

Reviews

The Use of Ultrasound in Industrial Chemical Synthesis and Crystallization. 1. Applications to Synthetic Chemistry

Peter W. Cains,* Peter D. Martin, and Christopher J. Price

AEA Technology plc, Harwell Laboratory, Didcot, Oxfordshire OX11 0RA, UK

Abstract:

Sonochemistry, or the application of power ultrasound to chemical processes, is a technology that has undergone very intensive research and development in the last 15–20 years, with respect to both its range of application and the methods employed for its implementation at industrial manufacturing scales. In a series of two papers, the authors review progress of the application of ultrasound to chemistry and chemical processing, and the development of equipment and scale-up methods. This first paper focuses on chemistry and also covers mechanisms of action of ultrasound and its *in situ* detection and measurement. Part 2 will deal with the application of ultrasound to crystallization processes (sonocrystallization) and with scale-up and equipment development.

1. Introduction

The application of power ultrasound to chemical processes is one of a number of intensification technologies that have undergone serious and wide-ranging development over the past 10–15 years. The driving force for these developments has many facets, but the increasing requirement for environmentally clean technology that minimises the production of waste at source is an important factor. Energy input via ultrasound offers possibilities for cleaner reactions through improved product yields and selectivities, and for enhanced product recovery and quality through application to crystallization and other product recovery and purification processes.

The earliest serious studies of the chemical effects of ultrasound were carried out in the 1950s, where the production of H₂O₂ was reported as evidence of radical formation on insonation of aqueous solutions.^{1,2} The more recent interest commenced with the outstanding enhancements that were observed in organometallic reactions in the early 1980s, and the field has expanded and developed dramatically in the late 1980s and early 1990s with an increasing volume of literature publications and conference proceedings.

To date, industrial interest in sonochemistry has somewhat lagged behind exploratory work investigating new applica-

tions and the fundamentals of how ultrasound influences chemical systems. A major factor in this delay is the difficulty that underlies scale-up. Although much work has been carried out in developing scaled-up systems, and many development modules and prototypes have been produced, large-scale processing is restricted by ultrasonic path lengths and the limitations in the power delivery systems. A more widespread adoption of sonochemistry has almost certainly been impeded by an inability to work at throughputs that are realistic for industrial production.

Since the mid-1980s, we have aimed to develop a broad, multidisciplinary view of the subject, from the standpoint of chemical manufacturing and processing and in close collaboration with industrial interests. It is through these latter contacts that we have detected a change in emphasis in recent years, away from the more traditional reaction chemistry and into the areas of processing associated with separation and purification, and particularly crystallization.

This review aims to summarize our views of the current state of industrial sonochemistry and sonocrystallization, and to indicate the directions that appear to offer the most promise for the future. It has been structured in two parts. This part outlines the range of applications of ultrasound to chemical synthesis. Part 2 will deal with sonocrystallization, with the major issues of scale-up, and with the development of equipment for carrying out sonochemistry and sonoprocessing at larger industrial scales.

2. Cavitation and the Physical Effects of Ultrasound

Acoustically induced cavitation is the primary phenomenon from which most sonochemical effects are derived. Cavitation occurs above a threshold level of insonation intensity that suffices to create voids by the shearing effect on a continuum fluid, and it follows that a minimum intensity must be applied for any consequent effects to be observed. However, the application of ultrasound at subcavitational intensities may induce mixing effects, which may account for some of the phenomena observed at high frequencies where the cavitation thresholds will be high. Sonic wavelengths in liquids are typically in the range 0.1–100 mm, well beyond molecular dimensions.

The relationship of acoustic cavitation to the physical effects directly associated with sonochemistry has been a

(1) Henglein, A. *Naturwissenschaften* **1957**, *44*, 179.

(2) Weissler, A. *J. Am. Chem. Soc.* **1959**, *81*, 1077.

subject of considerable debate, much of which has focused on the closely related topic of sonoluminescence. A detailed discussion of the latter is beyond the scope of this review, but Young³ has reviewed in detail the application of bubble dynamics to acoustically cavitating fluids and has summarized the various theories that have been advanced to relate luminescence to cavitation. A review of cavitation theory by Suslick⁴ differentiates effects in a homogeneous liquid from those occurring in heterogeneous systems. In the former, cavitation is a nucleated process, with voids forming at weak points such as gas-filled crevices in suspended particulate matter, or on transient bubbles from previous cavitation events. Bubble dynamics predicts that such cavities will grow and collapse under the oscillating pressure field. Chemical effects arise from the collapse phase of the cavitation cycle, which occurs when a cavity has grown to such an extent that it can no longer efficiently exchange energy with the sonic pressure field, and can no longer sustain itself mechanically with respect to surface tension and static pressure forces.

In heterogeneous solid–liquid systems,⁴ the interface produces a perturbation in the sonic field which induces an asymmetric collapse of the cavitation voids. At extended interfaces several times larger than the resonance cavity size, the result is a microjet of liquid passing through the cavity which impinges with the solid surface at velocities estimated around $100 \text{ m}\cdot\text{s}^{-1}$. This phenomenon has been verified experimentally and is the origin of the well-known erosion, pitting, and surface cleaning effects of ultrasound. Resonance cavity size depends on frequency, but at 20 kHz such extended interface effects are not observed with solid particles smaller than $\sim 200 \mu\text{m}$.

With powdered solids, such microjet impact phenomena do not occur, but shock waves from cavitation collapse exert large forces on small particles, producing high-velocity interparticle collisions.⁴ Brittle solids may be shock fragmented to give increased surface area,⁵ while for metal particles collisions may remove surface oxide coatings and induce local melting at the site of the impact. Insonation of $75 \mu\text{m}$ Cu spheres at 20 kHz and $500 \text{ kW}\cdot\text{m}^{-2}$ intensity for 4 h completely removed the oxide layer,⁶ while insonation of Zn powder smoothed the particle surfaces, substantially reduced the oxide layer thickness, and consolidated the particles into extended aggregates.⁷ Examination of these aggregates showed the particles to be joined by a neck of fused metal assumed to arise from local melting during high-velocity interparticle collisions.⁸ Similar experiments with mixtures of powdered Sn and Fe exhibited fusion of the dissimilar metals with the neck regions composed mainly of the low-melting Sn. Powdered Cr (mp $1857 \text{ }^\circ\text{C}$) fused into similar agglomerates, while Mo (mp $2617 \text{ }^\circ\text{C}$) aggregated with the neck formation reduced to the appearance of spot welds, and W (mp $3410 \text{ }^\circ\text{C}$) showed no aggregation

even after 4 h of insonation.⁸ These effects depended critically on particle size ($3\text{--}10 \mu\text{m}$) and the viscosity of the liquid medium (decane); no aggregation was observed with $160 \mu\text{m}$ Ni particles.

Whereas the physical effects of ultrasonic cavitation on solids in heterogeneous systems have been well characterized, the processes by which the chemical effects of free radical generation, and the promotion of radical ion formation, occur are less clear and have been a subject of considerable debate. The intuitively simplest approach has been the so-called “hot spot” theory, which postulates that the effects are induced by highly localized temperature and pressure transients brought about by the collapse of cavitation voids in the compression phase of the sonic cycle. The term “hot spot” characterizes the intense concentration of mechanical energy in the collapsing void, as illustrated by the detection of sonoluminescent photons of energy above 6 eV from an acoustic pressure field of average energy density $2.22 \text{ J}\cdot\text{m}^{-3}$, which represents an enhancement of over 10 orders of magnitude at an individual site of photon emission.⁹ Chemical evidence has been presented from experiments on sonochemical ligand substitutions of volatile metal carbonyles,⁴ which indicated that reaction takes place both in the vapour phase of the cavity and in the shell of liquid surrounding the cavity, in which rate data indicated transient temperatures of around 5000 and 2000 K, respectively. These temperatures are of the same order as those calculated for the adiabatic collapse of the voids.⁴

An alternative theory has been based on electrical microdischarge, and it postulates that charge separation occurs during the creation of cavitation voids.¹⁰ There are a number of theories as to how this may arise,³ some of which date back to the original discovery of sonoluminescent phenomena in the 1930s. Much of the debate about the two theoretical approaches centres on sonoluminescent phenomena, and on the mechanics of cavitation collapse and the viability of creating the extreme local temperature and pressure conditions predicted by the hot spot theory. According to the latter, sonoluminescence should increase with increasing cavitation intensity, decrease with increasing frequency, show a distinct threshold at low intensity, and decrease above certain critical values of both the overall hydrostatic pressure and the pressure amplitude of the insonating wave.³ All of these factors are borne out qualitatively by experiment. Furthermore, time-resolved measurements on a single, stable gas bubble,¹¹ albeit under restrictive conditions, have shown that the sonoluminescent flash corresponded to the time in the insonation cycle at which the bubble diameter was at the minimum.

Taken alone, the hot spot theory would predict a spectral distribution of sonoluminescent energy corresponding to black body radiation. This has been observed in some cases, such as the insonation of O_2 -saturated water at 800 kHz and air-saturated water at 500 kHz,³ but the fact that many sonoluminescent spectra deviate from the black body pattern

(3) Young, F. R. *Cavitation*; McGraw-Hill, 1989.

(4) Suslick, K. S.; Doktycz, S. J.; Flint, E. B. *Ultrasonics* **1990**, *28* (5), 291.

(5) Bates, D. M. Ph.D. Thesis, Coventry University, 1993.

(6) Suslick, K. S.; Casandonte, D. J.; Doktycz, S. J. *Chem. Mater.* **1989**, *1*, 6.

(7) Suslick, K. S.; Doktycz, S. J. *J. Am. Chem. Soc.* **1989**, *111* (6), 2342.

(8) Doktycz, S. J.; Suslick, K. S. *Science* **1990**, *247*, 1067.

(9) Roy, R. A. *Ultrason. Sonochem.* **1994**, *1* (1), S5.

(10) Margulis, M. A. *Akust. Zh.* **1970**, *16* (3), 434.

(11) Gaitan, D. F.; Crum, L. A.; Church, C. C.; Roy, R. A. *J. Acoust. Soc. Am.* **1992**, *91*, 3166.

has been used to criticize the theory.¹² However, analysis of the sonoluminescence from the single stable bubble above showed a spectrum consistent with a black body of notional temperature 4×10^4 K¹³ and a duration of less than 50 ps,¹⁴ consistent with hot spot calculations. It has also been observed¹² that luminescence is not quenched by solutions of α -naphthol or KI and, therefore, cannot arise from the transfer of excited species from the gas to the liquid phase.

The formation of radicals can be explained in principle by both hot spot and electrical discharge theories. H_2O_2 and HNO_2 are formed in air- and nitrogen-saturated water both under insonation and when subjected to an electrical discharge.¹⁵ ESR studies of insonated methanol–water mixtures¹⁶ indicated a pattern of radical formation consistent with an initial thermal pyrolysis step, followed by secondary radical abstraction processes. The pattern of radical yields with increasing methanol concentration was consistent with the qualitative variations in cavitation collapse conditions as prescribed by the hot spot theory for the changes in vapour specific heat ratio.

3. Measurement of Insonation Intensity

The characterization and measurement of insonation intensity is clearly important for the quantitative expression of reaction conditions and for the specification and development of efficient scaled-up processes. However, quantitative measurements that take account of relevant effects and their spatial distributions are usually difficult to identify and carry out in a simple and cost-effective manner.

