently, power US has been applied to biotechnology processes (O'Donnell et al. 2010). This technology has been used as an enzyme inactivation method for several years, but it has recently been reported that US does not inactivate all enzymes, especially under mild conditions (Gogate and Kabadi 2009).

Indeed, it has been shown that the use of ultrasonic treatment at appropriate frequencies and intensity levels can lead to enhanced enzyme activity (Subhedar and Gogate 2014b). US proved also to induce favourable conformational changes in protein molecules without altering the structural integrity of the enzymes. The ability of US to increase the enzymatic activity and reduce mass transfer resistance renders this treatment a potential option for the conversion of lignocellulosic biomass under mild conditions, using cellulase for the production of bioethanol. The name cellulase (endo-1,4-β-D-glucanase) refers to a group of enzymes that are chiefly produced by fungi, bacteria and protozoa and that catalyse the cellulose hydrolysis process. Cellulase either breaks down cellulose into smaller polysaccharides or completely into β-glucose units which can be further fermented to bioethanol. Considering the commercial importance of cellulase, the finding of an effective method to improve its activity is of crucial importance. However, the majority of the papers published in this area have evaluated the effectiveness of the US-aided processes, without focusing on the intensification of catalytic activity using US. More research is thus required in order to better understand the relationships behind 'sonication enzyme action'. This would facilitate the development of effective processes in the field of sono-biotechnology.

Lunelli et al. (2014) have evaluated the feasibility of using US irradiation to increase the yields after the enzymatic hydrolysis of sugarcane bagasse. The highest yield of fermentable sugars (0.26 g/g of dry material) was obtained after 240 min of hydrolysis, at 50 °C, with a moisture content of 75% mass and an enzyme concentration of 10% mass. Results displayed in Fig. 4.6 highlight that the US-assisted hydrolysis (40 kHz, 132 W) produced more than double the amount of fermentable sugars with simple hydrolysis (35.0 and 17.0% with and without US, respectively). Figure 4.6 also shows that the hydrolysis yield increased with temperature up to 50 °C, while a substantial decrease in the yield occurred at 60 and 70 °C. These results can be probably ascribed to enzyme denaturation. With US irradiation, it is possible to use lower amounts of enzyme to obtain higher fermentable sugar yields, as compared to hydrolysis without US.

Borah et al. (2016) have provided some mechanistic insights into US enzymatic biomass hydrolysis. They have explored the enzymatic hydrolysis of multiple invasive weeds [*S. spontaneum* (SS), *M. micrantha* (MM), *L. camara* (LC) and *E. crassipes* (EC)] under US conditions (Table 4.2). These waste biomasses can be used as feedstock for alcoholic biofuel production as their significant holocellulose content can be converted into fermentable sugars. The enzymatic hydrolysis of pretreated weeds has been conducted with mechanical agitation and sonication (US bath at 35 kHz and 35 W power input) under constant conditions. Sonication accelerates hydrolysis kinetics by a factor of around ten. This effect arises from a number of features that can be attributed to the intense micro-convection generated during sonication: (1) increase in reaction velocity, (2) increase in enzyme–substrate affinity, (3) reduction in product inhibition and (4) enhancement of enzyme activity due to conformational changes in its secondary structure. The sonication enhancement effect has been shown to be independent of the enzymatic hydrolysis conditions.

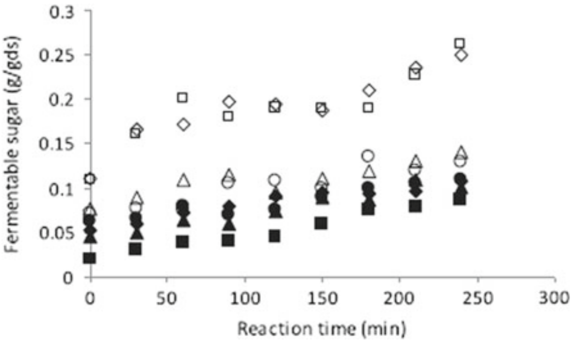


Fig. 4.6 Sugarcane bagasse hydrolysis as a function of temperature without (filled diamond 40 °C; filled square 50 °C; filled triangle 60 °C; filled circle 70 °C) and with US irradiation (white). Reprinted from Lunelli et al. (2014), Copyright (2014), with permission from Elsevier (License Number:4358700759597)

Table 4.2 Total reducing sugar yield (TRS) after enzymatic hydrolysis for various biomasses

Biomass	Sonication	Mechanical agitation
	Treatment period: 10 h	Treatment period: 36 h
SS	40.02 ± 0.42	35.77 ± 1.20
LC	36.09 ± 0.72	27.81 ± 0.42
EC	38.09 ± 0.45	31.86 ± 0.24
MM	35.90 ± 1.02	24.86 ± 0.65

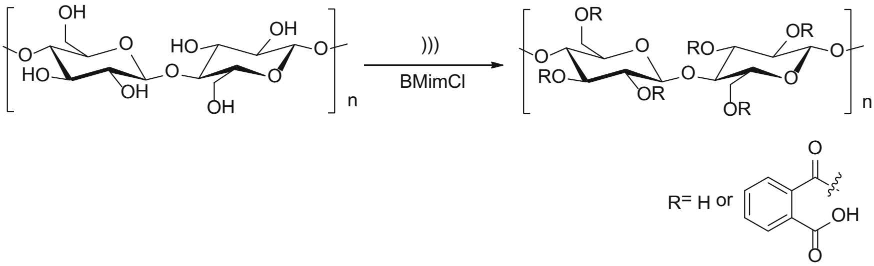
4.4 Ultrasound-Assisted Conversion of Biomass into Platform Molecules

Cellulose is one of the most renewable and biodegradable natural resources to originate from agricultural residue. As such, a great deal of attention has recently been focused on its modification as a promising method for the production of value-added products. Cellulose derivatives bearing benzene moieties are currently used as good thermoplastic and optical materials in a variety of fields, and are exploited as excellent chiral selectors in chromatography. However, the intrinsic insolubility of cellulose in water and majority of organic solvents is still the major drawback to homogeneous cellulose modification. In this context, Ma et al. (2013) have made use of ionic liquids (ILs) as a useful medium for cellulose derivatization. Moreover, they have successfully demonstrated that the combined use of US and ILs enhances the substitution degree (DS) of recovered cellulose derivatives.

In particular, cellulose phthalates were prepared under US irradiation (40 kHz, 180 W) from phthalic anhydride and beet pulp cellulose using 1-butyl-3-methylimidazolium chloride ([BMim]Cl) as the solvent (Scheme 4.1). The DS of reported cellulose derivatives increased from 0.76 to 1.56 with sonication time from 15 to 60 min, reaction time from 30 to 70 min and reaction temperature from 90 to 120 °C. Cellulose dissolution in [BMim]Cl was ascribed to the formation of hydrogen bonds between the cellulose hydroxyl protons and the chloride ions of the IL, which weakened the intra- and intermolecular hydrogen bonds network within the cellulose chains. The non-volatility of the IL and cellulose meant that the cavitation bubbles generated in the reaction system mainly consisted of phthalic anhydride vapour and that cavitational collapse dramatically enhanced the mass and heat transfer provided to the reaction.

2-hydroxyethyl cellulose (HEC) is one of the most important cellulose derivatives with numerous industrial applications, including in pharmaceuticals, paper, textiles and emulsion polymerization.

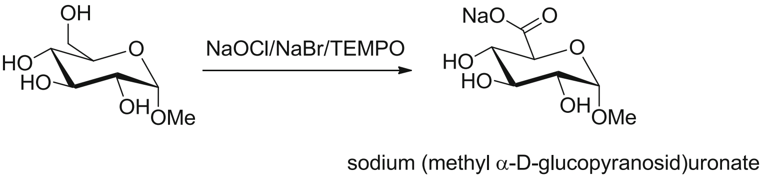
Surfactants (when a hydrophobic chain is attached to a carbohydrate moiety), and complexing agents (polyhydroxy-polycarboxylates) have recently attracted much more attention than other obtainable targets from biomass. Brochette-Lemoine et al. (2000) have therefore explored the effects of US on their production. They investigated on how US could direct the heterogeneous course of glucose with hydrophobic



Scheme 4.1 Reaction of cellulose with phthalic anhydride in [BMim]Cl under US irradiation

but different chain length alcohols (butanol and dodecanol), in an acidic medium (montmorillonite KSF/O), either towards surfactant glucosides or towards polyglucose oligomers. In the case of dodecanol use, US (Vibra-Cell apparatus coupled with a titanium horn with a 13 mm diameter working at 20 kHz under 300 W power) promoted the oligomerization of glucose instead of the formation of the surfactant glucoside because of the wetting of the glucose suspension caused by the efficiency of the sonophysical mixing. On the other hand, the same authors observed that US strongly promoted the oxidation of primary carbohydrate hydroxyl groups at higher frequencies (500 kHz under 0.08–0.22 W/ml acoustic power) in polyhydroxypolycarboxylate formation in the presence of a NaClO/TEMPO system (Scheme 4.2). They concluded that US was responsible for two distinct effects. On the one hand, US enhanced the oxidation rate of either methyl glucoside or sucrose in basic aqueous medium. On the other hand, US promoted also the formation of sodium (methyl α-D-glucopyranoside)urinate and sucrose tricarboxylate in the absence of sodium bromide, which is usually required for this purpose when the TEMPO reagent is used. This highlighted the pivotal role that US plays in the formation of the nitrosonium ion, which is the active oxidizing species in the considered catalytic cycle.

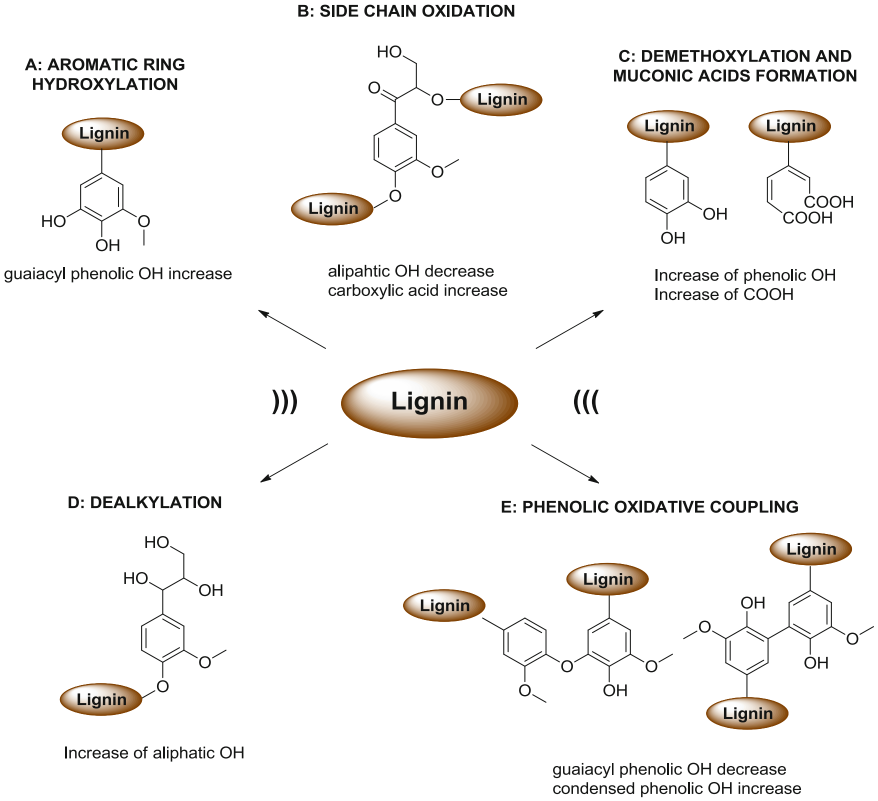
Interest in sugar alcohols has also increased considerably over the last few years. While D-Mannitol displays widespread natural distribution, its extraction from raw plant material is no longer economically viable, meaning that it is still produced from the catalytic hydrogenation of fructose or glucose (Makkee et al. 1985). For this reason, the development of new sustainable protocols for the production of mannitol is a great challenge.



Scheme 4.2 Effect of US on NaOCl/TEMPO oxidation

In this context, Toukoniitty et al. (2005) have investigated the effect of US on D-fructose hydrogenation to D-Mannitol over three different heterogeneous catalysts: Cu/SiO_2, $Cu/ZnO/Al_2O_3$ and Raney-Ni. The hydrogenation reactions were performed at 110 °C under 50 bar of hydrogen in a high-pressure autoclave equipped with an ultrasonic horn-type irradiation system working at 20 kHz and 50 W. The sonication significantly enhanced the reaction rate over Cu/SiO_2, although Raney-Ni remained the most active catalyst. The influence of pressure and temperature on the reaction over the Raney-Ni type catalyst was studied under sonication as well. Higher H_2 pressures (30–50 bar) and temperatures (90 and 110 °C) only brought moderate enhancements to reaction rates whereas variations in nominal ultrasonic power input (from 0 to 50 W) significantly affected catalyst activity. Moreover, catalyst deactivation was significantly hampered by the acoustic irradiation, as compared to experiments run under silent conditions.

Finally, lignin has recently been considered as a possible starting material for new nanostructured products that are suitable for textile fibre treatments or for use as



Scheme 4.3 Proposed mechanism for grass lignin degradation by US hydroxyl and superoxy radical species

biocide systems in wood protection. In this context, Gilca et al. (2015) have made use of the effect of US on lignin aggregation processes to obtain new nanoparticles from two different types of lignin (wheat straw and Sarkanda grass). Two main reaction patterns were postulated for US-assisted lignin nanoparticle preparation; a side chain cleavage/ depolymerization and an oxidative coupling/polymerization (Scheme 4.3). The depolymerization process was prevalent under the applied reaction conditions (20 kHz–600 W). Moreover, it was possible to tune the depolymerization process by modulating US irradiation time and/or power. An increase in the number of condensed units was observed in IR spectra and indirectly from QQ-HSQC analyses. Phenyl coumaran and pinoresinol subunits were found to be completely degraded and aryl glycerol aryl ether subunits (β–O–4) were found to be reduced in number. The results confirm that the compositional and structural changes in the nanoparticles obtained are not significantly modified at the intensity applied (20 kHz–600 W), but that they rather depend on lignin nature.

The production of suitable and cost-effective biopolymers is still another significant challenge for biomass valorization. The commercial success of biopolymer food packaging is somewhat limited at present, partially because of the high cost of biopolymer materials. Food processing waste could be utilized to produce biodegradable packaging film and address these issues. In fact, Borah et al. (2017) have developed a protocol that is based on the use of potato peel and sweet lime pulp to prepare composite films under US irradiation (40 kHz, 50 W). The biopolymers were prepared over 45–60 min by varying potato peel (PP) powder and sweet lime pomace (SLP) proportions across a 0:1 to 1:0 ratio range.

4.5 Conclusion

Extensive research has been carried out in support of sustainable biomass valorization using acoustic and hydrodynamic cavitation. Although it has not seen extensive use yet, hydrodynamic cavitation is a promising biomass conversion technique. More significant scientific breakthroughs in the field of biomass valorization are expected to occur in this innovative field in the near future.

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Chapter 5
Gone with the Flow: Miniaturization and Safer Chemistry

Abstract Like other enabling technologies, ultrasonication has moved progressively from batch to flow conditions, which are more suitable for large-scale applications and industrial purposes. Without discussing comprehensively, the subject of sonochemistry underflow, this chapter provides some background and practical considerations with a focus on chemical synthesis in following the heading of this monograph. A deeper analysis is presented for miniaturized systems as microfluidics and machine-assisted approaches will doubtless be the future of chemistry. Ultrasound in microchannels helps to prevent clogging while enhancing considerably mass transfer. Moreover, such applications will require the design of more efficient micro-sonoreactors and an accurate control of external parameters.

5.1 Introduction: Batch Versus Flow

The advantages of using flow conditions in chemical reactions for synthesis, or chemistry in general, can be more relevant than thought at first sight. One day, it could become economically relevant for chemical production companies, to produce high-value chemicals in the pharmaceutical and fine chemistry industry among others. However, for scientists regularly not concerned with economic aspects, or future potential valorization of their findings, the most commonly preferred system is the batch reactor.

