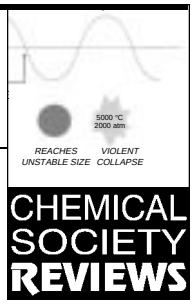
Ultrasound in synthetic organic chemistry



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High-power ultrasound can generate cavitation within a liquid and through cavitation provide a source of energy which can be used to enhance a wide range of chemical processes. Such uses of ultrasound have been grouped under the general name sonochemistry. This review will concentrate on applications in organic synthesis where ultrasound seems to provide a distinct alternative to other, more traditional, techniques of improving reaction rates and product yields. In some cases it has also provided new synthetic pathways.

1 Introduction

The use of ultrasound in chemistry (sonochemistry) offers the synthetic chemist a method of chemical activation which has broad applications and uses equipment which is relatively inexpensive. The driving force for sonochemistry is cavitation and so a general requirement is that at least one of the phases of the reaction mixture should be a liquid. When laboratory research in sonochemistry began it seemed to be mainly a method of initiating intransigent reactions especially those which depended upon the activation of metallic or solid reagents. Its development in the past 15 years however has revealed that it has far wider applicability than this and also that it presents a significant scientific challenge to understanding its underlying physical phenomenon—acoustic cavitation. The ever expanding number of applications of sonochemistry in synthesis has made the subject attractive to many experimentalists and interest has spread beyond academic laboratories into industry and chemical engineering.[1–5]

It was in 1986 that the first ever International Symposium on Sonochemistry was held at Warwick University UK as part of the Autumn Meeting of the Royal Society of Chemistry.[6] This meeting was significant in that it was the beginning of serious interest in the uses of ultrasound in chemistry as a study in itself. Of course sonochemistry dates back much further than this. Its origins can be traced to the early part of this century with the discoveries of echo sounding and the mechanical use of power ultrasound for emulsification. The formation of the Royal Society of Chemistry Sonochemistry Group in 1987 followed by a European Society in 1990 and then other national groups has meant that the subject has expanded greatly over the last few years.

There are a range of applications for the uses of ultrasound in chemistry which include synthesis, environmental protection (the destruction of both biological and chemical contaminants) and process engineering (improved extraction, crystallisation, electroplating and new methods in polymer technology).

Professor Mason obtained a BSc (1967) in chemistry and PhD (1970) in organic chemistry from Southampton University. After periods at Amherst College, USA, York University and Bradford University he joined Coventry Polytechnic (now University) in 1975. He is currently chairman of the RSC Sonochemistry group and President of the European Society of Sonochemistry and was awarded a DSc in 1996.

2 Fundamental aspects

Ultrasound is defined as sound of a frequency beyond that to which the human ear can respond. The normal range of hearing is between 16 Hz and about 18 kHz and ultrasound is generally considered to lie between 20 kHz to beyond 100 MHz. Sonochemistry generally uses frequencies between 20 and 40 kHz because this is the range employed in common laboratory equipment. However since acoustic cavitation can be generated well above these frequencies, recent researches into sonochemistry use a much broader range (Fig. 1). High frequency ultrasound from around 5 MHz and above does not produce cavitation and this is the frequency range used in medical imaging.

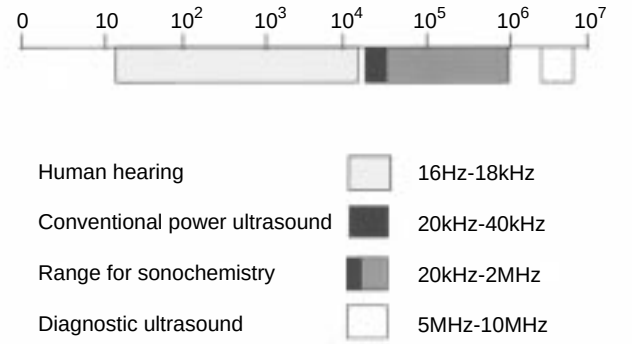


Fig. 1 Sound frequency ranges

Like all sound energy, ultrasound is propagated *via* a series of compression and rarefaction waves induced in the molecules of the medium through which it passes. At sufficiently high power the rarefaction cycle may exceed the attractive forces of the molecules of the liquid and cavitation bubbles will form. These bubbles will grow over a few cycles taking in some vapour or gas from the medium (rectified diffusion) to an equilibrium size which matches the frequency of bubble resonance to that of the sound frequency applied. The acoustic field experienced by the bubble is not stable because of the interference of other bubbles forming and resonating around it. As a result some bubbles suffer sudden expansion to an unstable size and collapse violently. It is the fate of these cavities when they collapse which generates the energy for chemical and mechanical effects (Fig. 2). There are several theories which have been advanced to explain the energy release involved with cavitation of which the most understandable in a qualitative sense is the 'hot spot' approach. Each cavitation bubble acts as a localised microreactor which, in aqueous systems, generates temperatures of

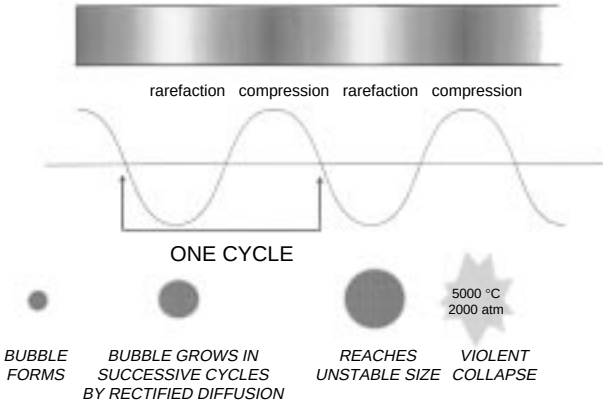


Fig. 2 Sound propagation in a liquid showing cavitation bubble formation and collapse

several thousand degrees and pressures in excess of one thousand atmospheres.

In addition to the generation of extreme conditions within the bubble there are also major mechanical effects produced as a result of its rapid collapse. These are also of significance in synthesis and include very rapid degassing of the cavitating liquid (in the rarefaction cycle the newly formed bubbles will fill with gas and be expelled from the liquid) and rapid crystallisation (brought about through seed crystal generation on implosion).

