CHAPTER 8. Sustainable Activation of Chemical Substrates Under Sonochemical Conditions

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X. Sustainable Activation of Chemical Substrates Under Sonochemical Conditions

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ABSTRACT

Ultrasound activation has been widely explored in organic chemistry to improve the yields of reaction or their kinetics. The sonochemical approach can also allow changing the selectivities or limiting the use of hazardous solvents or the amount of catalyst, in accordance with the principle of green chemistry. However, a rigorous control of the sonochemical parameters is necessary to better understand the mechanisms involved under ultrasonic activation.

X. 1. Introduction

Sonochemistry is the use of power ultrasound for chemical reactions. Some chemists reported the first reaction involving ultrasound in 1927,[1,2] although the term "sonochemistry" has only been used since 1980.[3] Ultrasound is often viewed, and particularly in organic chemistry, as a simple and efficient mixing tool in the lab. However, a control of the sonochemical parameters and experimental conditions have made it possible to demonstrate, in many cases, significant improvements in terms of reaction yields and/or reaction speed, thanks to the use of ultrasound. In some cases, unexpected reactivities and selectivities have also been observed under ultrasound, making it possible to imagine new perspectives and applications of sonochemistry in organic chemistry. After having introduced sonochemistry by presenting its basic theoretical and practical aspects, some case studies from recent literature are summarized to show the major advantages of using ultrasound in an organic reaction. At last, this chapter aims to highlight the current and future challenges of organic sonochemistry.

X. 2. Sonochemistry, a chemistry based on power ultrasound

X. 2. 1. Acoustic cavitation and associated effects

Acoustic cavitation in liquid media is the phenomenon of formation, growth and violent collapse induced by sound waves that generate fluctuation of pressure. Liquid media usually contains free gas bubbles or gas molecules trapped in solid impurities, which can act as nuclei for cavitation[4]. Once the cavitation bubble is formed, its diameter increases throughout the expansion and compression phases to achieve a critical size at which it violently collapses. Indeed, expansion phases being isotherm and compression phases adiabatic, a large amount of acoustic energy is

accumulated inside the bubble. At the moment of bubble implosion, temperatures of about 5,000 K and pressures close to 1,000 bar are then reached within the bubble (see Figure X.1). These extremes conditions lead to different local effects such as radicals' formation, shock waves, acoustic micro-currents and violent liquid microjets, which are at the origin of application of sonochemistry[5,6].

[Insert Figure X.1 here]

X. 2. 2. Ultrasonic parameters and experimental factors affecting cavitation

The ambient conditions of a reaction system can strongly influence acoustic cavitation threshold and its intensity, which then directly affects the kinetic and/or the yield of the chemical reaction. The acoustic cavitation in the liquid may be affected by several parameters such as the frequency and power of the ultrasounds, the hydrostatic and external pressures, the temperature, the nature of the solvent and dissolved gas.

X. 2. 2. 1. Ultrasonic frequency

Ultrasound is a sound wave with a frequency (f, Eq. X.1) greater than the upper limit of human hearing, which is generally over 20 kHz and below 10 MHz. When it propagates in an elastic medium it presents all the general properties of periodic progressive waves such as propagation, attenuation and reflection[7].

[Insert Equation X.1 here]

In water low frequencies, ranging between 20 and 80 kHz, lead to relatively few and large transient cavitation bubbles; Physical effects such as micromixing, erosion, etc. predominate over chemical effects. High frequencies, ranging between 150 and

2,000 kHz, produce many small transient cavitation bubbles; Chemical effects such as production of hydroxyl radicals in water predominate over physical effects. It is noteworthy that, when the frequency increases, the depth of penetration of the ultrasonic wave decreases, decreasing the maximum pressure reached during implosion. It is therefore necessary to increase the sound power to obtain the same effects as at low frequency[7,8].

X. 2. 2 .2. Dissipated ultrasonic power

A piezoelectric transducer converts electrical energy into mechanical energy that is thus transmitted to the liquid, which is irradiated[9]. No transducer is 100% efficient in converting electrical to mechanical power. To determine the power output (P_{out}) for a given power input (P_{in}), it is necessary to know the transducer efficiency (h), according to Eq. X.2.

[Insert Equation X.2 here]

The mechanical energy is then converted into acoustical energy generating acoustic cavitation if the minimum power required is reached, *i.e.,* at the Blake threshold, which is 0.5 $W.cm^{-2}$ at 20 kHz in pure water and at atmospheric pressure[7]. It is relatively easy to measure the electrical energy delivered by a transducer, but this value in no way reflects the acoustic energy absorbed by the medium, which is the only that can be active. Different methods are proposed for the determination of ultrasonic power (P_{acous}) such as thermoacoustic sensor[10], acousto-optic interaction[11], piezoelectric hydrophone[12], sonoluminescence, and chemical dosimetry[8]. Nevertheless, one of the most useful methods has been found to be the calorimetric one[8,13]. Therefore, the absorbed acoustic power P_{acous} in $W.mL^{-1}$, transmitted to the solution can be measured using a conventional thermal probe

method[14,15]. Using this method, all energy delivered to the system is considered as dissipated as heat (Eq. 3).

[Insert Equation X.3 here]

X. 2. 2. 3. Hydrostatic Pressure

Hydrostatic pressure is a crucial parameter as the conditions within a collapsing cavitation bubble become more extreme as it increases[16]. Thus, it has been shown that, cavitation threshold in ultrapure water increases linearly with the hydrostatic pressure as well as intensity of bubble collapse[8]. Thereby, an optimal hydrostatic pressure is required to increase the efficiency of ultrasound when used in sonochemical processes[17].

X. 2. 1. 4. Temperature

When increasing temperature of a liquid, the solubility of gases it contains decreases whereas its vapor pressure increases decreasing the cavitation efficiency[18]. The influence of temperature on cavitation threshold is especially noticeable at elevated hydrostatic pressures and for fluids with large amounts of dissolved gases[19].

X. 2. 1. 5. Nature of the solvent

Properties such as (1) solvent viscosity, (2) its vapor pressure, and (3) its surface tension can impact ultrasound intensity. For pure solvents the most determining parameter is the vapor pressure, which when high, decreases cavitation effects[8]. Thus, combination of a high surface tension with a low viscosity and a low vapor pressure favors cavitation[18].

X. 2. 1. 6. Dissolved gas

After few acoustic cycles, transient bubbles violently collapse into smaller tiny bubbles that act as nuclei of new bubbles and create a hot spot with temperatures of up to 10,000 K[19]. This adiabatic collapse of the bubbles is assumed to allow the calculation of the temperature and the pressure inside the bubbles according the equations X4 and X5[20]. Whereas Eq. X.6 allows the calculation of pressure inside the bubble at the moment of the collapse.