This preference for batch over continuous flow reactors can be given by different reasons. Batch systems are easier to explain to students, or to adapt in real-world scenarios from textbooks or laboratory practices. For example, ‘making a beaker bigger’ and scaling the stirring or cooling needed for a bench reaction up to industrial scales seem logical; and for many centuries, it has proven to be successful. The idealized concept of controlling the volume, pressure, temperature and residence time in a batch reactor is more appealing than a continuous flow reactor whose content is constantly moving as it changes. Furthermore, mathematical models for

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David Fernandez Rivas contributed to this chapter.

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process control and design are easier to implement for classical unit operations, e.g. continuous stirred tank reactors. The availability of large empirical databases built over years represents a comfortable choice for most companies in contrast with new risky types of unit operations.

If we abstract ourselves for a moment, it becomes evident that even for batch systems, flow is crucial. Not only the reactants and products in a batch reactor need to be brought in and out of the vessel, but cooling media, electricity and data retrieved by sensors monitoring the relevant parameters are continuously flowing. Then, we could agree that there are many more similarities between batch and continuous flow reactors; with the particularity that in the latter, the reactants and products move with respect to our point of observation, and not only around a stirring axis. Clearly, if we travel together with our reaction as it is transported, we can make use of techniques and phenomena that its stationary batch counterpart cannot benefit from. For example, the geometry defined by the conduct through which the fluid is circulated brings certain advantages, e.g. provide close-to-homogeneous heat transfer by wrapping a resistance around a tube, or couple optical fibres to monitor process in-line.

There is ample technical information compiled over the last decades concerning the advantages of using continuous flow. A few inflection points have marked a modest increase on the popularity among scientists, although we have also observed a timid corresponding time-delayed adoption by the industry. Perhaps, the strongest impulses to the continuous flow concepts and popularity, among scientists at least, were inspired by the Green Chemistry idea, as we shall discuss later in certain detail (Elvira et al. 2013). Within this context, a key inflection point comes from the adoption of microfluidics in the general chemical engineering communities, as every argument linked to 'small' is invariably appealing in terms of costs and risks (Whitesides 2006; Jensen 2017). Unfortunately, the *miniaturization* trend that has occurred in parallel with the Green hype might have been difficult to understand, and consequently, has hampered its utilization by the broad scientific community not specialized in any of the two. Industry-paid research has logically been cautious not to jump too early into these promising concepts and technology, in order not to get affected by hypes or under-delivering promises of the academic colleagues. A lengthy and tortuous increase in understanding and use of continuous flow microfluidics has been accompanied by the use of ultrasound, and sonochemistry more specifically.

Our goal with this chapter is to provide new ideas and summarize a selection of well-established elements for the better understanding of the advantages of using flow, microfluidics and ultrasound in the particular contexts of organic chemistry and synthetic chemistry. We also aim at providing a few examples while warning of pitfalls and potential hyped promises. The discipline of continuous flow synthesis, ranging from chemicals and pharmaceuticals to materials and biofuels, has grown in a spectacular fashion in recent years, and the readership is referred to a wide literature that includes numerous and excellent reviews (Yoshida et al. 2013; Wiles and Watts 2014; Gutmann et al. 2015; Porta et al. 2016; Britton and Raston 2017).

Moreover, a recent and detailed protocol describing the assembly and use of a continuous flow system in an expeditious manner has been reported recently and should help to eliminate fears and misconceptions on the adoption of this technology (Britton and Jamison 2017).

5.2 Miniaturized Continuous Flow Systems: Some Remarks

The term ‘flow chemistry’ usually applies to the adoption of continuous flow systems through the assembly of numerous parts in a modular fashion consisting of single reactor coils, stainless-steel syringes, pumping systems, pressure and temperature regulators, and multiple junctions (see Fig. 5.1). Further implementation can also include, among others, liquid–liquid separators, membranes, mixers, drying columns, packed-bed reactors, etc, and all in all contrasts with conventional and traditional technology using round-bottomed flasks, stirrers, heaters and reflux condensers. Continuous flow systems now enable the preparation of numerous organic compounds, especially active pharmaceutical ingredients. Typically, enhanced reaction kinetics and accurate levels of control and automation can be achieved in contrast with batch conditions. Additional benefits provided by the small path occupied by liquids or gas in channels of microscopic diameters include improvements in heat and mass transfers, homogeneization, facile penetration of external activation sources such as microwaves, ultrasound, light or plasma (Bruggeman et al. 2016), and improved reaction safety. The latter represents a key concern as continuous flow allows the safe handling of hazardous compounds. Moreover, the sequential generation and consumption of such species, formed in small amounts, avoids risks associated with their manipulation, isolation and storage. These pluses are not only linked to increased reaction efficiency and reduced costs but also to sustainability and low environmental impact.

A clear-cut illustration of how flow synthetic chemistry works is shown in Fig. 5.2, where a commercially available aryl tribromide undergoes a cascade of couplings involving toxic and hazardous organometallic reagents without any separation leading to a more elaborated structure, which is finally subjected to aqueous alkaline treatment to afford the desired target (Yoshida et al. 2013). This fast strategy, often tolerating a variety of functional groups, has become an ideal companion in the pharmaceutical industry. In fact, numerous patents aimed at preparing active pharmaceutical ingredients (APIs) or bioactive substances in general have adopted flow processes as routine protocols (Hughes 2018).

A dramatic advantage of miniaturized flow chemistry relative to batch technology can be appreciated in the continuous synthesis of a key antibiotic, ciprofloxacin hydrochloride. The overall transformation consists of six telescoped steps followed by filtration and crystallization to give the ciprofloxacin salt in 60% yield (Lin et al. 2017). A telescoped route is that in which the flow is not interrupted for offline purifications. Remarkably, the flow synthesis takes nine minutes, which contrasts

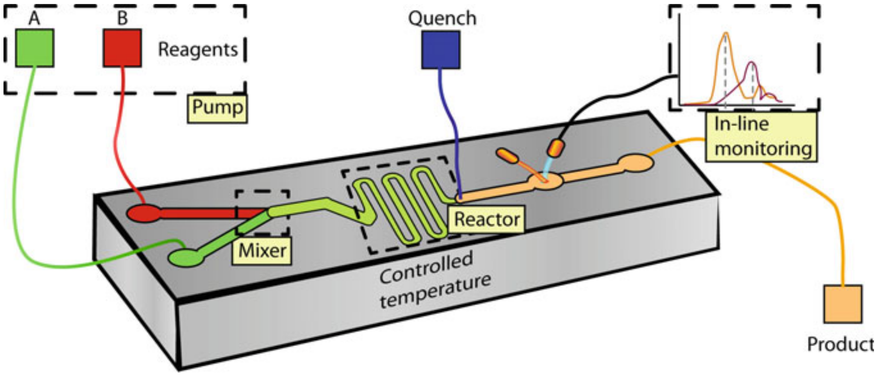

Fig. 5.1 Schematic diagram showing the main components and assembly of a microreactor system. The materials typically used for the different parts of the reactor are glass, silicon, stainless steel, ceramics and polymers. The reagents can be pumped to the reactor by several means (syringe or HPLC pumps, pressurized containers, etc.). Different types of mixers can be used such as passive (based on structure of the channel walls) or active (ultrasound, magnetic, dielectric, etc.). The reaction can be quenched by addition of a specific molecule, or by changing the temperature. The in-line monitoring can be based on Raman, UV–Vis, FTIR, magnetic, etc.

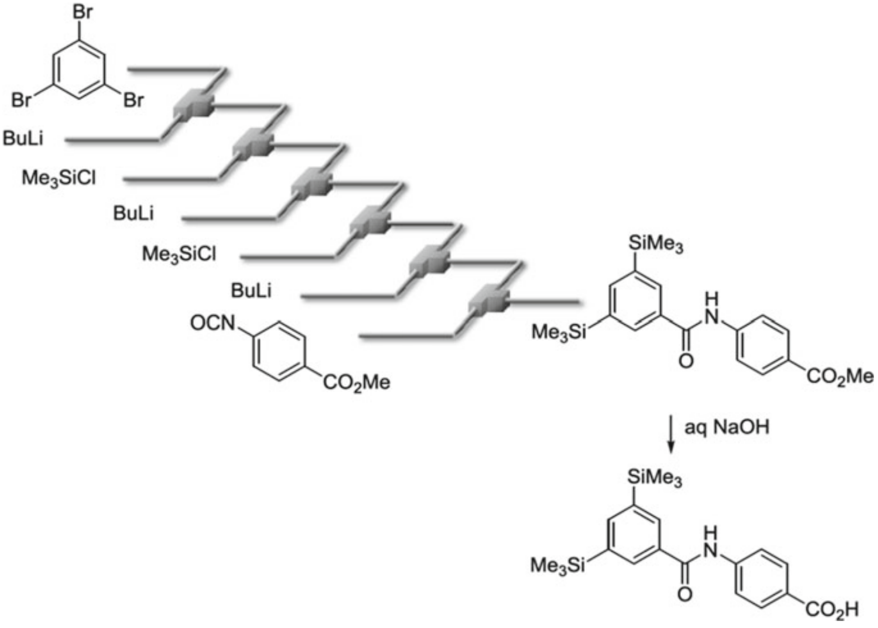

Fig. 5.2 Linear sequence of telescoped flow steps leading to a functionalized diaryl amide. Copyright 2013 the Royal Society of Chemistry. Reproduced with permission

with the conventional batch process that makes ciprofloxacin in more than 100 h to achieve a similar throughput.

Practitioners moving from batch to flow systems face invariably the challenges of miniaturization as flow reactors are usually smaller than flasks, even if a given product can ultimately be obtained in significant amount or concentration after several cycles. Another well-known challenge is mixing, for which non-dimensional analysis can assist, based on the Reynolds, Peclet and Dämkholer numbers, among others (Günther and Jensen 2006; Nagy et al. 2012). Perhaps, a curious exception can be seen in the case of segmented liquid–liquid and gas–liquid flows, which provide enhanced mixing, when liquid slugs or microdroplets are obtained without any special device fabrication features (Kashid et al. 2005). These 'quantified' or segmented flows have spawned a great body of research, and are known among other terms as digital microfluidics, or ultrahigh throughput microfluidics when millions of picoliter droplets are created (Fig. 5.3, Kaminski and Garstecki 2017).

That said, the concept of 'small dimension' should be taken with caution, at least clarified in diagrams and experimental protocols. Most flow systems do not necessarily involve micro-dimensions, or those employed in microfluidics and microchips (*vide infra*). Thus, reactors and pumps tolerating volumes of a few mL allow the safe preparation of organic compounds at appreciable reaction rates.

We can arrange sonication physico-chemical effects in two groups: (a) motion-inducing and (b) static (Fig. 5.4). For example, acoustic streaming, jetting and shock waves influence mixing, and hence belong to the former classification, whereas the latter refers to sonoluminescence, radical reactions and sonochemiluminescence. Though not verified by us, one could argue that the local concentration gradients that can be established as a result of sonochemistry could induce some kind of flow. Cavitation should be understood in this context as the formation of a gas cavity, i.e. a bubble in a liquid (not to be confused with pitting of a solid material as a result of erosion) (Lohse 2005).

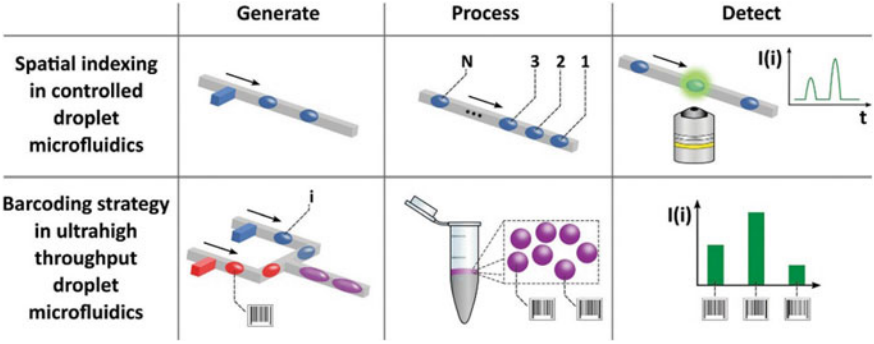

Fig. 5.3 Scheme illustrating comparative strategies for tracking of the identity of droplets in the screen: either using spatial indexing or barcoding based on fluorescent dyes or biomolecular reporters such as nucleic acids. Copyright 2017 the Royal Society of Chemistry. Reproduced with permission

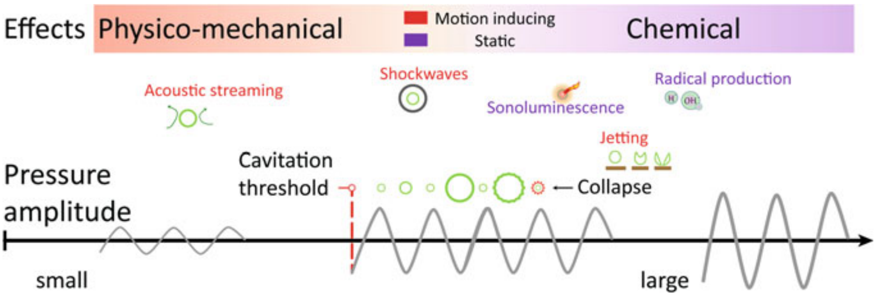

Fig. 5.4 Schematic overview of mechanical and chemical effects arising from acoustic irradiation, which may largely influence flow systems

The application of sonication to continuous flow has multiple benefits, which are particularly noticeable when one moves to smaller scales (*microfluidics*). In general, the use of tubular sonoreactors having tubes with diameter and length optimized for ensuring a proper transfer of energy allows a convenient industrial extrapolation. Furthermore, the wall of the tube serves as the ultrasonic emission surface, thus focusing cavitation on the centre of the tube and hence limiting corrosion (Chatel 2017). One evident drawback of microfluidic systems is the fact that clogging or obstruction of small channels can occur for some undesired reason, or a product of a given reaction generates it. The use of ultrasonic agitation often suffices as technical solution by enhancing considerably mass and heat transfer. In practice, the limitations inherent to flow operations dealing with large volumes of liquid, which would require large-scale ultrasonic transducers (Vinatoru 2001; Leonelli and Mason 2010; Peshkovsky and Bystryak 2014), can be mitigated by means of so-called loop (sono)reactors, i.e. a flow system where a small, yet powerful, ultrasonic source is mounted on a reactor through which the bulk reaction mixture is pumped in a continuous fashion. Such devices, suitable for scaling-up purposes (see also Chap. 8), represent convenient strategies for the synthesis and processing of large amounts of chemicals, like fuels/biofuels among others (Cintas et al. 2010; Calcio Gaudino et al. 2014). A recent study casts doubt on naming such loop reactors a continuous flow reactor (Vinatoru and Mason 2017). Since ultrasound is applied to a small volume of the total mixture, there is an obvious uncertainty as the number of passes through the loop required to achieve completion is not defined. The problem, however, has little to do with the loop reactor set-up itself, but rather with the fact that numerical estimations of working parameters should be specified in order to determine the real sonication time and the total power density delivered to the system.

5.3 Microflow Sonoreactors in Chemical Synthesis

As noted in the preceding section, early studies combining sonication and any type of continuous flow were focused essentially on solving a major technical trouble: clogging. Other pluses that cavitation might induce in the reaction mixture have been often overlooked. For example, given the omnipresence of ultrasonic baths in most chemical labs for cleaning activities, scientist see sonication as a non-invasive method for removing contamination from delicate objects. Unfortunately, its chemical effects are barely known to them. As shown in Fig. 5.5, such designs can be easily accomplished by immersing the microchannel tubing in an ultrasonic bath. The device was employed to carry out the phase-transfer reaction of benzyl chloride and sodium sulphide in the presence of an ammonium salt as catalyst (Aljbour et al. 2009).