3 Laboratory equipment

The first requirement for sonochemistry is a source of ultrasound and whatever type of commercial instrument is used the energy will be generated *via* an ultrasonic transducer—a device by which mechanical or electrical energy can be converted to sound energy. There are three main types of ultrasonic transducer used in sonochemistry: liquid-driven (effectively liquid whistles), magnetostrictive (based on the reduction in size of certain metals, *e.g.* nickel, when placed in a magnetic field) and piezoelectric. Most of the current equipment used for sonochemistry utilises transducers constructed of piezoelectric ceramics. These are brittle and so it is normal practise to clamp them between metal blocks for protection. The overall structure is known as a piezoelectric 'sandwich'. Usually two ceramic elements are combined so that their overall mechanical motion is additive (Fig. 3). Piezoelectric transducers are very efficient and, depending on their dimensions, can be made to operate over the whole ultrasonic range.

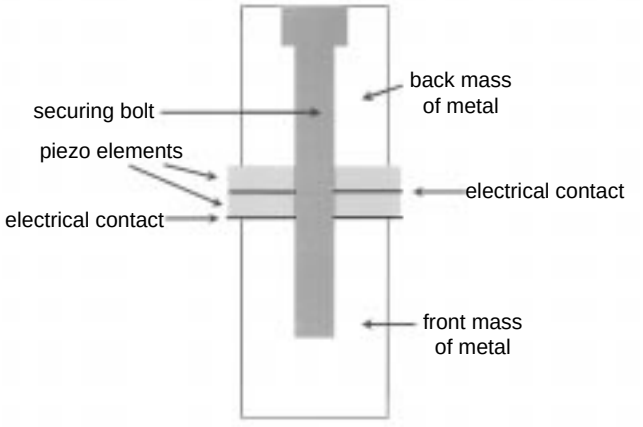


Fig. 3 Construction of a piezoelectric sandwich transducer

The two most common sources of ultrasound for laboratory sonochemistry are the ultrasonic cleaning bath and the ultrasonic horn or probe system.[7] These generally operate at frequencies of around 40 and 20 kHz, respectively.

3.1 The ultrasonic cleaning bath

The simple ultrasonic cleaning bath is by far the most widely available and cheapest source of ultrasonic irradiation for the chemical laboratory. Although it is possible to use the bath itself as a reaction vessel this is seldom done because of problems associated with corrosion of the bath walls and containment of any evolved vapours and gases. The normal usage therefore involves the immersion of standard glass reaction vessels into the bath which provides a fairly even distribution of energy into the reaction medium (Fig. 4). The reaction vessel does not need any special adaptation, it can be placed into the bath, thus an inert atmosphere or pressure can be readily maintained throughout a sonochemical reaction. The amount of energy which reaches the reaction through the vessel walls is low—normally between 1 and 5 W cm^{-2}. Temperature control in commercial cleaning baths is generally poor and so the system may require additional thermostatic control.

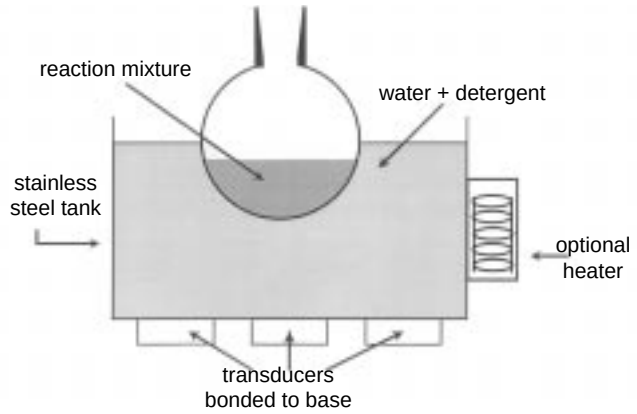


Fig. 4 The ultrasonic cleaning bath in sonochemistry

3.2 The ultrasonic probe

This apparatus allows acoustic energy to be introduced directly into the system rather than rely on its transfer through the water of a tank and the reaction vessel walls (Fig. 5). The power of such systems is controllable and the maximum can be several hundred W cm^{-2}. The probe system is more expensive than the bath and it is slightly less convenient in use because special seals will be needed if the horn is to be used in reactions which involve reflux, inert atmospheres or pressures above (or below) ambient.

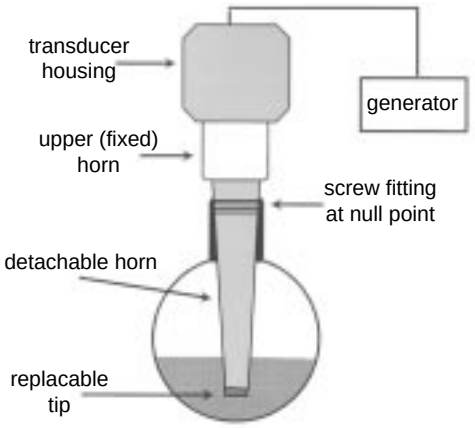


Fig. 5 The ultrasonic probe system in sonochemistry

4 An attempt to formulate some rules governing sonochemical activity

One of the earliest tenets of sonochemistry was that it is particularly good at assisting reactions involving solid reagents.

This is generally but not exclusively correct. A number of groups are attempting to gain an understanding of the underlying principles of sonochemistry in order to be able to predict which type of reaction would be most susceptible to sonication. As a result of these efforts some guidelines have been identified. An empirical classification of sonochemical reactions into three types was proposed by J.-L. Luche and was based upon the purely chemical effects induced by cavitation.[8] Other (mechanical) effects of cavitation bubble collapse (*e.g.* emulsification) were considered to be physical rather than chemical and judged to be 'false' sonochemistry. These so-called 'false' effects are often important and have been included in the following interpretation of the three original types of reaction susceptible to sonochemical enhancement.

Type 1 Homogeneous systems which proceed *via* radical or radical-ion intermediates. This implies that sonication is able to effect reactions proceeding through radicals and further that it is unlikely to effect ionic reactions.

Type 2 Heterogeneous systems proceeding *via* ionic intermediates. Here the reaction is influenced primarily through the mechanical effects of cavitation such as surface cleaning, particle size reduction and improved mass transfer. This is what has sometimes been referred to as 'false sonochemistry'.

Type 3 Heterogeneous reactions which include a radical pathway or a mixed mechanism *i.e.* radical and ionic. Radical reactions will be chemically enhanced by sonication but the general mechanical effect referred to above may well still apply. If the radical and ionic mechanisms lead to different products ultrasound should favour the radical pathway and this could lead to a switch in the nature of the reaction products.

