Power ultrasound in organic synthesis: moving cavitational chemistry from academia to innovative and large-scale applications

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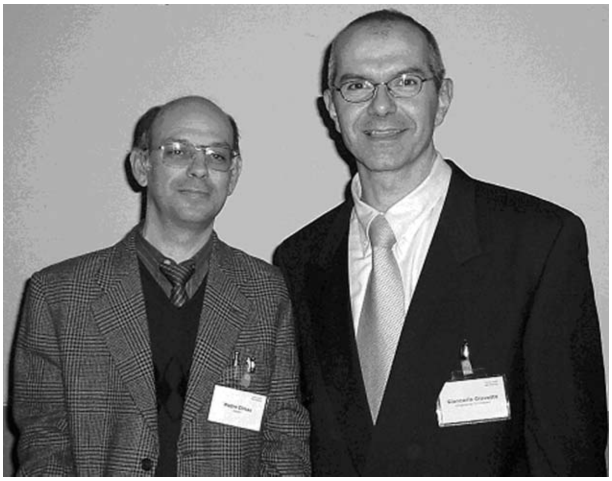
Ultrasound, an efficient and virtually innocuous means of activation in synthetic chemistry, has been employed for decades with varied success. Not only can this high-energy input enhance mechanical effects in heterogeneous processes, but it is also known to induce new reactivities leading to the formation of unexpected chemical species. What makes sonochemistry unique is the remarkable phenomenon of cavitation, currently the subject of intense research which has already yielded thought-provoking results. This *critical review* is aimed at discussing the present status of cavitational chemistry and some of the underlying phenomena, and to highlight some recent applications and trends in organic sonochemistry, especially in combination with other sustainable technologies. (151 references.)

1. Introduction and scope

Ultrasonic irradiation is widely used in chemistry and elsewhere. Imaging techniques using echolocation, such as SONAR systems for target detection or echography in health care, represent perhaps the best known use of ultrasound. Chemical applications extend to such varied areas as organic and organometallic chemistry, materials science, aerogels, food chemistry and medicinal research. The reader is referred to some recent series and monographs for an in-depth coverage of these subjects.[1–4] Although readers are likely to be acquainted with the use of common ultrasonic apparatus such as baths and probes, the advantages and disadvantages of a particular device and the ways to maximize its efficiency and usefulness are often overlooked. Moreover, the interaction of acoustic waves with a chemical system is not merely an improved way of achieving agitation or surface cleaning, as it involves complex physico-chemical phenomena which are currently a matter of advanced research. Nevertheless the enhanced reactivity induced by this type of radiation stems, in many cases, from mechanical and physical effects, namely the dispersion of materials in a finely divided form and the breakage of a passive coating. It is not surprising that most of the synthetic studies have focused on heterogeneous metal reactions, partly owing to the importance of these processes and partly in the search for milder and faster procedures in organic synthesis.[2,5]



Pedro Cintas (left) and Giancarlo Cravotto (right)

Giancarlo Cravotto, a graduate in Pharmacy as well as in Pharmaceutical Chemistry and Technology, after a 3-year stint in the pharmaceutical industry became a researcher and then Associate Professor of Organic Chemistry at the University of Torino. In 1992 he spent 10 months at the TU-Berlin working with Prof. Weyerstahl. His research activity has been centered on the synthesis of natural products and the development of new sonochemical procedures. He has authored 85 scientific papers and is currently co-ordinator in COST Action D32 (Microwave and high-intensity ultrasound in the synthesis of fine chemicals).

Pedro Cintas earned his PhD degree (1987) from the University of Extremadura (UEX, Spain). He did postdoctoral studies at the University of Geneva (Switzerland) with Professor Wolfgang Oppolzer on asymmetric methodologies (1988–1989). He joined the UEX as Associate Professor and later as Organic Chemistry Professor. He was Visiting Professor at the Université Paris Sud-Orsay (2002). His research concentrates on stereochemistry and physical activation of chemical reactions. A member of the European Society of Sonochemistry (ESS), he was fortunate to chair the 9th Meeting of the ESS, held in Spain (Badajoz, April 2004) for the first time.

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Sonochemistry shares with sustainable chemistry such aims as the use of less hazardous chemicals and solvents, a reduced energy consumption and an increased product selectivity.[6,7] In this regard, ultrasound and microwave heating are in many instances complementary techniques for driving chemical reactions. Our first aim is to introduce readers to ultrasound and its effects, and to make them aware that sonochemistry is in fact a unique and distinctive chemistry, in which the physical properties of the medium may have a decisive effect on chemical reactivity. Although the extreme conditions inside an acoustic bubble have been a matter of controversy, recent findings have provided an accurate estimate of local temperatures and clarified the chemical events to be expected. In addition, it has become possible to rationalize sonochemical reactions following an analysis of experiments. The knowledge thus gained confirms that the bubbles behave as special microreactors in which outcome of the reactions is predictable.

From our scope we excluded some synthetic applications such as the preparation of micro- and nanomaterials, largely of inorganic nature, which make up a significant portion of the current literature and are covered in more specific reviews,[8–11] as well as the multifaceted field of sonoelectrochemistry. We concentrated instead on showing how sonochemistry can be usefully applied to organic synthesis and the development of environmentally benign protocols. Particular attention will be paid to the combined use of ultrasound and other methodologies such as photochemistry, ionic liquids, and microwaves.

2. Sonochemistry: where does it come from?

Sonochemistry is a branch of chemical research dealing with the chemical effects and applications of ultrasonic waves, *i.e.* sound with frequencies above 20 kHz that lie beyond the upper limit of human hearing. Although the range of ultrasonic frequencies can be extended up to 100 MHz, it is customary to divide ultrasound into two distinct regions: *conventional power ultrasound*, up to 100 kHz, that especially affects chemical reactivity in liquids (although higher frequencies can also do so), and *diagnostic ultrasound* (above 2 MHz and up to 10 MHz) with applications in both medicine and materials processing (Fig. 1). For the sake of comparison it can be mentioned that microwaves lie in a higher frequency range, from 0.3 to 300 GHz, although most devices operate at a single frequency of 2.45 GHz (2450 MHz) to avoid interference with telecommunications.

Over 80 years have passed since Richards and Loomis published the first report describing the influence of ultrasounds on reaction rates.[12] It is not surprising that their paper attracted scarce attention because these pioneers worked with very high frequencies, from 100 to 500 kHz, which in the late 1920s were uncommonly employed. It is interesting to point out that this group also reported some physical effects of ultrasound as well as biological alterations it caused on animals.[12,13] Subsequent work expanded on mechanical and chemical effects of ultrasounds such as cleaning of surfaces and formation of free radicals by sonolysis of water. Similarities between sonochemistry and radiation chemistry were explored by numerous investigators from the early 1950s. Cavitational implosion (*vide infra*) generates solvent radicals; in the case of water these are $H^•$ and $OH^•$ that can combine to give hydrogen and hydrogen peroxide (Scheme 1). They can also react with other substances to induce secondary reduction and oxidation reactions.[14] For example, iodide can be sonochemically oxidized to triiodide by $OH^•$ radicals or by H_2O_2 produced during cavitation. This so-called Weissler reaction constitutes a standard dosimetric method in sonochemistry since the rate of triiodide formation can be determined spectrophotometrically. If aqueous solutions contain chlorocarbons (*e.g.* CCl_4), $Cl^•$ and Cl_2 are also generated in high yields, which increases the rate of iodide oxidation. Molecular oxygen, if present, can also be broken down, and the subsequent radical pathways parallel those found in flame chemistry, particularly those leading to oxygen production. Yields of these short-lived species are less than those found in radiolysis experiments; moreover, a certain skepticism persisted about the existence of some intermediates. Only recently has electrochemical evidence provided confirmation for ultrasound-generated hydrogen radicals.[15]

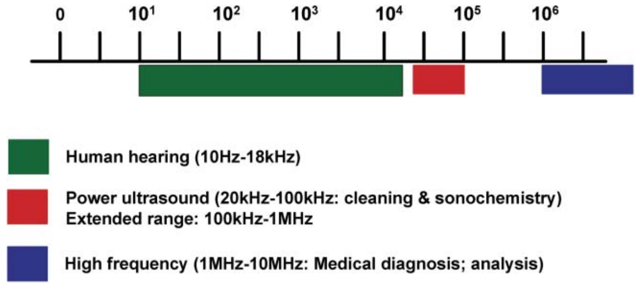
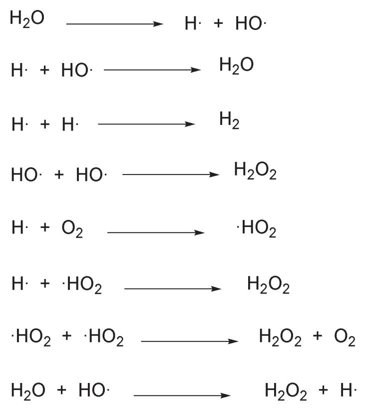


Fig. 1 Sound frequencies (in Hz).

Schultes and Gohr were the first to outline a possible mechanism for the fixation of atmospheric nitrogen when they showed that ultrasonic irradiation at 540 kHz produced hydrogen peroxide in water saturated with oxygen. When air was present instead, nitrous acid was also formed. If enough oxygen was available, further oxidation took place and nitric acid was produced.[16] Interestingly, some reactions caused by sonication of aqueous solutions may have relevance to prebiotic chemistry. Thus, ultrasonic irradiation of a mixture of gases such as N_2, H_2, CH_4 and CO dissolved in water resulted in formation of formaldehyde, hydrogen cyanide, imidazole and amino acids.[17]



$$H_2O \longrightarrow H\cdot + HO\cdot$$
$$H\cdot + HO\cdot \longrightarrow H_2O$$
$$H\cdot + H\cdot \longrightarrow H_2$$
$$HO\cdot + HO\cdot \longrightarrow H_2O_2$$
$$H\cdot + O_2 \longrightarrow \cdot HO_2$$
$$H\cdot + \cdot HO_2 \longrightarrow H_2O_2$$
$$\cdot HO_2 + \cdot HO_2 \longrightarrow H_2O_2 + O_2$$
$$H_2O + HO\cdot \longrightarrow H_2O_2 + H\cdot$$

Scheme 1 Sonolytic production and recombination of radical species.

Research on aqueous media still holds important developments in store concerning the effects of sound waves on biomolecules and polymers.[14] In solutions of DNA, degradation of sugars[18] and base damage[19,20] may be induced by ultrasonic cavitation. These studies are also of paramount importance in assessing the influence of high-frequency waves on living cells and tissues, the domain of medical ultrasonics.