A further example that discloses several pluses is provided by the well-known Barton decarboxylation performed and optimized under ultrasonic continuous flow, which enabled bulkier synthesis (Fig. 5.6). The reductive decarboxylation of hexanoic acid was chosen as model reaction, reaching up to 53% yield at 35 °C (Banaszak-Léonard et al. 2016). All the reactants were dissolved in a mixture of CH_2Cl_2–MeOH and pumped into the system (HPLC pump) below 35 °C. Then, the solution was entered into a tubular reactor (Teflon coil, 0.8 mm internal diameter, 40 m length, $V = 20.1$ mL) heated in an ultrasonic bath (from room temperature to 35 °C), with power (10–100% of 330 W) and frequency (37 or 80 kHz) regulators. To keep the reaction mixture in liquid state, the pressure was set to 0.1 MPa by a back-pressure valve. The process was quenched by cooling the solution in a cooling bath. As a radical process, the Barton decarboxylation benefited from both

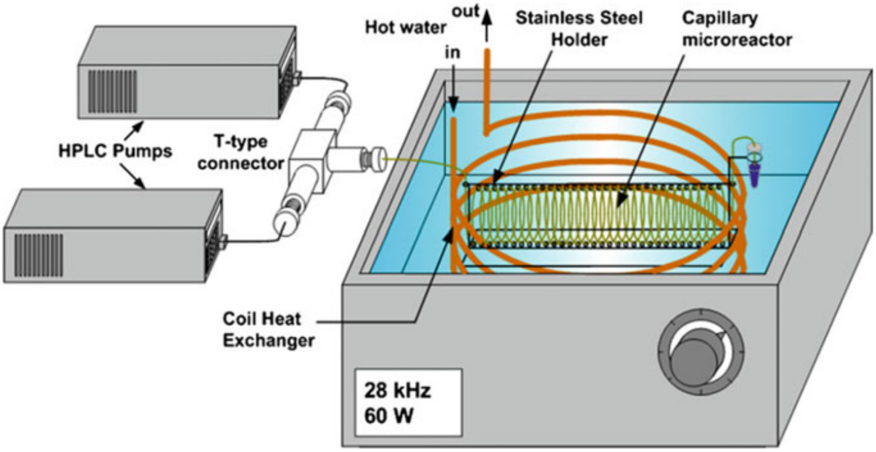

Fig. 5.5 Ultrasonic capillary microreactor for the phase-transfer catalysis of benzyl chloride and sodium sulphide in the presence of a surfactant. Copyright 2009 Elsevier BV. Reproduced with permission

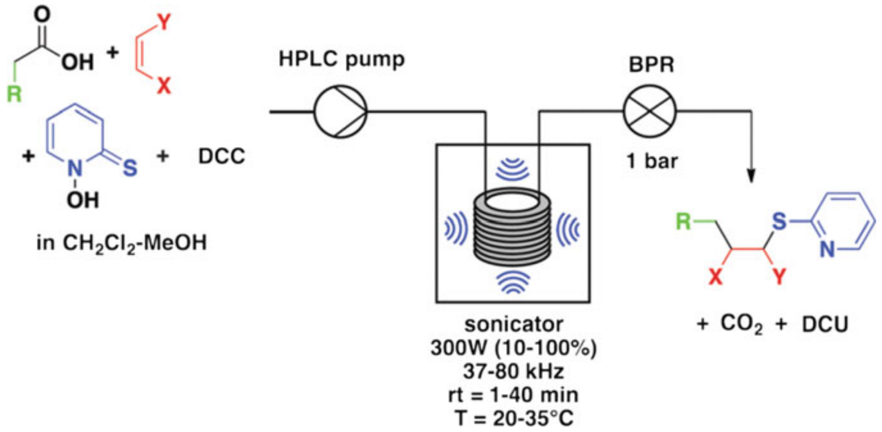

Fig. 5.6 Barton decarboxylation of carboxylic acids conducted under sonication and continuous flow (general synthetic scheme). The process was optimized for hexanoic acid and *N*-phenylmaleimide. DCC = dicyclohexylcarbodiimide, DCU = dicyclohexylurea. Copyright 2016 the Royal Society of Chemistry. Reproduced with permission

physical and chemical effects induced by cavitation, i.e. bringing energy for radical formation (e.g. OH$^\cdot$, H$^\cdot$) and removing oxygen and releasing CO_2 from the solution (by-products are CO_2 and dicyclohexylurea).

Running reactions under continuous flow enables safe preparation of hazardous substances, like the potentially explosive polynitrophenol displayed in Fig. 5.7 (Cantillo et al. 2014). The nitration reaction also requires a mixture of toxic and oxidizing mineral acids, even if employed in dilute conditions. The transformation usually leads to a mixture of mono- and trinitro-phloroglucinols. Optimal results for the latter (98% yield as determined by HPLC) were achieved at 40 °C using a thermostated ultrasonic bath.

Notably, continuous processing enables the incorporation of automated machinery to replace conventional glassware and separation/purification protocols conducted in batch mode. The adoption of machines to perform complex multistep syntheses that involve routine workup steps too, not only avoids risks inherent to chemical manipulation but also reduces the discovery-to-manufacturing time frame (Fitzpatrick et al. 2016). No less important is the fact that the total footprint of miniaturized versions of conventional plants can be significantly reduced.

In an impressive example of chemical synthesis to form a biologically active intermediate from a tricyclic ketone (Ingham et al. 2015), a single researcher was able to execute and control a fully telescoped eight-step synthesis (actually comprising three synthetic transformations with five intermediate downstream processing steps). A machined set-up was controlled with a low-cost computer-assisted monitoring (e.g. webcams). Note in Fig. 5.8 the use of sonication in two critical points (steps 1 and 2) of the tubing system to ameliorate continuous flow of heterogeneous mixtures.

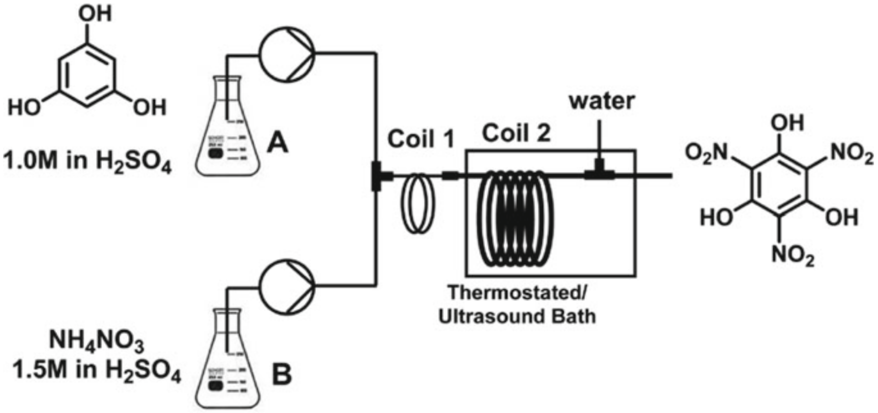

Fig. 5.7 Continuous flow nitration of phloroglucinol. Copyright 2014 the American Chemical Society. Reproduced with permission

As one goes down in scale, the miniaturization of reactors or components are ideally translated into a chip (see Fig. 5.1). The incorporation of sonication into microdevices needs to overcome the drawback of 'the small', because conventional equipment employed in batch and even continuous flow should be replaced by transducing elements that can be fabricated on a chip scale; perhaps, the most widely used are piezoelectric materials. In chemical synthesis, the use of surface acoustic waves (SAWs), i.e. standing waves that propagate along the surface of a piezoelectric material, is quite promising and permits reactions in microdroplets (Kulkarni et al. 2009). However, the working frequencies are much greater (a few MHz) than those employed usually in power ultrasonics, where cavitation effects are desired. The observed enhancements are largely, if not purely, thermal, as greater intensities are required to induce cavitation of a liquid at high frequencies.

5.4 Micro-Sonoreactors: Miscellaneous Applications

The preceding sections provide presumably a good overview on the benefits stemming from combining sonication and flow in microchannels (microfluidics), often leading to synergetic results. This has been discussed in recent perspectives and has been highlighted as a Process Intensification approach (Fernandez Rivas et al. 2012a; Fernandez Rivas and Kuhn 2016). This section will therefore concentrate on a few applications other than chemical synthesis. There is a vast literature covering the so-called field of acoustofluidics en route to the design of acoustic sensor and actuators, which are beyond the scope of this chapter (Friend and Yeo 2011). A further understanding of microfluidics also requires some knowledge of physics because different phenomena and forces dominate mass transport, which are markedly different

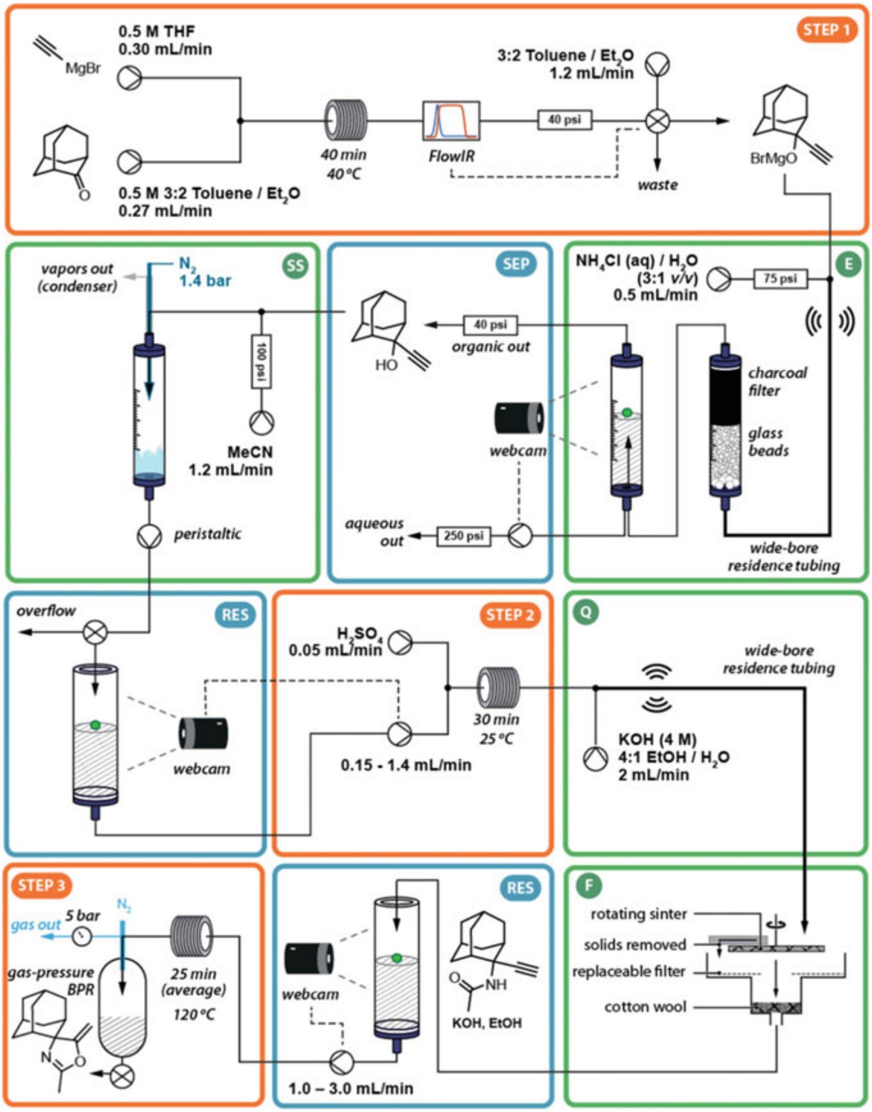

Fig. 5.8 A telescoped eight-step system with adoption of machine assistance leading to a polycyclic intermediate of biological interest. Copyright 2016 the American Chemical Society. Reproduced with permission

from those of larger scales (Bruus 2012). In particular, laminar flow characterized by low numbers of Reynolds takes place in microchannels. Acoustic cavitation does not occur easily in microfluidics because of the high static pressure inside the microchannel, which promotes the fast dissolution of microbubbles. In practice, small particles or impurities in liquids suffice to create gas bubbles at pressures much lower than those required to overcome cohesion forces in liquids (the Blake threshold pressure). In addition, acoustically driven capillary waves travelling on the liquid surface can induce cavitation in narrow channels as well (Fernandez Rivas and Kuhn 2016).

As mentioned before, standing waves represent a convenient tool for the fabrication of microactuators and microsensors, which are suitable for analytical and bioanalytical applications. The acoustic radiation pressure along with other secondary forces arising from such high ultrasonic frequencies causes the levitation of suspended matter that can further be concentrated and separated. This acoustophoresis has been employed in the fractionation and separation of particles, including blood cells in continuous flow (Lenshof et al. 2012), and dynamic photobioreactor systems that enhance the medium replacement process in concentrated microalgae cultivation (Lee and Li 2017). In routine proteomics protocols, a microscale in-gel processing and tryptic digestion of proteins takes no more than 30 min (overall) using SAWs (at ~20 MHz). The method competes favourably with the standard experiment that involves overnight digestion (Kulkarni et al. 2010).

Ultrasonic equipment, such as bath or probes (also known as horns), can be considerably inefficient to transmit the acoustic power as the system becomes smaller if done without a proper understanding of the phenomena behind acoustic cavitation. The miniaturization of these devices is also a technical challenge often overlooked. In contrast, integrating a piezoelectric actuator directly into the microfluidic system has been proven to be more energetically efficient, but design considerations need to be followed (Navarro-Brull et al. 2014). The diagram shown in Fig. 5.9 shows a home-made design, where a piezo-element (transducer) converts electricity into mechanical vibrations that are transferred to the liquid contained in the microreactor. Typical phenomena resulting from acoustic cavitation are summarized on the top, namely, formation of radical species, shock waves, streaming or sonoluminescence (Fernandez Rivas et al. 2012a, b, c; Fernandez Rivas and Kuhn 2016). The presence of artificially created crevices ensures the formation of bubbles at desired spots, which resulted in lowering the energy threshold for cavitation, and a significant increase in the energy efficiency measured in terms of radical production (Fernandez Rivas et al. 2010). Such microreactors are ideal for studying fundamental aspects of sonochemistry under spatial control, and other mechanisms or effects of cavitation, such as bubble nucleation, erosion, surface cleaning and sonoluminescence (Fernandez Rivas et al. 2012b, c, 2013a, b). Additionally, bubble structures generated from micromachined crevices on surfaces show more homogeneous size and distribution, as inferred from luminol luminescence, than the multibubble configuration arising from bath or horns at a given power and frequency (Fernandez Rivas et al. 2010).

The same microreactor principle based on artificial crevices has been used for improving mixing when acoustic pressures lower than required for bubble nucleation are employed (Bolaños-Jiménez et al. 2017). As shown in Fig. 5.9b), this reactor has also been scaled-up and numbered up, though still as a batch type. The authors have proposed further studies to attain continuous flow conditions.

In a different multilayered design, shown in Fig. 5.10, a piezoelectric actuator is integrated with a Teflon microreactor that was employed for handling solid-forming

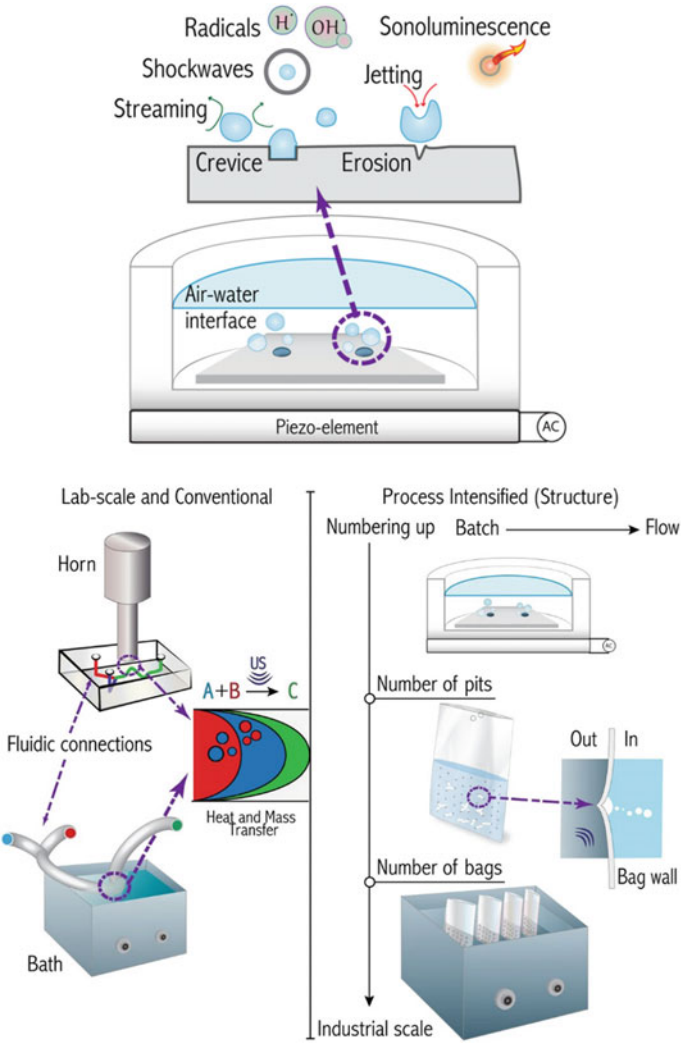

Fig. 5.9 Top: A tailor-made ultrasonic device of the bath type with a total volume of 250 µL. A miniaturized transducer is coupled to the bath, and the microreactor is completed by a substrate onto which artificial crevices have been etched. Bubbles are formed from the natural and artificial crevices in the wall of the reactor or dissolved solid particles. Bottom: A scale-up and numbering up process has been also described based on the same principle. Copyright 2012a the Royal Society of Chemistry, and 2016 Springer. Reproduced with permission

reactions (Kuhn et al. 2011). Stable cavitation appears to be responsible for the formation of gas bubbles upon ultrasonic irradiation, which also contributes to the breakage of particle agglomerates. This can be viewed in the same Figure (right) depicting the rapid fragmentation and dissolution of solid particles after bubble collapse.