In this article the term sonochemistry will be used to encompass any beneficial effect on synthesis induced by cavitation whether it is chemical or physical.

4.1 Reactions which exemplify the 'rules' of sonochemistry

4.1.1 Homogeneous liquid-phase reactions

Any system involving a homogeneous liquid in which bubbles are produced is not strictly homogeneous, however, in sonochemistry it is normal to consider the state of the system to which the ultrasound is applied. Sonochemical syntheses in homogeneous conditions are not extensively reported which suggests that cavitation is less effective in promoting reactions under these conditions. The few studies which have appeared indicate that sonochemical effects generally occur either inside the collapsing bubble where extreme conditions are produced, at the interface between the cavity and the bulk liquid where the conditions are far less extreme or in the bulk liquid immediately surrounding the bubble where the predominant effects will be mechanical (Fig. 6).

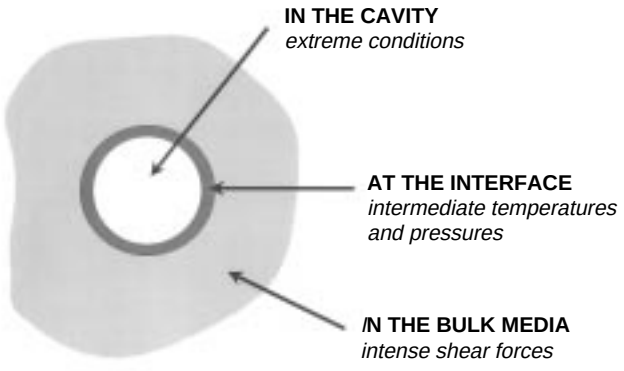


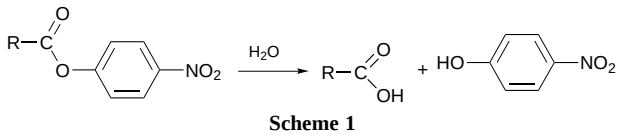
Fig. 6 Cavitation in a homogeneous liquid

In order for a chemical to experience the extreme conditions generated inside the cavitation bubble during collapse it must enter the bubble and so should be volatile. The 'concentration' of cavitation bubbles produced by sonication using conventional laboratory equipment is very small and so overall yields in this type of reaction are low. Thus in the sonication of water small quantities of $OH^{\cdot}$ and $H^{\cdot}$ radicals are generated in the bubble and these undergo a range of subsequent reactions including the generation of H_2O_2. The highly oxidising $HO^{\cdot}$ species can react with other moieties in the bubble or migrate to the bulk solution where they have only transient existence. Such radicals can have a significant effect on both biological and chemical species in aqueous solution and can be detected chemically.[9] Organic solvents will also slowly decompose on sonication but solvent decomposition is normally only a minor contribution to any sonochemical reaction taking place in the medium.

A synthetically useful reaction which takes place in the collapsing bubble is the production of amorphous iron from the sonolysis of $Fe(CO)_5$ (0.4 M) in decane under argon.[10] Volatile iron pentacarbonyl enters the bubble and is decomposed during collapse. The fact that an amorphous (rather than crystalline) material is produced confirms that very high temperatures are generated in the bubble and that extreme cooling rates are involved. Conventional production of amorphous iron requires rapid cooling from the vapour to solid state of the order of 10^6 K s^{-1}. Sonolytic decomposition of iron pentacarbonyl in pentane (a more volatile solvent) yields $Fe_3(CO)_{12}$ rather than the metal indicating that the cavitation collapse is not so extreme in this solvent. Since this original report the study of cavitation induced decomposition of iron and other metal carbonyls has continued and expanded. In the case of molybdenum hexacarbonyl the product is nanostructured molybdenum carbide which has proved to be an excellent dehydrogenation catalyst.[11]

Sucrose has a negligible vapour pressure and so cannot enter the bubble during sonication. A study of the effect of sonication on the rate of acid catalysed inversion of this material revealed no appreciable effect. It is tempting to conclude from this that sonochemistry has no effect on involatile materials in solution. This is not entirely correct because bubble collapse produces very large shear forces in the surrounding liquid capable of breaking the chemical bonding in polymeric materials dissolved in the fluid.[1] Over the last few years, increasing interest has been shown in this procedure since the net result of polymer-chain rupture is a pair of macroradicals, which may recombine randomly (resulting in a reduction in molar mass and possibly leading to a monodispersed system) or act as a radical site on which to polymerise another monomer added to the solution (resulting in block copolymerization).

Small accelerations, in the range 4–15%, have been found for the rate of acid catalysed hydrolysis of a number of esters of carboxylic acids.[1] In the case of methyl ethanoate the effects (at 23 kHz) were attributed to the increased molecular motion induced by the pressure gradients associated with bubble collapse. Similarly, the hydrolysis of the 4-nitrophenyl esters of a number of aliphatic carboxylic acids at 35 °C showed ultrasonically (20 kHz) induced rate enhancements which were all in the range of 14–15% (Scheme 1). The activation energy for the hydrolysis of each of the substrates varied considerably with the alkyl substituent (R = Me, Et, Pr^i, Bu^t) on the carboxylic acid and so the uniform increase in rate could not be associated with any cavitational heating effect. Here again, the modest sonochemical effect was considered to be the result of mechanical effects.



Scheme 1

The effect of ultrasonic irradiation on the hydrolysis of 2-chloro-2-methylpropane in mixed aqueous ethanolic solvents

of different compositions revealed more evidence for the influence of mechanical effects.[1] The rate enhancement induced by ultrasound (at 20 kHz) was found to increase with increase in the alcohol content and to decrease as the reaction temperature was raised. A maximum rate increase of 20-fold was observed at 10 °C in 50% (m/m) solvent composition. This composition is closely coincident with the structural maximum for the binary ethanol–water solvent system. It is logical to suppose that if the sonochemical enhancement is associated with solvent disruption then the maximum effect would be observed at this composition.

4.1.2 Heterogeneous systems

In any heterogeneous system cavitation which occurs in the liquid phase will be subject to the same conditions as have been described above for homogeneous reactions. There will be a difference however when bubbles collapse at or near any interface and this will depend upon the phases involved.