The important area of organometallic sonochemistry was pioneered in 1950 by Renaud, who reported that certain organometallics could be prepared in undried solvents, with unactivated metals, in shorter reaction times, using a simple cleaning bath.[21] At the time ultrasonic transducers were not commonly available and therefore this work, which was also a toehold on non-aqueous sonochemistry, remained unknown. Thirty years later, Luche and Damiano described the facile sonochemical preparation of organolithium and Grignard reagents and their Barbier-type coupling with carbonyls.[22] This, together with the reductive dehalogenation of dibromoketones with ultrasonically dispersed mercury,[23] was the jumping-off point of modern sonochemistry. After the 1980s the number of synthetic applications has been impressive, but in many cases the conjecture that cavitational collapse was inducing truly new chemical reactions has not been confirmed.

As early as 1934 Frenzel and Schultes discovered that ultrasonic irradiation of liquids can produce light in the UV/VIS window (200 to 700 nm).[24] This intriguing phenomenon, known as *sonoluminescence*, can be observed in both aqueous and non-aqueous liquids. As with other sonochemical effects, sonoluminescence arises from acoustic cavitation generating excited-state species.

3. What is cavitation?

That ultrasound can induce chemical effects would at first glance appear surprising since its energies are too low to alter electronic, vibrational, or rotational molecular states. The same consideration applies to microwaves, as the energy of photons in this electromagnetic region is too low to break chemical bonds.[25]

An acoustic pressure wave consists of alternate compressions and rarefactions in the transmitting medium along the wave propagation direction. When a large negative pressure is applied to a liquid, intermolecular van der Waals forces are not strong enough to maintain cohesion and small cavities or gas-filled microbubbles are formed. The rapid nucleation, growth and collapse of these micrometer-scale bubbles constitutes the phenomenon of *cavitation*, accidentally observed towards the end of the 19th century by Thorneycroft and Barnaby when they noticed the poor speed performance of the screw-driven destroyer *H.M.S. Daring*.[14,26] It was found that owing to the rapid motion of the propeller blade in water, the trailing edge created enough negative pressure to pull the water molecules apart, thus originating microbubbles. When collapsing near the metal surface, the bubbles released enough energy to cause erosion of the blade. Thorneycroft and Barnaby envisaged a solution to the problem by modifying the propeller surface, thereby decreasing its angular velocity and, consequently, reducing bubble formation. Thus, the origin of cavitational bubbles is associated with turbulent flow and also during ultrasonic irradiation in liquids. Microbubbles are not spherical and undergo radial and tangential deformations before collapsing. This phenomenon is also responsible for sonoluminescence, when the energy of a sound wave becomes so highly concentrated as to generate light flashes in a liquid. The collapse of a bubble formed by cavitation occurs in an adiabatic manner in such a small volume that the energy of collapse is delivered to a relatively small number of molecules; these are thus excited or dissociated so as to emit light when they return to their ground state, a mechanism similar to that of chemiluminescence.

3.1. Stable and transient cavitation

In general, theoretical sonochemists distinguish between two types of cavitation: stable and transient.[27,28] Stable cavitation takes place when microbubbles mainly contain a gas (*e.g.* air) and their mean life is very much longer than a cycle of the ultrasound. During their growth, as long as their resonance frequency is higher than that of the ultrasound, they are driven into pressure antinodes, where they induce chemical reactions. Conversely, transient cavitation is a phenomenon of shorter duration: a cavity is rapidly formed which contains mainly vapor of the liquid and vigorously collapses after a few cycles. At ultrasound intensities of a few W cm^{-2}, probably both kinds of cavitation take place. As most theoretical work has been devoted to transient cavitation, this is often considered the most efficient way of producing chemical reactions, which is probably true for experiments conducted with high ultrasound intensities and avoiding the formation of standing waves. Nevertheless, at low intensities, when standing waves must occur if high bubble numbers and significant yields are to be achieved, most chemical reactions are induced through stable cavitation.

3.2. Temperatures of cavitation

In a simplified description, two different theories have been proposed to explain sonochemistry and sonoluminescence, the so-called "hot spot"[29] and electrical discharge[30] theories. Most experimental evidence supports the former, although given the complex nature of cavitation, electrical phenomena cannot be completely ruled out. At any rate, practitioners of microwave-assisted reactions often refer to the existence of hot spots to rationalize the observable heating of reaction mixtures.[31]

According to the thermal "hot spot" theory, extreme local temperatures and pressures are produced inside the cavitating bubbles and at their interfaces when they collapse. The effective temperature of the resulting transient, local "hot spots" was estimated to be in the range of 4500–5000 K.[32] Assuming such value, the pressure during collapse, as inferred from the van der Waals equation, would be approximately 1700 atm. Sonoluminescence studies also estimated the duration of the cavitation event (less than 100 ns) and found that cooling rates for hot spots exceeded 10^{10} K s^{-1}.[33] Accordingly, this near-adiabatic high energy process supplies the kinetic energy that drives the chemical reaction. The cavitation bubble model presented in Fig. 2 highlights three different temperature domains, in which peculiar chemical processes will take place.

This simple picture provides an intuitive handle for understanding how sonochemical reactions occur and why they may

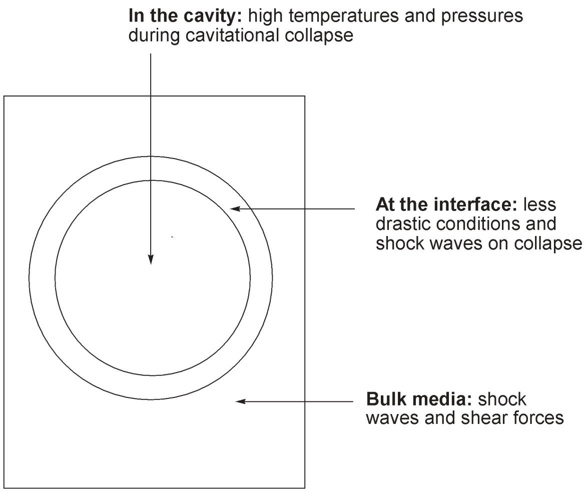


Fig. 2 Cavitation bubble in a homogeneous medium.

yield products that are inaccessible by other methods. After volatile molecules enter microbubbles and the high temperatures and pressures produced during cavitation break their chemical bonds, short-lived chemical species are returned to the bulk liquid at room temperature, the thermal gradient extending over less than 500 Å. Compounds of low volatility, which are unlikely to enter bubbles and thus be directly exposed to these extreme conditions, still experience a high-energy environment resulting from the pressure changes associated with the propagation of the acoustic wave (a few bars) or with bubble collapse (shock waves); or they can react with radical species generated by sonolysis of the solvent. The passage of a sound wave or a shock wave through a medium displaces the system from equilibrium by the combined action of pressure and temperature changes. At the shock front mechanical energy of mass flow is converted to kinetic energy of random molecular translation and rotation. Consequently, conditions created by cavitation are comparable to those of flash thermolysis.

It is obvious that the negative pressure required for cavitation and the resulting temperature change must be largely solvent-dependent. Thus, measured cavitation bubble temperatures in aqueous solutions of aliphatic alcohols range from 4600 K (for pure water) to 2300 K. The mean temperature falls with increasing concentration, also with increasing molecular weight (or decreasing vapor pressure) of the alcohol. This finding was based on the yield of hydrocarbons arising from recombination of methyl radicals generated by thermal decomposition of alcohols.[34]

The electrical theory claims that lower temperatures and pressures are involved but electrical discharges accompany the collapse. However, this theory based on a double layer model has been the target of much criticism.[29,35,36] Perhaps the major objection lies in the fact that, hydrated electrons, $e^-_{(aq)}$, which would be generated by electrical discharge, have not been unambiguously detected. Solvated electrons may be formed by the interaction of high-energy radiation with liquids, the initial step being the production of ionized and excited solvent molecules. In fact, the pulsed radiolysis of water yields $e^-_{(aq)}$ which can be identified by its broad absorption spectrum, peaking around 700 nm.[37] In pure water it is initially free, but in a matter of picoseconds it is rapidly trapped in solvent cavities, and further stabilized by the orientation of solvent dipoles. It has a half-life of $\sim 5 \times 10^{-4}$ s and decays by reaction with water. Sonolysis of alkaline aqueous solutions generates hydrated electrons,[29,38] but in neutral solutions negative evidence has emerged.[38,39] If hydrated (or solvated) electrons were formed by ultrasonic irradiation, their reaction with spin traps would give rise to radical anions, thereby leading to reaction products which can be obtained in radiation chemistry. However, these substances could alternatively be formed by direct pyrolysis (in agreement with the hot spot theory) rather than by the reaction with hydrated electrons.[38]

Chemistry associated with multibubble cavitation (MBC) cannot be treated quantitatively as there are many unknown parameters such as the number of active bubbles, the acoustic pressure on each bubble and the bubble size distribution. An important breakthrough in understanding the physicochemistry of cavitation occurred in 1990 when Gaitan and Crum showed that in degassed water a single air bubble can levitate in a standing acoustic wave until light is emitted on critically increasing the acoustic stress; this unusual phenomenon is called single-bubble sonoluminescence (SBSL).[40] It is characterized by very short light flashes (less than 50 ps), a regular light emission, and the appearance of light immediately before collapse. Under appropriate conditions, a stable levitating bubble may luminesce for several hours, which contrasts with a transient cavitation event that ends within a few acoustic cycles. Moreover, the ultrashort duration of SBSL flashes is not consistent with an almost adiabatic compression. An alternative explanation hinges on a plasma diagnostics analysis of experimental sonoluminescence spectra, which gives higher than expected values for cavitation temperatures.[41] Thus, sonoluminescence is shown to arise from chemiluminescent reactions of seed molecules (inner gas such as N_2 or solvents such as water) with their dissociation products. Theoretical calculations also predict that chemical reactions in an air bubble under SBSL conditions should produce appreciable amounts of $H^•$, $OH^•$, $HOO^•$, H_2O_2, O_3 and H_2, but smaller amounts of nitrogen-containing compounds (NO_x, NH_x and HNO_x).[42] The chemical activity of SBSL has been difficult to monitor because of the tiny amount of reacting gas within a single bubble ($<10^{-13}$ mol). However, Suslick and his group demonstrated the occurrence of molecular excited states and chemical reactions during single-bubble cavitation in polar aprotic solvents[43] as well as in water at different ultrasound frequencies (28 and 52 kHz) and temperatures.[44] The energy efficiency of $OH^•$ formation was comparable to that in MB cavitation, but the efficiency of light emission was much higher. Nitrite formation correlated well with the diffusion rate of N_2 in the bubble. Remarkably, temperatures attained during SBSL in liquids with significant vapor pressures extended over a wide range (from 1,600 to 15,000 K) and were significantly limited by the endothermic chemical reactions of the polyatomic species present inside the bubble.[43,44] A further study suggesting a plasma-like scenario showed that using Xe- or Ar-filled bubbles in concentrated sulfuric acid, SBSL could be even more intense than in water.[45]

The resulting spectra contained lines from atomic and molecular species; from their intensities cavitational temperatures above 15,000 K were inferred (consider that the temperature at the Sun's surface is roughly 5,500 K).