Most laboratory insonation experiments are carried out with transducer and probe assemblies, and these units serve to illustrate some of the difficulties in measuring effective intensity, as well as some of the important geometric factors relevant to scale-up. Probes oscillate longitudinally, producing a very high energy density immediately below the tip which is transmitted in a forward direction. Thus, the intensity distribution is forward-directed and falls off with increasing distance from the tip according to the usual inverse-square law. In regions away from the forward-scatter zone, the insonation energy may be close to zero, and vessels containing such “dead zones” must be stirred to ensure a reasonably uniform insonation of the working volume. A very simple and common “intensity” measurement is the energy dissipated by the probe tip per unit area of probe surface, expressed as $\text{W}\cdot\text{cm}^{-2}$ or $\text{kW}\cdot\text{m}^{-2}$. Most commercially available transducer–probe systems give a readout of the tip amplitude and the corresponding energy dispersal; the measurement is simply derived using the tip diameter. Such a measurement is useful for characterizing laboratory conditions for repeatability, but it says nothing about what is happening in the working fluid or about how the energy is dispersed and distributed.

The most absolute measure of energy dispersion is that obtained calorimetrically, which is normally carried out by

insonating the liquid system in an insulated enclosure and measuring the temperature rise. It assumes the conversion of all energy entering the reactor to heat, can be used for all systems regardless of whether or not cavitation is occurring, and gives no information about cavitation. It cannot normally be used *in situ*, without special experimental arrangements.

A simple qualitative test for cavitation is to introduce a metal foil into the insonated fluid for a few seconds; cavitation will induce visible pitting in relation to its intensity. This simple test is useful in testing and commissioning equipment, and for estimating the spatial distribution of insonation intensity, but it has no use as a quantitative measurement or an intensity reference.

More quantitative measurements of effects induced by ultrasonic cavitation are given by various dosimeter techniques. These measure the yields of chemical effects and entities that are created by insonation in some sort of quantitative relation to intensity. The results obtained will always be dependent on the geometry of both the insonator and the working liquid or solution. An example commonly employed is the terephthalic acid dosimeter, which provides a luminescence measurement of $\cdot\text{OH}$ radical yields from the addition product 2-hydroxyterephthalic acid. This system is useful for measurements on aqueous systems where the creation of $\cdot\text{OH}$ and similar radicals is the primary means by which the ultrasonic effect is mediated. Alternative dosimeters have also been proposed, including the liberation of iodine from a 4% KI solution (the Weissler reaction)¹⁷ and the *cis*–*trans* isomerization of maleate to fumarate mediated by $\cdot\text{Br}$ radicals.^{18,19}

Reisse¹⁹ has discussed the need for reliable characterization and also for stable, well-characterized equipment in order to establish sonochemistry on a quantitative basis. His group have developed their own generators of 18–22 kHz ultrasound, and they claim stabilities of $\pm 10^{-4}$ and total harmonic distortions as low as 0.1%. The aim of these developments has been to obtain purely sinusoidal signals, frequency stability, and accurate intensity adjustment. Intensity measurements have been carried out using a Brüel & Kjær hydrophone with a sensitivity of $27 \mu\text{V}\cdot\text{Pa}^{-1}$, and with a Hewlett-Packard 3516A signal analyzer with an FFT facility.

4. Ultrasound in Chemistry

Ultrasound has been applied to a very wide range of chemical reactions, and the most important general groups are given below. The mechanisms of enhancement, as discussed above, generally comprise one or more of the following effects:

(a) Mechanical and dispersive effects on powdered solids. The mechanical effects described above can be employed to remove passivating layers from metals in organometallic

(12) Margulis, M. A. *Adv. Sonochem.* **1990**, *1*, 39.

(13) Hiller, R.; Putterman, S. J.; Barber, B. P. *Phys. Rev. Lett.* **1992**, *69*, 1182.

(14) Barber, B. P.; Putterman, S. J. *Nature* **1991**, *352*, 318.

(15) Margulis, M. A. *Ultrason. Sonochem.* **1994**, *1* (2), S87.

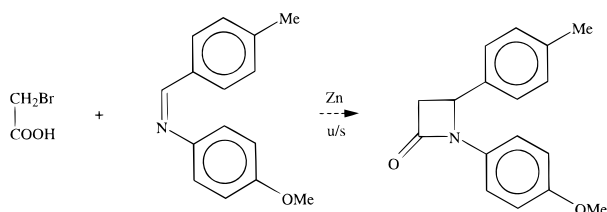
(16) Riesz, P.; Kondo, T.; Krishna, C. M. *Ultrasonics* **1990**, *28* (5), 295.

(17) Lorimer, J. P.; Mason, T. J.; Paniwnyk, L. Unpublished work, **1992**.

(18) Reisse, J.; Yang, D. H.; Maeck, M.; Vandercammen, J.; Van der Donck, E. *Ultrasonics* **1992**, *30* (6), 397.

(19) Reisse, J. Quantitative Homogeneous Sonochemistry—Scope and Limitations. Presented at the Interdivisional Sonochemistry Symposium, Annual Chemical Congress of the Royal Society of Chemistry, UMIST Manchester, April 13–16, 1992.

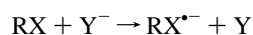
Scheme 1



reactions, and to break down brittle solids such as bases and catalysts to increase surface areas, mass transfer, and reaction rates.

(b) Generation of free radicals. Reactions that are either initiated or mediated by free radicals, including polymerizations and oxidations in aqueous solution, may be promoted by the application of ultrasound.

(c) Promotion of electron transfer. It was suggested in the late 1980s²⁰ that a large number of displacement reactions hitherto thought of as classical bimolecular nucleophilic substitutions (S_N2) take place by a radical mechanism, with radical formation by transfer of a single electron from the nucleophile to the lowest lying antibonding (σ^*) orbital of the recipient substrate:



It has been further suggested²¹ that insonation accelerates such single electron transfer (SET) processes. In this way, the application of ultrasound can alter reaction pathways and selectivities in cases where reaction may proceed by either a SET or a classical ionic S_N2 mechanism; examples are given below.

4.1. Organometallic Reactions. The outstanding results obtained in early work on the application of ultrasound to a range of standard organometallic reactions provided much of the stimulus for the more recent development of sonochemistry. A simple Reformatsky reaction of Zn, octanal, and ethyl bromoacetate gave a 95% yield of the β -hydroxy ester product in 5 min at room temperature under insonation, compared with 69% after 12 h at 80 °C without insonation.²² A similar insonated reaction for the preparation of a β -lactam from Zn, ethyl bromoacetate, and a diaryl Schiff base²³ gave a 95% yield within 4 h at room temperature, whereas the conventional method of refluxing in toluene gives yields of only 60% (Scheme 1).

Rate enhancements in organometallic reactions have been largely associated with the disruption of passivating oxide layers on the metal surfaces, which is most dramatically demonstrated by the reduction or elimination of induction periods. In the Ullmann coupling of two 2-nitroiodobenzene moieties to form 2,2'-dinitro biphenyl, preinsonation of the Cu powder for 12 h at 20 kHz produced a 50-fold enhancement in the initial rate⁶ and a 10-fold rate increase in the later stages of reaction. We have investigated the formation

of Grignards²⁴ from 1- and 2-bromopropanes, 2-bromo-2-methylpropane, and benzyl bromide; in all cases induction periods were reduced or eliminated, but the final yields of ~80% were unaffected. Benzylmagnesium bromide was also prepared in a "wet" solvent of THF with 0.2% water, and Figure 1 shows the marked reduction in induction period brought about by insonation under these conditions.

Another simple organometallic reaction exhibiting marked improvement under insonation is the Barbier reaction: the coupling of benzaldehyde and 1-bromoheptane in the presence of Li gave a 90% product yield on insonation at 50 kHz for 25 min, compared with only 8% after 7 h at room temperature without insonation²⁵ (Scheme 2). We have investigated the analogous reaction with 1-bromopropane, which we have used as a model system for scale-up studies and equipment development²⁶ and which will be described in more detail in Part 2 of this review. Our work indicated that insonation removed passivating hydroxide and halide layers from the Li, but that the effects on particle size were not great. We were also able to carry out this reaction in a THF solvent containing up to 0.2% water, as for the Grignard above.

There is also a considerable body of evidence²⁷ that insonation influences the coupling reaction of the lithiated alkyl and the keto function, probably by promoting electron transfer. The uninsonated Barbier reaction of (*S*)-(+)-2-bromooctane with Li and cyclohexanone²⁸ gives a small (6%) excess of the inverted *R* enantiomer product, which is increased to 19–24% on insonation. It is suggested²⁷ that the coupling reaction occurs by a dual mechanism, consisting of the standard S_N2 organometallic pathway and an electron transfer pathway via a radical anion (Scheme 3). Under insonation, the rate of formation of the radical ion of pathway (A) is increased due to the accelerated SET, giving an enhanced yield of the *R* enantiomer.

Other organometallic reactions to which ultrasound has been applied beneficially include the Simmons-Smith cyclopropanation of alkenes with diiodomethane and Zn;²⁹ for example, see Scheme 4. Using methyl oleate as the alkene, a 98% yield of cyclopropanated adduct was obtained after 2 h of insonation, compared with 50% without insonation.³⁰

The Bouveault reaction of alkyl, cycloalkyl, and aryl bromides with Li and dimethylformamide in an ether solvent to form the corresponding aldehydes conventionally suffers from numerous side reactions which restrict the overall yield to around 50%. Insonation of the reaction with bromocyclohexane at 50 kHz in a THF or THP (tetrahydropyran) solvent increased the aldehyde yield to 70% and reduced the reaction time from 2 h to less than 30 min³¹ (Scheme 5). Raising the ultrasonic frequency to 500 kHz also enabled

(20) Ashby, E. C.; Pham, T. N. *Tetrahedron Lett.* **1987**, 28 (28), 3183. Ashby, E. C. *Acc. Chem. Res.* **1988**, 21, 414.

(21) Luche, J.-L.; Einhorn, C.; Einhorn, J.; Sinisterra-Gago, J. V. *Tetrahedron Lett.* **1990**, 31 (29), 4125.

(22) Han, B. H.; Boudjouk, P. *J. Org. Chem.* **1982**, 47, 5030.

(23) Bose, A. K.; Gupta, K.; Manhas, M. S. *J. Chem. Soc., Chem. Commun.* **1984**, 86.

(24) Cains, P. W.; Goodwin, T. W. AEA Technology. Unpublished work.

(25) Luche, J.-L.; Damiano, J. C. *J. Am. Chem. Soc.* **1980**, 102, 7926.

(26) Martin, P. D.; Ward, L. D. *Chem. Eng. Res. Des.* **1992**, 70A, 296.

(27) Luche, J.-L.; Einhorn, C.; Einhorn, J.; de Souza-Barboza, J. C.; Petrier, C.; Dupuy, C.; Delair, P.; Allavena, C.; Tuschl, T. *Ultrasonics* **1990**, 28 (5), 316.

(28) de Souza-Barboza, J. C.; Luche, J.-L.; Petrier, C. *Tetrahedron Lett.* **1987**, 28, 2013.

(29) Repic, O.; Vogt, S. *Tetrahedron Lett.* **1982**, 23, 2729.

(30) Repic, O.; Lee, P. G.; Giger, U. *Org. Prep. Proced. Int.* **1984**, 16, 25.

(31) Petrier, C.; Gemal, A. L.; Luche, J.-L. *Tetrahedron Lett.* **1982**, 23, 3361.