If cavitation bubbles are formed at or near to any large solid surface the bubble collapse will no longer be symmetrical. The large solid surface hinders liquid movement from that side and so the major liquid flow into the collapsing bubble will be from the other side of the bubble. As a result of this a liquid jet will be formed which is targeted at the surface with speeds in excess of 100 m s^{-1} (Fig. 7). The mechanical effect of this is equivalent to high pressure jetting and is the reason why ultrasound is so effective in cleaning. Depending upon the conditions used this powerful jet can activate surface catalysis, force the impregnation of catalytic material into porous supports and generally increase mass and heat transfer to the surface by disruption of interfacial boundary layers.

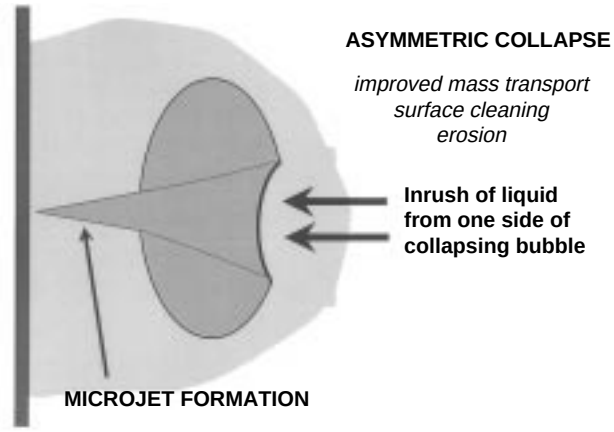


Fig. 7 Cavitation near to a solid surface

For this reason the use of ultrasound in conjunction with almost any electrochemical process will be beneficial and has been the subject of extensive study. The subject has become known as sonoelectrochemistry.[12] The particular advantages which accrue include (*a*) degassing at the electrode surface, (*b*) disruption of the diffusion layer which reduces depletion of electroactive species, (*c*) improved mass transport of ions across the double layer and (*d*) continuous cleaning and activation of the electrode surfaces. All of these effects combine to provide enhanced yield and improved electrical efficiency.

When the solid is particulate in nature, cavitation can produce a variety of effects depending on the size and type of the material (Fig. 8). These include mechanical deaggregation and dispersion of loosely held clusters, the removal of surface coatings by abrasion and improved mass transfer to the surface. Mechanical deagglomeration is a useful processing aid and is illustrated in the effect of sonication (in a bath) of titanium dioxide pigment in water. A powder sample made up in water consisting initially of agglomerates (volume mean diameter *ca.* 19 μm) was rapidly broken apart (< 30 s) to provide a limiting size of 1.6 μm particles. Furthermore, the sonicated sample showed no sign of re-agglomeration even after being allowed to stand for a period of 24 h.

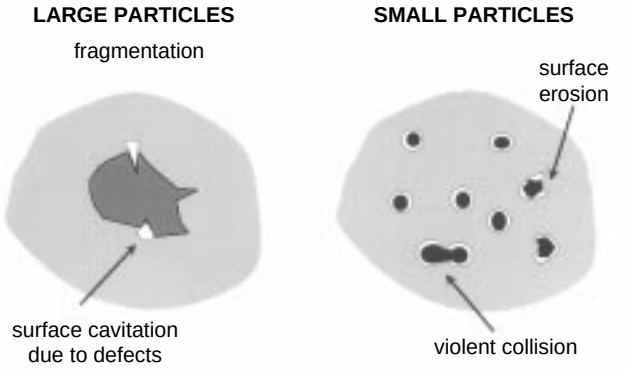
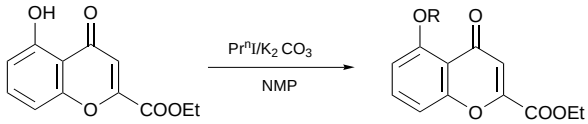


Fig. 8 Cavitation in a particulate medium

The *O*-alkylation of 5-hydroxychromones is a difficult process probably as a result of hindrance to ionisation caused by hydrogen bonding between the carbonyl and OH group coupled with some dispersion of the resulting phenoxide O^- charge. Thus, using 5-hydroxy-4-oxo-4*H*-1-benzopyran-2-carboxylic acid ethyl ester as substrate in *N*-methylpyrrolidinone (NMP) a low yield (28%) of the *O*-propyl product is obtained after 1.5 h at 65 °C using 1-iodopropane and potassium carbonate as base (Scheme 2).[7] The yield was greatly increased under sonication



Scheme 2

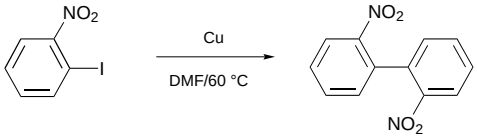
(probe 20 kHz) and the scope of the reaction was expanded by using a range of different haloalkanes (Table 1). Power ultrasound would be expected to be effective in enhancing this reaction *via* the reduction of the particle size of K_2CO_3 powder. This factor was investigated by first sonicating NMP containing K_2CO_3 at 65 °C. The appropriate proportions of 1-iodopropane and chromone were then added to the resulting very fine suspension and the reaction was run under conventional conditions. This resulted in around 90% product formation in 90 min at 65 °C, a reactivity similar to that obtained under continuous ultrasonic irradiation except that the reaction was approaching a definite limit at 90% yield. The fall-off suggests that the surface of the remaining K_2CO_3 had become deactivated, and this was confirmed when sonication of the residual mixture rapidly completed the reaction.

Table 1 *O*-Alkylation of a hydroxychromone

Alkyl group	Yield (stirred) (%)	Yield (sonicated) (%)
Pr^{n}I	28	100
Bu^{n}I	57	97
BnBr	59	97

[a] GLC yields, 90 min in NMP at 65 °C, sonication with 20 kHz probe system.

A study of the Ullmann coupling reaction has provided evidence that the mechanical effects of surface cleaning coupled with an increase in surface area cannot fully explain the extent of the sonochemically enhanced reactivity. The reaction of 2-iodonitrobenzene to give a dinitrobiphenyl using conventional methodology requires heating for 48 h and the use of a tenfold excess of copper powder (Scheme 3). The use of power ultrasound affords a similar (80%) yield in a much shorter time (1.5 h) using only a fourfold excess of copper.[7] During these



Scheme 3

studies it was observed that the average particle size of the copper fell from 87 to 25 μm but this increase in surface area was shown to be insufficient to explain the large (50-fold) enhancement in reactivity produced by ultrasonic irradiation. The studies suggested that sonication assisted in either the breaking down of intermediates and/or the desorption of products from the surface. An additional practical advantage was that sonication prevented the adsorption of copper on the walls of reaction vessels, a common problem when using conventional methodology.