[Insert Equations X.4, X.5 and X.6 here]

Thus, according to equations X.4 and X.5, a monatomic gas leads to higher maximum temperatures and pressures and thereby to more violent collapse of the bubble than a polyatomic gas because its γ value is greater. Thermal effects consecutive to the collapse of the bubble mainly depend on gas phase thermal properties such as heat capacity and thermal conduction.

In the presence of gas with high thermal conduction, the temperature reached at the time of implosion is lower than in the presence of a gas with low thermal conduction, decreasing thus T_{max}. In addition, increasing the gas content, *i.e.* the number of gas nuclei of a liquid, leads to lowering of both the cavitational threshold and the intensity of the shock wave released on the collapse of the bubble.

X. 2. 2. 7. External pressure

An increase of P_h leads to an increase of P_m, which is the pressure of the medium (Eq. X.6). In equations X.4 and X.5, when P_m increases T_m and P_m *increase*, leading to an increase in the cavitation threshold and the intensity of cavity collapse.

X. 2. 2. 8. Ultrasonic intensity

The ultrasonic intensity, I_{max}, can be expressed as Eq. X.7[7]:

[Insert Equations X.7 here]

If considering ρ and c constant in the medium where the sound propagates, then I_{max} is proportional to the square of the acoustic amplitude P_A. Thus, an increase in P_A leads to an increase of the ultrasonic intensity, which increases the sonochemical effects up to an optimal value. Indeed, an increase of P_A, leads to a decrease of the time available for the collapse of the too large bubble formed that may become thus insufficient.

Likewise, during their propagation through a medium, the intensity of ultrasound waves decreases when their distance from the emitting source increases (Eq. X.8). Indeed, sound is attenuated in a liquid medium due to reflection, refraction, diffraction and/or scattering of the waves, or the conversion of some of their mechanical energy into heat.

[Insert Equation X.8 here]

In addition, if too many bubbles are produced at the transducer/liquid interface, the ultrasonic energy entering the system is attenuated, decreasing the efficiency by decoupling of the system.

X. 2. 3. Mode of irradiation and sonoreactors

X. 2. 3. 1. Modes of irradiation

Two physic phenomena are widely used to generate ultrasonic waves from ultrasonic devices: magnetostriction and piezoelectricity. Phenomenon of magnetostriction takes place when ferromagnetic materials transform an oscillating magnetic field into mechanical vibration[7]. Piezoelectric effect is the ability of certain crystalline materials when subjected to an electric field to convert electrical energy

into mechanical energy. The strain is then proportional to the applied field and the mechanical vibrations may lead to ultrasonic sound[21]. This phenomenon is the most widely used in ultrasound devices.

The main materials used are barium titanate ($BaTiO_3$), synthetic cristals of lithium nobiate ($LiNbO_4$) and lead zirconate titanate ($PbTiZrO_3$). These materials are separated from the reactor by metal or glass and ultrasound waves irradiate directly or indirectly the reaction medium (see Figure X.2). An immerged titanium probe is often used as a waveguide.

[Insert Figure X.2 here]

X. 2. 3. 2. Equipment

Three major sonoreactors are used at lab: ultrasonic bath, cup horn and probe (Figures X.2, and X.3)[22,23,24].

[Insert Figure X.3 here]

Ultrasonic bath, which represents the most common source of ultrasound in laboratories, is widely used for its low cost. With a frequency of 20 to 60 kHz and acoustic intensities of 1 to 5 $W.cm^{-2}$, this device is not well adapted to organic reactions due to the non-homogeneous dissipation of ultrasound energy and the associated lack of reproducibility of the experiments[25].

Cup-horn reactors present high intensity, which is generally 50 times more intense than in US baths, and directly irradiate the liquid medium[26]. Their geometry allows a good distribution of the ultrasonic field. This device is able to produce low and high frequencies depending of the piezoelectric ceramic chosen and positioned at the bottom of the reactor for upward irradiation.

Ultrasonic probes provide intense ultrasonic energy, which is concentrated at their tip and approximately 100 times higher compared to ultrasonic baths; they allow a direct irradiation of the medium.

In both cases, the use of a jacketed reactors is recommended to control the temperature of the medium during the study of organic reactions at lab[6].

In addition, a study of the shape of the reactor may be relevant to avoid dead zones or to optimize certain physical, thermal and / or chemical effects. Thus, the tubular reactors, providing radial irradiations, make it possible to focus the high-intensity ultrasonic field in the heart of the tube and to develop continuous processes.[27].

X. 2. 3. 3. Characterization of the ultrasonic parameters

A rigorous characterization of sonochemical parameters is crucial to facilitate the comparison between each study reported in the literature and to understand the involved mechanisms[6]. Indeed, the used frequency, electric and acoustic powers, ultrasonic intensity, radical production, shape and geometry of the reactor and other experimental conditions (temperature, pressure, gas atmosphere, nature and volume of solvent, etc.) have to be rigorously reported in the experimental part of scientific publications.

The frequency, inherent to the equipment used, is the first parameter to report to identify which range is used between low frequency (20-80 kHz) and high frequency (200-2,000 kHz). The electric power also called “nominal electric power” or “electric power input” is the energy delivered by the device, measured by a wattmeter (in W). The absorbed acoustical power (P_{acous}, expressed in W or $W.mL^{-1}$) can be estimated through a calorimetric method using Equation X.3. Acoustic

intensity (I_{acous}) is defined as the acoustic power per unit area of the probe (Equation X.9, $W.cm^{-2}$).

[Insert Equation X.9 here]

As previously mentioned, the extreme conditions during the collapse of bubbles lead to radical production. For example, the sonolysis of water (Scheme X.1) and the recombination of radical species into hydrogen peroxide (Scheme X.2) are observed under ultrasonic conditions.

[Insert Schemes X.1 and X.2 here]

The radical species production can be experimentally estimated or measured by dosimetry methods[28,29], Electron Paramagnetic Resonance (EPR),[30] spin-trapping and/or sonochemiluminescence experiments[31,32,33]. Chemical dosimetry is the most convenient and employed method. For example, KI dosimetry involves the oxidation of iodide ions into iodine by hydroxyl radicals formed under ultrasound, through the reaction shown in Scheme X.3. The concentration of I_3^- can be easily measured using UV-Visible spectrophotometry at a wavelength of 355 nm (ε_λ = 26,303 $L.mol^{-1}.cm^{-1}$) to deduce the concentration of $HO^\bullet$ radicals.