3.3. Cold sono-fusion?

Recent work claiming evidence for nuclear emissions during acoustic cavitation in deuterated acetone (C_3D_6O) met with considerable skepticism. The authors announced the observation of tritium decay and neutron emission near 2.5 MeV, an energy level expected for D–D fusion. In addition, temperatures from 10^6 to 10^7 K for bubble implosion were suggested from hydrodynamic studies.[46] In a further, peer-reviewed paper, neutron and gamma ray emissions were reported during cavitation in deuterated acetone.[47] However, the extreme conditions required to initiate nuclear fusion would be unlikely to occur in solvents with a significant vapor pressure such as acetone ($P = 30$ kPa at 298 K *versus* $P = 3.2$ kPa for water at the same temperature), as the collapsing bubbles will then contain many polyatomic molecules.[44] Sono-fusion might only be possible in solvents of very low volatility. At any rate other authors failed to detect neutron emission, even at plasma temperatures.[45] At this stage, solid evidence for bubble fusion is lacking, although this possibility should not be completely excluded.[48]

3.4. Hydrodynamic cavitation

While the chemical effects of acoustic cavitation generated by the action of pressure waves on a fluid have been extensively investigated, surprisingly scarce attention has been paid to the chemical consequences of *hydrodynamic* cavitation which occurs during turbulent flow of liquids. This type of cavitation should be important in waterfalls, fast streaming rivers, and stormy seas; *i.e.* whenever water impinges on water at relatively low linear velocities.[49] In addition, hydrodynamic cavitation appears to play an important role in water transport in trees.[50]

With the advent of commercially available high-pressure jet fluidizers (with liquid pressures of $\sim$2 kbar and jet velocities of $\sim$200 $\mathrm{ms^{-1}}$), hydrodynamic cavitation experiments have become possible.[51–53] The study of the hydrodynamically induced Weissler reaction reveal that the chemical effects of hydrodynamic and acoustic cavitation can be identically correlated with such experimental parameters as the bulk temperature and the nature of the dissolved gas.[52] Reaction rates decrease with increasing liquid temperatures owing to the increased vapor pressure inside the bubble which attenuates the cavitational collapse. Likewise, the triiodide formation rate decreases exponentially as the thermal conductivity of the dissolved gas increases. Both observations are consistent with the hot spot model for cavitation. It is also noteworthy that no chemical reaction was observed at hydrostatic pressures below 150 bar; this very likely represents the threshold jet velocity to induce cavitation. Pandit and his group applied hydrodynamic cavitation to some industrially important reactions, such as the oxidative degradation of aromatics and transesterification of fatty acids for the preparation of biodiesel.[54] They also evaluated a series of operating and system parameters that should help to optimize the design of large-scale hydrodynamic cavitational reactors.[54,55]

3.5. From cavitation to chemistry

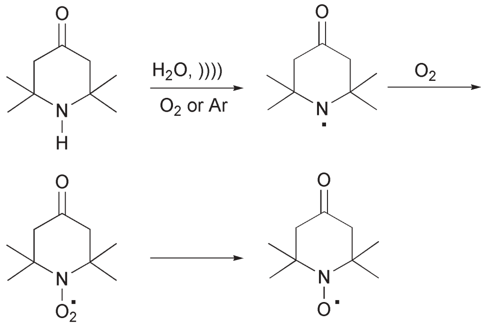
Although the fundamentals of cavitation outlined above may seem irrelevant from a practical viewpoint, they highlight the uniqueness of sonochemistry and show that factors affecting cavitation, such as the nature of solvents or the volatility of substrates, may be crucial to understanding how this high-energy chemistry can be performed in a simple flask. What is more important, solvent effects in sonochemistry should not be reckoned in terms of such parameters as acidity, basicity, dipole moments *etc.*, but rather taking into account volatility, viscosity, surface tension and dissolved gas, all of them directly involved in bubble formation and energy.[56] Two physical parameters, ultrasonic frequency and intensity, are often poorly understood from a chemical perspective. Unlike electromagnetic radiation, sound is not quantized, therefore a direct relationship between its energy and frequency cannot be established. A simplified form of the temporal evolution of the pressure $P(t)$ at a given point of an elastic medium is given by:

$$P(t) = P_A \sin(2\pi f t + \theta) \qquad (1)$$

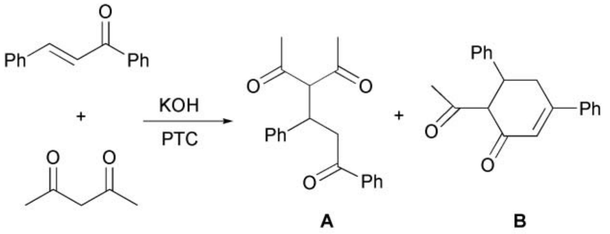
where P_A is the acoustic pressure amplitude (in Pa or bars) and f the frequency of the alternating pressure wave. As frequency is increased, it is necessary to increase the amplitude (or the power) of irradiation to maintain the same amount of cavitational energy. This is why it becomes more difficult to produce cavitation at higher frequencies, especially in the MHz region. Intuitively, this can be explained in terms of shorter cycles of compression and rarefaction at very high frequencies: since the creation of cavities requires enough time for molecules to be pulled apart, cavitation can be extremely difficult to achieve with very short cycles.

If predictions are to be made, it must be borne in mind that reactions induced by cavitation will depend on the lifetimes of primary radicals relative to bubble lifetime. Frequency will influence the time taken by a bubble to collapse, although studies on this aspect are few. At high frequencies, say 500 kHz, collapse occurs in 4×10^{-7} s, less than the lifetime of most radicals. These will then diffuse into the liquid phase and interact with other species. At a frequency of 20 kHz, however, bubble collapse occurs in approximately 10^{-5} s, a time long enough for $^{\bullet}OH$ radicals to undergo recombination reactions (yielding hydrogen peroxide, superoxides, excited water molecules) or other reactions in which dissolved gases may also participate. This suggests that "primary" sonochemistry will be observed only at high frequencies, while the chemistry of low frequencies will be determined by sequential transformations of radicals.

To test the above predictions, the sono-oxidation of 2,2,6,6-tetramethylpiperidin-4-one was investigated at 520 and 20 kHz and the formation of its stable nitroxide was monitored by ESR (Scheme 2).[57] The reaction requires the presence of $^{\bullet}OH$ and either molecular oxygen or superoxide radical anion. At 520 kHz a higher rate of nitroxide formation was observed with an oxygen-saturated solution, while it was not under argon. In contrast, the same reaction run at 20 kHz proceeded



Scheme 2 Sonochemical oxidation of 2,2,6,6-tetramethylpiperidin-4-one.



Conditions	A (%)	B (%)
Stirring	52	0
US, Cup-horn	69	0
US, Probe	72	12

Scheme 3 Effect of ultrasonic energy on product distribution in a Michael reaction under phase-transfer catalysis conditions.

more slowly under oxygen than under argon. As it requires oxygen, at low frequency under argon this must be produced by reaction pathways involving $^{\bullet}$OH recombination (*vide supra*, Scheme 1).

The next important parameter is acoustic intensity, or the amplitude of the pressure wave which is linked to our perception of sound strength. Acoustic pressure and intensity (in W m^{-2}) of ultrasound are related by the following expression:

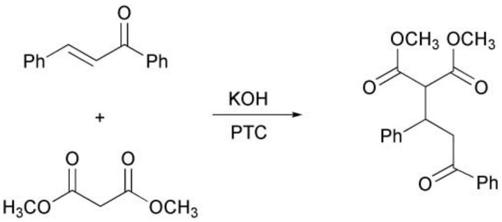
$$I = P_A{}^2/2\rho c \qquad (2)$$

where ρ is the density of the fluid and c the speed of transmission (the term ρc describes the acoustic impedance of the medium). In general, an increase in intensity will give rise to stronger sonochemical effects. A minimum intensity value is required to reach the cavitational threshold, which also depends upon the frequency. Since the intensity of sound, as it propagates through a medium, is attenuated to an extent that is inversely related to its frequency, a higher power output will be required with a higher frequency.[56] For a proper comparison, sonochemical effects should be evaluated at different power levels; this can be done by varying the applied potential (in Volts) at the piezoelectric transducer. Sonochemical efficiency will depend on how efficiently the ultrasonic device transforms electrical power into mechanical energy and the latter is then transmitted to the reaction mixture. An interesting synthetic study addresses this issue in an excellent way.[58] In the Michael addition to chalcone of the pentan-2,4-dione anion under solid–liquid phase-transfer conditions, an adduct is formed that can further react to give a cyclohexenone derivative (Scheme 3). This reaction is accelerated by sonication, but both its yield and selectivity depend on the ultrasonic power. The initial adduct is only generated without ultrasound or using a cup-horn, whereas the cyclic product is only formed under sonication using a probe. A likely explanation is that at the smaller probe surface the ultrasonic intensity is higher than at the larger cup-horn surface, therefore more drastic conditions exist in the small reaction volume under the probe.

This sort of addition reaction also offered further insights into reactor design and scale-up. Thus, the addition of diethylmalonate to chalcone was investigated in the absence of solvent under solid–liquid phase-transfer conditions. High yields and good reaction rates were obtained on a laboratory scale without stirring. However, the scale-up was seriously hindered by poor mass and heat transfers, a hurdle that could likely be overcome by the addition of a solvent. As expected, sonication (cup-horn, 1.3 W cm^{-2}) with a minimal amount of toluene gave satisfactory results (Scheme 4).[58] Furthermore, the reaction was scaled-up by placing in a hexagonal ultrasonic bath a concentric cylindrical reactor with a capacity of 750 cm^3. The authors estimated that if the reactor were used in continuous mode at a flow rate of 250 cm^3 min^{-1}, the annual production would be around 15 tons, a realistic figure in industry.