The collapse of cavitation bubbles at or near the interface of immiscible liquids will cause disruption and mixing, resulting in the formation of very fine emulsions (Fig. 9). This is essentially a mechanical effect but it has been utilised in the hydrolysis of benzoate esters where the emulsion was produced by a probe system.[13] Using 10% NaOH the conventional hydrolysis (Scheme 4) under reflux, gave a very low yield after 90 min; however sonication at room temperature afforded near complete hydrolysis in 1 h.

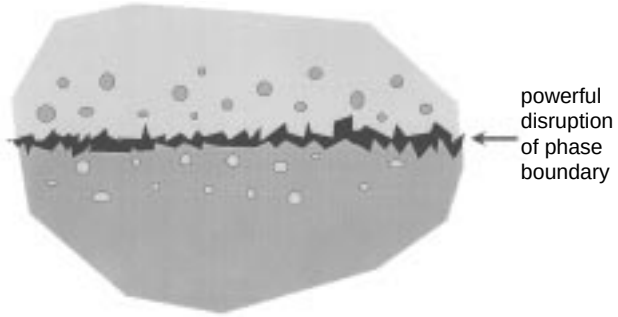
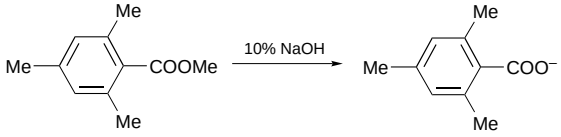


Fig. 9 Cavitation in a two phase liquid medium

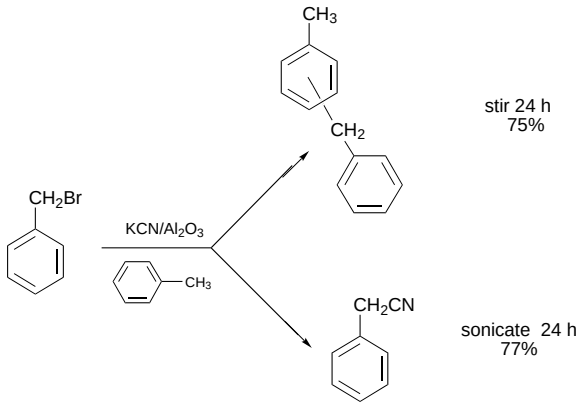


Scheme 4

Other applications of sonochemically induced emulsification are in phase transfer catalysis, emulsion polymerisation and two phase enzymatic syntheses.

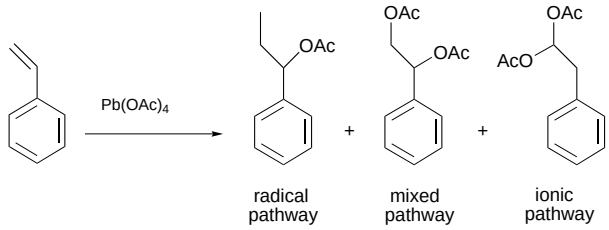
4.1.3 Reactions 'switched' by ultrasound

An extremely good way of demonstrating that sonochemistry is different from other methods of enhancing chemical reactions is to find specific reactions for which ultrasound has changed the product distribution. The first report of a reaction exhibiting 'sonochemical switching' came from Ando *et al.*[14] The system consisted of a suspension of benzyl bromide and alumina-supported potassium cyanide in toluene as solvent (Scheme 5). The aim was to produce benzyl cyanide by nucleophilic displacement of the bromine by supported cyanide. Under stirring alone the reaction provided diphenylmethane products *via* a Friedel–Crafts reaction between the bromo compound and the solvent, catalysed by Lewis acid sites on the surface of the solid phase reagent. In contrast, sonication of the same constituents produced only the substitution product, benzyl cyanide. The explanation for this was based upon cavitation producing a structural change to the catalytic sites of the solid support, possibly by masking them through cavitationally induced cyanide absorption.



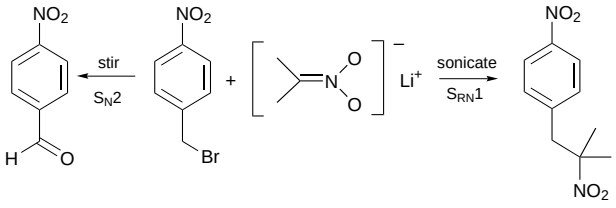
Scheme 5

The same group have reported an example of sonochemical switching in a homogeneous reaction. The decomposition of lead tetraacetate in acetic acid the presence of styrene at 50 °C generates a small quantity of diacetate *via* an ionic mechanism. Under otherwise identical conditions sonication of the mixture gives 1-phenylpropyl acetate predominantly through an intermediate methyl radical which adds to the double bond (Scheme 6).[15] These results are in accord with the proposition that radical processes are favoured by sonication.



Scheme 6

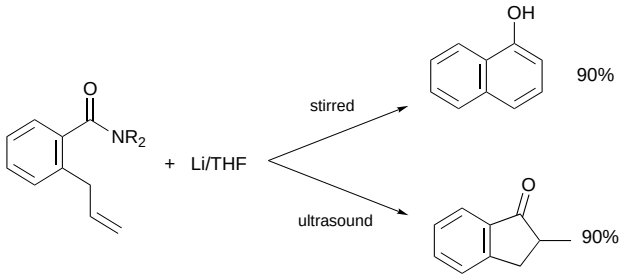
Another example of sonochemical switching and is found in the Kornblum–Russell reaction (Scheme 7). 4-Nitrobenzyl bromide reacts with 2-lithio-2-nitro-propane *via* a predominantly polar mechanism to give, as a final product, 4-nitrobenzaldehyde.[16] An alternative SET pathway exists in this reaction leading to the formation of a dinitro compound. Sonication changes the normal course of the reaction and gives preferentially the latter compound, in amounts depending on the irradiation conditions and the acoustic intensity.