[Insert Scheme X.3 here]

Other methods are used such as Fricke dosimetry (oxidation of Fe^{2+} to Fe^{3+}), terephthalate dosimetry (use of terephthalic acid in alkaline solution) or nitrite and nitrate dosimetry[6]. The Sonochemical Efficiency (SE) can be defined combining electric/acoustic power and rate of radicals formation determined by dosimetry (Equation X10). It constitutes an efficient assessment method to compare different ultrasonic conditions/reactors.

[Insert Equation X.10 here]

In EPR spin-trapping experiments diamagnetic nitroso or nitrone compounds are used as spin trap for the conversion short-lived radicals into relatively longer lived nitroxyl radicals that are observable by EPR spectroscopy[30,34]. This accurate characterization method is limited by the non-availability of the equipment at lab.

The sonoluminescence is the emission of photons during the collapse of bubbles. The activity of radical or excited species formed in the gas phase of the bubbles during this collapse can be explored using specific detectors by observing the UV-Visible spectra of the sonoluminescence[35,36]. The use of luminol solution (3-aminophtalhydrazide) oxidized by $HO^{\bullet}$ radical formed in water under sonochemical activation leads to the formation of 3-aminophthalic acid with electrons in an excited state. The visible blue light emission (λ = 430 nm) due to the de-energization of these electrons allows the mapping of effective zones in a sonoreactor, through this chemiluminescence method[36].

X. 3. Organic sonochemistry: beneficial effects and new reactivities

X. 3. 1. Green organic sonochemistry

The effects of ultrasound during organic reactions have led to serious improvements in terms of reactivity and performance, often under mild conditions, in accordance with a green chemistry approach[37]. Sonochemical reactions in water or biphasic aqueous systems constitute a great potential for further developments.

Sonocatalysis often allows using environmentally friendly conditions, and to decrease reaction times and reach higher yields. In addition, cavitation phenomenon leads to physical and chemical effects, which consequences are interesting for catalyst surface cleaning and free reactive radicals production[38,39]. In the most

general cases, the combination of ultrasound activation and a catalyst can lead to synergistic effects, mainly observed through the physical effects of US on solid catalysts. Indeed, the physical effects generated by cavitation bubble collapse leads to improved mass transfer that contributes to permanent cleaning of the catalyst's surface and increases the probability for compounds to meet and react. Shear forces induced by shock waves and microstreaming provoke the de-agglomeration of catalyst, the reduction of particle size, which implies an increase in surface area[40]. For these reason, poisoning of catalyst can be avoided, the active surface of catalyst is increased, which leads to higher reaction rates, improved yields and lower chemicals consumption; this makes sonocatalysis an effective tool for green chemistry[41,42,43,44,45]. As an example, the S-alkylation of hetaryl thiols was performed at room temperature six times faster and led to increased yield under US (74% in 30 min) compared to silent conditions (66% in 3 h)[42]. Another synergistic aspect relies in the microbubbles present in the crevices of solid catalysts. They constitute nuclei for cavitational bubble, increasing the number of collapsing events[46]. When bubble collapse near a solid surface such as a solid catalyst particle or vessel, the inrush of liquid generates an "asymmetrical collapse" disaggregation of the catalyst but also the fragmentation of the bubble in smaller bubbles that constitute new nuclei for more cavitation bubbles and collapsing events[47,48].

In the case of semiconductor catalyst such as TiO_2, electron/hole pairs can be generated at its surface through the absorption of energy: (UV-)light in the case of sonoluminescence from cavitation bubbles, or by heat from the extreme temperature resulting from the collapse of bubbles[41,49]. These charges (electron and hole) operate in redox reactions with the solvent to form radical species or directly with organic compounds of the medium. In sonicated reaction medium, the generation of

radical species will favor reaction mechanism implying electron transfer rather than ionic path[23]. For example, the heterocyclization of 1,2-propanediol with fullerene to form fullerene-fused dioxane adduct was enabled by the improved mixing of the non-miscible liquid phases, provided by US and also possibly by secondary radical reaction in the reaction bulk that would react with the C60 fullerene structure[50]. A change in mechanism and selectivity was describe by Ando where benzyl bromide reacted with potassium cyanide and alumina in toluene with a Friedel-Crafts mechanism to afford *o*- and *p*-benzyltoluene when stirred mechanically at 50 °C. Under 45 kHz US irradiation, the mechanism switched to a nucleophilic substitution and lead to the production of benzyl cyanide in 71% yield[51]. Bubbles generated by acoustic waves in the reaction medium are influenced by the presence of solid catalyst particles and *vice versa*, justifying the beneficial effect of their combination, called synergy.

Another meaning of sonocatalysis is the activation of a reaction by US, through physical and chemical effects generated by cavitation activity[23]. In that case, the origin for the effects observed are separated into two categories: true and false sonocatalysis, “true” being linked to chemical effects such as the generation of radicals, and false referring to mechanical effects of US[52].

X. 3. 2. Cases studies in organic sonochemistry

X. 3. 2. 1. Examples of oxidation reactions

Many oxidation reactions such as aldehyde[53] or alcohol[54] oxidations have been studied under ultrasonic irradiation because their mechanisms pass through a radical route.

The aerobic oxidation of D-glucose into D-glucuronic acid was investigated under high frequency ultrasound (550 kHz, P_{acous} = 0.36 $W.mL^{-1}$) (see Scheme X.4)[55]. In absence of oxygen, D-glucose was oxidized into D-gluconic acid as main product (40% yield), while D-glucose under oxygen bubbling was oxidized into D-glucuronic acid with excellent yield and selectivity (94% and 98%, respectively). The presence of oxygen bubbling into reaction media allows to increase production rate of radicals $HO^{\bullet}$. In this case, mechanisms involving $HO^{\bullet}$ and $HOO^{\bullet}$ were suspected.

[Insert Scheme X.4 here]

In a very recent study, the H_2O_2-mediated epoxidation of *cis*-cyclooctene performed under high frequency ultrasonic irradiation (800 kHz, P_{acous} = 0.58 $W.mL^{-1}$) led to improve results compared to silent conditions and revealed important mechanistic insights of the studied reaction (see Scheme X.5)[56]. Indeed, while a maximum yield of 89% and a selectivity of 91% were observed under silent conditions, better results were obtained (96% yield and 98% selectivity) in 30 min under high frequency ultrasound induced by a good thermoregulation and mild mixing brought by the sonoreactor. In addition, the non-radical nature of *cis*-cyclooctene epoxidation mechanism has been demonstrated.

[Insert Scheme X.5 here]

At last, the oxidative cleavage of double bond of olefins has been studied under ultrasonic irradiation (see Scheme X.6)[56]. Simultaneous use of ultrasound and Aliquat 336® as phase transfer catalyst was essential to perform the oxidative cleavage of olefins without organic solvent and in less than 1 h. At room temperature and thanks to 20 kHz ultrasound probe, mono- and diacids derived from linear and cyclic olefins are obtained with good to excellent yields, from 65 to 96%.