4. Sonochemical reactions

In what way does ultrasound affect chemical reactions? The analysis of numerous experiments revealed that ultrasound had no effect on chemical pathways and reaction rates were often comparable to those of non-irradiated (or silent) processes. Thus, in many heterogeneous reactions the application of ultrasound, whether by bath or probe, has the same effect as a high-speed agitator or a homogenizer in which fluids do not cavitate.[59] Enhanced yields and rates can be observed owing to the mechanical effects of shock waves. Chemical effects of ultrasound ("true sonochemistry") will occur only if



Conditions	Time (min)	Yield (%)
Stirring, solventless	5	91
US, solventless	2	97 (98)*
Stirring, toluene	10	52
US, toluene	2	98

US: Cup-horn, volume = 50 cm^3
*Hexagonal bath, volume = 750 cm^3

Scheme 4 Effect of sonication on a phase-transfer reaction: power source and scaling-up.

an elemental reaction is the sonication-sensitive step or when the high-energy species released after cavitational collapse do indeed participate as reaction intermediates. In this context, it is appropriate to speak of ultrasonic activation and sonocatalysis. Then changes in product distribution upon irradiation, switching of mechanisms, and in some instances changes of regio- and diastereoselectivity[60] suggest, although do not explicitly prove, that a true activation is occurring. A set of empirical rules (a–c) have been established to distinguish between true and false sonochemistry;[61] they represent a first rational approach to sonochemical reactions and can provide clues for future work. In the following we will quote some recent examples to illustrate these specific situations and to give an indication of what is possible in modern synthetic sonochemistry.

a) *Type I*: In homogeneous reactions chemical effects can be rationalized by assuming that sequential electron transfers are favored by ultrasonic irradiation. Transition metal complexes will undergo ligand–metal bond cleavage producing coordinatively unsaturated species. In general, homogeneous ionic reactions will not be affected by sonication.

b) *Type II*: In heterogeneous liquid–liquid or liquid–solid ionic reactions, mechanical effects associated with sound waves can affect both rates and yields to an extent depending on surface tension, density, temperature and nature of participant solids. These are in fact cases of false sonochemistry.

c) *Type III*: In heterogeneous reactions which can follow either an ionic or an electron-transfer path, the latter will be preferentially induced by ultrasound. These biphasic systems will also be sensitive to the mechanical component of shock waves in addition to chemical activation.

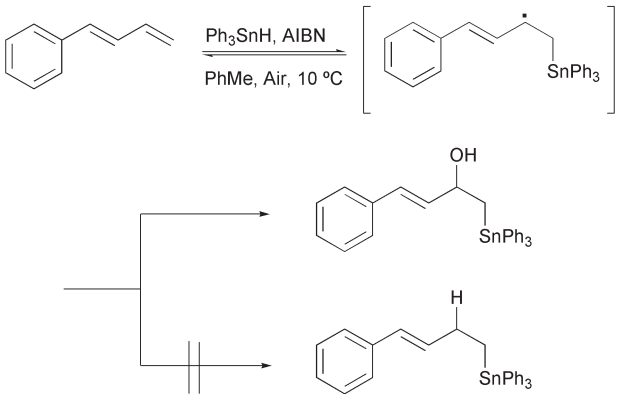
At this point one should emphasize that most organic chemists are only interested in using ultrasound as a convenient tool to enhance the yields and rates of many chemical reactions. The high temperatures and pressures developed locally by cavitation prove advantageous in a multitude of common reactions, in which conventional conditions or high-speed stirring cannot achieve the same results. Whether these effects fall under the heading of true or false sonochemistry (*vide infra*), they all contribute to the current trend to adopt this technology.

Probably, one of the most telling examples of true sonochemistry was the report by Ando and coworkers of a sonochemical switching in the reaction of benzyl bromide, potassium cyanide and alumina (*Type III* reaction). This system, when stirred mechanically in toluene at 50 °C, gave rise to a mixture of *o*- and *p*-benzyltoluene in 75% yield. In contrast, when irradiated with ultrasound (45 kHz) at the same temperature it afforded benzyl cyanide in 71% yield.[62] The reaction switch from a Friedel–Crafts to a nucleophilic substitution course was attributed to the acceleration by ultrasound of a specific poisoning by potassium cyanide of the catalytically active sites of alumina.[63] Alternatively, benzyl cyanide might be formed through a SET pathway, since sonication should yield a higher density of free radical species than mechanical stirring.[64]

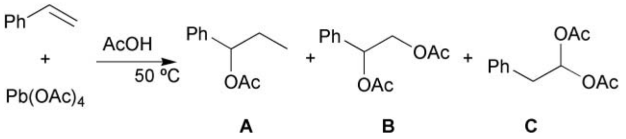
A more convincing example of sonochemical switching is the initiation of radical chain reactions with tin radicals, a case that illustrates well the differences between radical sonochemistry and classical free-radical chemistry. When an aerated solution of R_3SnH and an olefin was sonicated at low temperature (0 to 10 °C), *hydroxystannation* of the double bond occurred instead of the conventional hydrostannation achieved under silent conditions (Scheme 5).[65] The result was attributed to the generation, in the region of hot cavities, of tin and peroxy radicals, which underwent synthetic reactions in the bulk liquid phase. We may also quote the sonochemical synthesis of alkyl hydroperoxides by reductive oxygenation of alkyl halides,[66] and the catalytic conversion of alkyl halides to alcohols by trialkyltin halides,[67] in both cases under an atmosphere of air.

A homogeneous process involving C_{60} is worth mentioning because the sonochemistry of fullerenes is relatively underexploited.[68,69] The ultrasonic irradiation at 20 kHz of a solution of C_{60} in decahydronaphthalene resulted in the formation of $C_{60}H_2$.[70] Owing to its low vapor pressure at room temperature, C_{60} will not enter the cavitation bubbles, although it will experience secondary reactions in the liquid phase. Dihydrofullerene resulted from its reaction with atomic hydrogen generated by sonolysis of the solvent. Although there are already many studies on hydrogenated fullerenes, it is remarkable that sonication does not give rise to more highly hydrogenated derivatives. Moreover, upon continued sonication both C_{60} and $C_{60}H_2$ disappeared from the solution, presumably by fragmentation into smaller hydrocarbons or by formation of polymeric structures.

Another case of switching is the reaction of lead tetraacetate with styrene.[71] The addition may follow either an ionic or a radical course affording the products shown in Scheme 6. In the former, lead tetraacetate adds to styrene leading to a *gem*-diacetate *via* a carbocation, while the radical pathway probably starts by the decomposition of the lead reagent to give the methyl radical, which then reacts with styrene. The use of an ultrasonic horn enhances yields of products resulting from homolytic processes, while the same cannot be obtained at all under mechanical stirring. Moreover, the sonochemical reactivity of styrenes correlated well with their vapor pressures, while no correlation was found with the usual Hammett parameters that account for electronic effects.[72,73] In a further study, radical species formed in the sonochemical activation of styrenes were scavenged with pyrocatechol. A linear free-energy relationship could be established between rates of decomposition and vapor pressures of styrenes.[74]

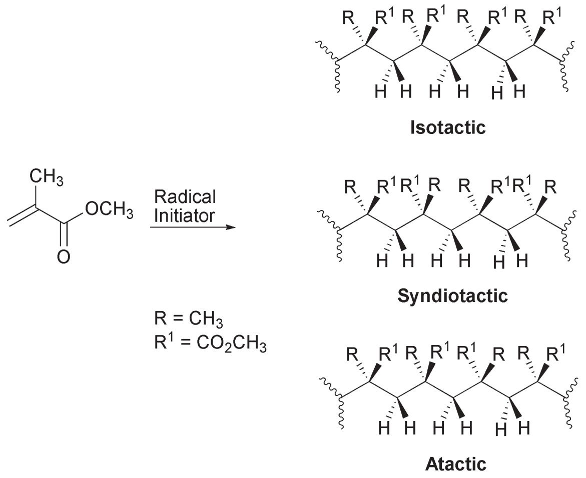


Scheme 5 Ultrasound-induced hydroxystannation of olefins.



Conditions	A (%)	B (%)	C (%)
Stirring, 1h	0	0	5
US, 1h	38	12	3
US, 1h, radical scavenger	38	12	3

Scheme 6 Effects of stirring and sonication on the composite pathway of the reaction of lead tetraacetate with styrene.



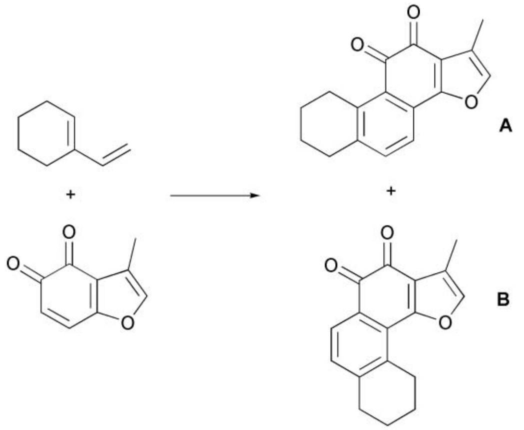
Conditions	Isotactic (%)	Syndiotactic (%)	Atactic (%)
Stirring, 100 °C	9	54	38
Stirring, 50 °C	6	56	38
Sonication, 60 °C	4	55	41
Sonication, 40 °C	4	56	40
Sonication, 25 °C	3	63	34
Sonication, 0 °C	2	65	34
Sonication, -10 °C	1	74	26

Scheme 7 Stereochemical ratios obtained in the radical polymerization of PMMA.

Polymerizations undoubtedly present suitable test cases for cavitational effects, as it is well known that these reactions can be initiated by ionic or radical intermediates, and some monomers are volatile enough to undergo activation inside the bubbles. The field has been the subject of recent studies, both on the synthetic side[75,76] and on the depolymerizing effect of ultrasound,[77] the latter being relevant to the degradation and detoxification of waste materials.