Scheme 7

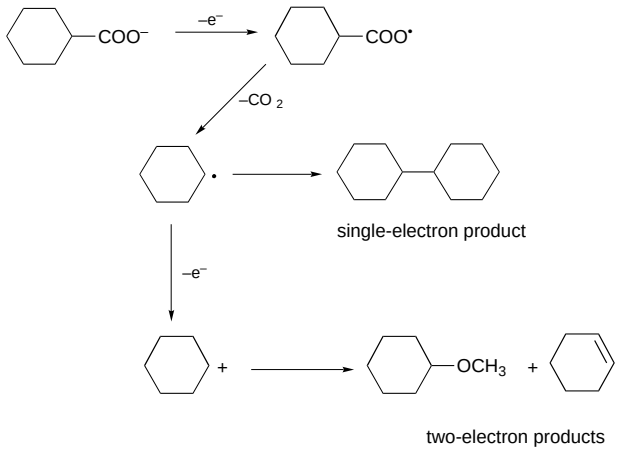
A sonochemical switch has also been observed in the formation of the indanone nucleus from *o*-allyl benzamides (Scheme 8).[17] The ketyl radical anion cyclizes to 2-methylindanone and liberates an amide ion which deprotonates the allyl moiety. The resulting carbanion then undergoes cyclization to α-naphthol. Under sonication the first step of the process is accelerated and the ketyl is generated much more rapidly so that only the cyclization to 2-methylindanone occurs.

The Kolbe electrolysis of cyclohexanecarboxylate in aqueous methanol generates a mixture of products in which bicyclohexyl



Scheme 8

predominates (49%). In the presence of ultrasound (38 kHz) however the product distribution was changed quite significantly reducing the yield of bicyclohexyl to only 7.7% (Scheme 9).[12] The major products were the result of two electron processes through a cyclohexane carbocation which gave cyclohexene (34%) by elimination and cyclohexyl methyl ether (32%) by solvent attack. A characteristic of many sonoelectrochemical processes is that the average cell potential under sonication is less than that required conventionally. In this case a current density of 200 mA cm^{-2} could be maintained at a potential of 7.3 V with ultrasound compared with 8.3 V under silent conditions.



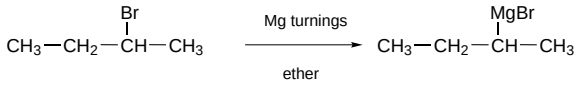
Scheme 9

5 Some applications of ultrasound in synthesis

5.1 The activation of metals

Ultrasound can be used to accelerate reactions involving metals through surface activation which can be achieved in three ways (*a*) by sonication during the reaction, (*b*) as a pre-treatment before the metal is used in a conventional reaction or (*c*) to generate metals in a different and more reactive form.

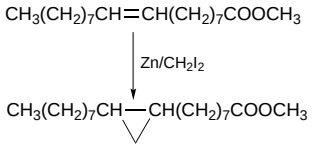
A classic use of ultrasound is in the initiation and enhancement of synthetic reactions involving metals as a reagent or catalyst. One such example is the preparation of a Grignard reagent. A long-standing problem associated with Grignard reagent synthesis is that in order to facilitate reaction between the organic halide and the metal in an ether solvent all of the reagents must be dry and the surface of the magnesium must be clean and oxide free. Such conditions are difficult to achieve and so many methods of initiating the reaction have been developed most of which rely on adding activating chemicals to the reaction mixture. A very simple method of initiating the reaction is by sonication of the reaction mixture in an ultrasonic bath which avoids the need for the addition of chemical activators. The quantitative effects of ultrasound on the induction times for the formation of a Grignard reagent using magnesium turnings in various grades of ether have been examined (Scheme 10).[18] Using damp, technical grade ether



Scheme 10

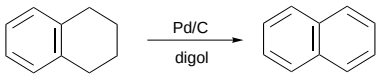
ultrasonic irradiation is able to initiate Grignard formation in under 4 min compared with several hours using the traditional method involving periodic crushing of the metal.

The formation of cyclopropanes through the Simmons–Smith reaction involving zinc dust and CH_2I_2 and an alkene suffers from several experimental drawbacks some of the major ones being the sudden exotherm which occurs after an unpredictable induction period, foaming and the difficulties in removing finely divided metal from the reaction products. The conventional method for enhancing this reaction relies upon activation of the zinc metal by using it in the form of a zinc–silver or zinc–copper couple and/or using iodine or lithium in conjunction with the metal. The experimental difficulties have been eliminated using a sonochemical procedure where no special activation of the zinc was required and good and reproducible yields were obtained using zinc metal in the form of mossy rods or foil (Scheme 11).[19]



Scheme 11

The dehydrogenation of tetrahydronaphthalene to naphthalene using 3% Pd/C in digol under the influence of sonication is accelerated by ultrasonic irradiation (Scheme 12).[20] The conventional thermal reaction in digol at 200 °C reached 55% conversion in 6 h (but thereafter reaction ceased) and only 17% reaction was obtained in the same time at the lower temperature of 180 °C. Under sonication at 180 °C the reaction reached completion in 6 h. Pulsed ultrasound (at 50% cycle) was as effective as continuous sonication and even a 10% cycle gave over 80% yield. These results offer considerable energy savings, particularly on processes carried out on a large scale.

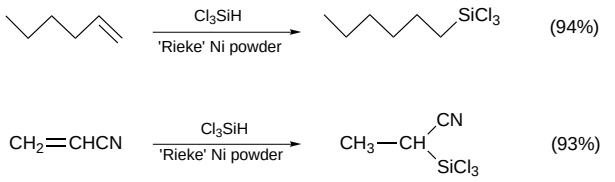


Scheme 12

Surface activation is of great use in catalysis where metal powders such as nickel, which are generally poor catalysts, can be activated by sonication before use. Normally, simple nickel powder is a reluctant catalyst for the hydrogenation of alkenes yet ultrasonic irradiation offered a reactivity comparable with Raney nickel.[21] In this case, ultrasound gave an unexpected decrease in surface area due to aggregation of particles, with electron micrographs indicating a smoothing of the nickel surface. Auger electron spectroscopy revealed an increase in the nickel/oxygen ratio at the surface. The explanation suggested was that abrasion from interparticle collisions removes the oxide layer of the nickel giving the observed increased reactivity. A simple pre-sonication of 3 μm nickel in ethanol prior to use is quite capable of converting this powder from an extremely poor into an acceptable catalyst for the conventional hydrogenation of oct-1-ene.