[Insert Scheme X.6 here]

X. 3. 2. 2. Examples of reduction reactions

Amines are important molecules that are involved in the synthesis of amino acids[57] or vitamins[58] and many of them exhibit interesting biological activities. Therefore, they are used as antihistaminics, analgesics, antiglycemics[59], anesthesic[60], decongestant[61], pyschostimulant[62] or antidepressant[63]. Classical preparation of amine derivatives relies on the reduction of nitro precursors using different methods. Among them hydrogenation catalyzed by metals, is still the most used in the petrochemical and pharmaceutical industries[64]. However, these methods are often associated with a lack of chemoselectivity in the presence of other reducible functions. In addition, the reaction is exothermic, and involves pressurized hydrogen and flammable solvents, requiring thus particular precautions in terms of safety[65]. The research of more selective, safe and environmentally friendly method of reduction is thus an important issue. It is well known that low frequency ultrasonic irradiation (20 kHz < f < 80 kHz) may enhance catalyst activity and chemical reactions' kinetic and selectivity[66]. Thus, in 2000, Basu *et al.* described the reduction of nitroaromatic compounds to the corresponding amines using a Sm/NH_4Cl reducing agent under 10 to 25 min of ultrasonic irradiation (see Table X.1)[67].

[Insert Table X.1 here]

In Table X.1, 86% of 6-aminochrysene were obtained from 6-nitrochrysene (Table X.1, compound **2**) after 10 min of sonication using a Sm/NH_4Cl reducing agent in methanol, whereas no reaction was observed under silent conditions. 2-nitro-9H-fluorene (Table X.1, compound **3**) was reduced to 2-aminofluorene in 10 min under ultrasonic irradiation whereas no transformation was observed when the

reducing agent was changed for In/NH_4Cl or for Fe powder/NH_4Cl. Under silent conditions, 10 h under methanol reflux were required to reduce 2-nitro-9H-fluorene (Table X.1, compound **3**) to the corresponding amine. In addition, the reaction was shown to be selective towards sensitive functional groups such as bromo (Table X.1, compound **4**), cyano (Table X.1, compound **5**), ester (Table X.1, compound **6**), unsaturated bonds (Table X.1, compound **7**) and heterocycles (Table X.1, compound **8**). Unfortunately, ultrasonic frequency and power are not given, making it impossible to reproduce the experiments under identical conditions.

Hypophosphorous acid and its salts are mild, cheap and powerful reducing agents commonly used for electrochemical applications[68]. Furthermore, sodium hypophosphite seems has been registered as a non-hazardous substance for Man and for the Environment in 2010 by REACH[69]. In that context, with sodium hypophosphite/hypophosphorous acid as reducing system and Pd/C as catalyst, Letort *et al.* studied the reduction of nitro compounds to the corresponding amines in H_2O/2-MeTHF at 60 °C[70]. The authors studied the reaction in terms of solvent effect, NaH_2PO_2/H_3PO_2 ratio, temperature, Pd/C catalyst loading, with 2-nitroethylbenzene as model substrate. The methodology scope was then extended to other aliphatic nitro compounds (see Table X.2) and the results obtained were compared to those obtained under ultrasonic irradiation.

[Insert Table X.2 here]

Under the same conditions and even with 1.25 mol% of Pd/C the reduction of β-nitrostyrene did not lead to the corresponding unsaturated amines nor to the saturated one, but to a mixture of 44 % of (*Z*)- and 38 % of (*E*)-2-phenylacetaldehyde oximes[70]. The reaction was found to be faster under ultrasonic irradiation and especially in the mixture H_2O/Me-THF (2:1). Thus, a maximum yield of 92% of 2-

phenylethan-1-amine was obtained at 60 °C in only 15 min under ultrasonic irradiation compared to 90 min required under silent conditions. In water as solvent 90 min were required to obtain 35% of amine under silent conditions whereas almost the double was obtained under ultrasonic irradiation. In water and under ultrasonic irradiation, a maximal yield of 90% was obtained in 15 min when the temperature was increased to 70 °C. The use of a vibromixer allowed the authors to attribute the effects of ultrasound to the formation of an intense micro-emulsion and classified the reaction as a type II reaction termed as “false sonochemistry”.

X. 3. 2. 3. Examples of fused heterocycles

N-containing heterocycles are essential building blocks for the synthesis of many biologically active compounds[71,72]. In that context, Nongrum *et al.* described the synthesis of fused benzo *N,N*-containing heterocycles under ultrasonic activation and using 1-désoxy-1-(méthylamino)-D-glucitol, *i.e.,* meglumine, as organocatalyst[73]. The authors used meglumine, an environmental water-soluble amino sugar, to catalyze the reaction in association with ultrasound as alternative activation technic with mixture ethanol-water as solvent. The reaction was optimized in terms of catalyst loading, solvent and activation technique with 1,2-phenyldiamine, dimedone and tolualdehyde as substrates. The scope of the reaction was then extended to aromatic aldehydes bearing electron–withdrawing and –donating substituents, leading to excellent yields under 20 to 30 min of ultrasonic irradiation (see Table X.3)[73]. Two hypotheses have been formulated to explain the role of meglumine, which is suggested to act via electrophilic or nucleophilic activation of dimedone. Under the same conditions, 85 to 90% of quinoxaline derivatives were synthesized under 25 to 35 min of ultrasonic irradiation at 50 °C.

[Insert Table X.1 here]

Using an acidic ionic liquid, the 1,4-diazabicyclo[2,2,2]octanium diacetate, *i.e.,* DABCO diacetate, Fekri *et al.* synthesized 93 to 97 % of various benzodiazepines under 8 to 17 min of ultrasonic irradiation (see Table X.4)[74]. The reaction under silent conditions and at 90 °C afforded the products in higher reaction times and lower yields. A mechanism involving the ionic liquid for increasing the electrophilicity of the carbonyl substrates is then proposed.

[Insert Table X.4 here]

X. 3. 2. 4. Examples of organometallic reactions

Sonochemistry is a green alternative method to classical methods to promote the synthesis of organic compounds, offering then versatile and easy pathways for a wide variety of transformations such as Reformatsky, Barbier-Grignard or Michael reactions[75].

The Reformatsky reaction, which converts aldehydes and ketones to β-hydroxyesters, is one of the first organometallic reactions with problems of metal activation under silent conditions that was studied under ultrasound. In 1982, it was shown that the addition of ultrasound resulted in better reaction yields in less time compared to silent conditions[76]. In fact, for a reaction time of 12 h, the yield was 58% while with ultrasound (ultrasonic bath, frequency not indicated), it rose to 98% in only 30 min. Several studies were carried out in order to understand the role of ultrasound in this reaction[77,78,79]. Authors reported successful syntheses with quantitative yields of β-hydroxyester by reacting phenylketons, α-bromoesters, zinc dust and a catalytic amount of iodine under high intensity ultrasonic irradiation[80]. But, the role of iodine was not fully understood. Reformatsky reactions could then be carried out using non-traditional electrophiles such as glyoxylic oximes[81].