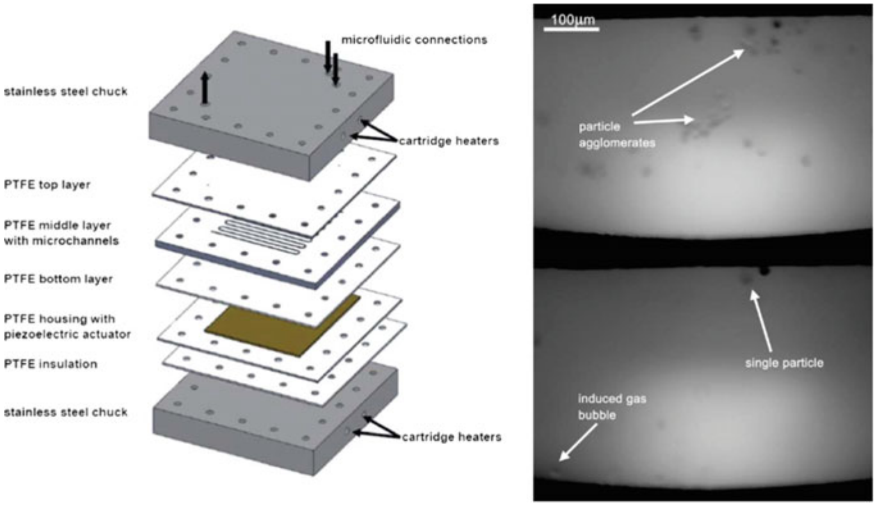

Fig. 5.10 Multilayer assembly of a micro-sonoreactor using a piezoelectric actuator with teflon (PTFE) components (left). Right: microscopic images showing the rapid dissolution of solid particles after sonication (50 kHz, 30 W). Copyright 2011 the Royal Society of Chemistry. Reproduced with permission

Counter-intuitively, these novel devices not only overcome clogging of the microchannels but can also enable kinetic control of nucleation and further aggregation, which are key issues in crystallization. Such phenomena are still poorly explored and hence understood in microfluidics, although recent studies on hydroxyapatite crystallization show significant advantages over batch processes: particles are more crystalline and less contaminated (Castro et al. 2013). Transient cavitation is presumably the driving force in crystal nucleation under ultrasound as evidenced by sonocrystallization of adipic acid (Rossi et al. 2015).

An interesting application of the mechanical effects of sonication in microchannels that we consider an appropriate epilogue here targeting infectious pathologies is the facile bacterial sonolysis with oscillating cavitational bubbles in a microfluidic device (Tandiono et al. 2012). The latter consists of a microchannel and four piezoelectric transducers mounted on a glass substrate. Complete lysis could be achieved quickly after ultrasound exposure with an increase in temperature of less than 3 °C. Rod-shaped *E. coli* bacteria were fragmented into small particles in less than 0.4 s, while more robust *P. pastoris* yeast cells were disrupted completely in ca. 1.0 s.

5.5 Conclusion

The combined use of sonication and continuous flow, especially in microchannels as outlined through this chapter, could one day be an easy and reliable protocol in complex chemical synthesis. Reactors composed of multiple compartments can be assembled into small machines with complete automation, integrating ultrasonic transducers in critical points to prevent solid formation and ensuring kinetic control. Ultrasound can be used with several parameters (frequency, acoustic pressure) that allow the fine-tuning of many physico-chemical effects (radical production, sonoluminescence). With the right knowledge, it is possible to discriminate when only mechanical or chemical effects are desired, and similarly, into motion-inducing or static. While this is going to enable us to standardize numerous protocols in synthesis and processing, other applications of acoustofluidics have also shown enormous versatility in particle separation, cell disruption or crystallization to name a few. In a reference to this chapter's title, we expect that the times where microfluidics and ultrasound were overlooked are now gone. We also hope that its combination will be a step forward towards a digitized, safer and greener chemistry.

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Chapter 6
Ultrasound as Mechanical Force

Abstract Acoustic cavitation invariably combines chemical and mechanical effects that stem from bubble collapse in liquids. Strategies to harness preferentially the role of mechanochemistry in sonochemistry have been invented and developed in recent years, demonstrating enormous versatility from synthesis and catalysis to biology and analytical monitoring. Most cases involve polymers containing weak bonds that can be fragmented by sonication. The effects are dependent largely on both the nature of substrates and the strength of cavitational collapse.

6.1 Introduction: What Mechanochemistry Is

Mechanochemistry is the branch of chemistry that deals with the mechanical activation of molecules and materials. These everyday actions and phenomena, such as stretching, milling and grinding, date back to the origins of human civilization and have long been used to induce chemical reactions. In fact, rubbing sticks together to make fire is probably one of the earliest mechanochemical transformations to have been discovered by man. According to IUPAC definitions, a mechanochemical reaction involves a chemical reaction that is induced by the direct absorption of mechanical energy (Fernández-Bertran 1999). Some authors have argued that this rather broad definition is inappropriate and that the term should only be used when mechanical energy directly breaks strong bonds, for example, in polymers or in single molecule (Kaupp 2009). This restriction may mislead some readers as the literature often alludes to mechanochemistry in the broader sense. After all, nature itself harnesses mechanotransduction processes to transform mechanical force into chemical/biochemical signals. The motion of cells and bacteria, the interactions of cells with their environment, ion channel opening in membranes and conformational changes in biomolecules are all manifestations of chemical responses induced by weak forces (Gillespie and Walker 2001; Chalfie 2009). Mechanical effects that induce changes in atomic positions and molecular structure, which are characteristic of polymorphism and conformational equilibria, for instance, could then be accurately described in terms of *mechanophysics* (Kaupp 2009). This semantic distinction is not usually

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used, although it has resulted in two distinctive domains being defined: *covalent* and *non-covalent* mechanochemistry, the latter of which is also called *soft mechanochemistry* (Ribas-Arino and Marx 2012; Zhang et al. 2015; Lavalle et al. 2016; Stauch and Dreuw 2016; Garcia-Manyes and Beedle 2017). In covalent mechanochemistry, a mechanical action causes ruptures at the molecular level (although as we shall see later bond formation can occur as well), leading to a new substance or a material with different properties. These processes are usually irreversible, meaning that the force causes a permanent change in the molecules which do not revert to their initial state when the force is removed. On the other hand, non-covalent mechanochemistry does not affect chemical bonds and its processes are generally reversible, relying on conformational processes that affect small fragments and supramolecular entities. Both fields are important, complementary and are involved in the development of chemo-mechanoresponsive systems.

Mechanochemistry offers inherent advantages and opportunities for cleaner syntheses and environmentally compatible chemistry. Reactions in the field generally occur between solids, often in fast and quantitative protocols, require either no or reduced amounts of volatile solvents, while purification and recycling are greatly facilitated. Accordingly, most mechanochemical applications involve solvent-free transformations or slurries containing low solvent quantities, which sets them apart from ultrasonic reactions that require a liquid phase for the propagation of sound waves and the induction of cavitation.

6.2 Sonochemistry: Tribochemical Interpretations

Sonochemists are of course aware of the intertwined chemical and mechanical effects caused by cavitational collapse, with the latter being largely due to the shear forces and shock waves experienced at the bubble–bulk liquid interface that are capable of dramatically influencing heterogeneous reactions (Mason and Lorimer 2002). Useful analogies between sonochemistry and mechanochemistry can be drawn from tribochemistry, the subdiscipline that deals with the stimulation of chemical transformations through friction at boundary surfaces, leading to mechanical-energy-caused physico-chemical changes in solids (Boldyrev 1995). For example, atomic dislocations and structural defects in solids often serve as the preferred reaction sites under ultrasonic action. As expected, mechanical effects, such as chemical production, are strongly dependent on the parameters that influence cavitational events. In particular, there is an inverse dependence between mechanical and chemical effects and the frequency of ultrasound (Mason et al. 2011). Moreover, the estimated thresholds for cavitational, chemical and mechanical effects to occur are also dependent on acoustic frequency (Nguyen et al. 2017). At frequencies lower than 100 kHz, the mechanical effect threshold, determined using the erosion of aluminium foil, nearly equals the threshold required for cavitation. However, the threshold for mechanical effects is much higher than the cavitation threshold at high frequency.

Unlike solid–solid contact, during which even plasma states can be created, the generation and transmission of large tensile forces in liquids is a more complex process, one in which molecular control is difficult to attain. In fact, most scissions in liquids stem from the radical species formed inside the bubbles, so long as the parent reagents are volatile enough. However, shear forces may homolytically fragment large molecules (e.g. polymers) into smaller monomers, which can undergo further reactions and/or recombination (Teo et al. 2012). The mechanical properties of ultrasonic irradiation can be compared to those of an elongational flow field, in that its strain rate depends on the time passed since the onset of bubble collapse, and hence the radius of the imploding void, as well as on the distance to the bubble (Nguyen et al. 1997). Ultrasonic agitation provides high strain rates (up to 10^7 s^{-1}), compared to other flow fields, while the average masses required for chain scission or mechanophore activation (Sect. 6.3) are significantly lower, at *ca.* 10^4–10^5 Da, and are synthetically attainable molecular weights. Polymers are therefore more sensitive to the mechanical effects of sonication than small molecules, which may undergo fragmentation induced by secondary radical species. The rest of the chapter will give these issues the detailed attention they deserve as polymer mechanochemistry (Sohma 1989) is currently enjoying a significant resurgence, thanks, in part, to ultrasound technology, and is becoming a solid foundation upon which a number of innovations are being built (Cravotto et al. 2013; Li et al. 2015; Cintas et al. 2015).

6.3 The Mechanophore Concept: Ultrasonication of Polymers

Although thermal and mechanical effects coexist during bubble collapse, bond rupture is not selective and thus limits the scope of sonication in site-selective reactions in which numerous functional groups are present. Nevertheless, strained molecules and weak bonds will undergo more facile fragmentation than others and this effect may be amplified in molecules that have been adsorbed onto surfaces (i.e. heterogeneous sonochemistry), and when such groups are incorporated into polymer chains that can act as tweezers and propagate the mechanical action further (Encina et al. 1980).

As early as the 1950s, Melville and Murray performed ultrasonication experiments on a styrene-containing poly(methacrylate) solution, which resulted in polymer degradation and repolymerization (Melville and Murray 1950). This clearly provided indirect evidence of homolytic bond breaking to produce radical species initiators. Cavitation-induced cleavage in polymers is not completely random and, although it does depend somewhat on molecular weight (MW) and chain length (*vide infra*), polymer chains tend to break near the middle of large chains. This tendency can be harnessed by inserting small structural units between polymer chains, as demonstrated by Moore and associates when they placed an azo group near the centre of poly(ethyleneglycol) as it undergoes specific cleavage under sonication (Berkowski

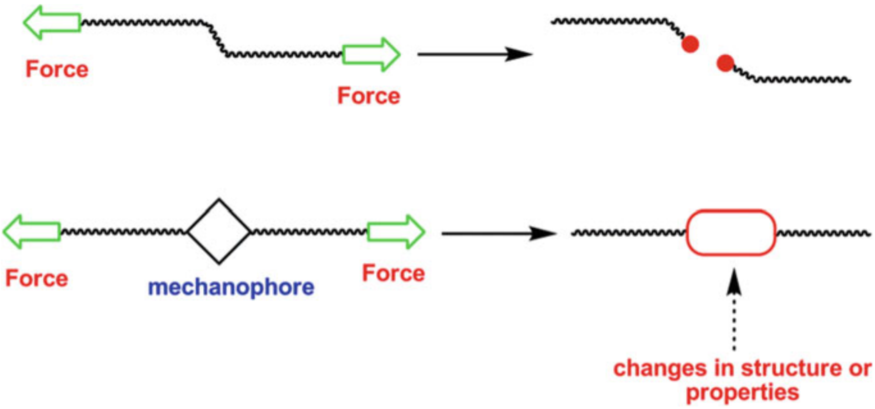

Fig. 6.1 Mechanical activation of polymers under tensile/elongational forces: (top) causing bond rupture and (bottom) activating labile units (*mechanophores*) placed near the middle point of the chain

et al. 2005). This discovery gave birth to the concept of *mechanophore*; a force-sensitive molecular unit that possesses mechanically labile bonds. As mentioned above, the adjacent long chains play a pivotal role in transmitting and propagating the shear forces generated in the reaction mixture to a small unit embedded in a larger framework. In fact, mechanical activation fails in mechanophore-end-capped polymers, thus proving that force transduction does not occur if chains are not attached at both ends of the mechanophore.

Mechanophore activation may lead to salient physico-chemical changes in colour, luminescence, isomerization, the release of small molecules and the generation of latent catalysts, etc., which can be employed in numerous applications, such as the design of sensors/actuators, material monitoring, chemical catalysis and *in vivo* delivery (Fig. 6.1). These technologies are generally 'constructive' (productive), rather than destructive (i.e. merely the fragmentation of polymer chains or mechanophore cleavage).

A striking result obtained via the sonication of a benzocyclobutene mechanophore is an apparent violation of the Woodward–Hoffmann rules, which are a fundamental cornerstone of physical organic chemistry (Hickenboth et al. 2007). In this experiment, both *cis*- and *trans*-derivatives undergo ring opening furnishing an *E,E*-configured diene, the presence of which was further corroborated by spectroscopic methods after derivatization with a chromophore-containing molecule (Fig. 6.2). This result is unexpected from a thermal activation viewpoint. In fact, only the *trans* isomer is expected to give the *E,Z*-diene. However, photochemical activation reverses this stereochemical outcome.