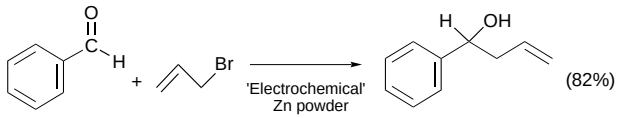
The reduction of metal salts to a finely divided very reactive free metal generally involves refluxing the metal salt in THF with a very active metal like potassium. The conditions for the production of these so-called Rieke powders can be ameliorated using ultrasound such that equally reactive metal powders can be produced using lithium in THF at room temperature. An

example of the use of sonochemically generated Rieke powders is in the preparation of organosilicon compounds (Scheme 13).[22]



Scheme 13

A novel method of generated finely divided zinc metal is by the use of pulsed sonoelectrochemistry using an ultrasonic horn as the cathode.[23] Normal electrolysis of $ZnCl_2$ in aqueous NH_4Cl affords a zinc deposit on the cathode. When the electrolysis is pulsed at 300 ms on/off and the cathode is pulsed ultrasonically at a 100 : 200 ms on/off ratio the zinc is produced as a fine powder. This powder is considerably more active than commercial zinc powder, *e.g.* in the addition of allyl bromide to benzaldehyde (Scheme 14).

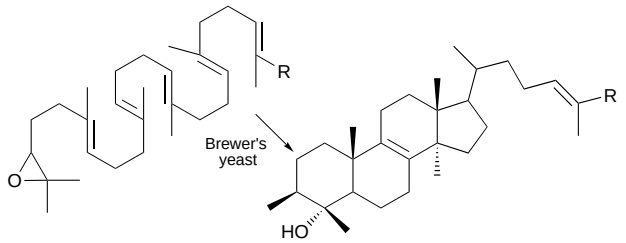


Scheme 14

5.2 Enzymatic syntheses

An area of sonochemistry which is deserving of far greater attention is the use of ultrasound to modify enzyme or whole cell reactivity. High power ultrasound will break biological cell walls releasing the contents but it can also denature enzymes. It is therefore very important that when ultrasound is used in conjunction with biological material the conditions of sonication must be carefully regulated.

Controlled sonication has been used to 'stimulate' a suspension of baker's yeast to provide an inexpensive source of sterol cyclase (Scheme 15, Table 2).[24] This technique provides an



Scheme 15

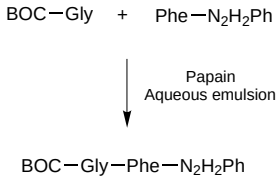
enantioselective enzymatic synthesis of a sterol in gram quantities. Significantly, sonication has no effect on the activity of the isolated cell-free cyclase system, a result which demonstrates how cell membrane disruption can occur without damage to the contents.

Table 2 Conversion of squalene oxide to sterol with baker's yeast

Enzyme source	Conversion (%)	Enantiomer conversion (%)
Whole yeast	9.5	19
Pre-treated yeast[a]	41.9	83.9

[a] Presonication at 0 °C using a probe system (20 kHz) for 2 h. [b] Enzymatic reaction at 37 °C, 12 h.

When an enzyme is used in a two phase synthesis one of the important requirements is an efficient emulsification/mixing system. Sonication provides such a method which has been used in the synthesis of peptides (Scheme 16).[25] The methodology is effective using different solvent combinations (Table 3).



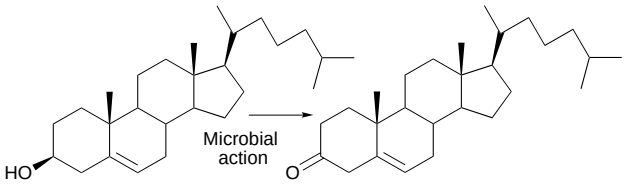
Scheme 16

Table 3 Dipeptide synthesis in an aqueous emulsion[a]

Organic phase	Stir	Sonicate
Diethyl ether	71	89
Light petroleum	12	62

[a] Water (75%) with organic solvent (25%) at 37 °C 12 h, 38 kHz ultrasonic bath.

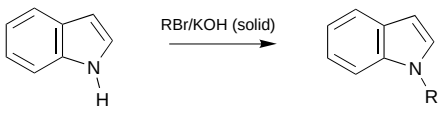
Another and probably the most spectacular example of the correct choice of optimized sonicating conditions has been reported for the microbial conversion of cholesterol to cholestenone (Scheme 17).[26] Optimum conditions involved irradiation pulses of 2.8 W power applied for 5 s each 10 min and this gave a 40% yield increase.



Scheme 17

5.3 Phase transfer and related reactions

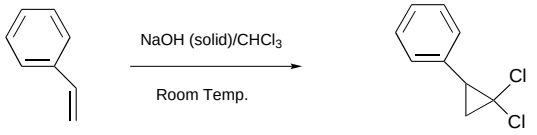
The effect of cavitation on a suspended solid has been described above (section 4.1.2). Such effects become very important in the case of reactions involving solid–liquid phase transfer catalysis. The *N*-alkylation of indole with RBr [R = $CH_3(CH_2)_{11}$] in toluene at 25 °C in the presence of solid KOH produces a 19% yield in 3 h using *tert*-butylammonium nitrate (Scheme 18). This yield is substantially improved by sonication to around 90% after only 80 min.[27]



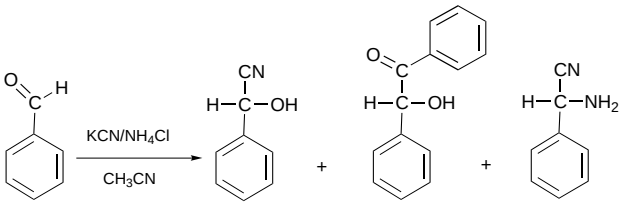
Scheme 18

In some cases sonochemistry can completely remove the need for PTC as is the case in the generation of dichlorocarbene by the direct reaction between powdered sodium hydroxide and chloroform at 40 °C using an ultrasonic bath.[28] Under these conditions styrene can be cyclopropanated in 96% yield in 1 h when a combination of both sonication and mechanical stirring is used. Significantly the yield is much reduced to 38% in 20 h with sonication alone because the power of the bath is not sufficient to disperse the solid reagent into the dense chloroform (Scheme 19).