In the Barbier-Grignard type reaction, the organometallic reagent, which intervenes, serves as a nucleophile for the formation of a carbon-carbon bond[82]. The zinc-mediated Barbier reaction was carried out in a biphasic CO_2/H_2O system allowing a preferential partitioning of the desired homoallyl alcoholic product[83]. Here, pulsed ultrasound is efficient for dispersing and mixing the two phases creating thus an emulsion while ensuring the kinetic control.

The Michael reaction is often a first choice organic transformation because there are a large number of Michael acceptors and nucleophiles. Indeed, almost all activated alkenes such as α,β-unsaturated ketones can act as acceptors. It is also possible in a single step to form stereogenic centers[84]. Numerous studies have demonstrated the need for basic or acidic catalysts in the reaction of addition of nucleophiles 1,4-conjugated to unsaturated carbonyl compounds[85]. However, these conditions gave way to side reactions. The effects of ultrasound then allowed a more efficient approach when adding the conjugate[86]. In a recent study, researchers studied the chemical behavior of 3-diethyl phosphonocoumarin in an ultrasound-assisted Michael-type reaction[87]. Several organometallic compounds have been selected to react with this coumarin as hard nucleophiles isomers (see Scheme X.7). This approach allowed the use of a simpler experimental set and milder reaction conditions. Excellent reproducibility of yield is reported as well as high diastereoselective activity of isolated *trans* isomers[87].

[Insert Scheme X.7 here]

X. 3. 3. Scale-up and industrial applications

In organic sonochemistry, a series of macroscopic characteristics, namely the use of less toxic/hazardous chemicals, eco-friendly solvents, alternative or renewable raw

materials, the development of reaction conditions to increase the selectivity of the product or even the minimization of consumption energy during transformations reinforce the aspect sought in green chemistry and encourage the use of ultrasound on a larger scale[6,88].

As presented previously, lab scale experiments in organic chemistry are very promising to create green processes in industry[23,89]. However, to our knowledge, no industrial scale sonoreactor was successfully employed for organic synthesis. Large scale transfers require adjustments concerning various parameters and a scale-up methodology is lacking[90].

The efficiency of sonochemical reactions relies on hydrodynamics, mixing and mass transfer. Two types of parameters need to be studied when scaling up a lab-scale experiment to industrial purpose: (i) the operating parameters such as the frequency, the intensity and the initial radius of bubble nuclei and (ii) the geometric parameters such as the size and location of transducers, the shape and dimensions of the reactor. Both types of parameters will impact the mixing and hydrodynamic characteristics that define the cavitation field. The main problems in intensifying organic reactions relate to the fact that the yield and selectivity of the chemical reaction are non-linearly based on operating parameters and geometry; a proportional amplification of the dimension of the reactor is therefore not sufficient to reproduce the same experimental conditions. Fine predictions of many parameters such as pressure, temperature, and cavitational activity distribution are required to achieve chemical reaction effectiveness. Another problem frequently encountered is that cavitation events happen mainly near the irradiating surfaces. The adjustment of lab-scale reaction at large-scale requires higher energy input to counterbalance energy dissipation in wider bulk media leading to fast erosion of the sonication

surfaces[90]. Large-scale reactors contain larger volumes, which bring the issue of US attenuation, due to reflection, refraction or absorption of the incident sound wave and leads to spatial variation of the cavitational activity, creating active and passive zones in the reactor. This needs to be avoided to perform chemical reactions at an industrial scale[91].

To anticipate the problematics related to large scale sonoreactors, experimental measurements and theoretical techniques exist to predict the cavitational activity distribution. The mapping of a sonoreactor can contribute to upscale chemical reactions. It consists in the characterization of the cavitational phenomena and implies the quantification of primary effects (generated at the same time as the bubble collapse) and secondary effects (generated after bubble collapse). Parameters like pressure can be quantified using a hydrophone while changes in local temperature can be measured with a thermocouple[92] and gives information on the local cavitation activity and is used to quantify the efficacy of the sonochemical reactor in term of energy transfer. The quantification of secondary parameters as radical production can be assessed through dosimetry. Chemical reaction implying hydroxyl radicals enable an indirect measure of their concentration and they can have large measurement errors[93]. The modelling of cavitational parameters such as pressure, temperature but also the bubble radius and the chemical species formed can be predicted through modelling[94,95]. Large scale reactors imply specific studies as for example, the pressure of the reaction medium is a function of depth and impacts the conditions of cavitation bubble collapse like pressure and temperature, and thus the physical and chemical effects on chemical reactions[96,97]. Concerning sonochemical efficiency assessment, most studies are conducted on single bubble

model[98,99] which does not take account of neighbor bubbles behavior mutually influencing the other bubble behavior[100,101].

The scaling-up of organic reaction under US would enable great energy and chemical savings. The main difficulty to design large scale reactors is to ensure a uniform distribution of cavitational activity. Empirical methods and theoretical modelling can be used to work on this aspect and contribute to the industrialization of US for organic synthesis.

4. Conclusions: from the challenges to new perspectives of organic sonochemistry

Since the evaluation of the eco-compatibility of a process cannot be done subjectively, there are a certain number of calculations of green chemistry such as the economy of atoms, the mass reaction efficiency, the intensity mass, effective mass yield, carbon efficiency, the E-factor, the Eco-Scale or other green metrics[102,103]. These tools are still little exploited by sonochemists and the systematization of their use is recommended. The systematic comparison between silent and ultrasonic conditions are necessary, under the same conditions, to highlight the improvements brought by ultrasound in terms of efficiency and eco-compatibility. For example, the energy consumption should be also measured. At lab scale, *in situ* data monitoring can be collected to extrapolated the ultrasound conditions at a higher scale[104].

In terms of equipment, the combined efforts of chemists, physicists and equipment manufacturers will be needed for the chemical process industry to exploit cavitation as a more viable option for chemical transformations.

As a perspective, the combination of ultrasound with other physical and chemical methods of activation seems promising. For example, the use of subcritical H_2O (hydrothermal, 200 °C) under ultrasonic irradiation (20 kHz) shows stable cavitation with nonlinear bubble oscillations. On the other hand, formation of hydrogen peroxide H_2O_2 thermally instable is not observed[105]. Sonohydrothermal synthesis is described for the synthesis of inorganic nanomaterial[106], but not yet for organic synthesis. Indeed, the combination of ultrasound with supercritical CO_2 has not been used in organic chemistry due to high pressure and lack of phase boundaries observed in the supercritical state [107]. Hence, for biomass valorization, positive influence of ultrasound in supercritical CO_2 is observed thanks to mechanical effects (micro- and macro-mixing, cell damage) that could be useful in organic synthesis[108].