Additional applications of ultrasound-assisted mechanophore activation are presented in Fig. 6.3, which illustrate the broad scope of the process. For example, a spiropyran unit undergoes C–O bond cleavage and further isomerization, which translates into pronounced colour change (Davis et al. 2009). A similar case can be

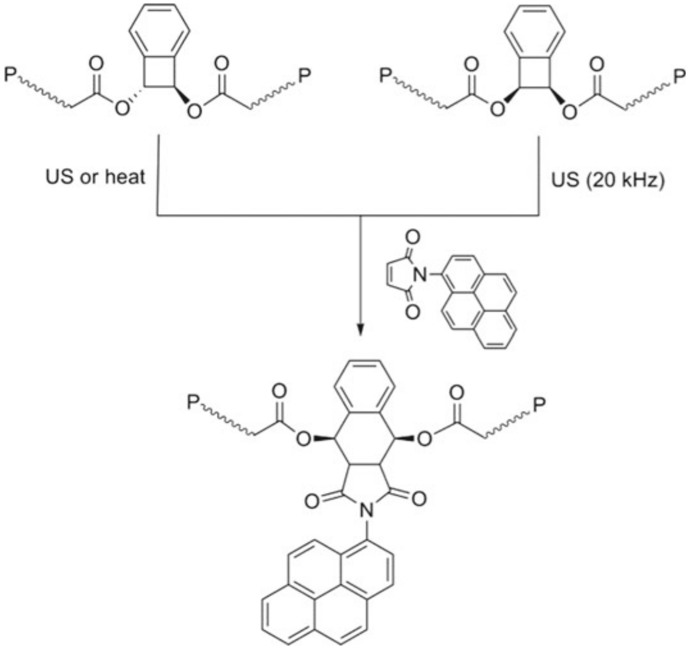

Fig. 6.2 Ultrasound-induced forbidden ring-opening transformations of benzocyclobutene mechanophores within polymer chains (denoted as P)

found in the generation of chemiluminescence from a polymer-centred 1,2-dioxetane mechanophore (not shown), which undergoes facile ring opening under mechanical stress via sonication (Chen et al. 2012). Such visual changes may be of interest when assessing the homogeneity of polymeric structures or in the development of mechanoresponsive sensors. For example, Moore and co-workers have developed an acid-masked mechanophore, based on a *gem*-dichlorocyclopropyl indene derivative, which releases HCl through bond cleavage and rearrangement followed by elimination–aromatization upon ultrasonication of the polymeric chains (Diesendruck et al. 2012). This work took advantage of previous findings by Craig and co-workers who reported the mechanical rearrangement of *gem*-dihalocyclopropanes to 2,3-dihaloalkenes (Lenhardt et al. 2009). Moreover, when *gem*-difluorocyclopropanes, embedded along a polybutadiene chain, undergo mechanochemical tension, the cyclopropyl ring opens and traps a 1,3-diradical that lives long enough to participate in further addition reactions (Lenhardt et al. 2010). In the last application highlighted in Fig. 6.3, a latent catalyst can also be generated from mechanophore-containing polymers and then released into the bulk medium, thus participating in organic transformations, such as ring-opening polymerization and ring-closing metathesis (Piermattei et al. 2009).

A recent, eye-catching application is the ability of sonication to drive and fine-tune polymer mechanochemistry and this has been harnessed in the preparation

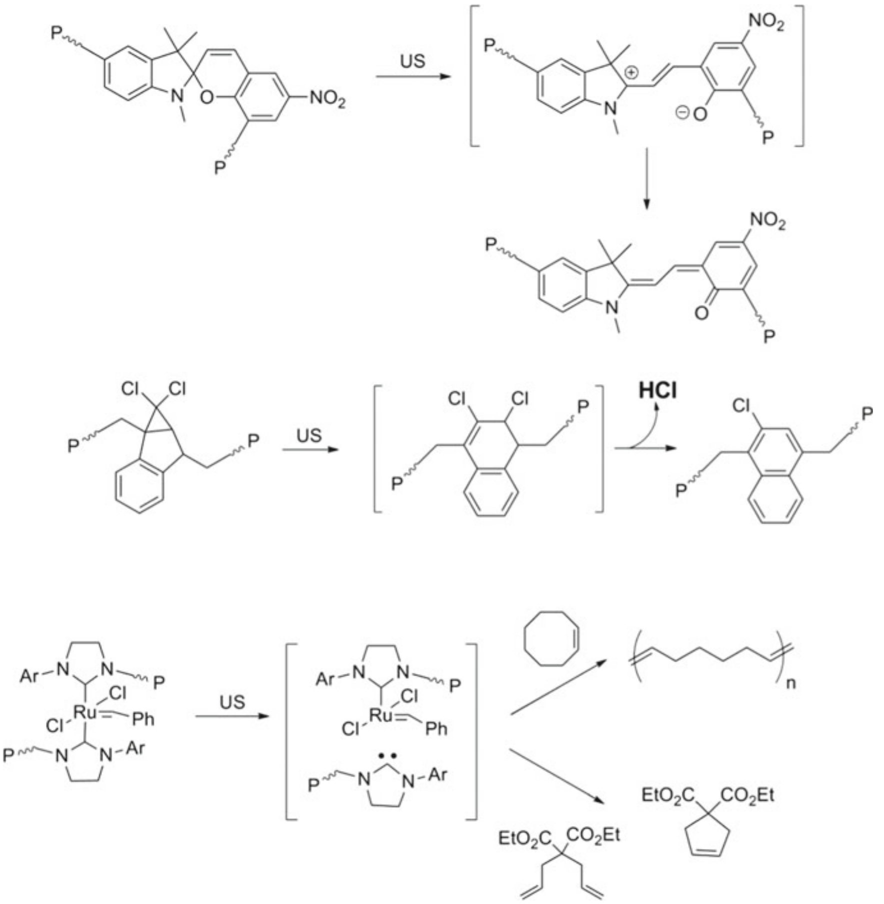

Fig. 6.3 Merging sonication and polymer mechanochemistry: activation of a variety of mechanophores embedded in the middle of chains. The symbol P stands for a polymer chain of variable length. No stereochemical features are shown

of plastic ladderene-based semiconductors which have emerged as a new class of sensitive mechanophores that are susceptible to facile ring opening in a similar way to intrinsically weak disulfides or azo groups. A ladderene consists of fused cyclobutyl rings that adopt a staircase-type conformation and exhibits enough strain to undergo rapid ring fragmentation. The strain of the terminal cyclobutene unit of a chloro-substituted [5] ladderene monomer can be alleviated through ring-opening metathesis polymerization (ROMP), triggered by a Grubbs ruthenium carbene catalyst (Fig. 6.4). Further dehydrohalogenation results in hydrocarbon homopolymers, with high-mechanophore loading along the backbone, which are then subjected to the action of mechanical force. To this end, acoustic sonication of the polyladderene causes fragmentation to give polyacetylene, a characteristic organic semiconductor,

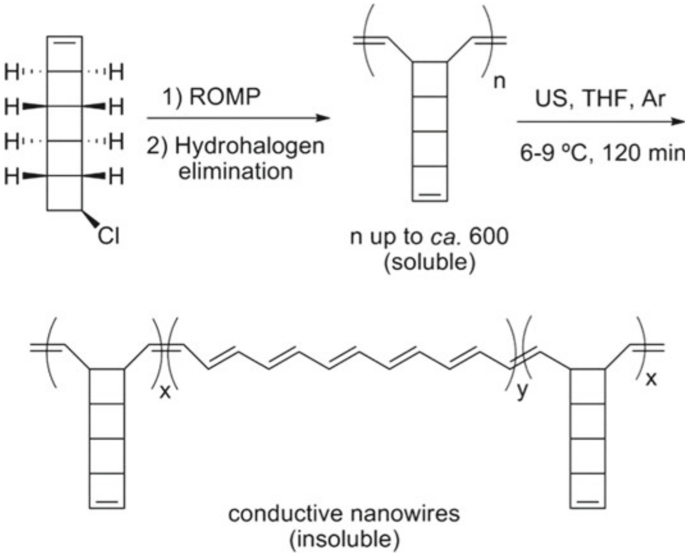

Fig. 6.4 Mechanochemical generation of polyladderene–polyacetylene copolymers that self-assemble into conductive nanowires

which undergoes subsequent aggregation after prolonged sonication. The effect is clearly visible as ultrasonication transforms a soluble and almost colourless system into an insoluble polymer that develops an intense blue colour (Chen et al. 2017).

As we shall briefly discuss in the next subsection, claims of mechanochemical reactivity induced by sonication also imply discarding other essentially thermal-activation-based mechanisms. The authors of the ladderene-to-polyacetylene study observed a correlation between the degree of polymerization and the observed rate of polyacetylene formation, as occurs with other mechanochemically sensitive polymers; longer chains gave polyacetylene copolymers faster than shorter chains during sonication. On the other hand, the rates of unimolecular, thermally activated polymerization reactions do not depend on the degree of polymerization.

6.4 Structure–Property Relationships

An in-depth understanding of how sonication induces mechanochemical transduction would allow us to elaborate a series of structural parameters that account for the observed reactivity. Sonication appears to exert a critical role above a threshold polymer mass. However, the distinction between average molecular weight (MW), and the degree of polymerization (i.e. polymer chain length), is often subtle and the literature contains contradictory results and conclusions. Early work on the ultrasonic degradation of polymers pointed to chain length as the principle parameter governing

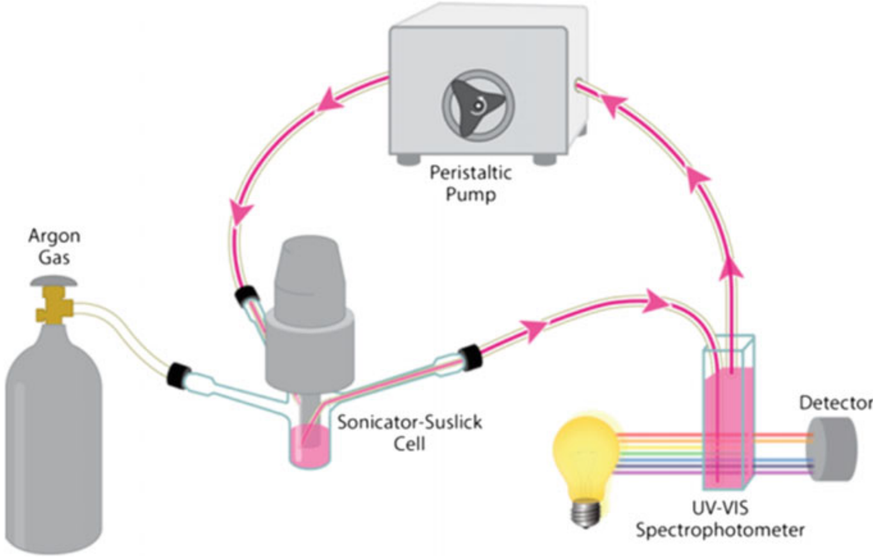

Fig. 6.5 Schematic diagram of the flow cell employed for measuring real-time ultrasonic activation rates of the spiropyran mechanophore. Copyright 2016 by the American Chemical Society. Reproduced with permission

the rate of polymer chain scission (Thomas 1959). With the advent of mechanophores, the effect of structure on chain breakage can be re-assessed in detail, while the effects of MW and polymerization degree can be decoupled. In fact, Moore and co-workers have investigated the mechanochemical ring opening of spiropyran, which was used as a model mechanophore and embedded into a variety of acrylate polymers with different repeating units and side chain compositions, as well as its conversion into the merocyanine form (Fig. 6.3, top). Kinetic information was obtained using real-time changes in UV–Vis absorption spectra (May et al. 2016). Continuous ultrasound irradiation (10.7 W/cm^2 at 3–5 °C), in methyl ethyl ketone (in which all of the polymers had good solubility), was implemented in a flow set-up at a constant flow rate of 4.5 mL/min (Fig. 6.5).

As shown by plots of kinetic constants *versus* degree of polymerization, for which all data collapse onto a single linear relationship, it is polymerization degree that was found to be the crucial descriptor of mechanochemical activity, regardless of MW and side chain constitution. Conversely, plots of rate constant against MW gave rise to differing linear regressions depending on the pendant group (Fig. 6.6).

Cavitation is a prototypical example of mechanochemistry in solution as it exerts its mechanical action through solvodynamic shear forces. While mass and degree of polymerization are the principle characteristics at play, polymer architectures can also be decorated with other structural motifs, such as cross-linking and hydrogen bonding, which ultimately determine folding properties, like in proteins and their analogues. In fact, sonication has been applied to dilute samples and the changes in

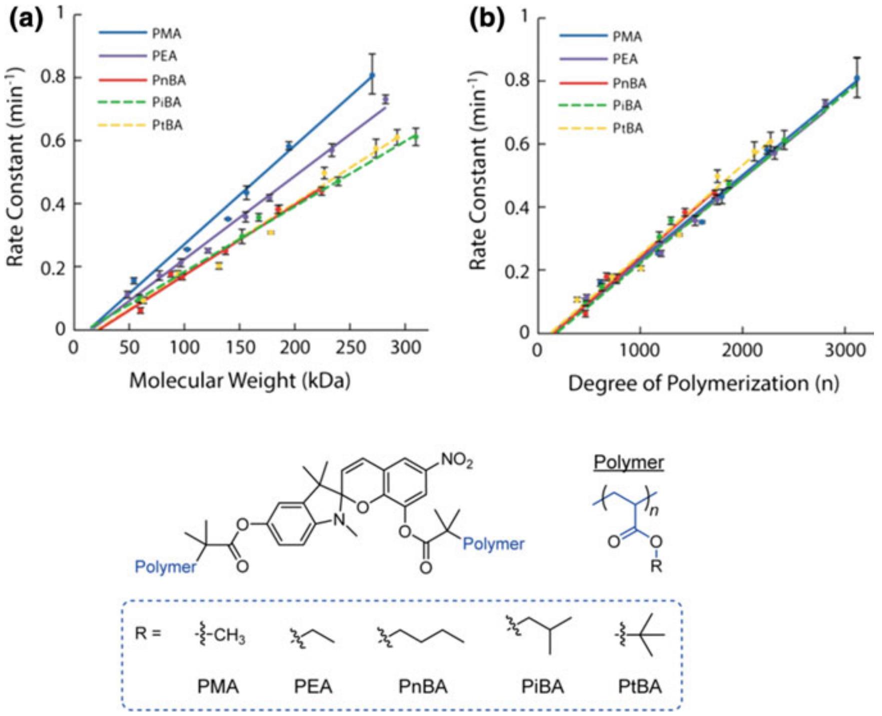

Fig. 6.6 Rate of mechanochemical activation induced by the sonication of the spiropyran mechanophore as a function of **a** number average molecular weight, and **b** degree of polymerization. Each point represents the average of two measurements with the error bar denoting the range of the two values. Copyright 2016 by the American Chemical Society. Reproduced with permission

MW, hydrodynamic radius and intrinsic viscosity were monitored in order to test the relative stability of single-chain polymer nanoparticles in solution (Levy et al. 2017). Surprisingly, an increase in the amount of cross-linking enhanced the structural stability of the polymer. The average molecular weight for linear polymers decreased from 99 to 64 kDa after ~2 h-sonication, while polymers containing 10 and 15 mol% of cross-linked features remained almost unchanged after similar sonication exposure, with average masses changing from 132 and 136 kDa to 117 and 127 kDa, respectively. Intrinsic viscosity followed similar trends, with little variation being observed. It can be concluded that the presence of additional bonds does not reduce the extent of mechanochemical reactions, but delays the fragmentation events. The collapsed structure of the polymers (increasing cross-link density) undergoes mechanochemical reactions faster, although the scission takes place in sacrificial bonds that do not involve chain fragmentation. These aspects are much more noticeable in low molecular weight polymers, which experience less tensile force than their higher molecular weight homologues. For a 100 kDa polymer, even a small amount of intramolecular cross-linkage enhances the stability of the chains and the polymer becomes essentially insensitive to solvodynamic shear when containing above 10 mol% cross-link density.

As mentioned earlier, it is not easy to distinguish thermal effects from purely mechanical ones during cavitation because thermal activation will inevitably occur at the bubble interface and in the bulk solution, even though high polymers will not be activated inside the microbubble. Sijbesma and associates addressed this issue by generating active carbene catalyst after mechanophore scission (see Fig. 6.3, bottom), and by performing the reaction under methane (CH_4), instead of argon. The change in gas largely suppresses the thermal effects of ultrasound and concomitantly enhances the activity of the in situ generated catalyst, as displayed by the performance of mechanochemically activated transesterification and alkene metathesis (Groote et al. 2012). The suppression of thermal effects caused by using CH_4 as the saturation gas apparently increases catalyst lifetime and hence, catalytic activity. The role that CH_4 plays can be rationalized using well-known sonochemical arguments. First, the use of a polyatomic, instead of a monoatomic, gas makes liquid cavitation difficult (Mason 1991). Accordingly, the enhanced survival of the free catalyst arises from its avoiding secondary sonochemical reactions, such as the formation of radical species or products derived from solvent pyrolysis. Moreover, methane is more soluble in organic solvents, hydrocarbons in particular, than argon, and this greater solubility leads to less violent bubble collapse, which also translates into slower polymer scission (Price and Smith 1993).