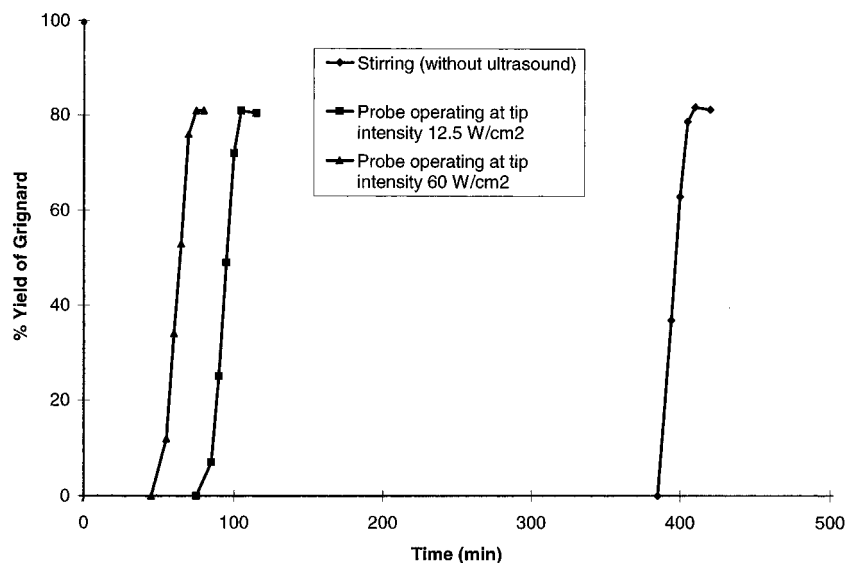
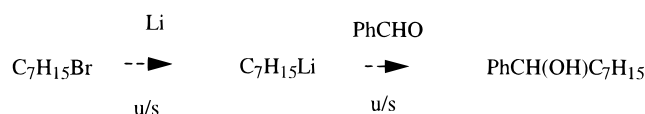


Figure 1. Preparation of benzylmagnesium bromide Grignard in “wet” THF containing 0.2% water.²⁴

Scheme 2



the reaction to be carried out in diethyl ether.³² This suggests that cavitation, which is unlikely to occur in diethyl ether at 500 kHz, may not be the sole source of enhancement of this reaction.

Ultrasound has also been applied to reactions with Na and K. K may be dispersed by insonation in xylene and toluene but not in THF; Na is dispersed in xylene but not in toluene or THF; while Li is not dispersed in any of these solvents.³² Such a K dispersion has been used to enhance the Dieckmann condensation³³ (Scheme 6), and an insonated dispersion of Na has been used in Wurtz couplings³⁴ (Scheme 7) and in the generation of aryl radical anions³⁵ (Scheme 8).

Generally, the application of ultrasound allows organometallic reactions to proceed more rapidly under milder conditions than those required in conventional synthesis, and it is this latter characteristic that is attractive in the preparation of delicate compounds. Thus, organometallic sonochemical techniques have been applied in steroid synthesis,³⁶ in organosilicon chemistry,³⁷ and in the preparation of vitamin D₃ metabolites.³⁸ Novel applications continue to be reported, including recently the preparation of arylstannanes by reaction of aryl bromides with Mg and (Bu₃Sn)₂O in THF,³⁹ the synthesis of aromatic α -disulphones from Li and an

arenesulphonyl chloride in THF,⁴⁰ and the direct formation of ketones from chloroalkanes, Li carboxylates, and Li metal in THF.⁴¹

4.2. Metal-Catalyzed Hydrogenation. Ultrasound has been applied to powdered metal catalysts to promote reactions mediated by adsorption at the catalyst surfaces. The hydrogenation of alkenes using formic acid and hydrazine as hydrogen sources and a Pd/C catalyst has been considerably enhanced by insonation, which is believed to increase the effective surface area of the catalyst by fragmenting the support.^{42,43} The hydrosilylation of styrene to alkylsilanes in the presence of Pt/C is reported to 95% yield within 2 h at room temperature under insonation, whereas the conventional reaction requires elevated temperatures (> 100 °C) and pressures (> 5 bar) to produce a reasonable yield of product.⁴⁴

Catalytic hydrogenation with gaseous hydrogen represents a more complex system physically, with the dispersive effects of ultrasound on the catalysts counterbalanced to some extent by its degassing effect on the solution. We have found that the initial rate of reduction of acetophenone to 1-cyclohexylethanol over Pd/C and Rh/C in ethanol increased in proportion to the adsorptive uptake of H₂ on the catalyst; for Pd/C this increased from 0.45 mmol·g⁻¹ without insonation to 1.8 mmol·g⁻¹ on insonation with a probe at maximum intensity (180 W·cm⁻²).²⁴ The solubility of H₂ in ethanol reduced from 1.5 mmol·L⁻¹ to zero under these conditions. The rate of reduction of α -methylstyrene to cumene under the same conditions exhibited a decrease in initial rate, assigned to the degassing effect.

The hydrogenation of 1-octene with H₂ over Pd/C in ethanol was carried out with and without a 1 h preinsonation of the catalyst suspension.²⁴ The preinsonation reduced the time for complete conversion from 1 h to 30 min. Using the same conditions with preinsonation, the alkene function

(32) Luche, J.-L. *Ultrasonics* **1987**, 25, 40.

(33) Luche, J.-L.; Petrier, C.; Dupuy, C. *Tetrahedron Lett.* **1984**, 25, 753.

(34) Matyjaszewski, K.; Kim, H. K. *Polym. Bull. (Berlin)* **1989**, 22 (3), 253.

(35) Azuma, T.; Yanagida, S.; Sakurai, H. *Synth. Commun.* **1982**, 12, 137.

(36) Salvador, J. A. R.; Sa e Melo, M. L.; Campos Neves, A. S. *Tetrahedron Lett.* **1993**, 34 (2), 357.

(37) Lukevics, E. Organosilicon sonochemistry. Presented at the 3rd Meeting of the European Society of Sonochemistry, Figueira da Foz, Portugal, March 28 to April 1, 1993.

(38) Mascarenas, J. L.; Perez-Sestelo, J.; Castedo, L. Moureño, A. *Tetrahedron Lett.* **1991**, 32 (24), 2813.

(39) Shih-Yuan, A.; Dai, W.-C. *Tetrahedron Lett.* **1996**, 37 (4), 495.

(40) Prokes, I.; Toma, S.; Luche, J.-L. *Tetrahedron Lett.* **1995**, 36 (22), 3849.

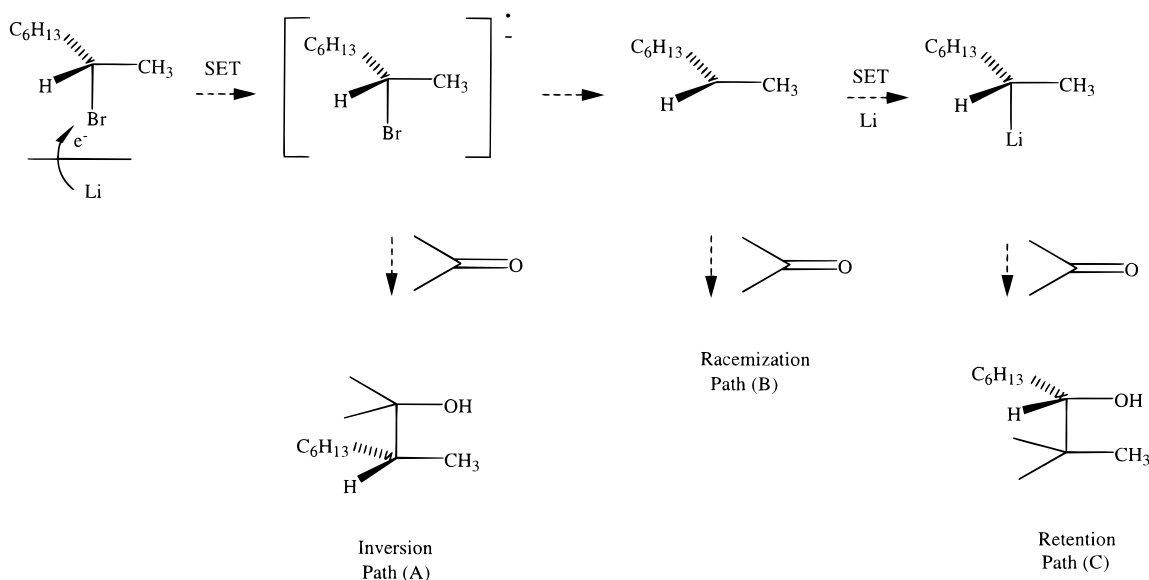
(41) Aurell, M. J.; Danhui, Y.; Einhorn, C.; Luche, J.-L. *Synlett* **1995**, No. 5, 459.

(42) Boudjouk, P.; Han, B. H. *J. Catal.* **1983**, 79, 489.

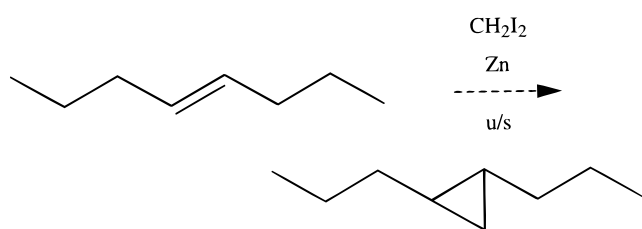
(43) Shin, D. H.; Han, B. H. *Bull. Korean Chem. Soc.* **1985**, 6, 247.

(44) Han, B. H.; Boudjouk, P. *Organometallics* **1983**, 2, 770.

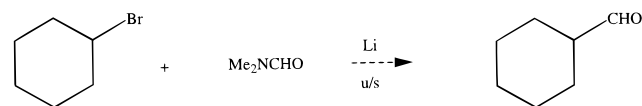
Scheme 3



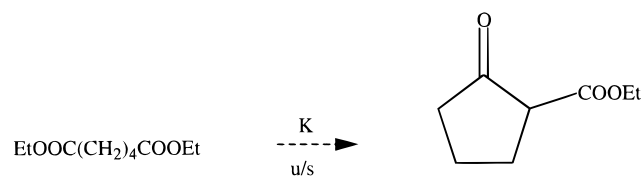
Scheme 4



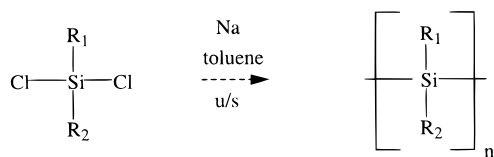
Scheme 5



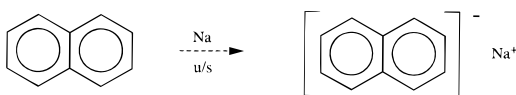
Scheme 6



Scheme 7



Scheme 8



in *trans*-4-phenyl-3-buten-2-one was quantitatively and selectively reduced in 30 min. Selective hydrogenation of alkene functions by H₂ and Pd/C under insonation are also reported at yields >92% in the presence of CN, CO, COOMe, and CHO groups.⁴⁵

Ultrasound has also been effective in activating simple Ni powders as hydrogenation catalysts.⁴⁶ A 3 μm Ni powder has been activated for the reduction of 1-octene with H₂, but the effects and yields appear to be very sensitive to the physical and insonation conditions employed.⁴⁷ The activation of a submicron Ni powder was much less marked under the conditions optimum for the coarser powder. Insonation of a Raney Ni catalyst gave results inferior to those in an uninsonated control, which were presumed due to the insonation agglomerating and consolidating the catalyst.