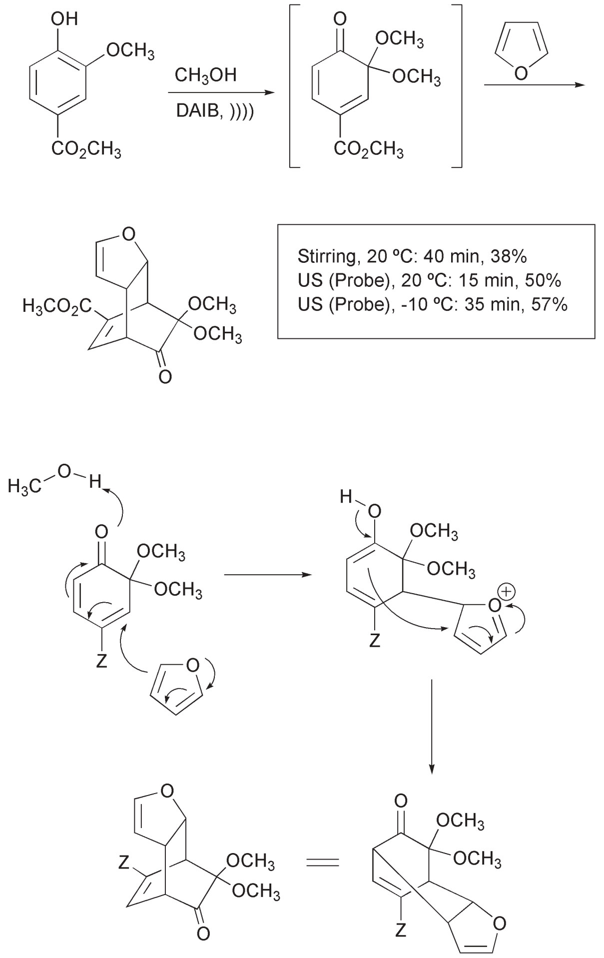
It is interesting to note that ultrasound can induce radical polymerization (*e.g.* of vinyl monomers) even in the absence of chemical initiators.[8,75] The early 1950s saw the first examples of sonochemically induced polymerizations, those of acrylonitrile[78] and acrylamide,[79] both in aqueous solutions. Further studies in organic media, especially aromatic hydrocarbons, were disappointing as sonication led to high-molecular weight colored products resembling coal, often referred to as *chars*.[75] Formation of normal polymers, such as those derived from polystyrene or poly(methyl methacrylate) requires stable cavitation stages, while under transient cavitation higher local temperatures can be reached breaking the C–H bonds and leading to pyrolytic degradation.[80] Experiments with radical scavengers strongly prove that sonochemical polymerizations are due to free radicals formed from thermal scission of monomers in bubbles, or from an intense shock wave in the liquid immediately surrounding the bubble; this induces shear forces that fragment polymer chains already present. Many useful macromolecules can easily be obtained by sonochemical methods, such as acrylamide,[81] methacrylamide,[82] and copolymers of styrene with maleic anhydride.[83] Ultrasound has also been exploited for graft copolymerization of methyl methacrylate onto regenerated cellulose film.[84] Ultrasonic irradiation not only alters kinetic parameters in polymer synthesis, but also affects polymer properties, resulting for example in a more homogeneous chain growth, hence a narrower distribution of molecular weight. As for heterogeneous and emulsion polymerizations, sonication affects them most likely by physical rather than chemical activation, by increasing mass transfer and continuously sweeping the polymer surface resulting in a greater number of propagation sites.[76] A remarkable possibility is that ultrasound may alter the conformation[60] of the resulting polymer chains, namely the *tacticity*, a key factor in determining the physical properties of these products. Atactic polymers have a random arrangement of side chains whereas in isotactic and syndiotactic products the substituents lie either all on the same side of the polymer chain or regularly alternate on the two sides. Scheme 7 shows the tacticity ratios obtained in the sonochemical polymerization of poly(methyl methacrylate), PMMA, in the presence of peroxide as initiator. At room or high temperatures, sonication had little effect on tacticity ratios, as the yields of atactic and syndiotactic products were comparable to those obtained under silent conditions. However, syndiotacticity was increased by lowering the temperature.[76] This result was explained in terms of a lower propagation rate, that should increase the thermodynamically favored syndiotactic addition. In addition, one should keep in mind the so-called *anti-Arrhenius effect* of temperature in sonochemical reactions: increasing the temperature will raise the vapor pressure of the liquid and lead to an easier cavitation but a less violent collapse.[56] Accordingly, enhanced sonochemical effects, including a higher reaction rate, would be expected on lowering the temperature, at least up to the limit imposed by the viscosity of the liquid.

A limiting, borderline case among homogeneous reactions are the Diels–Alder and other thermal symmetry-allowed cycloadditions, a current challenge to sonochemists. Surprisingly scarce success has so far met Diels–Alder reactions under ultrasonic irradiation, although they are very sensitive to heat and pressure. For some recently reviewed exceptions to this inertness[85] non-concerted mechanisms with the intermediacy of radical ions were suggested. Other experiments should be interpreted with caution because they were carried out under heterogeneous conditions, although they offer some clues to cavitational effects. In this context, the most frequently cited work is found in a series of papers by Snyder and his associates on the synthesis of *o*-quinonic derivatives that are present in plants used by traditional Chinese medicine (Scheme 8).[86–89] In all their experiments, carried out in a cleaning bath, the reaction mixtures were



Conditions	Yield (%)	A/B Ratio
Sealed tube, 110 °C, C_6H_6, 12 h	< 10	-
Reflux, MeOH, 16 h	40	2.5 : 1
11 kbar, MeOH, rt, 2 h	67	6 : 1
US, neat, 45 °C, 2 h	65	7: 2

Scheme 8 Cycloadditive strategies for the construction of quinonic abietanoids.



Scheme 9 Addition of furan to masked *o*-quinones and its probable stepwise mechanism.

heterogeneous due to the insolubility of quinones in the diene taken in excess. Conventional activation (heating in a solvent or in a sealed vessel) gives poor yields, especially with thermally labile substrates. Moreover, the presence of an organic solvent (benzene or toluene) is undesirable, as it cuts down the sonochemical effect. Addition of just enough methanol to make the mixture homogeneous, improved yields. Notably, either under sonication or under a pressure of 11 kbar, rates and yields were substantially enhanced and the regioselection also changed. Thus, the naturally-occurring isomer (A) was favored by ultrasonic irradiation at the expense of the unnatural one (B), except when methanol was replaced by a less polar medium (*e.g.* dioxane).

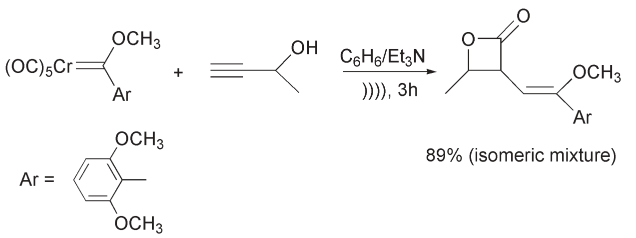
Purely chemical effects, unrelated to cavitational implosion, can be observed in some sonochemical cycloadditions. Small amounts of $TiCl_4$ or $TiBr_4$, Lewis acids that are good cycloaddition catalysts, can be generated when a titanium horn is used in combination with halocarbon solvents.[90]

Positive results for sonochemical cycloadditions can be found even when radical pathways are ruled out. Thus, the addition of furan to masked *o*-benzoquinones, generated *in situ* by oxidation of the corresponding phenol with (diacetoxyiodo)benzene (DAIB), was accelerated under sonochemical irradiation.[91,92] Yields were dependent on acoustic energy, temperature and solvent composition. The presence of radical scavengers gave no conclusive results, and the overall process could satisfactorily be explained by a double Michael addition (Scheme 9). The sonochemical effect should be ascribed to the mixing role of cavitation, which has been usually invoked only for non-homogeneous conditions. However, spectroscopic (UV/VIS) monitoring reveals that the quinone undergoes a faster dispersion, favoring the probability of encounter between the reaction partners and minimizing side reactions.

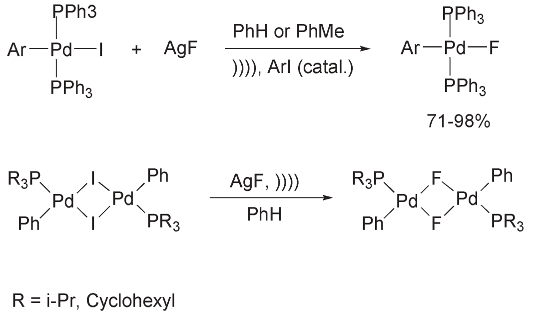
The reactivity of transition metal complexes can often be enhanced by ultrasound under homogeneous conditions. Chromium aryl(alkoxy)carbenes react with propargylic alcohols under sonication (Ti horn, 20 kHz) to afford β-lactones in good yields. These Dötz cyclizations also take place under thermal activation, but sonication works faster and, in addition, favors the formation of less heavily substituted β-lactones (Scheme 10).[93,94]

Palladium fluoride complexes, which have become important and useful organometallics, can be prepared by a new ultrasound-promoted ligand exchange between $[(Ph_3P)_2Pd(Ar)I]$ and AgF in aromatic solvents. No I–F exchange occurs without sonication. The process can also be conducted in the presence of a catalytic amount (5–10 mol%) of the corresponding aryl iodide, a variant that is beneficial for the purity of the product. By the ultrasonic procedure the first dinuclear organopalladium μ-fluorides and their mononuclear analogs stabilized by trialkylphosphine ligands have been synthesized (Scheme 11).[95,96]

In heterogeneous polar reactions (*Type II*) only the mechanical role of ultrasonic waves can possibly lead to enhanced reaction rates and yields. This "false sonochemistry" comprises numerous transformations such as alkylations, acylations, oxidations and reductions. Owing to its dispersing and microstreaming effects, ultrasound constitutes an advantageous alternative to the use of phase-transfer catalysts.[97] A

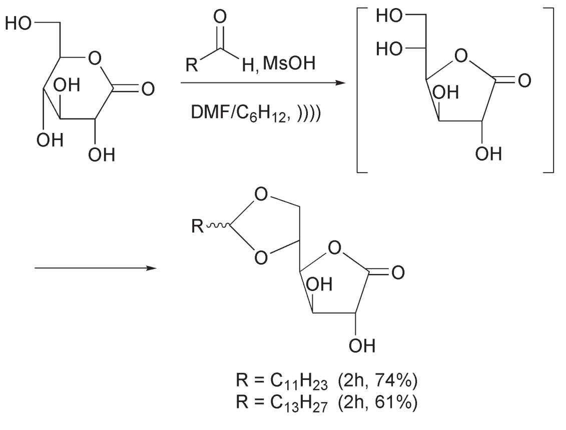


Scheme 10 Sonochemical Dötz cyclization reactions leading to β-lactones.