6.5 Conclusion

The last decade has seen numerous studies that have focused on the action of ultrasound on polymer chains that contain weak bonds or functional groups (*mechanophores*), revealing the mechanical effects of cavitational collapse. This relatively new ultrasound-induced chemistry can be tailored for multiple productive purposes, which include the design of smart and stimuli-responsive materials and the high performance of sonochemically activated latent catalysts, among others. Such mechanical effects depend strongly on molecular structure (degree of polymerization in particular) and can be advantageously decoupled from thermal effects via accurate control of working parameters, such as temperature, intensity and the nature of dissolved gases.

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Chapter 7
Hybrid Technologies in Action: Sonochemistry and Beyond

Abstract In the search for new forms of synergism, chemists have always looked for novel combinations of tools and processes that may produce improvements in efficiency and selectivity, principally, but also time frame, safety, costs and sustainability. Ultrasound has been combined with microwave heating either in loop or in flow mode or simultaneously in batch. Relevant examples are reported on the use of hybrid reactors under combined ultrasound and microwave irradiation.

7.1 Combined Microwaves/Ultrasound; A Brief Introduction

The first evidence of the synergistic effect produced by simultaneous microwave/ultrasound (MW/US) irradiation was found in 1995 (Maeda and Amemiya 1995). The two techniques are complementary with acoustic cavitation providing a large amount of concentrated energy that is released by hotspots and MW providing the dielectric and selective heating of solid particles. Combined MW/US irradiation can be performed either sequentially, by circulating the reacting mixture through the two compartments, or in simultaneous mode. This latter, synchronous system, in which the ultrasound horn is placed deep into the reaction liquid within the MW cavity, is the method of choice.

The yearly number of publications on this subject has been steadily increasing over the last 20–25 years, as can be seen in Fig. 7.1. This is representative of the large and constant growth in interest in the widespread applications of simultaneous MW and US irradiation. The majority of publications deal with extraction, while organic synthesis, biodiesel production and sample preparation for chemical analysis attract constant attention. Furthermore, interest in food applications and nanoparticle production has been growing over the last decade.

Katia Martina contributed to this chapter.

J.-M. Lévêque et al., *Organic Sonochemistry*, Ultrasound and Sonochemistry,
https://doi.org/10.1007/978-3-319-98554-1_7

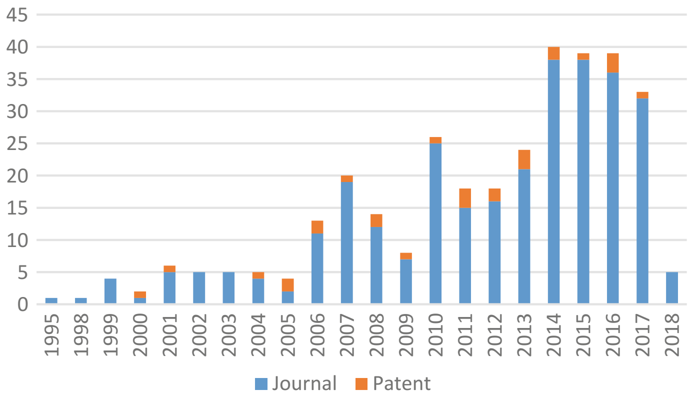


Fig. 7.1 Yearly number of publications (1995–2018) relative to the combination of US and MW

7.2 Combined MW/US Reactors

A prototype of a combined MW/US system that conveyed US waves to the reaction mixture via decalin (a low viscosity apolar liquid) was published by Chemat et al. in 1996. The reactor was placed in a double-jacketed Pyrex® vessel inside the MW oven (Chemat et al. 1996).

A further pioneering system, this time for sequential MW/US treatment, was designed using a domestic oven and flow loop reactors. A pump circulated the reacting mixture through the two separate US and MW reaction cells, as depicted in Fig. 7.2. Commercially available metallic horns were used (Cravotto et al. 2005).

More complete technical considerations have recently been taken into consideration when designing simultaneous MW and US irradiation protocols. In fact, US irradiation can be delivered by a non-metallic-horn inserted into a modified MW oven. The first generation of simultaneous MW/US irradiation devices used quartz horns despite the fact that their fragility makes them far from ideal for use as a piezoelectric material. Nowadays, US horns are typically made of ceramic materials, quartz, Pyrex® or special PEEK®, which contains glass fibre. Palmisano et al. have created a system using a professional MW oven (Fig. 7.3) which can monitor and record all the main parameters (Palmisano et al. 2007). Furthermore, constant cooling can be provided, when required, by a circulating refrigerating fluid that is transparent to MW and thus prevents the reaction from reaching boiling point, which would result in negligible cavitation.

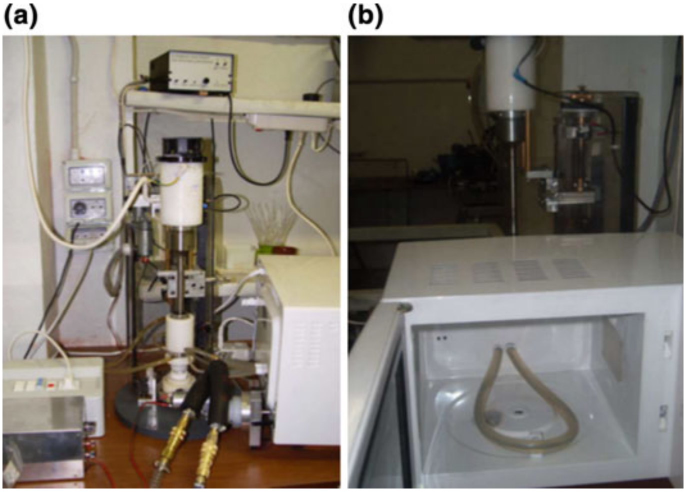


Fig. 7.2 A reactor prototype featuring combined US/MW irradiation. **a** US horn and reaction vessel made of titanium. The reaction vessel is cooled by a flow of refrigerated oil, **b** the reaction mixture circulates between the US-cell and the MW oven. Copyright 2005 © Elsevier. Reproduced with permission

Fig. 7.3 Set-up for simultaneous MW/US irradiation in a professional oven, Microsynth-Milestone (Italy) equipped with a Pyrex® horn

7.3 Combined MW/US and US/Flow Production of Nanoparticles

Ultrasonic irradiation has been used to improve the efficiency of spray pyrolysis, which is a continuous flow process that operates at ambient pressure for the production of inorganic powders and films. Atomization by US has the advantage of

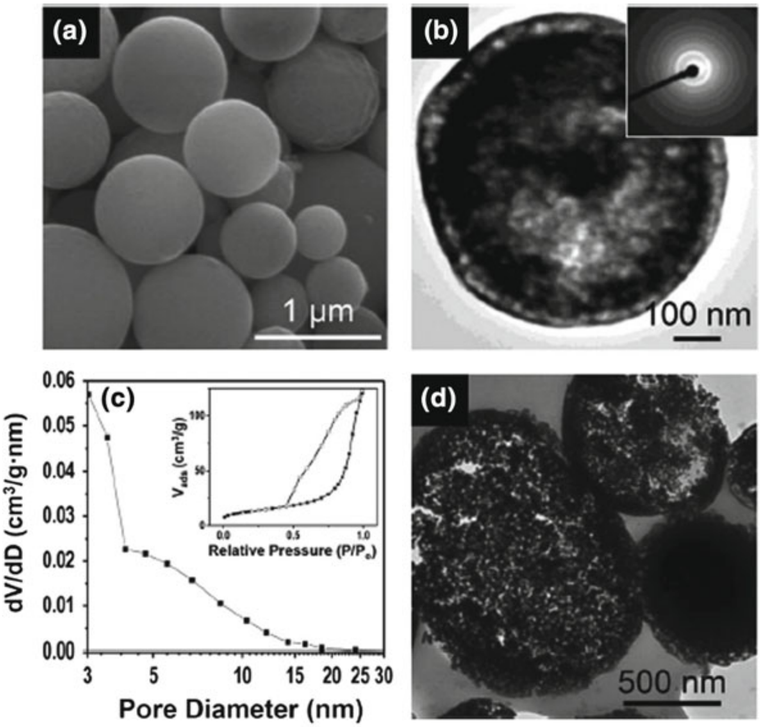


Fig. 1 (a) SEM image, (b) TEM image with inset SAED, (c) BJH pore size distribution with inset N_2 isotherm, and (d) TEM image of microtomed LTO-USS particle.

Fig. 7.4 SEM and TEM images of La–Ti–O particles. Copyright 2017 Royal Society of Chemistry. Reproduced with permission

narrowing drop size distribution, although its low throughput is considered to be the main disadvantage.

Ultrasonic spray pyrolysis was carried out in Milošević et al. (1996), for the production of micrometric and sub-micrometric spherical particles of $BaTiO_3$ and $TiCl_4$ (Milošević et al. 1996). When the technique was implemented in the form of air-assisted ultrasonic atomization, it produced much smaller particles than those produced by conventional ultrasonic spray pyrolysis, despite the significantly larger precursor drop size (Tsai et al. 2004). This continuous scalable route has also seen to be used in the production of materials with complex compositions, such as porous polycrystalline microspheres of La–Ti–O and $LaTiO_2N$, as shown in Fig. 7.4 (Rugen et al. 2017).

Fu et al. have recently attempted the preparation of single-crystalline $NaSbO_3$ nanoplates and have developed a facile and general synthetic strategy. The published protocol describes the design and assembly of components for a simple ultrasonic spray pyrolysis reactor (Fu et al. 2017). The same research group prepared luminescent carbon dots and used the chemical aerosol flow method to maximize productivity (Fu et al. 2014).

Another example of high-quality nanoparticle production has been carried out giving tuned particle properties and size in short production times using simultaneous US and MW irradiation (Cravotto and Boffa 2014).

Nanoscaled ZnO is of very great interest because it is a common photocatalyst that exhibits enhanced performance. The synergic effect that MW and US grant to the preparation of well-defined flower-like nanostructures in surfactant-free conditions has been described by Li et al. The optimized procedure was performed via a 5 min sonication at 1000 W of a zinc acetate solution in hydroxide aqueous solution, followed by MW heating combined with pulsed US irradiation (1 s on and 2 s off) at a power of 500 W for 30 min (Li et al. 2011). More recently, the same authors prepared hexagonal hourglass-like microstructures from the MW irradiation of ZnO with UV assistance and double sonication provided by two transducers working at different frequencies (25 and 40 kHz) and fixed 220 W power (Li et al. 2013a, b). Ultrafine and highly crystalline particles of uniform size were obtained by combining the MW oscillating field with the US acoustic streaming preventing local overheating to afford more uniform microstructures. Li et al. (2013a, b) demonstrated another valuable example of the fine-tuning of the size and morphology of ZnO nanostructures under combined MW and US irradiations. In that study, pH value, zinc precursor and Zn/2-[4-(2-hydroxyethyll)-1-piperazinyl] ethanesulfonic acid molar ratio were varied to afford a variety of ZnO micro- and nanostructures (grenade-like, round-prism-like, spindle-like, rod-like, shuttle-like and flower-like).

A number of $BiVO_4$ nanostructures have been reported to promote the degradation of numerous organic pollutants and microorganisms under visible light irradiation. It has been also documented that both the shape and size of the nanostructures have a significant effect on activity. The controlled fabrication of monocyclic $BiVO_4$ nanostructures generally requires harsh conditions, high temperature, long reaction times and either the addition of organic additives or a specific template. Combined MW/US irradiation is an attractive technique here as it enables $BiVO_4$ nanoparticles (Zhang et al. 2013) with an average size of 150 nm to be prepared at pH 2. The optimized procedure for $BiVO_4$ micro-/nanostructure preparation is performed in a combined MW/US reactor at 110 °C (HC-300A, Beijing Xianghu Technology CO., Ltd, MW power 500 W, US 800 W, 2 s sonication and 1 interruption).

Porous manganese dioxide (MnO_2) has been synthesized by P. Wang et al. Their detailed manuscript reported that the network structure varied according to its means of preparation, either via US alone or in combination with MW irradiation. An MW and US irradiation-intensified precipitation reaction has been used, in the presence of the structure-directing agent P123, to obtain manganese dioxide particles with a looser network structure, more uniform dispersion, enlarged surface area and enhanced electrochemical pseudocapacitance (Wang et al. 2014).

7.4 Simultaneous US/MW-Promoted Organic Syntheses

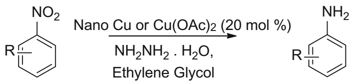
The MW and US irradiation combination has been investigated as a means of providing a reliable and cost-effective strategy for an increasing number of synthetic transformations (Cravotto and Cintas 2007).

The benign effects that simultaneous MW and US irradiation (SMUI) can provide have been proven in catalyst activations and heterogeneous catalysis as well as in a number of chemical reactions, where they have provided improved results (Carmona et al. 2015, Chowdhury and Abd Hamid 2016; Cintas et al. 2007, Cravotto et al. 2011). They have also granted further benefits to C–C coupling, Pd-catalysed reactions and in a number of other organometallic protocols.

Pd-catalysed C–C couplings have been efficiently performed under SMUI conditions. Examples of ligand-free Heck reactions have been performed using $Pd(OAc)_2$ (0.01–0.1 mol%) and Pd/C (1.0–2.0 mol% range) to give stilbene derivatives in high yields at 120 °C in 30 min (Palmisano et al. 2007). A Pyrex® horn (20.3 kHz, 35 W) together with 50 W of MW power was used during the reaction with a short initiating 200 W MW irradiation time to reach 120 °C.

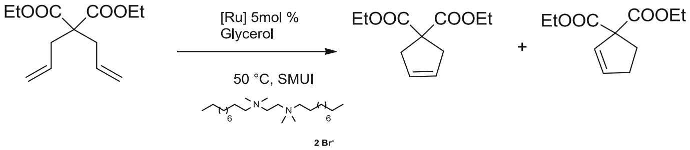
SMUI has been used to generate copper nanoparticles, for use as a catalyst, in a nitrobenzene reduction with hydrazine hydrate. The reaction was performed with $Cu(OAc)_2$ hydrazine hydrate at 105–110 °C in ethylene glycol. SMUI promoted reactions took 4.5 min to complete, while a 52% yield was obtained after 12 h under conventional conditions (Feng et al. 2014) (Scheme 7.1).

The fascinating possibility of applying SMUI hybrid technology to micellar catalysis could lead to a much wider use of green protocols. An example of this can be found in a ring-closing metathesis reaction that was performed successfully in glycerol micellar systems with Ru complexes. The SMUI reaction occurred in around 18 min under 200 W US power and 10 W MW power. The SMUI reaction was faster than the one performed with MW alone (Sacco et al. 2015) (Scheme 7.2).

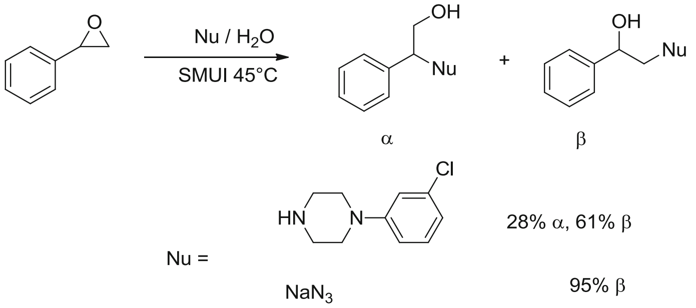


Entry	Catalyst	Method	Time	Conv (%)
1	$Cu(OAc)_2$	MW+US	4.5 min	97
2	$Cu(OAc)_2$	Conventional heating	12 h	52
3	$Cu(OAc)_2$	MW	30 min	83
4	$Cu(OAc)_2$	US	3 h	48
5	Metallic Cu	MW + US	5 min	35

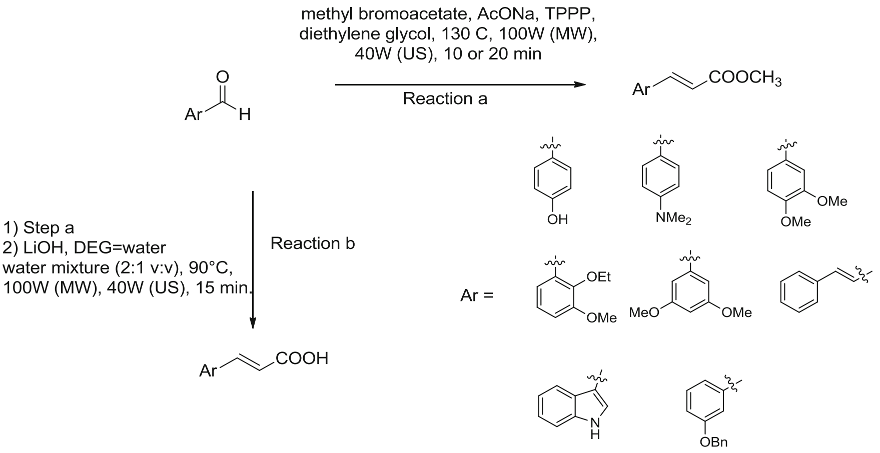
Scheme 7.1 Graphical scheme of the copper-catalysed reduction of nitrobenzene



Scheme 7.2 Graphical scheme of ring-closing metathesis



Scheme 7.3 Schematic representation of epoxide opening under SMUI



Scheme 7.4 Schematic representation of Wittig reaction and hydrolysis

Another example of SMUI use in organic synthesis is the search for new methodologies for highly regio- and stereo-selective epoxide cleavage by nucleophiles in aqueous media. A comparison of reaction conditions (conventional and MW alone at 50 °C, US alone at 45 °C, and SMUI at 45 °C) led to the finding that simultaneous irradiation provided extremely fast and regioselective epoxide opening with NaN_3 and that water media did not compete with the nucleophile (Scheme 7.3).