4.3. Preparation of Metal and Ceramic Powders. In recent years, ultrasonic methods have been employed to produce a range of ultrafine, amorphous, and nanostructured powdered materials for use in catalysis and other applications. Amorphous iron has been prepared by insonating a 4 M solution of pure Fe(CO)₅ in decane at 0 °C, which exhibited catalytic activity 10 times more intense than that of 5 μm crystalline Fe powder for the Fischer–Tropsch conversion of CO + H₂ to low molecular weight alkanes.⁴⁸ Nanostructured Co has also been prepared from Co(CO)₃(NO), Fe–Co alloys have been prepared from mixtures of Fe(CO)₅ and Co(CO)₃(NO), and an effective Fe/SiO₂ Fischer–Tropsch catalyst was prepared from a slurry of Fe(CO)₅ and SiO₂.⁴⁹ Insonation of Mo(CO)₆ in hexadecane under Ar at 90 °C yielded a fcc Mo₂C of very high surface area (BET 188 m²·g⁻¹), which exhibited catalytic activity comparable to that of Pt powder for the dehydrogenation of cyclohexane with 100% conversion to benzene and no hydrogenolysis to methane.⁵⁰ Amorphous Ni of particle size ~10 nm has also been prepared by sonolysis of Ni(CO)₄ and its solution in decane.⁵¹

(45) Kim, T. Y.; Yim, E. S.; Lee, S. J.; Park, M. K.; Han, B. H. *J. Korean Chem. Soc.* **1996**, *40* (3), 216.

(46) Suslick, K. S.; Casandonte, D. J.; Doktycz, S. J. *Solid State Ionics* **1989**, *32/33*, 444.

(47) Cains, P. W.; McCausland, L. J.; Bates, D. M.; Mason, T. J. *Ultrason. Sonochem.* **1994**, *1* (1), S45.

(48) Suslick, K. S.; Choe, S. B.; Cichowlas, A. A.; Grinstaff, M. W. *Nature* **1991**, *353*, 414.

(49) Suslick, K. S.; Hyeon, T.; Fang, M. *Chem. Mater.* **1996**, *8* (8), 2172.

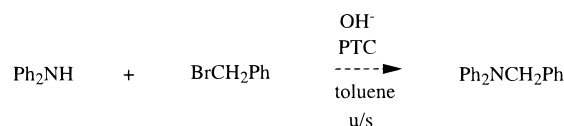
Insonation has been employed as a pretreatment in the production of ultrafine 40–80 nm Fe particles by liquid phase reduction with KBH_4 ,⁵² and also in the production of goethite ($\alpha\text{-FeOOH}$) and magnetite (Fe_3O_4) from precipitated $\text{Fe}(\text{OH})_2$.⁵³ The process involved dissolution, oxidation, and the reprecipitation of the products. Where sufficient O_2 was present, insonation increased the rate of appearance and growth of the products; with insufficient O_2 , the formation of the goethite phase was favoured at the expense of the magnetite.

Ultrasonic methods for the preparation of finely divided precious metal products have also been reported. The formation of gold metal sols has been initiated by insonation of solutions containing AuCl_4^- at concentrations of 1–20 mM;^{54,55} best results were obtained in the presence of organic additives such as aliphatic alcohols, ketones, surfactants, and water-soluble polymers. Ultrafine Pd particles of particle sizes of 6–7.5 nm have been prepared by the insonation of aqueous PdCl_2 solutions in the concentration range 0.1–0.5 mM in the presence of a protective agent such as poly(vinylpyrrolidone).⁵⁶ The main reaction pathway of Pd(II) to Pd(0) appeared to be reduction by radicals formed by the thermal degradation of the protecting agents in the regions of ultrasonic cavitation.

The application of ultrasound has been employed to modify the crystal lattice constants of titanium silicides in their production by the self-propagating, high-temperature synthesis (SVS) technique.⁵⁷ Preparations with stoichiometric Si:Ti ratios between 0.5 and 1.0 contained the Ti_5Si_3 phase and an increasing quantity of TiSi_2 as the ratio increased. Insonation at ultrasonic amplitudes up to 15 μm caused the Ti_5Si_3 lattice constants to approach reference values but those for TiSi_2 to deviate more widely. Ultrasound has also been employed in the preparation of semiconducting Q-ZnO,⁵⁸ where control of particle size is an important facet since the density of electronic states decreases and the band-gap energy increases as the particles become smaller. A relatively concentrated colloid was prepared by boiling $\text{Zn}(\text{OAc})_2$ in absolute ethanol, adding LiOH, and insonating in a bath. The effects of ultrasound are believed to arise from enhanced phase transfer (see below) via the liberation of OH^- ions from the base.

4.4. Phase Transfer Reactions. The last example demonstrates the other major physical dispersive effect that ultrasound can bring to bear to promote chemical reaction, the mixing of heterogeneous phases. From a physical standpoint, there are two main reaction classes of this type;

Scheme 9



those involving the dispersion of an insoluble solid reactant, commonly a base, in a liquid medium, and those requiring the intimate mixing of two immiscible liquid media. Many of these reactions are conventionally carried out in the presence of a surfactant, or phase transfer catalyst (PTC), which is likely to be difficult to remove in subsequent workup and product purification stages. The reduction or elimination of such catalysts has been a strong incentive in applying ultrasound to these systems.

We have investigated the effects of ultrasound on the *N*-alkylation of diphenylamine (20 mmol) with benzyl bromide (20 mmol) (Scheme 9) in toluene (50 mL) using KOH as the anion source (50 mmol) and polyethylene glycol methyl ether (20 mmol) as the PTC.²⁴ In the absence of insonation, the reaction proceeds to completion under reflux in 48 h, but vigorous mechanical agitation reduces the reaction time to less than 1 h. These latter conditions have been employed for reference, and the effects of insonating at 20 and 40 kHz are shown in Figure 2. Saturation effects with intensity were observed with both ultrasonic frequencies, and both insonated and noninsonated reactions were zero order with respect to Ph_2NH and BrCH_2Ph and first order with respect to KOH. Decreasing the PTC to one-quarter of its original level slowed down the initial reaction rate and reduced product yields to 15% in both uninsonated and insonated cases.

A number of important reactions of this type involving amines and *N*-heterocycles have been reported. The yield and rate of the *N*-benzylation of indole in the presence of KOH and polyethylene glycol methyl ether have been improved from 80% in 8 h to 95% in 2 h by the application of ultrasound.⁵⁹ A very important reaction of this type is the *tert*-butoxycarbonylation of amines, used to confer protection on the amine by the large and relatively unreactive *t*-BOC group⁶⁰ (Scheme 10). Without ultrasound, stirring the amine in ethanol or methanol solution with di-*tert*-butyl dicarbonate in the presence of a weak base such as NaHCO_3 led to complete reaction over long contact times (>24 h) without the addition of a phase transfer catalyst. Insonation caused the reaction to run to completion in a few minutes, and its progress could be monitored by the evolution of CO_2 . The procedure has been applied to a range of amino acids and amino acid esters, giving yields between 84% and 100%.

The *O*-alkylation of the hindered phenol 5-hydroxychromone has been carried out using insonation with a base and an alkyl halide in an aprotic solvent.⁶¹ An alternative

(50) Hyeon, T.; Fang, M.; Suslick, K. S. *J. Am. Chem. Soc.* **1996**, *118* (23), 5492.

(51) Koltypin, Yu.; Katabi, G.; Cao, X.; Prozorov, R.; Gedanken, A. *J. Non-Cryst. Solids* **1996**, *201* (1, 2), 159.

(52) Kikuchi, E.; Itoh, H. *Sekiyu Gakkaishi* **1991**, *34* (5), 407.

(53) Enomoto, N.; Akagi, J.; Nakagawa, Z. *Ultrason. Sonochem.* **1996**, *3* (2), S97.

(54) Grieser, F.; Hobson, R.; Sostaric, J.; Mulvaney, P. *Ultrasonics* **1996**, *34* (2–5), 547.

(55) Nagata, Y.; Mizukoshi, Y.; Okitsu, K.; Maeda, Y. *Radiat. Res.* **1996**, *146* (3), 333.

(56) Okitsu, K.; Bandow, H.; Maeda, Y.; Nagata, Y. *Chem. Mater.* **1996**, *8* (2), 315.

(57) Klubovich, V. V.; Kulak, M. M.; Chebot'ko, I. S. *Vestsi Akad. Navuk BSSR, Ser. Fiz.-Tekh. Navuk* **1991**, No. 1, 67.

(58) Spanhel, L.; Anderson, M. A. *J. Am. Chem. Soc.* **1991**, *113* (8), 2826.

(59) Davidson, R. S.; Patel, A. M.; Safdar, A.; Thornthwaite, D. *Tetrahedron Lett.* **1983**, *24*, 5907. Davidson, R. S.; Safdar, A.; Spencer, J. D.; Robinson, B. *Ultrasonics* **1987**, *25*, 35.

(60) Einhorn, J.; Einhorn, C.; Luche, J.-L. *Synlett* **1991**, No. 1, 37.

(61) Mason, T. J.; Lorimer, J. P.; Paniwnyk, L.; Harris, A. R.; Wright, P. W.; Bram, G.; Loupy, A.; Ferradou, G.; Sansoulet, J. *Synth. Commun.* **1990**, *20* (22), 3411.

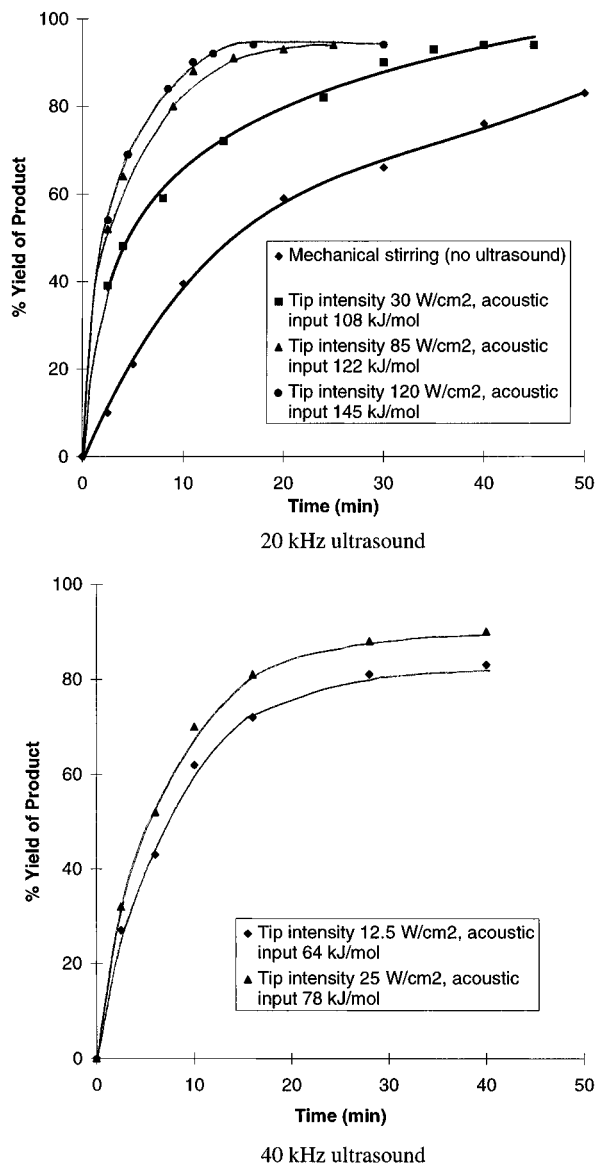
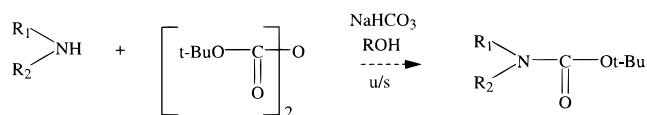


Figure 2. Effects of 20 and 40 kHz ultrasound on the *N*-benzylation of diphenylamine.²⁴ Acoustic input refers to estimated total ultrasonic energy input at 75% conversion.