In organic synthesis, the use of US and microwaves in tandem or simultaneously at laboratory scale improves selectivity, yield and lowers reaction times[109,110], satisfying some principles of green chemistry criteria. The synergistic effects observed are commonly attributed to the improved heat transfer provided by microwaves and the intense mass transfer resulting from US. Each irradiation technology compensates the weakness of the other, which justifies the added value of their simultaneous use, especially in heterogeneous systems[110,111].

Despite the many advantages of microreactors, one major drawback is the potential clogging of their channels[112] In that context, the synergy of ultrasound and microfluidics has shown its potential. Thus, Sedelmeier *et al*.[113] used an ultrasonic bath to avoid the fouling of the microreactor due to the deposition of manganese dioxide used for the oxidation of nitralkanes into their corresponding carboxylic acids. Recently, Delacour *et al*.[114] developed a scaled-up ultrasonic reactor to prevent

clogging in particle forming reactions. The millireactor was used for the synthesis of barium sulphate. Results showed that only 0.48 $W.mL^{-1}$ was required to prevent channel clogging and to increase the productivity by two orders of magnitude compared to a microreactor.

Sonophotocatalysis, which is the combination of sonochemistry and photocatalysis, has mainly been used as an advanced oxidation process for the removal of pollutants. Its recent use in organic synthesis showed promising results as a synergistic effect of both activation methods afforded an alkyl carbon chain elongation from 3 C (malonic acid) to 4 C (succinic acid). The carbon chain elongation was observed only when US and UV irradiations were combined[115].

At last, the physicochemical properties of some ionic liquids (ILs), such as their large thermal stability, their wide liquid domain or even their low vapor pressure make them very interesting reaction media for green chemistry. The combination of ultrasound with the appropriate ionic liquid is a powerful tool for performing various organic transformations[116]. The rate of reactions, selectivity and yields are often improved. Their combination with US then makes it possible to obtain the desired products without using inorganic of organic catalysts, even at room temperature[117]. The possible degradation phenomena (few ppm) of ILs under US conditions have nevertheless to be considered[118]. Deep eutectic solvents are also very promising as a green alternative in synergy with ultrasound in organic syntheses[119].

When combining processes, technologies, tools or reagents, an interesting way to assess to efficiency of the coupling is to calculate its synergy. Synergy corresponds to a beneficial effect from a coupling that is positive if the results obtained with the coupling of processes is superior to the sum of the results obtained

with each independent process[109]. Several indicators of synergy can be found in the literature but their definition and the equations that are used should always be detailed to avoid confusion. Among indicators for synergy the following can be found: synergy, synergy effect, synergistic effect, %synergy or synergy index[120,121,122]. For example, the equation for percentage of synergy (Equation X.11) and the synergy index (Equation X.12) for n processes leading to chemical reactions with k as rate constant, are detailed below.

[Insert Equations X.11 and X.12 here]

The calculation of the %synergy and synergy index are recommended when ultrasound are combined in an organic reaction with another physical or chemical activation method in order to prove the advantages of the used combination.

FIGURE AND TABLE CAPTIONS

Figure X.1: Schematic representation of bubble formation, growth and collapsing.

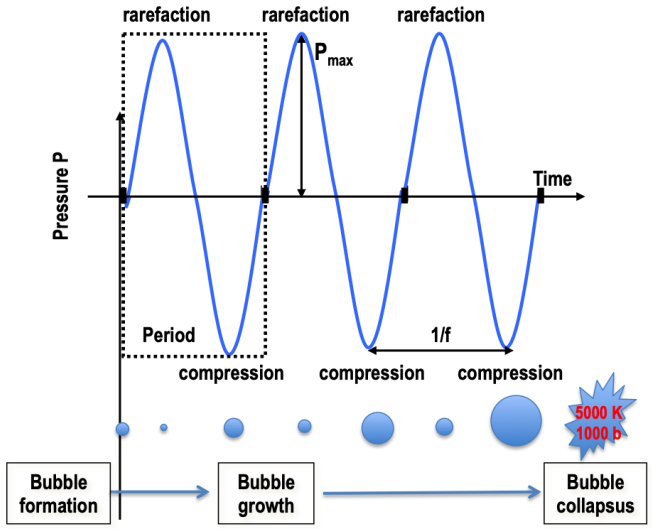


Figure X.2: Schematic representation of mode of irradiation depending on the main device used in laboratories (adapted from reference [123]).

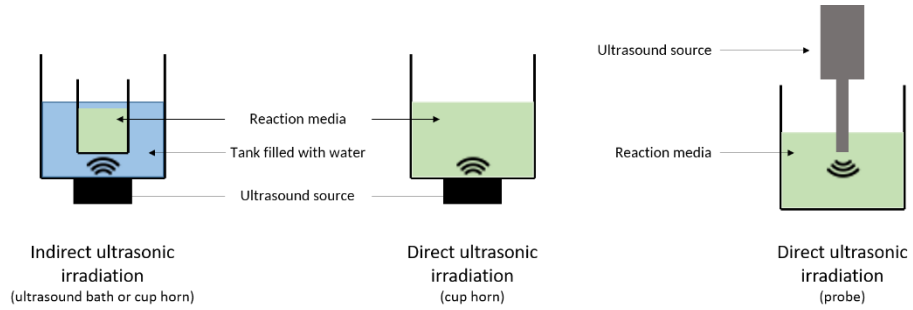
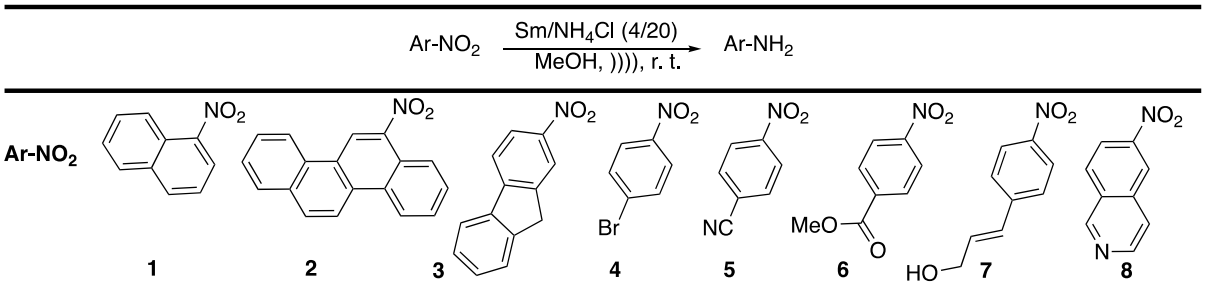


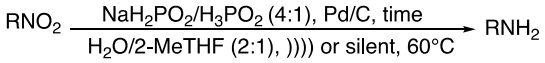
Figure X.3: Cup horn system (left) and ultrasonic probe (right) at lab.