The Wittig olefination, using polymer-bound triphenylphosphine (TPPP), has been optimized under combined US–MW irradiation and in a tandem procedure made up of a Wittig reaction and the hydrolysis of the ester intermediates to obtain α,β-unsaturated carboxylic acids (Rossi et al. 2009) (Scheme 7.4).

7.5 Combined MW/US Transesterification Reaction

The use of combined MW/US in the process intensification of biodiesel production leads to increased mass and heat transfer in the transesterification of vegetable oil. In 2014, Soni et al. demonstrated that cavitation efficiently sped up the transesterification of vegetable castor oil in the presence of symmetrical acidic ionic liquid as the catalyst. Lower catalyst loading was required as the methanol was efficiently suspended in the oil and the reaction occurred at the interfacial phase (Soni et al. 2014). Response surface methodology (RSM) has been used by Safieddin et al. to analyse the influence of reaction conditions, including methanol/palm oil molar ratio, catalyst concentration, reaction temperature and irradiation time on biodiesel yield. RSM analyses indicated 136 and 129 s as the optimal MW/US irradiation times, respectively. Optimized parameters for full conversion (97.53%) are as follows: 1.09% catalyst concentration and a 7:3.1 methanol/oil molar ratio at 58.4 °C. Simultaneous MW/US irradiation dramatically accelerates the palm oil transesterification reaction. Pure biodiesel was obtained after only 2.2 min (Safieddin et al. 2015).

Martinez-Guerra et al. have developed an optimized protocol for the production of biodiesel from waste vegetable oil under simultaneous MW/US irradiation. While their first study focused on methanol, their second one investigated the effect of simultaneous MW and US irradiation on methanol and ethanol-based transesterifications at different alcohol-to-oil ratios in the presence of varying catalyst amounts and reaction times (Martinez-Guerra and Gude 2014, 2016). As depicted in Fig. 7.5, high US power was required to improve mass transfer efficiency with methanol. The optimized reaction was performed with a 9:1 alcohol-to-oil ratio, 0.75% catalyst, reaction time of 2 min and resulted in maximum biodiesel yields of 97 and 96% for methanol and ethanol, respectively.

Another example is soybean oil transesterification by combined MW/US irradiation using methanol and KOH. The reaction reached 98% yield under continuous ultrasonic irradiation (Yu et al. 2017).

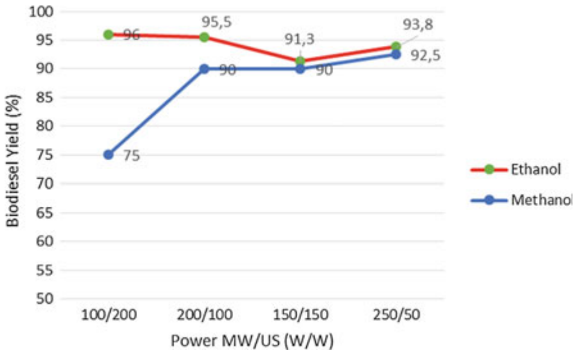


Fig. 7.5 The effect of simultaneous MW/US irradiation combinations on biodiesel yields for methanol and ethanol reactants

7.6 Combined MW/US in the Preparation of Adsorbents

The US/MW synergistic method has been used to reduce Graphene Oxide (GO) to rGO (Song et al 2016). A suspension of GO and ethylenediamine was heated to 110 °C under MW irradiation (2450 MHz, 300 W) and discontinuous ultrasonic irradiation (25 kHz, 750 W, 2 s US and 1 s interruption) for 30 min. Raman spectra were compared with those of rGO from the liquid phase exfoliation of graphite and the results confirmed that reduction had occurred. After the treatment of rGO with melamine foam, under the previously described conditions (MW/US combined irradiation), the rGO-modified melamine foam showed high porosity, superhydrophobicity and superoleophilicity. After a test, it was shown to possess high selectivity and an improved ability to collect a variety of oils and organic solvents from water.

While subsequent MW and US irradiation has been used for the preparation of a number of adsorbents, a recent study makes use of simultaneous irradiation to prepare amine-functionalized MIL-53(Al) (Ge et al. 2016). As depicted in Table 7.1, combined MW/US irradiation gave significant rate enhancements and improved yields, as compared to the hydrothermal method, and contributed to the decreased external surface areas of the monocrystals that may be due to increased crystal size. In adsorbency tests, the MW/US irradiation-prepared MIL-53(Al) showed a substantial increase in CO_2 adsorption capacity over those prepared under conventional conditions.

The effect of US and MW irradiation pretreatment on the biogas production, solids removal and dewaterability of anaerobically digested sludge has been studied by Yeneneh et al. (2013). Combined MW/US pretreatment significantly improved biogas production and specific methane yield after 17 days of the anaerobic degradation of a synthetic sludge sample that had been inoculated with digested sewage sludge. US pretreatment released extracellular polymeric substances which consist of short-chain organic matter and facilitated the release of exo-enzymes from cells that assist in the breakdown of organic materials into readily biodegradable fractions. MW irradiation enhanced the degradation of organic compounds and the formation of volatile acid. Furthermore, MW/US-treated sludge showed significantly higher dewaterability and shorter capillary suction time than the other pretreatment protocol. The optimum operating conditions were found to be 2 min of MW irradiation followed by 6 min of US.

The use of US and MW technologies has also been considered an appropriate, rapid, safe and sustainable method for the depolymerization of starch into sugars.

The delignification of lignocellulosic biomass is a matter of great interest (Singh et al. 2014). With the advent of nanoscience, researchers and industries have paid significant attention to the production of nanocellulose (NC). This high value-added product has applications that range from composites, paper, packaging, paints and oil to personal and medical care (Rajinipriya et al. 2018). The MW-promoted liquefaction of wood residues has provided a new approach to the extraction of cellulose-enriched residues from lignocellulosic biomass. In addition, US nanofibrillation can be used to isolate cellulose nanofibers from chemically purified cellulose fibres (Xie

Table 7.1 [a]NH_2–H_2BDC = 2-aminoterephthalic acid; [b]SBET is the BET specific surface area; [c]Micropore volume is the total specific pore volume determined using the adsorption branch of the N_2 isotherm at $P/P_0 = 0.99$

Sample name	Molar ratio NH_2–H_2BDC[a]:$Al(NO_3)_3$:DMF	Time	Yield (%)	SBET/(m^2 g^{-1})[b]	Micropore volume/(cm_3 g^{-1})[c]
a	4.5:3:30	10 min	68	499	1.03
b	4.5:3:30	15 min	84	529	2.10
c	4.5:3:30	20 min	91	568	3.78
d	4.5:3:30	25 min	95	636	3.53
Hydrothermal	4.5:3:30	72 h	90	1036	3.0

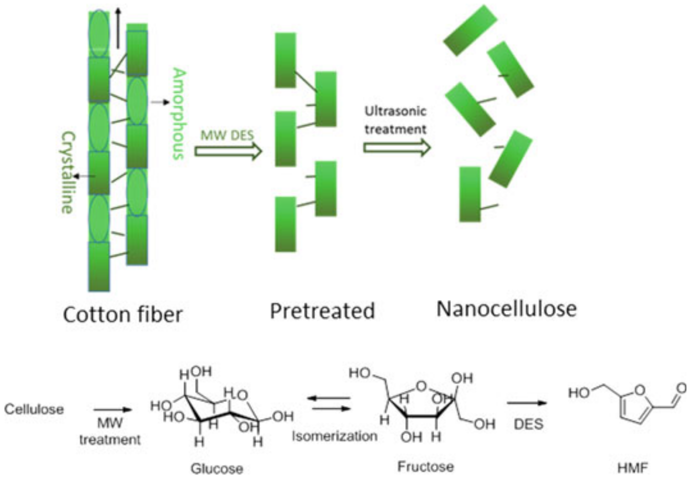


Fig. 7.6 Schematic diagram of the fabrication of CNCs using MW irradiation with DES and a subsequent high-intensity ultrasonication process

et al. 2016). Although cotton fibres contain the highest percentage (≈95%) of cellulose of the various biomass resources available, the presence of strong hydrogen bonding between the cellulose chains limits the possibility of using a facile and mild process for the production of nanocellulose. Conventional processing methods (Zheng et al. 2014) with H_2SO_4, NaOH and $NaClO_2$ thus have no significant pretreatment effects, which drove Y. Liu et al. to demonstrate that strong US cavitation improves the disintegration of cotton fibre fragments and generates cellulose nanocrystals (Liu et al. 2017). Choline chloride/oxalic acid dihydrate-based deep eutectic solvent (DES) pretreatment and high-intensity US processes were combined for the fabrication of NC. The dissolution of heterogeneous cotton fractions and the cleavage of the strong hydrogen bonds were investigated using DES under heating at $80 - 100$ °C and 800 W MW radiation for 3 min. The oxalic acid solvent was able to dissolve most of the oligosaccharides and cellulose glucose. A possible mechanism for the fabrication of NC from cotton using the presented method is illustrated in Fig. 7.6. The MWDES pretreatment was followed by US at 1200 W for 30 min. The NC crystals (74.2% yield) showed uniform morphology, with diameters in the 3–25 nm range and 100–350 nm lengths. They also displayed a relative crystallinity of 82% and high thermal stability (>320 °C). The obtained NC crystals were characterized using transmission electron microscopy (TEM), X-ray diffraction (XRD) and thermogravimetric (TG) analysis.

Chowdhury Z. and Abd Hamid SB have reported a green and sustainable synthesis of crystalline NC from dried jute stalk using a novel method that combines MW-assisted alkali pretreatment with US. The dried biomass sample (S-1) was pretreated with 2.5 M NaOH under MW irradiation at a constant power setting of 350 W over 45 min. In order to complete the delignification, the alkali-pretreated sample (S-2)

Table 7.2 Chemical composition of untreated, MW-assisted alkaline-treated, $[EMIM]^+Cl^-$ treated, bleached and H_2SO_4-treated jute stalk

Sample	α-cellulose (%)	Hemicellulose (%)	Lignin (%)	Moisture content (%)	Yield (%)
Untreated jute stalk S-1	64.30 ± 1.7	17.5 ± 1.4	6.9 ± 0.45	11.3 ± 0.3	–
MW-assisted alkaline-treated jute stalk (S-2)	76.07 ± 1.5	11.21 ± 0.89	1.21 ± 0.66	11.5 ± 0.2	68.65
Bleached jute stalk (S-3)	84.32 ± 1.12	2.98 ± 0.77	0.72 ± 0.31	11.6 ± 0.3	59.63
$[EMIM]^+Cl^-$ treated jute stalk (S-4)	87.09 ± 1.34	0.57 ± 0.21	0.54 ± 0.21	11.8 ± 0.4	48.33
H_2SO_4-treated jute stalk (S-5)	93.89 ± 1.03	0.32 ± 0.12	0.22 ± 0.13	11.7 ± 0.5	42.98

was bleached for 4 h at 55 °C using 30% H_2O_2 (S-3). The resulting crude cellulose was hydrolyzed with further US in the presence of ionic liquid [EMIM]Cl (S-4) and, separately, with traditional H_2SO_4 (S-5), in order to compare the NC, Table 7.2 shows the chemical composition of the sample at different stages. The percentage yield obtained using ionic liquid hydrolysis (48.33%) was higher than that of the H_2SO_4 process (42.98%), while the crystallinity index was higher in the presence of [EMIM]Cl (88.32%). The NC showed uniform morphology with diameters in the 10–15 nm range and 92–105 nm lengths. The sequential chemical stages were analysed using FTIR, SEM, TEM, TGA and XRD analyses.

7.7 Conclusion

Combined MW–US irradiation is a fast emerging technique that has applications in a number of fields, including pollutant degradation, organic synthesis, nanoparticle preparation and even plant extraction. The excellent results achieved mean that process implementation and scale-up to pilot plants should be envisaged for the future, although industrial applications will require specialized engineering and design.

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Chapter 8
Scaling-Up Enabling the Full Potential of Industrial Applications of Ultrasound and Hydrodynamic Cavitation

Abstract Nowadays, the requirement for process intensification in the chemical industry no longer only meets the economic considerations but also at the necessity to anchoring the industrial production in a sustainable approach, cleaner and more energy efficient technology. As we have seen in previous chapters, the phenomenon of cavitation, whether of hydrodynamic or ultrasonic origin, is likely to generate beneficial effects recognized as conducive for scale-up operations. Technically, the extrapolation of laboratory experiments on an industrial scale consists in taking into account the numerous constraints related to the production of large quantities of materials (impurities of the raw materials, duration of process, reliability, etc.) in large reactors. Thus, the development of a production line requires the realization of a pilot unit that will solve the problems encountered during the climb to scale-up. These miniaturized replicas have variable production capacities ranging from kilogram to several tens of kilograms and can be carried out in a research unit. Therefore, many laboratories have been engaged in this way for a few years and the number of publications on pilot units, whether dedicated to ultrasonic or hydrodynamic processes, has considerably increased these last years. This chapter is meant to be didactic and is not the object of a detailed development of cavitation phenomenon scaling operations. In this sense, he is interested in the basic considerations of cavitation phenomena on the industrial scale through some reminders and representative examples.

8.1 Introduction

Hydrodynamic and ultrasonic cavitation phenomena have in common that they aroused the interest of scientists during the World War I with the inception of the first submarine war. Thus, the physical theoretical foundations of cavitation were relatively discussed early, but chemists looked at the subject at different times. First, the concept of sonochemistry was stated by A. Loomis which published in 1927 a study on the 'physical and biological effects of high-frequency sound waves'. Although large-scale experiments were the subject of early research, industrial sonochemistry was born in the 1960s. The industrial sonochemical reactors were pioneered more

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than 40 years ago by Saracco and Arzano, who described an optimized reactor for the hydrogenation of unsaturated oils. They demonstrated the enormous influence of the reactor geometry on the kinetics of the reaction (Saracco and Arzano 1968). In the 90s, a major breakthrough in the industrialization of sonochemistry was found with the introduction of new loop reactors (Harwell reactor), new cylindrical pipe reactors and reactors with modular units combined in series (Branson Reactor) (Thompson and Doraiswamy 1999). About the hydrodynamic cavitation, it was not until the pioneer group appears in 80–90s that a substantial development took place especially towards industry (Hunicke 1990; Pandit and Joshi 1993; Suslick et al. 1997).