Scheme 10



noninsonated technique with a phase transfer catalyst and no solvent was also employed for comparison (Scheme 11). With reactive halides (allyl and benzyl bromides), the *O*-alkylated product (**A**) was dominant using both techniques. With less reactive halides, some transesterification occurred at the ester group in the 2-position, giving products **B** and **C**. With 1-bromobutane, product **A** was predominant, but the phase transfer method produced larger amounts of **B** and **C**, while with 2-bromobutane the insonated method gave all three products, and the phase transfer method gave **A** or **B** depending on the catalyst used.

Other examples of insonated phase transfer reactions involving solids include the *trans*-halofluorination of alkenes

using a hydrogen fluoride salt NH_4HF_2 combined with porous AlF_3 as the fluorinating agent and a *N*-halosuccinimide electrophile⁶² (Scheme 12) and the addition of perfluoroalkyl iodides to alkenes or alkynes catalyzed by sodium dithionite⁶³ (Scheme 13). The best results for the latter were obtained in an acetonitrile–water solvent; stereoselectivity generally favoured a *trans* (*Z*) configuration.

The other principal category of phase transfer reaction amenable to ultrasonic enhancement involves the intimate mixing of two immiscible liquid phases. Most of these reactions involve the generation of intermediate radical species, such as dichlorocarbene produced by the reaction of CHCl_3 and an aqueous alkali (Scheme 14). The dichlorocarbene can be added to an alkene to yield a *gem*-dichlorocyclopropane⁶⁴ (Scheme 15). The insonation of this reaction eliminated the requirement for a phase transfer catalyst. Similar results have been obtained for analogous reactions with CHBr_3 .⁶⁵

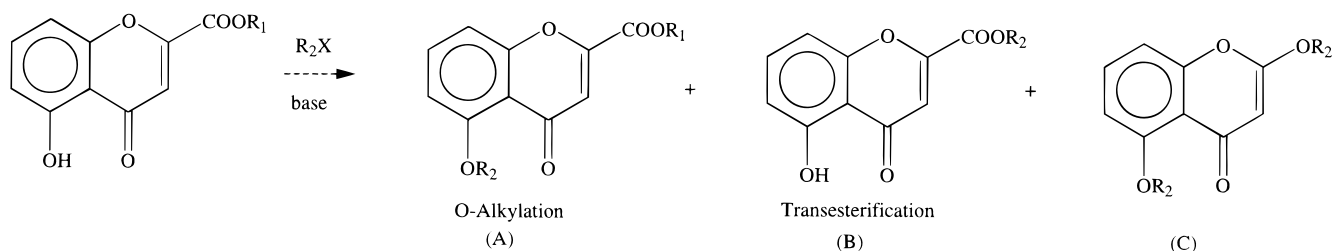
The insertion of dihalocarbenes into C–H alkane functions has also been investigated.⁶⁶ Insertions into primary and secondary functions produce very low yields, and moderate yields from insertion into tertiary C–H bonds have only been obtained with ball-shaped molecules such as adamantane and dodecahedrane. Insertion into C–H bonds α to a three-membered ring has been more successful, owing to activation arising from the interaction of the Walsh orbitals of the cyclopropane ring with the C–H bond orbitals. Thus, insonation of bicyclo[4.1.0]heptane with CHCl_3 , powdered NaOH , and 0.5% **TEBAC** (triethylbenzylammonium chloride, **PTC**) for 3 h yielded 83% 2-(dichloromethyl)bicyclo[4.1.0]heptanes in an *endo:exo* ratio of 4.3:1 (Scheme 16). A similar insertion into bicyclo[3.1.0]hexane gave an adduct yield of 40%, but with the *exo* isomer dominating by 3:1. A regioselective monhaloalkylation of arylidioxacycloalkanes via the halocarbenes $:\text{CHCl}$ and $:\text{CHBr}$ has also been reported⁶⁷ on insonation with KOH and **TEBAC** in a dihalomethane solvent (Scheme 17).

A reaction similar in principle to dihalocarbene addition is the preparation of *N*-carboxylated aziridines from alkenes and *in situ* generated ethoxycarbonylnitrene⁶⁸ (Scheme 18). The $:\text{NCOOEt}$ was created by the α -elimination of the 4-nitrobenzenesulphonate anion from ethyl *N*-[[4-(nitrophenyl)sulphonyl]oxy]carbamate on insonation in the presence of a base in a mixed dichloromethane–water system. The use of ultrasound eliminated the requirement for a phase transfer catalyst.

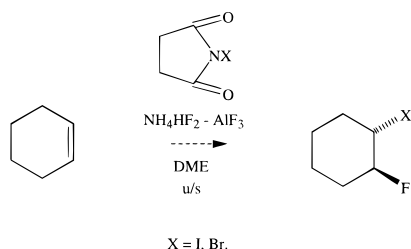
4.5. Generation of Free Radicals. The homolytic generation of free radicals by ultrasonic cavitation is well established and gives rise to a number of chemical processes. In aqueous solutions, $\cdot\text{OH}$ and $\cdot\text{OOH}$ radicals are formed as

- (62) Ichihara, J.; Funakibi, K.; Hanafusa, T. *Tetrahedron Lett.* **1990**, 31 (22), 3167.
 (63) Rong, G.; Keese, R. *Tetrahedron Lett.* **1990**, 31 (39), 5615.
 (64) Regan, S. L.; Singh, A. J. *Org. Chem.* **1982**, 47, 1587.
 (65) Xu, L.; Tao, F. *Synth. Commun.* **1988**, 18, 2117.
 (66) Xu, L.; Smith, W. B.; Brinker, U. H. *J. Am. Chem. Soc.* **1992**, 114 (3), 783.
 (67) Safiev, O. G.; Nazarov, D. V.; Zorin, V. V.; Rakhmankulov, D. L. *Lz. Fiz. Khim.* **1988**, 62 (11), 3137.
 (68) Dirnens, V. V.; Gol'dberg, Yu. Sh.; Lukevics, E. *Dokl. Akad. Nauk SSSR* **1988**, 298 (1), 116.

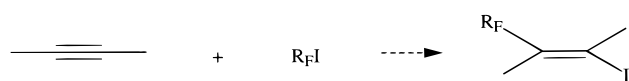
Scheme 11



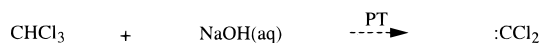
Scheme 12



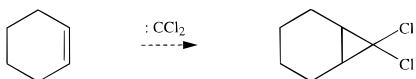
Scheme 13



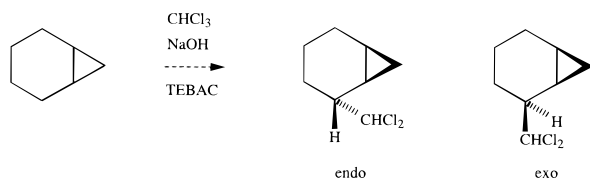
Scheme 14



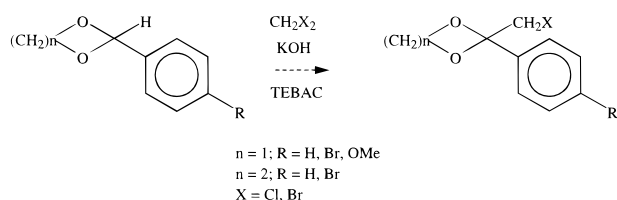
Scheme 15



Scheme 16



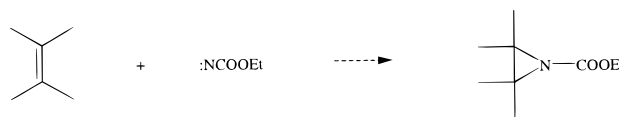
Scheme 17



shown by early reports of H_2O_2 formation,^{1,2} and attempts have been made to model the formation and propagation reactions in a similar fashion to radiolysis.¹² Investigation of $\cdot\text{OH}$ radical scavenging by the halide solutes I^- and Br^- indicated that the quantities of radicals and oxidizing intermediates formed on insonation were independent of the amounts of solute present.⁶⁹

4.5.1. Application to Effluent Treatment. An important potential application of the generation of oxidizing radicals has been in the treatment of waste waters containing toxic contaminants, particularly phenols and chlorinated aliphatic

Scheme 18



hydrocarbons. Tests with dichloromethane, trichloroethylene, 1,1,1-trichloroethane, and tetrachloromethane at 100–1000 $\text{mg}\cdot\text{L}^{-1}$ insonated at ~ 20 kHz showed a rapid initial decrease in solution pH brought about by the formation of HCl, which levelled off to an asymptotic value of 2.8 after 20–30 min.⁷⁰ Insonation at 250 W in a 2 L glass vessel showed an initial degradation rate following first-order kinetics with a rate constant of $3.93 \times 10^{-3} \text{ min}^{-1}$.

Insonation of O_2 -saturated phenol solutions ($5 \times 10^{-4} \text{ M}$) at 20 kHz and 500 kHz showed a high initial rate of phenol disappearance at the higher frequency, but an insignificant rate at 20 kHz.⁷¹ This result implies that $\cdot\text{OH}$ and $\cdot\text{OOH}$ generation and H_2O_2 formation are frequency dependent, and it appears to contradict the conventional notions relating to frequency and cavitation intensity and may be due to the way in which ultrasonic intensity is distributed in the reactor volume. Work on the degradation of anionic pentachlorophenate at concentrations of 10^{-4} – 10^{-3} M at various power levels and insonated volumes showed a direct relationship between degradation rate and power input density.⁷²

Addition of CCl_4 to the solution brought about a marked acceleration in phenol degradation at both frequencies, double at 500 kHz and 100-fold at 20 kHz, and the detection of chlorophenols indicated the formation of $\cdot\text{Cl}$ radicals and their participation in the degradation processes.⁷¹ Insonation of a solution of CCl_4 indicated that decomposition probably occurred within cavitation bubbles, with CO_2 and Cl^- as the main products.⁷³ Activated species, including $\cdot\text{Cl}$, $\cdot\text{CCl}_3$ and $\cdot\text{CCl}_2$, also appeared in the process.

We have investigated the application of ultrasound to decontaminate effluents containing phenols, nitroso- and aminobenzenes, and diazo compounds.²⁴ Most of these compounds should be reasonable candidates for degradation by radical attack because of their aromaticity; however, our tests showed at best only modest success. Using rate data from the generation of $\cdot\text{OH}$ and other oxidizing radicals from

(69) Gutierrez, M.; Henglein, A.; Ibanez, F. *J. Phys. Chem.* **1991**, *95* (15), 6044.

(70) Cheung, H. M.; Bhatnagar, A.; Jansen, G. *Environ. Sci. Technol.* **1991**, *25* (8), 1510.

(71) Petrier, C.; Lamy, M.-F.; Francony, A.; Benahcene, A.; David, B.; Renaudin, V.; Gondrexon, N. *J. Phys. Chem.* **1994**, *98* (41), 10514.

(72) Gondrexon, N.; Bernis, A.; Boldo, P.; Gonthier, Y.; Petrier, C. *Recents Prog. Genie Procédés* **1993**, *7* (30, Études de Conception d'Equipments), 383.

(73) Francony, A.; Petrier, C. *Ultrason. Sonochem.* **1996**, *3* (2), S77.