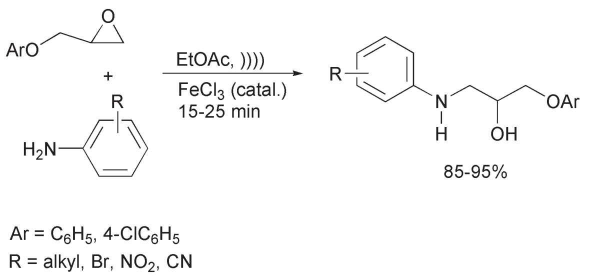


Scheme 11 Preparation of Pd–F organocomplexes under ultrasound.

typical example is the acid-catalyzed acetalization of sugars, involving cationic intermediates, which has been recently employed for the synthesis of biodegradable tensioactive agents.[98] In DMF-cyclohexane δ- and γ-gluconolactones reacted under heterogeneous conditions with dodecanal and tetradecanal to give the long-chain derivatives in good yields. Sonication promotes the reaction at room temperature, while comparable results are only obtained under reflux (Scheme 12). In another work related to carbohydrate chemistry, chitosan, a biodegradable polymer, underwent a facile and controlled depolymerization[77] under high-intensity ultrasound (17–18 kHz, horn) yielding a series of water-soluble intermediates that can be useful as building blocks.[99]



Scheme 12 Ultrasound-mediated acetalization of sugar lactones.

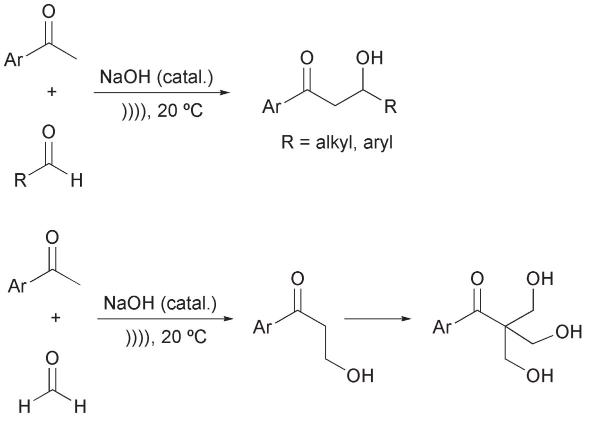


Scheme 13 Ring opening of aryloxy epoxides with aryl amines.

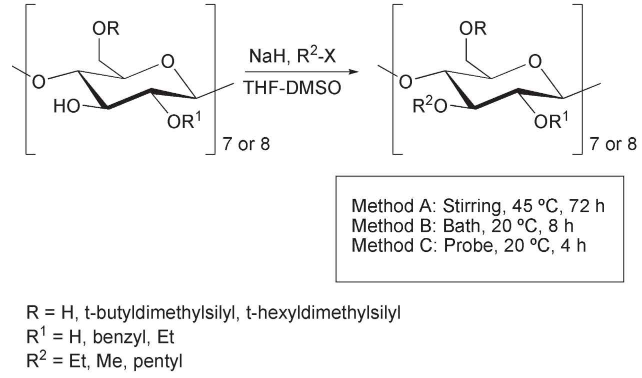
Some ionic reactions suffer from inherent reactivity troubles. Reduction of crowded nitroaromatics (*e.g.* 2,3,5,6-tetraalkylnitrobenzenes) could easily be accomplished in almost quantitative yields under sonication at 45–50 °C within 5–15 min, while it required from 2 h to 20 h and yields were somewhat lower if ultrasound was omitted.[100] Sonication also accelerated a useful Mitsunobu coupling between sterically hindered phenols and aliphatic alcohols, performed using highly concentrated reactants.[101] The cleavage of epoxides with weak nucleophiles such as aryl amines, in the presence of $FeCl_3$ as catalyst, was largely enhanced under ultrasonic irradiation. This synthetic procedure led to a series of interesting β-amino alcohols in excellent yields (85–95%) at room temperature and within 15–25 min (Scheme 13).[102] Some alkyl amines could also be employed with comparable success. The alternative silent transformation takes about 7–8 h for 70% conversions.

The aldol reaction of aldehydes and ketones, generally conducted under basic conditions, is a useful method in organic synthesis, but conversions are usually sluggish as the equilibrium lies well to the left, even with strong bases. When this transformation was re-investigated in water at room temperature under high-intensity ultrasound (18 kHz, 280 W), aldols were isolated in moderate to good yields in short reaction times (Scheme 14). Moreover, side products derived from the subsequent aldol dehydration were not observed.[103] The addition of a surfactant caused a dramatic effect affording exclusively the enone in every case.

Selectively persubstituted β- and γ-cyclodextrins are useful as chiral stationary phases in gas chromatography as well as drug carriers. The advantages of sonication were evident in the *O*-alkylation of positions 3 in 2,6-persubstituted cyclodextrins, that was studied under three different condition sets: A) at 45 °C under stirring, B) at 20 °C under sonication in a cleaning bath (35 kHz, 160 W), and C) at 20 °C with an ultrasonic



Scheme 14 Aldol reactions under high-intensity ultrasound and mild conditions.

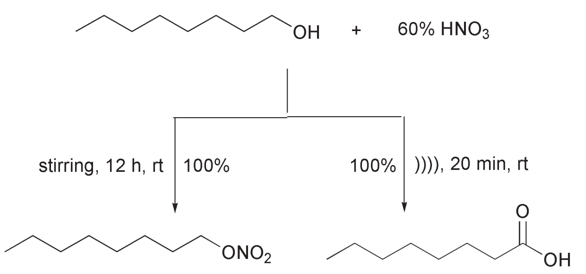


Scheme 15 Reactions of cyclodextrins with alkyl iodides under thermal and ultrasonic conditions.

probe operating at a higher power and intensity (20 kHz, 600 W). With conventional agitation, modest yields (14–41%) were obtained after 72 h and very often complete *O*-alkylation could not be achieved at all. The bath gave moderate to good yields (40–70%) in shorter reaction times (7–12 h), while the probe improved both yields and rates (50–80%, 3–5 h) still further (Scheme 15).[104]

Polar reactions of *Type I* or *Type II*, regardless of homogeneous or heterogeneous conditions (most sonochemical reactions are probably heterogeneous in nature), are susceptible of remarkable effects (including switching) that cannot be achieved thermally. For instance, switching was observed in the reaction of aqueous nitric acid with some (but not all) types of alcohols (Scheme 16).[105] Under mechanical stirring the reaction of 60% aqueous nitric acid with *n*-octanol and 3-bromo-2,2-dimethylpropanol proceeded slowly at room temperature affording nitrate esters quantitatively after 12 h, while under sonication it gave a quantitative yield of the carboxylic acid in 20 min. In close analogy to the sonolysis of water, the reaction should proceed *via* a radical pathway following the cleavage of nitric acid to the nitrogen dioxide radical or its protonated form (a radical cation).

Another example frequently invoked to the point was provided by Mason and his group when studying the solvolysis of *tert*-butyl chloride in aqueous ethanol.[106] The use of a probe generator increased the rate $\sim$20-fold. Remarkably, the sonochemical process also displayed the paradoxical temperature effect, *i.e.* it became more efficient on lowering the temperature.[56] This homogeneous reaction is difficult to interpret because the primary process is not very likely to occur inside the cavitation bubbles and a radical pathway should be ruled out. The authors attributed the acceleration to solvent cage effects[107] that would make sound absorption more efficient. Other local phenomena could facilitate bond breaking by raising the ground state energy of the halide.

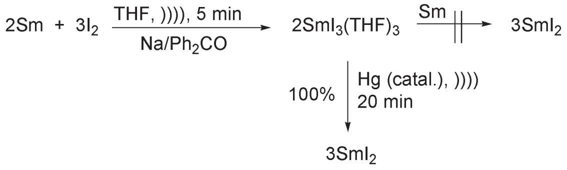


Scheme 16 A tale of two redox processes: the reaction of primary alcohols with nitric acid.

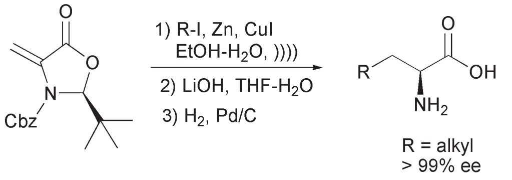
Results from the application of ultrasound to some nucleophilic displacements were more intriguing in view of the well-established duality of polar and radical mechanisms for bimolecular substitutions.[108] The *S*-alkylation of a thiocarbamate salt by alkyl halides in homogeneous ethanolic solutions was markedly accelerated by ultrasound, as the non-irradiated reaction proceeded 75 times slower at the same temperature.[109] The cavitational effect cannot be directly invoked as the salts are not volatile. Alternatively the reaction could occur *via* free radical species formed from the alkyl halide by electron transfers. However, *S*-alkylation reactions with alkyl chlorides most likely proceed by a polar mechanism.[110]

The study of heterogeneous radical or ambident reactions, that can follow either an ionic or a SET pathway (*Type III* reactions), represent the favorite domain of sonochemistry because they are influenced by sonication and sonochemical switching should be expected. Most studies have been focused on reactions involving metals.[3,5,111] Ultrasound favors mechanical depassivation and enhances both mass transfer and electron transfer from the metal to the organic acceptor. In this context it is fit to mention a theoretical study by Grechnev on the mechanochemical effects of ultrasound.[112] Under high frequencies ($\sim 10^{11}$ Hz) the energy of electrons in the valence and conduction bands of non-transition metals are so modified that the metal should display a greater reactivity than in the ground state. Although such frequencies are much higher than those of experimental sonochemistry, an acoustic field might enhance the reactivity of these metals by decreasing the band gap that electrons must cross in electron transfer processes.

The synergic effect of ultrasound associated with an electron carrier can be recognized in the facile preparation of radical anions and their propagation reactions, *e.g.* in the sonochemical formation of lithium amides in the presence of isoprene.[113] Likewise, useful organometallic reagents such as sodium phenylselenide, the important hydride $[(Ph_3P)CuH]$, and the versatile lanthanide SmI_2 can be easily prepared by sonication in the presence of sodium/benzophenone.[114] Since the rate-limiting step of these processes is the transfer of electrons from the metal surface, the acceleration of the reaction is due to the presence of the ketyl radical anion, a fact that reinforces again the chemical role of ultrasound. Thus, the yellow triiodide SmI_3 can be obtained within 5 min from samarium metal and iodine in THF using a simple cleaning bath. Further addition to the sonicated mixture of a catalytic amount of mercury leads to the quantitative formation of SmI_2 (Scheme 17). The overall process is complete is less than 30 min, which contrasts with the classical protocols requiring an inert atmosphere, dried solvents and longer reaction times. The same reagent can also be prepared by sonicating Sm metal and CHI_3 in dry THF, and employed straight away in organic reactions.[115]



Scheme 17 Sonochemical preparation of SmI_2.