Table X.1: Reduction of aromatic nitro compounds by Sm/NH_4Cl under ultrasonic irradiation (ultrasonic bath, frequency not indicated, room temperature)[67].



	1	2	3	4	5	6	7	8
Time, min	10	10	10	10	10	10	10	25
Yield, %	88	86	92	88	87	74	90	56

Table X.2: Reduction of aliphatic nitro compounds under silent and ultrasonic conditions (ultrasonic microtip, 20 kHz, P_{acous} = 3.94 W, 3 mL)[70].



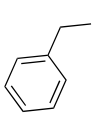
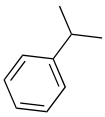
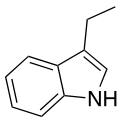
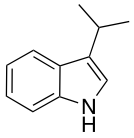
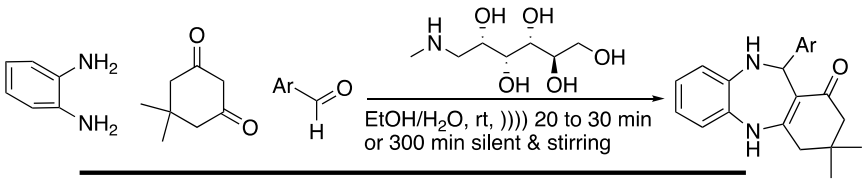
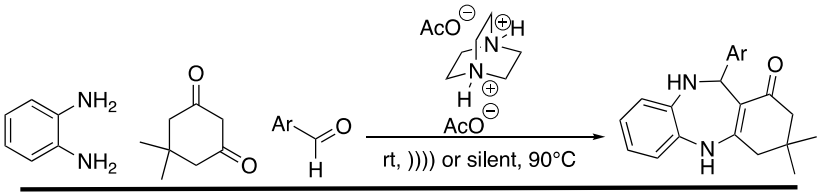
R				
Activation method	Silent /))))	Silent /))))	Silent /)))) /)))) /)))) /))))	Silent /)))) /)))) /)))) /))))
Time, min	90 / 15	90 / 15	90 / 10 / 20 / 30 / 30	90 / 15 / 20 / 30 / 30
Catalyst loading, mol%	0.6 / 0.6	0.6 / 0.6	0.6 / 0.6 / 0.6 / 0.6 / 1.25	0.6 / 0.6 / 0.6 / 0.6 / 1.25
Yield, %	90 / 90	84 / 84	98 / 61 / 78 / 84 / 98	80 / 78 / 80 / 85 / 85

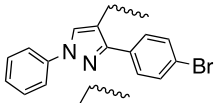
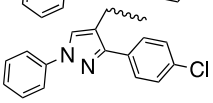
Table X.3: Synthesis of 1 *H*-dibenzo[b,e][1,4]diazepin-1-one derivatives with 5 mol% of meglumine as catalyst under silent and ultrasonic conditions (ultrasonic bath)[73].



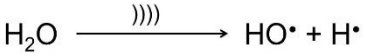
	))))		Silent 300 min
Ar	Time, min	Yield, %	Yield, %
C_6H_5	20	92	65
4-$CH_3C_6H_4$	20	92	68
4-$OCH_3C_6H_4$	20	88	65
4-ClC_6H_4	25	90	60
4-BrC_6H_4	25	92	68
4-$NO_2C_6H_4$	30	85	58
4-OHC_6H_4	25	88	60
4-$N(CH_3)_2C_6H_4$	30	88	64
2-ClC_6H_4	25	82	62
2-$NO_2C_6H_4$	30	85	55
1-Naphthyl	25	88	55
Furfuryl	30	88	64
$C_6H_5CH=CH$	30	82	60
4-(OH) and 3-$(OCH_3)C_6H_3$	25	90	65
3,4-$(OCH_3)2C_6H_3$	20	90	60

Table X.4: Synthesis of various benzodiazepines with 0.5 mmol of ionic liquid as catalyst under silent and ultrasonic conditions (ultrasonic bath, 45 kHz, P_{in} = 305 W)[74].

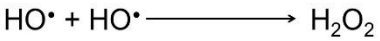


	))))		Silent, 90°C	
Ar	Time, min	Yield, %	Time, min	Yield, %
C_6H_5	10	95	75	82
4-ClC_6H_4	8	97	60	84
4-$OCH_3C_6H_4$	8	96	60	85
4-$NO_2C_6H_4$	8	98	60	89
3-$NO_2C_6H_4$	10	95	75	88
3-ClC_6H_4	10	96	75	89
4-$N(CH_3)_2C_6H_4$	12	93	90	85
2,4-diClC_6H_4	15	94	90	83
	6	95	60	82
	17	94	90	81

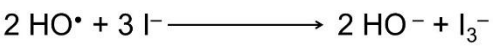
Scheme X.1:



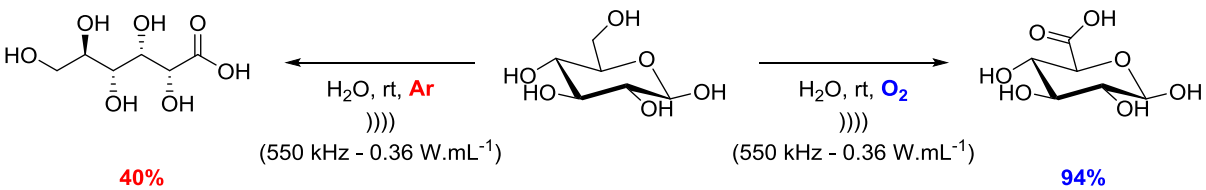
Scheme X.2:



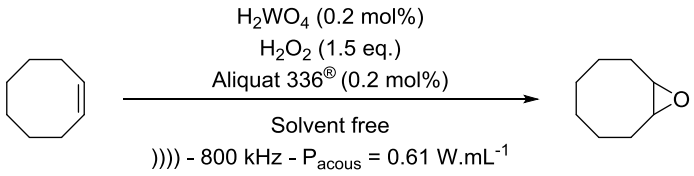
Scheme X.3:



Scheme X.4:

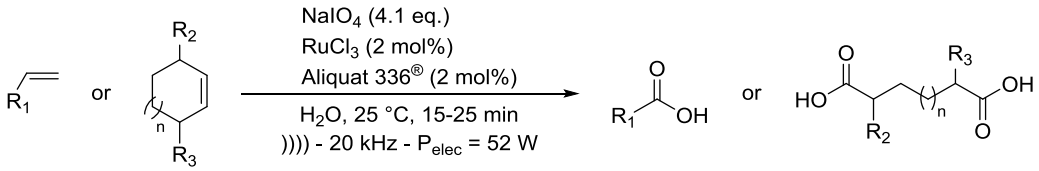


Scheme X..5:



624
625

626 **Scheme X.6:**

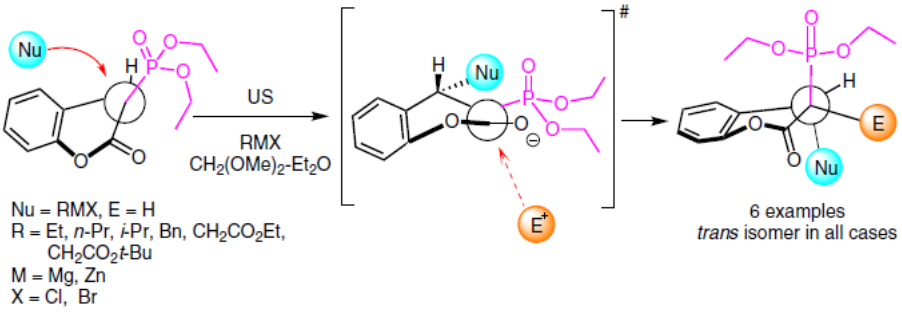


R_1 = CH_3-$(CH_2)_7$-, CO_2H-$(CH_2)_7$-, CO_2H-$(CH_2)_8$-
R_2,R_3 = H : n = 1-3 $R_2 = R_3 = CH_2$: n = 1

Yields : 65-96%

627
628

629 **Scheme X.7:**



Nu = RMX, E = H
R = Et, *n*-Pr, *i*-Pr, Bn, CH_2CO_2Et, CH_2CO_2t-Bu
M = Mg, Zn
X = Cl, Br

630

631 **Equation X.1.**

632 $$f = \frac{c}{\lambda}$$

633 where f is the frequency (Hz), c is the celerity of sound ($m.s^{-1}$) and λ the wavelength (m).

634

635 **Equation X.2.**

636 $$P_{out} = h \times P_{in}$$

637

638 **Equation X.3.**

639 $$P_{acous} = m \times c_p \times \left(\frac{dT}{dt}\right)_0$$

where P_{acous} is the absorbed acoustical power in W (or reported to the volume in $W.mL^{-1}$), m is the mass in kg of liquid in the sonoreactor, c_p is the specific heat capacity in $J.kg^{-1}.K^{-1}$, $\left(\frac{dT}{dt}\right)_0$ is the initial slope of the increase of the temperature of the solution versus time of ultrasonic irradiation.

Equations X.4., X.5 and X.6

$$P_{max} = P\left[\frac{P_m(\gamma-1)}{P}\right]^{\frac{\gamma}{\gamma-1}} \qquad \text{Eq. X.4}$$

$$T_{max} = T_0\left[P_m\frac{(\gamma-1)}{P}\right] \qquad \text{Eq. X.5}$$

$$P_m = P_a + P_h \qquad \text{Eq. X.6}$$

where P_{max} and T_{max} are the maximum pressure and temperature at the collapse, P is the pressure inside the bubble at its maximum size; it is usually equal to the vapor pressure P_v, P_m is the pressure inside the liquid at the moment of the collapse, T_0 is the ambient temperature, P_a is the acoustic pressure applied, P_h is the pressure within the fluid. It is usually taken to be ambient or atmospheric pressure. The polytropic factor γ is the ratio of the specific heat capacities of the gas or the gas vapor mixture.

Equation X.7.

$$I_{max} = \frac{P_A^2}{2\rho c}$$

where P_A is the acoustic amplitude, ρ is the density of the medium, and c is the velocity of the sound in the medium.

Equation X.8.

$$I_{max} = I_0 e^{-2\alpha d}$$

where I_0 is the initial sound intensity, α is the absorption coefficient of the medium and I_{max} is the ultrasonic intensity at the distance *d*.

Equation X.9.

$$I_{acous} = \frac{P_{acous}}{S_{probe}}$$

where I_{acous} is the acoustic intensity ($W.cm^{-2}$), P_{acous} is the acoustic power (W) and S_{probe} is the surface of the irradiating probe.

Equation X.10.

$$SE_{elec/acous} = \frac{n_{ions}}{E_{elec/acous}}$$

where SE is the Sonochemical Efficiency ($mol.J^{-1}$), n_{ions} is the number of moles of considered produced under ultrasonic irradiation (mol of I_3^-, NO_2^-, NO_3^- depending of the dosimetry method) and $E_{elec/acous}$ is the electrical or acoustic power (W, electric or acoustic).

Equation X.11.

$$\%synergy = 100\ \frac{k_{combined\ processes} - \sum_{i=1}^{n} k_{process\ i}}{k_{combined\ processes}}$$

Equation X.12.

$$synergy\ index = \frac{k_{combined\ processes}}{\sum_{i=1}^{n} k_{process\ i}}$$

ABBREVIATIONS:

c: celerity of sound

c_p: specific heat capacity

683 DABCO: 1,4-Diazabicyclo[2.2.2]octane

684 $E_{elec/acous}$: electrical or acoustic power

685 EPR: Electron Paramagnetic Resonance

686 f: frequency

687 I_0: initial sound intensity

688 I_{acous}: acoustic intensity

689 I_{max}: ultrasonic intensity

690 ILs: Ionic Liquids

691 m: mass of liquid in the sonoreactor

692 P: pressure inside the bubble at its maximum size

693 P_a is the acoustic pressure applied

694 P_A: acoustic amplitude

695 P_{acous}: acoustical power

696 P_h: pressure within the fluid

697 P_{in}: power input

698 P_m: pressure inside the liquid at the moment of the collapse

699 P_{max}: maximum pressure at the collapse

700 P_{out}: power output

701 P_v: vapor pressure at the moment of the collapse

702 REACH: Registration, Evaluation and Authorisation of Chemicals

703 SE: Sonochemical Efficiency

S_{probe}: surface of the irradiating probe

T_0: ambient temperature

T_{max}: temperature at the collapse

US: Ultrasound

UV: Ultraviolet

λ: wavelength

$\left(\frac{dT}{dt}\right)_0$: initial slope of the increase of the temperature of the solution versus time of ultrasonic irradiation

α: absorption coefficient of the medium

γ: polytropic factor

ρ: density of the medium

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