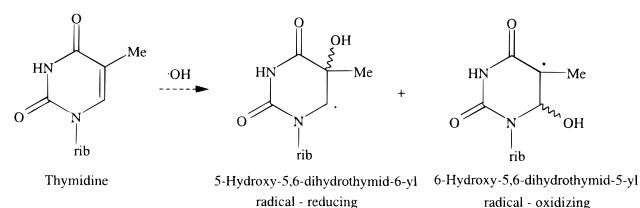
H₂O₂ and ozone,⁷⁴ we have estimated that •OH radical concentrations of at least 10⁻¹²–10⁻¹⁰ M are required to give degradation rates that are reasonable for practical applications. Although we have not attempted to measure radical yields from insonation, the production of these concentrations under controllable conditions is a major challenge in the development of this technology.

4.5.2. Reactions in Aqueous Solution. Insonation of aqueous solutions of glucose⁷⁵ and lactose⁷⁶ leads to degradation products that are largely a result of •OH radical generation. In glucose solutions,⁷⁵ these radicals abstract carbon-bonded hydrogen atoms, leading to glucosyl radicals. Where O₂ is present, i.e., the solution is aerated, the glucosyl radicals are converted to peroxy radicals, which do not abstract hydrogen from glucose and function as chain carriers. The peroxy radicals undergo a range of competitive unimolecular and bimolecular decompositions, leading to a range of oxidized hexoses and products containing fewer than six carbon atoms with combinations of CH₂OH, CHO, and COOH terminal groups. Where O₂ is absent, e.g., in Ar-saturated solutions, disproportionation and water elimination reactions of the glucosidic radicals occur, with the latter leading to deoxy compounds such as 2- and 5-deoxyhexonic acids.

Insonation of lactose solutions⁷⁶ gave glucose, galactose, and galactonic acid lactones as the primary products, resulting from an oxidative splitting of the glycosidic O-linkage. Other products were qualitatively consistent with a peroxy radical mechanism, but the product complementary to galactose arising from the radical at C₄, D-xylohexos-4-ulose, was only detected at levels corresponding to a secondary product. Secondary products derived from bimolecular degradation of peroxy radicals from the primary monosaccharide product units were also detected.

Studies of the sonolysis of nucleic acid components in aqueous solution also indicated that the active species of primary importance is the •OH radical.⁷⁷ Two 2'-deoxyribonucleosides, thymidine and 3',5'-di-O-acetyl-2'-deoxyguanosine, were insonated at 30 kHz in 0.5 mM aerated solutions. Thymidine was the more sensitive by far to ultrasonic degradation and was believed to degrade via the fast addition of an •OH radical across the 5,6-alkenic bond to give the reducing 5-hydroxy-5,6-dihydrothymid-6-yl and the oxidizing 6-hydroxy-5,6-dihydrothymid-5-yl radicals in roughly 70:30 proportions (Scheme 19). These radicals are believed to undergo O₂ addition to peroxy radicals, which degrade in ways similar to those created in glucose solutions, with β-scission opening the pyrimidine ring structure. Products detected included N-(2-deoxy-β-D-erythro-pentafuranosyl)formamide, the four diastereomers of 5,6-dihydroxy-5,6-dihydrothymidine, and the 5R and 5S diastereo-

Scheme 19



mers of 1-(2-deoxy-β-D-erythro-pentafuranosyl)-5-hydroxy-5-methylhydantoin.

The effects of ultrasound on solutions of proteins, enzymes, and nucleic acids have also been investigated with a view to identifying perturbations of both structure and related biocatalytic functions.⁷⁸ A wide range of effects were recorded, including the oxidation of purine bases in nucleotides and nucleosides, modifications to cytochrome *c*, a decline in the enzymatic activity of fibrillar protein myosin caused by mechanical damage to SH functions, and modifications to desoxyribonucleoprotein such as protein deamination and changes in peptide chain lengths. However, extrapolation of these results obtained *in vitro* to *in vivo* situations is difficult.

4.6. Polymer Synthesis. Ultrasound has been applied to polymer synthesis both in organometallic reactions and in the initiation of radical polymerisation and copolymerisation. The use of ultrasound as a radical polymerisation initiator has been investigated for styrene and methyl methacrylate.^{79,80} For styrene,⁷⁹ the radical generation at 60 °C appeared dependent on the presence of a gas (Ar) sparge; under these conditions, about 0.7% of the monomer polymerised over 1 h to give a product with a molecular mass peak at 5 × 10⁵ Da. Measurements with the radical scavenger DPPH (2,2-diphenyl-1-picrylhydrazyl) indicated a radical initiation rate of 3 × 10⁻⁹ mol·L⁻¹·s⁻¹ under these conditions, an order of magnitude higher than the thermal initiation rate normally occurring at 60 °C without insonation or chemical initiators. Where the gas sparge was discontinued, the molecular mass of the polymer dropped to 1 × 10⁵ Da over 2 h, indicating some degradation.

Insonation of methyl methacrylate at 25 °C gave monomer conversions up to 13% over 3–4 h, with the molecular mass of the polymer reaching a maximum of 2.5 × 10⁵ Da after 30 min and decreasing gradually to 1.7 × 10⁵ Da after 3 h.^{80,81} Radical trapping measurements using DPPH in methyl butyrate indicated that radical initiation rates were comparable with those commonly produced by the chemical initiator AIBN [azobis(isobutyronitrile)] at 70 °C.⁸⁰ The lowering of molecular mass at extended times is believed to arise from shear effects from collapsing cavitation voids; such shear effects principally affect polymer fragments of high molecular weight and lead to a narrower distribution.⁸¹

(74) Glaze, W. H.; Kang, J. W. *Ind. Eng. Chem. Res.* **1989**, 28 (11), 1573.

(75) Heusinger, H. Sonolysis of Aerated and Deaerated Glucose Solutions. Presented at the 1st Meeting of the European Society of Sonochemistry, Autrans, Grenoble, France, Sept 30 to Oct 4, 1990.

(76) Heusinger, H. *Ultrasonics* **1990**, 28 (1), 30.

(77) Berger, M.; Cadet, J. Ultrasonic Decomposition of 2'-Deoxyribonucleosides in Aerated Aqueous Solutions. Presented at the 1st Meeting of the European Society of Sonochemistry, Autrans, Grenoble, France, Sept 30 to Oct 4, 1990.

(78) Braginskaya, F. I. Sonochemical Effects on Proteins and Nucleic Acids. Kinetics and Biochemical Implications. Presented at the 3rd Meeting of the European Society of Sonochemistry, Figueira da Foz, Portugal, March 28 to April 1, 1993.

(79) Kruus, P.; O'Neill, M.; Robertson, D. *Ultrasonics* **1990**, 28 (5), 304.

(80) Price, G. J.; Norris, D. J.; West, P. J. *Macromolecules* **1992**, 25, 6447.

(81) Price, G. J. *Adv. Sonochem.* **1990**, 1, 231.

Ultrasound also promotes the decomposition of aqueous potassium persulphate,^{82,83} which is commonly used as an aqueous-phase initiator in emulsion polymerisation. A matrix of kinetic data has been generated for decomposition between 50 and 80 °C, with and without insonation,⁸² and the data has been fitted to a model representing the thermal effects of collapsing cavities according to the hot spot theory, assuming an Arrhenius temperature dependence. A recent radical-trapping investigation⁸³ has shown that the insonated decomposition rate at 25 °C is comparable with the uninsonated, purely thermal rate at 55 °C and that some control of reaction rate by insonation intensity is possible.

Ultrasound has also been used in the preparation of block copolymers.^{84,85} A major problem in this area is the control of block sizes; ultrasound has been used to degrade polymer chains in solution⁸⁴ and to produce terminal radicals which can be used to form copolymers either by reacting with a second monomer or by combining with a second macro-radical in the same solution. Block copolymers formed *in situ* in this way can also be used to prepare compatible blends of immiscible polymers, exemplified by polystyrene with *cis*-polybutadiene or poly(methylphenylsilane).⁸⁵

A single-step insonated process has been developed for the preparation of nylon 6 from ϵ -caprolactam.⁸⁶ Conventionally, the reaction occurs in two stages, with a ring-opening and addition stage requiring water addition, and a condensation polymerisation stage eliminating water. The application of 20 kHz ultrasound enables both reactions to be carried out using commercially available caprolactam with 1% water, without the need for separate stages of water addition and elimination. Good yields of high molecular mass polymer (1.6×10^4 Da) were obtained in 8 h of processing. A tubular insonated reactor has been developed for scale-up, and some modelling work on the chemical kinetics has been undertaken. An ultrasonic technique for cross-linking polymers *in situ* in manufacturing processes has also been patented.⁸⁷

4.7. Electron Transfer Reactions. The promotion of electron transfer reaction mechanisms via radical anions at the expense of ionic S_N2 pathways has been postulated²¹ as the basis of many so-called “sonochemical switches”, where the application of ultrasound leads to changes in selectivity and reaction pathway. It may also account for some of the examples where homogeneous reactions in solution are ultrasonically enhanced, and where there is no obvious pathway via free radical formation in the solution. An example of the latter is the Meerwein–Ponndorf reduction of benzaldehyde with aluminium isopropoxide in 2-propanol. This reaction has hitherto been thought to proceed via a cyclic intermediate, and is now believed to proceed also via a radical ion transition state²⁰ (Scheme 20). We have investigated the effects of ultrasound on this reaction,²⁴ which

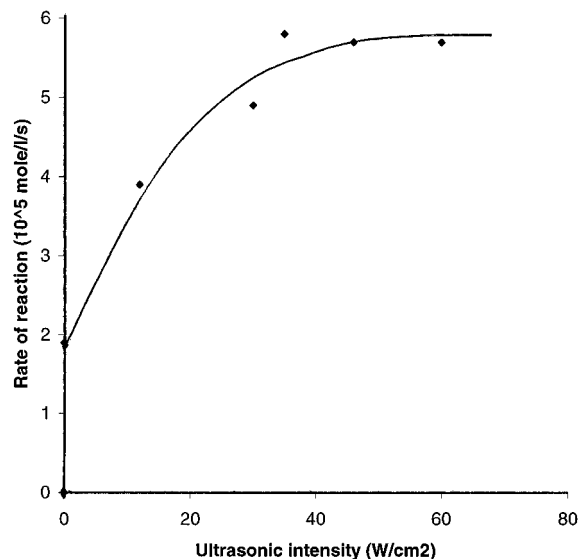
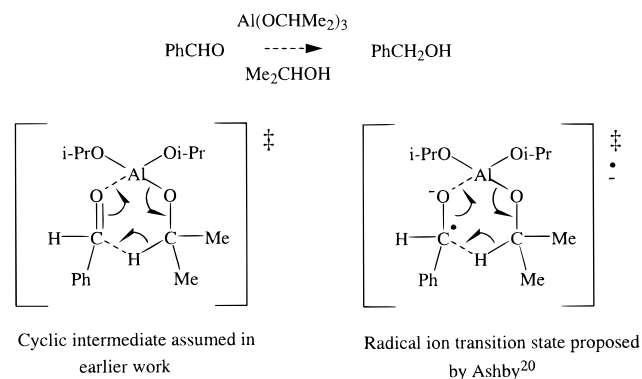


Figure 3. Effect of insonation (20 kHz) on the initial rate of the Meerwein–Ponndorf reduction of benzaldehyde, 50 °C.²⁴