As is known, the generation of ultrasonic and hydrodynamic cavitation effects is suitable to provoke different types of mechanical and chemical effects. Consequently, the process intensification of cavitation phenomenon can be easily classified between the applications requiring low energy per unit volume and those that demand high intensity. Though the production of collapse bubbles is of different origins, in chemical engineering, the fields of application of bubble cavitation are quite similar between those of hydrodynamic and ultrasonic origins and are often compared in terms of yields and energy consumption. Among industrial applications of ultrasonic and hydrodynamic processes, the treatment of wastewater and effluents is one of the most important applications of the cavitation processes intensification. Chemical pollutants can be efficiently oxidized by the intense production of hydroxyl radicals and hydrogen peroxide, the disintegrated microorganisms and bacteria destroyed by cell wall disruption. Food processing and bioprocesses also include many industrial applications based on cavitation. This broad range of uses, overwhelmingly dominated by heterogeneous sonochemistry, groups the formation of the emulsion, dispersion of various particles or food modifications (emulsification, extraction, crystallization, purification, etc.) (Masson et al. 2015). The cavitational assisted bioprocesses are involved with success in transesterification of triglicerydes and free fatty acids for biofuel production as well as enzymatic catalysis with improvements of the overall process. Otherwise, in sonochemistry, the cavitation phenomenon can allow green and soft synthesis conditions compared to conventional methods and consequently reduce energy consumption.

8.2 Requirement for Industrial Applications

It is obvious for perform a scale-up operation, it is imperative to know the effect of cavitation on the medium whether it an expected mechanical effect either sonochemical effect. In this context, the scaling-up interest of cavitational technology can be clearly established, at laboratory scale, in terms of saving time, reaction conditions, increasing yields and energy consumption saving (Paquin et al. 2013; Gonçalves et al. 2014; Peshkovsky and Tryak 2014; Cintas et al. 2010). For that, a thorough examination of the physico-chemical properties (viscosity, vapour pressure, dissolved gases, presence of particles) of bulk medium as well as the transformation conditions is necessary to hope for an effective scale-up. For this purpose, Patist and Bates (2011) have been compiled important considerations and examples which can be used as guideline for implementation of industrial applications.

8.2.1 Economical Aspects

We should keep in mind, whatever the performances of a small-scale implementation of a cavitation process, that the scale-up will be performed on the base of economic considerations. For instance, in the second half of 2015, the average price of industrial consumers in Europe was 0.119 euro/kWh and accounted for a sizable share of annual expenditure. Thus, many companies tend to improve their energy efficiency to reduce costs and their carbon footprint.

The treatment of large flows requires data on input energy per volume treated (kWh/L) and the needed intensity to successfully lead the chemical process, i.e. the actual output power per area (W/cm^2) of the cavitation devices. The introduction of a high power has technical limits and is not always the guarantee of success because there is a level beyond which the performances decline. The exposure time to cavitation should be minimized and there is a trade-off between input power and processing time which must be determined before scaling-up. This operation is usually performed with a semi-pilot system. Otherwise, the power consumption depends on the choice of the technology. For example, when cavitation is provided by piezoelectric transducers, the yields between output/input powers can range from 50 to 60% for clean-type transducers to 80% for bar probes.

8.2.2 Choosing a Technology

The choice of cavitation phenomenon in process intensification has technical limitations which must be taken into account from the origin of the scaling project. Depending on the expected objectives, bubble collapse can be carried out either by hydrodynamic cavitation or by ultrasonic cavitation.

Hydrodynamic cavitation is useful for processes that require low cavitation energy and is easily carried out at ambient temperature. This technique has the shortcoming of inducing a consequent loss of energy which must be compensated by a highly dimensioned pumping circuit and adequate geometry of the system. Although the erosion phenomenon is important for some applications, hydrodynamic cavitation is the cheapest technique compared to ultrasonic devices with regard to the generated cavitation energy, the rudimentary equipment and the low maintenance load (Carpenter et al. 2016). An innovative design of cavitator for process intensification was reported by Kumar and Pandit (1999), who used a high-speed homogenizer consisting of an impeller inside a cage-like stator with numerous slots where cavitation generates. Another rotor- and stator-based design was described by Badve et al. (2013), with a high-speed rotation cylindrical rotor with indentations generating cavitation with. A similar design with two counter spinning rotors was published by Petkovšek et al. (2013), which like all the other machines presented, needs an extra pump for operation. The same authors improved the system making it more energy efficient thanks to an extremely compact generator and pump used in wastewater treatment (Dular et al. 2016). Moreover, Cravotto's group experimented the rotor/stator apparatus made by E-PIC S.r.l. (Turin, Italy) successfully applied in biodiesel production (Crudo et al. 2016) and in the oxidative polymerization of waste cooking oil with air (Rinaldi et al. 2017).

The ultrasonic cavitation scale-up is mostly performed with piezoelectric technology compared to magnetostrictive transducers. The latter nevertheless benefit from a good coupling coefficient, strain performance, thermal and mechanical resistances superior to piezoelectric transducers. However, the magnetostritive devices have the drawback of being more expensive and difficult to manoeuvre because heavier and bulky. These are the main reasons why the development of ultrasonic cavitation is almost exclusively with piezoelectric transducers. Otherwise, one of the factors limiting the development of ultrasound is related to high power transducers and the limit that can reach the unit probes. Although advances have been made in recent years, the current maximum power of a single device is of the order of 3–4 kW_{eff}. At the industrial scale, it is therefore necessary to multiply the number of transducers to obtain the desired power and to rely on an adequate optimization of the reactor. Finally, the impact of ultrasonic noise, especially when using low frequencies, cannot be neglected in the case of exposure to operators in a work environment (Smagowska 2013). Thus, the sonochemical devices must be adapted to limit sound emission and propagation with specific noise protection.

8.3 Design Considerations

Critical examination of the numerous publications of the literature makes it possible to work out an operational strategy for scaling-up. Thus, once the benefits are established and the technology chosen, the reactor development stage can begin. First, we must consider that due to the introduction of large powers over large volumes, the control of temperature and pressure is crucial to ensure the expected effects on the chemical process, which highlights the preponderant aspect of chemical engineering. Among all the technical specifications of an industrial operation of the cavitation phenomenon, the following points should be carefully considered:

- Type and number of probes for ultrasonic cavitation and choice of venturi and orifices (number, size) for hydrodynamic cavitation,
- Intrinsic properties of the medium and its evolution over time,
- Temperature and pressure,
- Solid particles and dissolved gases,
- Geometry and sizing of reactor,
- Velocity of flow or agitation,
- Surfacing of the transmission system and erosion.

The operating conditions largely affect the cavitation physics and control some parameters such as the number of cavities, the magnitude of the collapse pressure, the intensity of the cavitation and its distribution of activity in the reactor (Gogate et al. 2011). In this section, only a few considerations are summarized in order to allow the understanding of the main lines of the optimization of parameters of the scaling-up of the cavitation phenomenon.

8.3.1 Optimization of Sonoreactor

As we have mentioned, the prerequisites for scaling-up are to obtain a high power on a maximum irradiation surface while taking into account the time required to enable the chemical process. The best solution to get ultrasonic high power is to use a horn system directly immersed in the solution. However, it also presents major drawbacks like the strong erosion of the tip, weak irradiative surface and a decreasing intensity as one move away from the device. In order to overcome these disadvantages, rod-type transducers can be used.

The most common devices use the transducers placed outside the sonochemical reactor. According to the required irradiation time to achieve the chemical process, the continuous flow systems and the loop reactors can be distinguished.

If the required cavitation collapse time is relatively short, a flow rate system can be selected. The generation of a continuous flow passing through venturi devices or orifices produces hydrodynamic cavitation phenomenon. To avoid pressure losses and cavitation energy, the process intensification requires a pumping system that can provide a high level of power. Otherwise, ultrasonic cavitation is produced either by the addition of transducers along the pipe (of tubular or hexagonal forms) or by the use of a vibrating bar whose useful length can be several tens of centimetres.

When a greater ultrasonic irradiation time is required, a reactor is added to form a loop with the continuous flow system. It has both the advantage of being able to conduct long irradiation times as well as control and adjust the medium during the transit of the treated material through the reactor.

8.3.2 Processing Parameters

Optimizing operating parameters when implementing a sonochemistry experiment is a crucial phase before scaling-up. Thus, among the input variables having the most influence on the cavitation during the intensification of the process are power dissipation, frequency, operating mode and the intensity of the irradiation as well as the geometry of the reactor.

- Introduction of High Power into Sonoreactor

An efficient scaling operation requires introducing large irradiating powers in large volumes and dissipating energy evenly over the reactor. Extensive literature shows that the range of energy needed to achieve various transformations ranges from a few hundred W/m^3 to several kW/m^3, which can induce technological limitations. An increase in the reactor volume leads to a simultaneous increase in the ultrasonic power to maintain the same power density. Owing to the power limitation of each single transducer, a large-scale reactor requires several ultrasonic transducers (Gonze et al. 1997) or as suggested by Gondrexon et al. (1999), a multistage reactor composed of a series of several smaller ultrasonic units.

For effective processing scale-up using cavitation phenomenon, it is important to maintain uniform cavitational activity distribution in the volume of processed materials since a non-homogeneous distribution of cavitation can skew the scale-up strategies. The sound wave streaming generates liquid circulation starting from the transducers towards the medium largely perturbed by multiple reflections at reactor walls and the surface of liquid or particles. The increase in the velocity of the liquid can be obtained by stirring but it can cause negative effects if the mixing system is placed near the transducers. Indeed, the bulk movement of the liquid due to stirring may disturb the pressure fields and interfere in the propagation of sound waves due to the scattering of ultrasound waves. Consequently, the diffusion of the acoustic wave undergoes a loss of intensity of the ultrasonic waves. Convenient measurement of the cavitation bubble fields is a significant stake to access a convenient mapping of the sonochemical reactor.

- Transducers

Ultrasonic transducers are elements whose function is not only to generate an ultrasonic wave but also to receive it and convert it into an electrical signal. The optimization of this device is an important factor in increasing the mechanical and chemical performance of the cavitational collapse. The positioning of the transducers must be optimal to allow irradiation of the maximum volume of raw materials and also to avoid disturbances related to the proximity of the ultrasonic capacitors.

Nowadays, for applications requiring high power, the most commonly used transducers are the prestressed sandwich piezoelectric ultrasonic transducers composed of the piezoelectric ceramic active elements placed between the front metal cylinder in contact with the medium and the back beam. The advantage of this technology is to offer the possibility to tune the shape and structure of transducers to optimize the electromechanical coupling coefficient. Nevertheless, these ultrasonic transducers are restricted in power capacity and in their dimensioning and may be inappropriate for large industrial applications. Indeed, the scaling of horn-type transducers is not optimal for use on large volumes due to a small acoustic wave transmission surface, erosion problems and a potential breakage of devices. Recent years have seen the birth of a new family of power transducers with extensive radiators in order to furnish high irradiative surface areas and good impedance. It consists of mounting a plate of various forms and profiles on the vibrating surface of a horn sandwich transducer.

An interesting point of these systems is the possibility to design and optimize the radiative surface as a function of the density of the medium in order to provide better radiation impedance improving the overall device (Gallego-Juárez et al. 2010).

- Use a Multifrequency System

The multiplication of the transducers number during the intensification of the process offers the possibility to associate elements of different operational frequencies and allows a great versatility of ultrasonic cavitation systems. It has been reported in the literature that the use of multifrequency reactors decreases the cavitation threshold and increases the number of cavitation bubbles. Moreover, the combination of low and high frequencies has positive effects on the nucleation of cavitation bubbles and increases the efficiency of mass transfer.

The use of a pilot system with several irradiation frequencies may in certain cases make it possible to improve cavitation. However, it is difficult to generalize because the positive effects of coupling depend on the frequencies used, the position of the transducers relative to each other and also the geometry of the reactor (De La Rochebrochard et al. 2012, Tiong et al. 2017).

- Pulsed Modes

Pulsed mode ultrasound can modify significantly the streaming velocity by sending a burst of n pulses during a period of time separated by a repetitive silent time. The residual cavitation bubbles, which occur in silent time between two irradiation exposures, may act as cavitation nuclei to enhance cavitation effects. However, at a high power level, the use of pulsing irradiation may cause a quenching effect due to excessive sound pressure. Moreover, the efficiency of pulse is higher at high frequencies than at low frequencies (Casadonte et al. 2005).

8.3.3 Measuring the Spatial Distribution of Cavitation

As previously shown, the optimization of a sonoreactor in scaling-up operation requires to control the spatial distribution of cavitation and the scattering of energy through the overall of important volume (Mhetre and Gogate 2014). In a synthetic way, the current investigative techniques measure the sound field, power and chemical activity associated with the cavitation field through optical, calorimetric and chemical methods, respectively.

The sound pressure field is measured by a hydrophone in order to access at the profile of sound pressure versus frequency (Leong et al. 2015). In transparent media, cavitation mapping by high-speed photography can achieve as high as 200 million frames per second in an exposure time of few nanoseconds to visualize multiple-bubble dynamic cavitation. For a bulk assessment of energy input, calorimetric measurements are based on the transformation by absorption of the acoustic energy to heat and are effective for measuring the mechanical effects of ultrasound. Although the implementation of a temperature measurement is relatively accurate at the laboratory scale, in large scales, the energy loss due to air convection and medium/wall interface should be taken into consideration by using a corrected model of calorimetric equation. In the intensification process, the measurement of power dissipation is often correlated with the determination of the chemical activity induced by ultrasound like KI method (Weissler reaction).

In the case where a purely chemical process is desired, it is preferable to rely on luminescence mapping as described in Chap. 1. The emission of photons is monitored by an ICCD camera whose exposure times depend on the mode of emission (the exposure time is higher for sonoluminescence but the intensity is lower than for sonochemiluminescence) (Cao et al. 2012). It should be noted that SCL spectra can be recorded with a fibre optics spectrofluorophotometer emerged in the sonoreator to access at the quantification of fluorescence emission.

8.3.4 Modelling Cavitational Process

In order to provide experimental data, the knowledge of the spatial distribution of bubble collapse allows to better understanding the physics of cavitation especially in large reactors. Indeed, the control of the cavitation field in the volume to be treated is a guarantee of success of the extrapolation of the chemical engineering system and the contribution of the modelling of bubble dynamic may help in predicting the cavitational activity. For this purpose, the computational models developed for the understanding of the distribution of collapse bubbles and the improvement of the mechanical properties of the transducers are compared with the experimental data collected by the types of measurement mentioned elsewhere.

The bubble dynamics and spatio-temporal variations can be modelled by using Rayleigh-type equations in order to predict the pressure and temperature after the bubble collapse as well as the radius of pulsation and their lifetime (Jamshidi et al. 2012). However, when the pressure amplitude increases, the cavitation phenomenon becomes highly non-linear (bubble oscillations, acoustic wave) which involves the use of models incorporating its considerations must be used as shown by the latest developments in this field (Louisnard 2012; Vanhille and Campos-Pozuelo 2014). Furthermore, the finite element method (FEM), due to the integration of both time domain and spatial domain, has become the most widely used methodology in the field of piezoelectric transducer innovation, numerical investigation of inhomogeneous bubble clouds and scaling-up investigations (Perincek et al. 2009).

8.4 Conclusion

Cavitation reactions are very effective tools for the intensification of processes in terms of reaction yields and energy saving especially for certain types of high value-added applications. The scale-up is more complex and costly for ultrasonic cavitation than for hydrodynamic cavitation and requires careful examination of the operating parameters. Although the roadmap for the intensification of cavitation processes in the chemical industry has been defined for 20 years by the pioneers in the field, the road is still long to lead to a generalization of these techniques. However, many efforts are made to complete the knowledge in the quantification of cavitational collapse intensity as well as in the development of reactors and the control of operational parameters. For this purpose, the laboratories are developing numerous semi-pilot or pilot reactors and much new multidisciplinary collaboration between experimenters and theoricians.

One of the undeniable contributions of recent years is the continuous progress of power electronics. Indeed, the control of the ultrasound systems is complex and nowadays is carried out by digital electronics, which is more efficient and furnishes better control through sophisticated calculation algorithms. Thus, the quality of the electronic control is important and aims to stabilize the functioning of the system in the space and in time. One of the most convincing examples is how to control the vibration of an axial probe. By setting the operating point exactly to the resonance of the system, the physics of piezoelectricity shows a direct relationship between the current supplied by the generator and the displacement at the end of the probe. Thus, the volume displacement of the fluid located at the end of the probe is constant whatever the nature of the liquid involved and the power will be the consequence of the effort to produce to maintain this displacement. This example illustrates that the control and control strategy of a device can have a major impact on the induced ultrasound phenomenon and its interpretation.

However, after highlighting the difficulties of dealing with large volumes, we must keep in mind that scaling can be carried out in an alternative and economical way by paralleling microfluidic devices.

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