One route to amino acids is *via* the synthesis of aminonitriles. The direct reaction between an aldehyde, KCN and NH_4Cl in acetonitrile leads to a mixture of products but in the presence of alumina and sonication the reaction can be made more specific (Scheme 20).[29] In the case of benzaldehyde the yield of the



Scheme 19



Scheme 20

target aminonitrile is poor under normal stirred conditions with benzoin and hydroxynitrile predominating (Table 4). The presence of alumina suspended in acetonitrile increases the proportion of aminonitrile but the overall results make it clear that the optimum reaction conditions require the presence of suspended alumina together with sonication and then the yield of target aminonitrile reaches 90%.

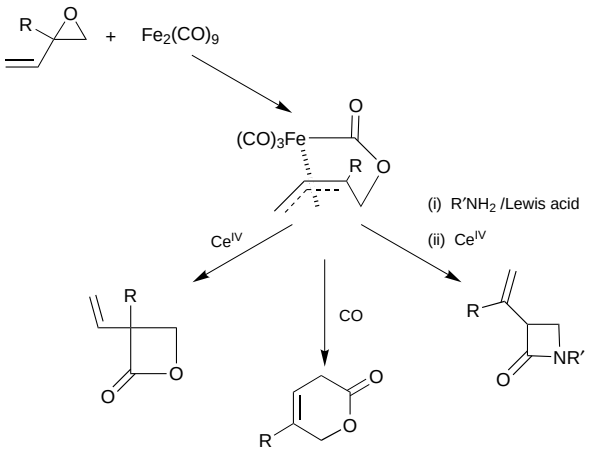
Table 4 Strecker synthesis of an aminonitrile[a]

Conditions	Cyanohydrin	Benzoin	Aminonitrile
Stir	38	21	6
Stir + Al_2O_3	19	9	64
Sonicate	45	22	23
Sonicate + Al_2O_3	3	7	90

[a] 25 °C, 38 kHz ultrasonic bath.

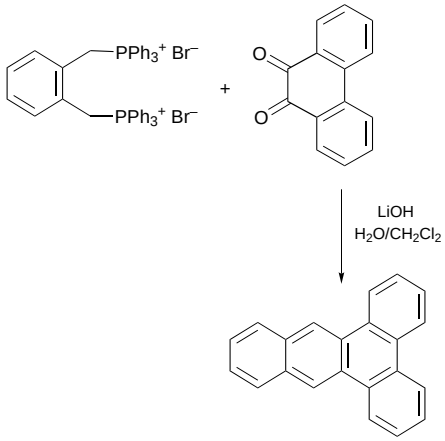
5.4 Miscellaneous syntheses

Synthetic applications of the sonolysis of iron carbonyl which lead to useful ferrilactones synthons have been described (Scheme 21). These are prepared easily and in good yields from vinyl epoxides and either iron pentacarbonyl or, for convenience and safety, diiron nonacarbonyl. The use of ferrilactones together with ultrasonically assisted reactions of samarium diodide and sodium phenylcyanide in natural product syntheses have been reviewed.[30]



Scheme 21

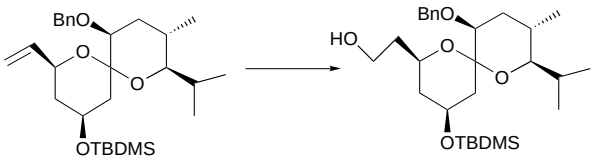
A rather difficult double Wittig reaction (Scheme 22) has been effected with enhanced efficiency under sonication.[31] The process constitutes a novel type of annelation of an aromatic ring when applied to *o*-quinones. It is possible to considerably simplify experimental procedures with ultrasound which allows the use of bases which are insensitive to moisture or air.



Scheme 22

Trialkylboranes are generally obtained through the stepwise reaction of borane with an alkene. With hindered alkenes however the reaction is very slow. Sonication promotes rapid reaction even with highly hindered substrates (Scheme 23).[32] Synthetic applications of this technique include the hydroboration/oxidation of vinyl groups.

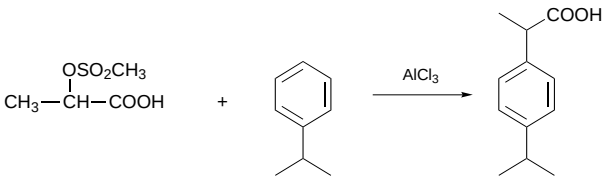
Neat 99% yield 1 h ultrasonic bath (5 h normal)



(i) 9-BBN , THF , ultrasound 89 %
(ii) NaOH , H_2O_2

Scheme 23

Sonochemistry has been used to improve a Friedel–Crafts alkylation reaction used for the synthesis of the anti-inflammatory agent ibuprofen (Scheme 24).[33] When performed under classical conditions (2 h at 25 °C) the reaction afforded only 17% yield and for this reason the normal synthesis is *via* a less direct route. Under the influence of ultrasound, using a cleaning bath, but under otherwise identical conditions the yield was improved to 50%.



Scheme 24

6 Conclusions

Sonochemistry is an expanding field of study which continues to thrive on outstanding laboratory results.[34] Applications can be found over a range of chemical systems, however it is in

heterogeneous reactions that sonochemical syntheses are most widely developed. The potential improvements afforded by sonication suggest that all chemical laboratories nowadays should be equipped with at least one small cleaning bath for simple trials.

While an empirical understanding of the subject has taken sonochemists a long way towards predicting possible applications considerable attention is currently being paid to gaining an understanding of what actually goes on in the collapsing bubble and in its immediate environment. In this area the chemists are finding very fruitful cooperation with engineers, physicists and mathematicians making sonochemistry a truly interdisciplinary study.

Recent laboratory studies have revealed that for a few heterogeneous reactions high speed stirring has a similar effect to sonication.[35] Thus in the cyclopropanation of styrene (Scheme 19) the yield can be improved from 3% with magnetic stirring through 20% at 8000 rpm to 70% at 24 000 rpm. Such results are intriguing in that they confirm the importance of mass transfer in sonochemistry and could suggest that high speed stirring involves hydrodynamic cavitation. Unlike sonication however stirring at such very high speeds is unlikely to become a viable prospect in industry.

Whatever the real laws of sonochemistry might be it is clear that sonochemistry has arrived, that sonochemistry is expanding and that chemists from all disciplines will find within the subject plenty that will be of interest to them.

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