Scheme 20



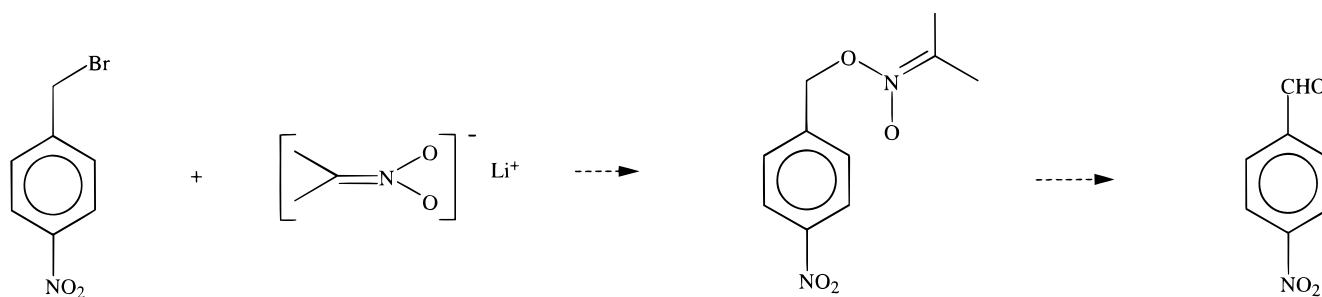
is reversible and is normally driven to completion by distilling off the by-product acetone. We did not remove the acetone product, and we measured the initial formation rate of benzyl alcohol with and without insonation. Results of the insonation of 9 mmol of benzaldehyde and 12 mmol of Al isopropoxide in 40 mL of 2-propanol at 20 kHz with a 3.2 mm probe tip at 50 °C are shown in Figure 3. The maximum initial rate enhancement was a factor of 3, with a saturation effect appearing at high intensities. At 80 °C, a similar pattern of rate enhancement to a maximum factor of 2.2 from an insonated rate of 1.5×10^{-4} mol·L⁻¹·s⁻¹ was measured. All equilibrated reaction solutions showed a 30% product yield independent of temperature and insonation-conditions. No discernible reaction occurred at 35 °C with or without ultrasound.

“Sonochemical switching” has been recorded in the Kornblum–Russel reaction of the lithium nitronate salt of 2-nitropropane with 4-nitrobenzyl bromide in deoxygenated ethanol.^{88,89} A simultaneous bielectronic mechanism gives an *O*-alkylated product that rearranges to an aldehyde (A), while a *C*-alkylated product is produced by a radical chain process⁸⁸ (Scheme 21). The radical anion intermediate in

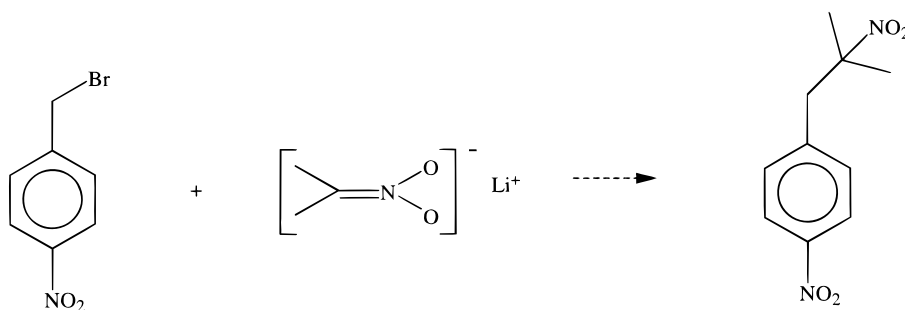
(82) Lorimer, J. P.; Mason, T. J.; Fiddy, K. *Ultrasonics* **1991**, 29 (4), 338.
 (83) Price, G. J.; Clifton, A. A. *Polymer* **1996**, 37 (17), 3971.
 (84) Smith, P. F.; Price, G. J. Synthesis and Characterization of Block Copolymers using Ultrasound. Presented at the 2nd Meeting of the European Society of Sonochemistry, Gargnano, Italy, Sept 15–19, 1991.
 (85) Price, G. J.; West, P. J. *Polymer* **1996**, 37 (17), 3975.
 (86) Ragaini, V. *PCT Int. Pat. Appl.* WO 91 18,941, Dec. 12, 1991.
 (87) Murphy, J. R. *Br. Pat. Appl.* GB 2,236,755, April 17, 1991.

(88) Einhorn, C.; Einhorn, J.; Dickens, M. J.; Luche, J.-L. *Tetrahedron Lett.* **1990**, 31 (29), 4129.

Scheme 21



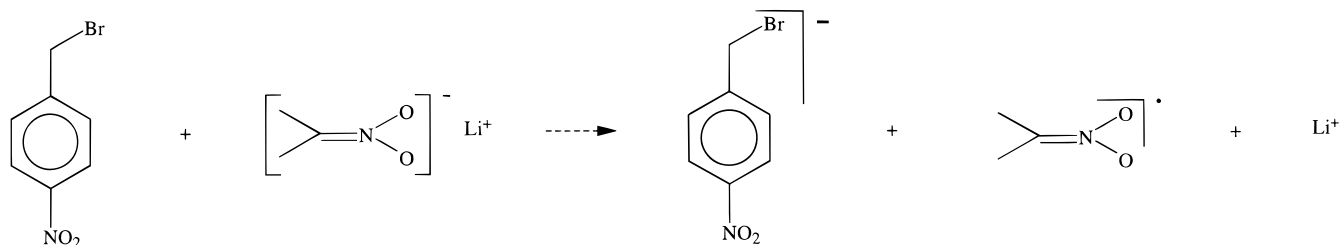
(A) O-Alkylation via bielectronic mechanism



(B) C-Alkylation via a radical chain mechanism

No insonation: 60% (A) + 13% (B)
 With insonation: 23% (A) + 48% (B)

Scheme 22

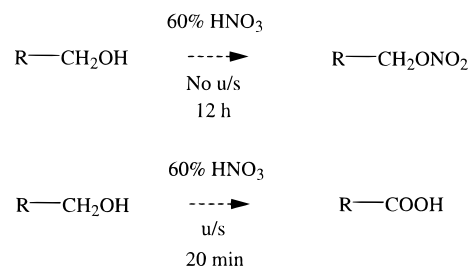


the latter case is thought to arise from an electron transfer from the nitropropane anion to the bromide⁸⁹ (Scheme 22), where one or both of the reactant species or a charge transfer complex is in an excited state.

Another reaction that is fundamentally altered by insonation is that between the primary alcohols 1-octanol and 3-bromo-2,2-dimethylpropan-1-ol and 60% HNO₃ at room temperature.⁸⁸ The stirred noninsonated reaction produced quantitative yields of the nitrate esters, while insonation induced rapid oxidation to the acids (Scheme 23). The second oxidation reaction is known to involve a protonated form of NO₂ as a radical or radical cation. Insonation of the nitrate esters did not yield the acids.

4.8. Cycloaddition Reactions. A number of Diels–Alder-type cycloadditions have been promoted by the application of ultrasound. A set of particularly dramatic results have been obtained in the synthesis of a series of tanshinones and related compounds via addition of dienes

Scheme 23



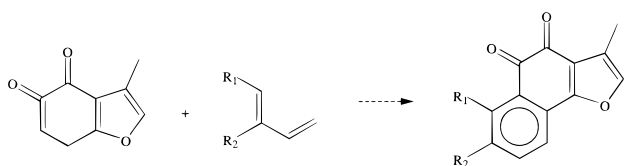
R = C₇H₁₅; BrCH₂CMe₂

to *o*-quinone dienophiles⁹⁰ (Scheme 24). With 1-vinylcyclohexene as the diene, the yield under insonation was 65% at atmospheric pressure, compared to a normal uninsonated yield of 67% under 11 kbar of pressure. A more recent and systematic study of Diels–Alder cycloaddition indicates that ultrasonic enhancement is most marked where

(89) Dickens, M. J.; Luche, J.-L. *Tetrahedron Lett.* **1991**, 32 (36), 4709.

(90) Lee, J.; Snyder, J. K. *J. Am. Chem. Soc.* **1989**, 111, 1522.

Scheme 24



quinones are the dienophiles and suggests that redox interaction between diene and dienophile gives rise to radical ion intermediates.⁹¹

The cycloaddition of quinoline-5,8-diones with 2-ethoxy-2-butenal *N,N*-dimethylhydrazone exhibited a sonochemical switch and thus provides further evidence of a radical transfer mechanism⁹² (Scheme 25). The uninsonated reaction favoured the [3 + 2] pathway and products (43%) proceeding via ionic intermediates, while insonation reversed the selectivity to give 45% of the [4 + 2] Diels–Alder products. Further chemical evidence suggested that the latter reaction proceeded via a radical mechanism.

The reaction between but-1-en-3-one (methyl vinyl ketone) and cyclopentadiene has been investigated under homogeneous conditions in trichloro-, dichloro-, and dibromomethane.⁹³ The effects of insonation on rates and product yields have been interpreted as arising from the sonolysis of the halogenated solvents to produce hydrogen halides, which subsequently catalyze the cycloaddition. Ultrasound has also been employed to enhance the rate of cycloaddition of a polar nitron function to an alkene to yield a substituted 2,3,4,5-tetrahydroisoxazole.⁹⁴

4.9. Sonoelectrochemistry. Combinations of ultrasound and electrochemistry have been employed in a number of reactions and syntheses. One application has been in the preparation of Se and Te alkyls.^{95,96} Powdered elemental chalcogen is reduced electrochemically to the anions E^{2-} and E_2^{2-} ($E = \text{Se, Te}$), which are employed *in situ* to prepare alkyl chalcogenides by nucleophilic displacement (Scheme 26). The effect of insonation was to disperse the chalcogen powders which were totally insoluble in the solvents employed.

The application of ultrasound to the electrochemical oxidation of cyclohexanecarboxylate influenced the reaction pathway and altered the product distribution.⁹⁷ The insonated reaction produced cyclohexene (32%) and methyl cyclohexyl ether (34%) via a two-electron pathway. The uninsonated reaction produced bicyclohexyl (49%), cyclohexanol (25%), and methyl cyclohexanoate (17%) via a one-electron pathway. The effect of ultrasound on the electrooxidation of phenylacetic acid that had been 50% converted to its Na

salt has also been investigated.⁹⁸ In the reaction without ultrasound, 13% pyridine had to be added to the methanol solvent to prevent anode fouling. Insonation produced a very similar effect to that of the pyridine additive, which complicated workup procedures and posed a potential environmental hazard in scale-up. The electrochemical oxidation of 4-chlorophenyl acetate followed a two-electron pathway both with and without insonation,⁹⁸ but the insonated reaction required a lower potential difference (4.82 V compared with 5.63 V) to maintain a current density of 100 $\text{mA}\cdot\text{cm}^{-2}$.

The application of ultrasound has also been found to alter the reaction pathway in the electrochemical oxidation of bis-(cyclopentadienyl)molybdenum(II) dichloride in an acetonitrile solution using Pt electrodes.⁹⁹ Without ultrasound, a simple single-electron oxidation with a half-wave potential of +0.5 V was obtained, with a much smaller second wave at +1.5 V. With insonation, the oxidation of the first wave involved more than one electron transfer, and the second wave disappeared.

4.10. Other Types of Reactions. The range of reactions to which ultrasound has been applied is very wide, and complete coverage would require a review many times longer than the present. The above has focused on cases that illustrate the mechanisms by which ultrasound may influence chemical processes. A few more general examples of the miscellaneous types of reactions and processes to which ultrasound has been applied are given below, but it is emphasized that this is illustrative and not exhaustive.