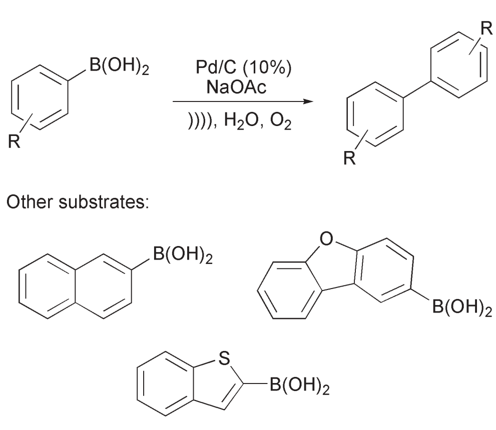
Scheme 18 Sonochemical conjugate additions *en route* to non-racemic amino acids.

A recent example that highlights the facile ultrasonic activation of metals in organic synthesis is an efficient enantioselective synthesis of α-amino acids in aqueous media.[116] Enantiomerically pure derivatives, both natural and unnatural, can be obtained by a highly diastereoselective 1,4-conjugate addition of alkyl iodides to a chiral methyleneoxazolidinone, mediated by an activated zinc/copper couple, followed by the usual deprotection steps (Scheme 18).

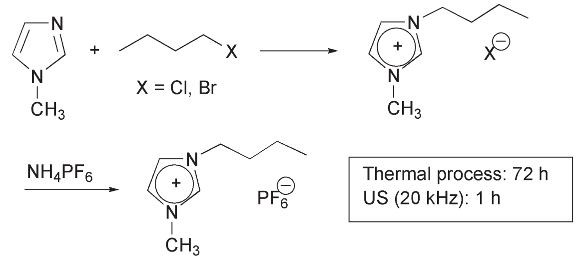
Transmetallations and heterogeneous processes following oxidative additions to metal centers are equally facilitated by sonication.[111] A recent example is the Pd-catalyzed Suzuki homocoupling of arylboronic acids in water under high-intensity ultrasound (18 kHz, 80 W cm^{-2}).[117] A catalytic amount of Pd/C was used without adding phosphine ligands, and oxygen could be employed as oxidant to generate the Pd(II) intermediate (Scheme 19).

4.1. Sonication in ionic liquids

Few topics in organic synthesis have experienced a more impressive and far-reaching development than ionic liquids. These substances, usually consisting of imidazolium or pyridinium cations associated with an anion of varied nature,[118] have negligible vapor pressures. This property, together with a higher viscosity and density than most conventional solvents, present the sonochemist with new challenges and opportunities. Although the correlation between vapor pressure and cavitation energy is not straightforward, the rates of sonochemical reactions can be increased, at least within limits, by lowering the vapor pressure of the solvent.[119] It is extremely difficult to induce cavitation in an ionic liquid where cohesive forces are large. Bar solvent cleavage, however, the reaction partners could then enter the cavitation bubble or the superheated liquid shell surrounding it, to undergo strong cavitational effects.



Scheme 19 Suzuki homocoupling of arylboronic acids under ultrasound.

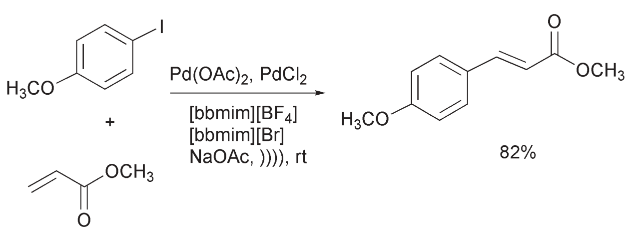


Scheme 20 The two-step route to imidazolium-based ionic liquids.

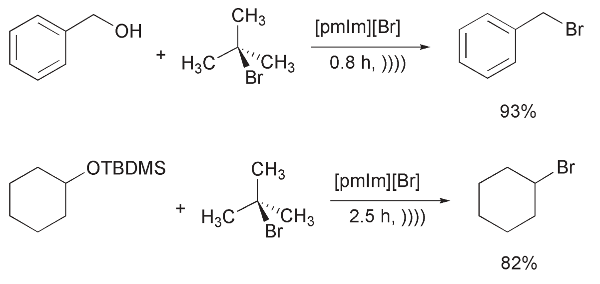
The preparation of ionic liquids usually involves two steps, namely a quaternization of the heterocyclic moiety and a subsequent anion metathesis (Scheme 20), that are both improved and accelerated by sonication.[120] The whole protocol can also be conducted under solvent-free conditions.[121]

A few important coupling reactions have so far been achieved under sonication in such ionic liquids as 1,3-di-*n*-butylimidazolium tetrafluoroborate or bromide. Heck reactions, for instance, go to completion at room temperature within 1.5–3 h in a bath (50 kHz) under argon (Scheme 21). This coupling is thought to involve the formation of Pd-biscarbene complexes and Pd(0) clusters, which would be stabilized by the ionic medium.[122] In fact, electron microscopy revealed that 20 nm Pd particles were formed. Sonochemical Suzuki reactions of phenylboronic acid and aryl halides were also carried out at room temperature in an ionic liquid plus methanol as cosolvent.[123] No phosphine ligands were required and chlorobenzenes could also be substrates under these conditions.

Ultrasonic irradiation in an ionic liquid was employed in the multicomponent synthesis of dihydropyrimidin-2-ones (the so-called Biginelli reaction),[124] and in the acetylation of alcohols.[125] These conditions also favor the *para*-selective nitration of phenols.[126] The direct halogenation of alcohols (or alcohol derivatives) with *tert*-butyl halides in [pmIm]Br has been reported (Scheme 22).[127] In the process, that works well



Scheme 21 Sonochemical Heck reactions in ionic liquids.



Scheme 22 Sonochemical halogenation of alcohols with *tert*-butyl halides in an ionic liquid.

for the bromination, iodination and chlorination of primary or secondary alcohols, a synergic effect of ultrasound and the ionic liquid was observed. Poor yields (below 20%) were observed with either the ionic liquid alone or ultrasound alone. Experimental evidence suggested that the *tert*-butyl halide in combination with ionic liquid generated 2-methylpropene and HX, which halogenated the alcohol.

The thermal stability of ionic liquids under sonication must be kept in perspective. Thus, when [bmIm]Cl was irradiated at 135 °C and the evolved gas was analyzed, chloromethane, chlorobutane (arising from nucleophilic substitutions), and decomposition products of imidazole were detected.[128] Although many sonochemical reactions are conducted at lower temperatures, the possibility of decomposition cannot be excluded. This would be relevant with certain anions, from which catalytic species like HX or BX_3 could arise. Compton and coworkers have detected some decomposition of an ionic liquid under ultrasound at 60 °C during the selective electroreduction of *N*-methylphthalimide. By the way ionic liquids, owing to their high polarity, should find a valuable niche in sonoelectrochemistry; actually a significant increase in the rate of electroreduction and high current efficiencies were observed under ultrasonic activation.[129]

Another difficulty stems from the acidity (pK_a = 21–23, comparable to some ketones or esters) of the H-2 hydrogen of the imidazolium nucleus. Deprotonation at the C-2 position would generate *N*-heterocyclic carbenes,[130] which may account for some experimental observations on sonicated ionic liquids. Although these drawbacks could limit the scope of ionic liquids in ultrasound- and microwave-assisted reactions, further study will be required for a proper assessment of their relative weights.

4.2. Ultrasound and photochemistry

Because radiolysis and sonolysis both promote homolytic pathways, one might expect to obtain comparable results from these techniques. The assumption however was disproved by Suslick and his associates working on the sonolysis of metal complexes and organometallics, which should give rise to coordinatively unsaturated transient species, possibly with switching. The sonolysis of iron pentacarbonyl led to selective formation of the $Fe_3(CO)_{12}$ cluster, while, remarkably, photo- and thermolysis gave different products.[131]

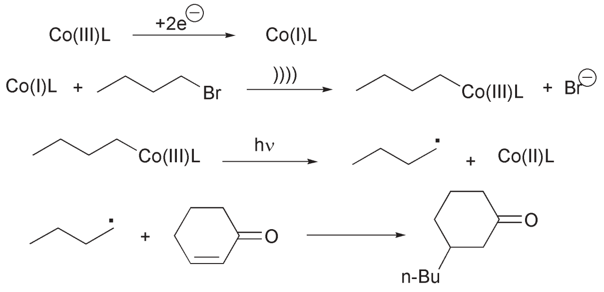
Further studies by Ando *et al.* on the sonolysis and photolysis of bromotrichloromethane ($CBrCl_3$) in the presence or the absence of *n*-alkenes also highlighted the difference in activation mechanisms. Thus, CCl_3 radicals generated in the gas phase during cavitation successively dimerized to give $Cl_3C–CCl_3$, while surviving radicals migrate into the liquid phase to initiate a radical chain process with alkenes. In contrast, the photochemical reaction in the absence of *n*-alkene did not generally give $Cl_3C–CCl_3$. Only when 1-octene was added could the dimer be detected in addition to alkene adducts. This suggests that under photolysis the dimerization of CCl_3 only occurred in the chain propagation step.[132] One could therefore envisage two different effects if both techniques were to be combined. UV light generates radicals in a homogeneous and dispersed state, cavitation in a heterogeneous and more localized state.

Sonication usually improves synthetically important photochemical addition reactions. As these processes should be occurring in the bulk solution, the homogenization provided by ultrasound favors the encounter of reactive intermediates. Thus, the addition of methyl disulfide to hexafluorobutadiene under UV irradiation is enhanced by ultrasound to give a mixture of adducts, *trans*-1,4-bis(methylthio)hexafluoro-2-butene being the major product.[133] The photochemical cycloaddition of olefins to the carbon–oxygen double bond of aldehydes and ketones constitutes the well-known Paternò–Büchi synthesis of oxetanes. A stepwise radical mechanism is suggested and formation of the more stable diradical accounts for the regiochemistry of the products.[134] Toma and coworkers reported that the Paternò-Büchi of acetone with ethyl vinyl ether gave a mixture of *cis*- and *trans*-oxetanes. Compared to the silent process, sonication accelerated the photochemical reaction and a higher yield was obtained. Moreover, a variation in the diastereomeric *cis*/*trans* ratio was observed under sonication.[135] In subsequent work by this group involving the photopinacolization of benzophenone in ethanol, both the reaction rate and yield of benzpinacol increased with irradiation.[136] A twofold effect has been suggested. Firstly, the light-absorbing transient species would undergo sonolytic decomposition making the photoconversion more efficient; on the other hand, sonication would also induce triplet state quenching.