4.10.1. Oxidation and Reduction. Many oxidation reactions have been promoted by ultrasound, the majority of which involve heterogeneous phases. Examples include the oxidation of a series of alcohols, alkenes, and alkylated aromatics to aldehydes, ketones, and carboxylic acids in nonpolar solvents by KMnO_4 ,¹⁰⁰ the conversion of pyrazole aryl alcohols to the corresponding ketones with pyridinium chlorochromate (PCC),¹⁰¹ and the oxidation of a series of homoallylic sterols including cholesterol to the corresponding 2-ene-1,4-diones using tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMMO).¹⁰² Ultrasound has also been employed to accelerate the mixed-phase oxidation of naphthalene to 1,4-naphthoquinone by aqueous Ce(IV) solutions.¹⁰³

A number of heterogeneous reductions have also been promoted by ultrasound including the hydrogenations

(91) Nebois, P.; Bouaziz, Z.; Fillion, H.; Moeini, L.; Piquer, M. J. A.; Luche, J.-L.; Riera, A.; Moyano, A.; Pericas, M. A. *Ultrason. Sonochem.* **1996**, *3* (1), 7.

(92) Nebois, P.; Fillion, H.; Luche, J.-L. Diels–Alder Reaction of 2-Ethoxy-2-Butenal-*N,N*-Dimethylhydrazone with Quinoline-5,8-diones. Its Mechanism Revealed by Sonochemical Methods. Presented at the 2nd Meeting of the European Society of Sonochemistry, Gargnano, Italy, Sept 15–19, 1991.

(93) Caulier, T. P.; Reisse, J. *J. Org. Chem.* **1996**, *61* (7), 2547.

(94) Borthakur, D.; Sandhu, J. *J. Chem. Soc., Chem. Commun.* **1988**, 1444.

(95) Degrand, C.; Prest, R.; Nour, M. *Phosphorus Sulfur Relat. Elem.* **1988**, *38*, 210.

(96) Mason, T. J.; Lorimer, J. P.; Walton, D. J. *Ultrasonics* **1990**, *28* (5), 333.

(97) Chyla, A.; Lorimer, J. P.; Mason, T. J.; Smith, G.; Walton, D. J. *J. Chem. Soc., Chem. Commun.* **1989**, 603.

(98) Walton, D. J.; Chyla, A.; Lorimer, J. P.; Mason, T. J. *Synth. Commun.* **1990**, *20* (12), 1843.

(99) Compton, R. G.; Eklund, J. C.; Page, S. D.; Rebbitt, T. O. *J. Chem. Soc., Dalton Trans.* **1995**, No. 3, 389.

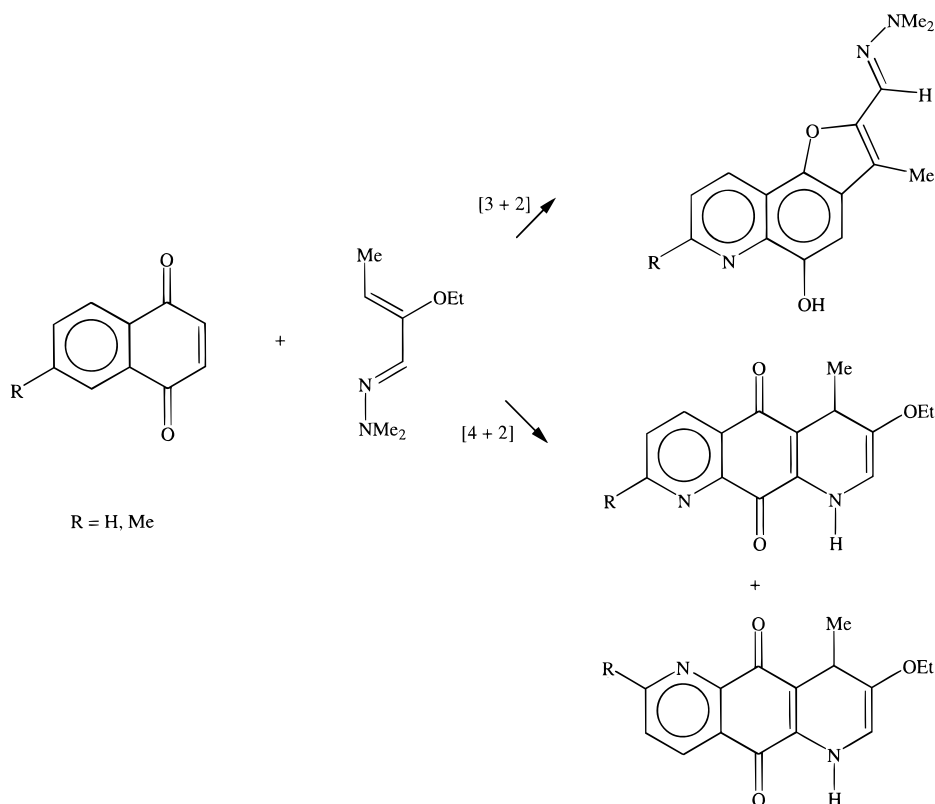
(100) Ando, T.; Kimura, T. *Ultrasonics* **1990**, *28* (5), 326.

(101) Murray, W. V.; Hadden, S. K.; Wachter, M. P. *J. Heterocycl. Chem.* **1990**, *27* (7), 1933.

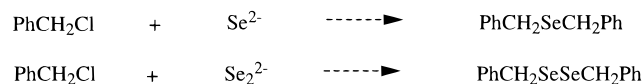
(102) Moreno, M. J. S.; Sa e Melo, M. L.; Campos Neves, A. S. *Tetrahedron Lett.* **1991**, *32* (27), 3201.

(103) Ikeda, N.; Sugishima, M.; Fujii, Y.; Ikuta, S.; Nakanishi, Y.; Inoue, A. *Jpn. Kokai Tokkyo Koho JP 63,264,428*, 1988.

Scheme 25



Scheme 26



promoted by heterogeneous catalysts described above. Others include the Clemmensen reduction of carbonyls to methylene functions¹⁰⁴ and reductions using Zn and acetic acid. The latter have been applied to the reduction of α -enone systems to alkenes and allylic alcohols in steroid synthesis¹⁰⁵ and to the selective hydrogenation of the C=C alkene bond in a number of α,β -unsaturated γ -dicarbonyl compounds.¹⁰⁶

4.10.2. Preparation of Transition Metal Complexes.

Ultrasound has been employed to promote the formation of a range of ferrilactone complexes by treatment of vinyl epoxides with $\text{Fe}_2(\text{CO})_9$ in THF solution.¹⁰⁷ The ferrilactones may be subsequently converted to biologically active lactones and lactams by oxidation, reduction, and reaction with CO or amines. Butene-1,4-diols have also been employed as alternative starting materials in place of the vinyl epoxides.¹⁰⁸

An ultrasonic dispersion of K metal in THF has been used to prepare the metalates $[\text{M}(\text{C}_5\text{Me}_5)(\text{CO})_n]^- \text{K}^+$ from the dimers $[\text{M}(\text{C}_5\text{Me}_5)(\text{CO})_n]_2$ (M = Fe, Ru, $n = 2$; M = Mo, n

= 3).¹⁰⁹ Under noninsonated conditions the reaction proceeded very slowly due to surface passivation of the metal, and it required 3 days at 20 °C with excess NaK alloy. The insonated reaction required only 30 min. The metalate was reacted *in situ* with an electrophilic haloalkane RX (X = I, Br, Cl) to yield the corresponding alkyl $[\text{M}(\text{C}_5\text{Me}_5)(\text{CO})_n\text{R}]$ at yields of 80–95%. A similar dispersion of K in an 80:20 toluene–THF mixture has been used to prepare the (pentaphenylcyclopentadienyl)iron(II) cationic complex $[\text{Fe}(\eta\text{-C}_5\text{Ph}_5)(\text{CO})_2(\text{C}_2\text{H}_4)]^+ \text{PF}_6^-$ from $[\text{Fe}(\eta\text{-C}_5\text{Ph}_5)(\text{CO})_2]\text{Br}$ and diiodoethane.¹¹⁰

Insonation has also been applied to the preparation of Ni(0) complexes with 2,2'-bipyridyl and cyclic oligoalkenes.¹¹¹ Preparations of $[(\text{bpy})\text{Ni}(\text{cyclooctadiene})]$ and $[(\text{bpy})\text{Ni}(\text{cyclododecatriene})]$ from $\text{Ni}(\text{acac})_2$, bpy, oligoalkene, and Na proceeded to 77–84% yields on insonation, compared to 15% under comparable conditions without insonation. The synthesis of monoalkylgallium diiodides $[\text{RGaI}_2]$ on insonation of I_2 , haloalkane, and Ga under N_2 at temperatures above the melting point of the latter (30 °C) have also been reported.¹¹²

Ultrasound has been employed in the synthesis of ruthenium–arene complexes. Insonation of $[(\text{C}_6\text{H}_6)_2\text{Ru}_2\text{Cl}_4]$ with Zn dust in dichloromethane under 2 bar of ethene at –10 °C gave a 50% yield of the mononuclear diethene

(104) Preston-Reeves, W.; Murray, J. A.; Wayne, D. *Synth. Commun.* **1988**, 18, 1961.

(105) Salvador, J. A. R.; Sa e Melo, M. L.; Campos Neves, A. S. *Tetrahedron Lett.* **1993**, 34 (2), 357.

(106) Marchand, A. P.; Madhusudham Reddy, G. *Synthesis* **1991**, No. 3, 198.

(107) Ley, S. V.; Low, C. M. R. *Ultrasound in Synthesis*; Springer-Verlag: New York, Berlin, Heidelberg, 1989.

(108) Bates, R. W.; Diez-Martín, D.; Kerr, W. J.; Knight, J. G.; Ley, S. V.; Sakellariadis, A. *Tetrahedron* **1990**, 46 (11), 4063.

(109) Roger, C.; Tudoret, M. J.; Guerschais, V.; Lapinte, C. *J. Organomet. Chem.* **1989**, 365 (3), 347.

(110) Brégañt, P.; Hamon, J. R.; Lapinte, C. *J. Organomet. Chem.* **1990**, 398 (3), C25.

(111) Walther, D.; Pfüetzenreuter, C. *Z. Chem.* **1989**, 29 (4), 146.

(112) Green, M. L. H.; Mountford, P.; Smout, G. L.; Speel, S. R. *Polyhedron* **1990**, 9 (22), 2763.

complex $[(C_6H_6)Ru(C_2H_4)_2]$.¹¹³ The related complex containing the *p*-cymene ligand in place of benzene was prepared in exactly the same way. Under similar conditions, but with an atmosphere of H_2 , the tetranuclear cluster $[(cymene)_4Ru_4H_4]^{2+}$ was formed. Insonation of the dimeric $[(arene)RuCl_2]_2$ with amines at room temperature gave mononuclear products, e.g., $[(C_6H_6)RuCl_2NH_2R]$ ($R = Et, C_6H_4Me, CMe_3$), resulting from simple ligand addition and dimer

cleavage.¹¹⁴ Reaction with the azide Me_3SiN_3 under the same conditions resulted in a simple Cl elimination to give $[(arene)Ru(N_3)Cl]_2$.

Received for review July 2, 1997.[⊗]

OP9700340

(113) Bates, R. S.; Wright, A. H. *J. Chem. Soc. Chem. Commun.* **1990**, No. 16, 1129.

(114) Bates, R. S.; Begley, M. J.; Wright, A. H. *Polyhedron* **1990**, 9 (8), 1113.

[⊗] Abstract published in *Advance ACS Abstracts*, November 15, 1997.