Emulsion electrosynthesis assisted by ultrasound was also successfully applied to the catalytic formation of carbon–carbon bonds.[137] The voltammetry of aqueous vitamin B_{12} (cyanocobalamin) solutions is modified by microscopic droplets of an organic reactant generated by applying power ultrasound. In some cases photochemical irradiation is also required, thus subjecting a chemical system to triple activation (electrolysis, ultrasound, and light). This concept was applied to bromoalkanes and activated alkenes to afford products with up to 50% yield. As depicted in Scheme 23 the mechanistic pathway involves electroreduction of vitamin B_{12}, denoted as [Co(III)L], yielding the nucleophilic species Co(I)L, which reacts with the bromoalkane *via* a SET process. Further photolysis produces an alkyl radical that adds to an α,β-unsaturated carbonyl compound.

4.3. Combined use of ultrasound and microwaves

Although the fundamentals of microwave-assisted reactions are not yet completely understood, most experts agree that in



Scheme 23 Electrosynthesis assisted by ultrasound and light and catalytic in cyanocobalamin.

the majority of cases the observed rate enhancements are due to a purely thermal/kinetic effect, that is, to the high reaction temperatures that are rapidly attained when polar materials are placed in a microwave field.[25,31] As already mentioned, the energy involved in dielectric heating (0.0016 eV) is too low to break chemical bonds and also lower than the energy of Brownian motion.

Combined irradiation with ultrasound and microwaves is a very promising innovation. Especially in heterogeneous catalysis, additional effects are to be expected when the large amount of energy released in cavitational collapse (causing particle fragmentation and molecular excitation) is associated with microwave polarization inducing dielectric volumetric heating and selective heating of solid particles. This combination of energy sources can promote or improve a number of chemical processes[138,139] such as synthesis, extraction of natural matrices and sample preparation in chemical analysis.[140] Because of technical hurdles it has not been systematically investigated for synthetic purposes as yet; only few reports have appeared concerning syntheses of ethers[141] and hydrazides,[142] esterifications[143] and the Knoevenagel–Doebner reaction.[144]

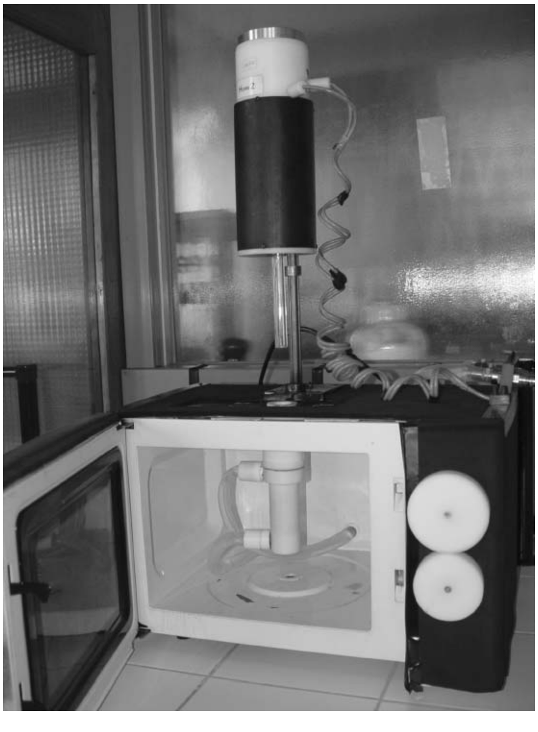
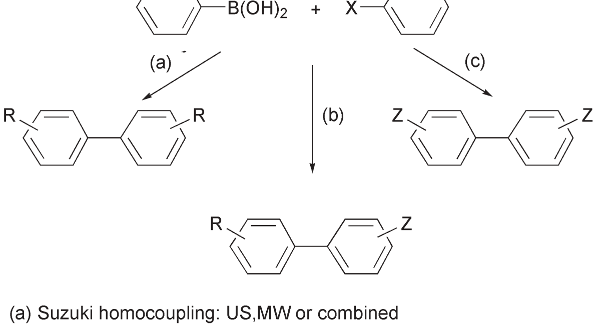


Fig. 3 Reactor featuring simultaneous ultrasound and microwave irradiation.

Fig. 4 Flow reactor combining ultrasound and microwaves.

Simultaneous irradiation in one reaction vessel can be achieved in a microwave oven where the horn (made of quartz or ceramic material) is directly inserted. Fig. 3 illustrates such a device, currently employed in our laboratories. In an alternative setup that avoids subjecting the horn to the high-frequency field, a low-viscosity apolar liquid (decalin), exposed to ultrasound waves outside the microwave oven, conveys them through a double-jacketed pyrex vessel to the reacting mixture.[145] A combined sequential irradiation can be achieved using flow reactors in which a pump circulates the reacting mixture through two separated reaction cells (Fig. 4). With the latter system a series of synthetically useful aryl–aryl couplings, catalyzed by Pd/C, gave better yields and shorter reaction times than individual irradiations with either ultrasound or microwaves (Scheme 24). Likewise homo- and cross-couplings of arylboronic acids and aryl halides were



(a) Suzuki homocoupling: US,MW or combined
(b) Suzuki cross-coupling: US,MW or combined
(c) Ullmann type coupling: US only

Scheme 24 Pd/C-catalyzed aryl–aryl couplings under ultrasound and microwave irradiations, alone or combined.

successfully conducted under high-intensity ultrasound (20.5 kHz) and microwave irradiation (2.45 GHz, 700 W) under heterogeneous conditions using Pd/C.[146] Neither phosphine ligands nor phase-transfer catalysts were required. Either energy source dramatically reduced reaction times giving biaryls in good yields from aryl bromides or iodides. Electron-deficient aryl chlorides also reacted when palladium(II) acetate was employed as catalyst. The Ullmann-type zinc-mediated homocoupling of iodo- or bromoaryls in the presence of Pd/C was also studied; although Ullmann reactions are sensitive to thermal activation, finely divided or activated catalysts are required and this could explain why ultrasound alone was effective in activating hard metal powders. At any rate the combined approach, still in its infancy, should permit all the potential advantages from both energy sources to be reaped.

5. Conclusions and perspectives

The open question "Quo Vadis Sonochemistry?" has been the common epilogue of recent meetings and monographs addressed to an audience of sonochemists.[147] A measure of optimism is justified as this discipline has gained acceptance and now sustains a wide range of applications in physical and life sciences. Sonochemistry has certainly moved a long way from its beginnings in the late 1920s through its renaissance in the 1980s to where it stands as a valuable store of knowledge, especially within the community of synthetic chemists. It is however still far from being ripe science. Once considered a laboratory trick and, to many newcomers, simply an efficient form of homogenization, most of them do not even suspect that they are actually brushing against a considerable scientific corpus. Although sonochemistry may offer simple solutions to synthetic problems, from a theoretical viewpoint it is really a complex topic, still growing thanks to a group of talented theoreticians that have gained insights into the key phenomena of cavitation and sonoluminescence. Recent studies on sonoluminescence suggesting the existence of a plasma-like state inside cavitation bubbles is both attractive and surprising. They envisage an ionized state of matter in which the electronic temperature of the molecules reaches several thousand K, revealing a new potential for creating ionized species by cavitation.

It may be advisable for all concerned to acquire some theoretical basis, leaving mathematics aside, in order to understand what can be expected in terms of success or failure. The first sections of this review gave a glimpse of such background, focusing on acoustic irradiation. They are also meant to show that cavitational chemistry is really unique, its substrates and media entering a particular marriage largely affected by parameters that are often irrelevant in conventional chemistry. Even if the overall picture of cavitation is still incomplete, it is now possible to rationalize sonochemical reactivities. Some reactions are accelerated without a change in the nature of the products; others, in stark contrast, exhibit switching phenomena, suggesting a more specific participation of the cavitational event and, sometimes, the occurrence of electron transfer processes. Although no general rules exist, the classification of sonochemical reactions according to *Types I–III* has offered a useful paradigm since it was introduced.

Sonochemistry has suffered from problems of reproducibility, especially with ultrasonic baths having an odd geometry in which frequency and power depend on the transducer employed. In this regard, sonochemistry and microwave-based chemistry share a common limitation, as domestic ovens also lacked reproducibility and are gradually being replaced by microwave reactors. Likewise, ultrasonic probes and standardized systems will become more and more the instruments of choice.

Besides broadening its own scope, sonochemistry has shown to great advantage when combined with another technique. In this context sonoelectrochemistry represents a successful combination carrying such advantages as an efficient cleaning and degassing of electrode surfaces along with an enhanced mass transport. It has found interesting analytical and synthetic applications,[148] and further improvements should be expected. In greater detail throughout this article we discussed combinations of ultrasound with photochemistry or microwaves. Practitioners will find that they may offer interesting synergic effects, a minimum easy-to-get practical knowledge being required. Such inroads should also benefit the search for new selective processes: we believe that very innovative applications are just round the corner. Practically unexplored, ultrasound-induced cavitation at increased pressures may open up new vistas in high-pressure chemistry. Sonication has largely been limited to atmospheric conditions, as an increased static pressure hinders the formation of bubbles in a liquid. However, cavitation does occur in liquid CO_2, where the vapor pressure in the bubble is considerably higher than in ordinary liquids. Polymerization reactions have been conducted in high-pressure CO_2 affording, for instance, poly(methyl methacrylate) of high molecular weight.[149]

Finally, the challenges of scale-up represent a current concern of non-conventional technologies. A series of commercially available ultrasonic rectors can be readily adapted for scale-up,[3,4] even operating below the ultrasonic threshold. Interestingly, a giant probe system using a large bar of steel as horn and operating with audible sound has found a variety of applications in processing and catalysis.[150] Because organics are invariably linked to biomaterials and pharmaceuticals, sonochemical reactions conducted on larger scales will doubtless have a wide impact. Besides improving numerous organic reactions, sonication also can initiate crystal nucleation, even selecting a particular polymorph.[151] Both sonosynthesis and sonocrystallization will be very useful in drug discovery. We hope that the present review may stimulate further progress of organic chemistry hand in hand with the harmless and greener sound energy.

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