Ultrasound

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Forcing and Controlling Chemical Reactions with Ultrasound**

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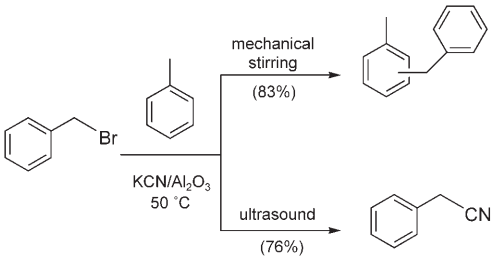
If one asks any synthetic sonochemist about the possibility of obtaining distinctive results, other than under conventional conditions, by applying ultrasound to a chemical reaction, he or she will probably give you the same answer: perhaps. This could seem surprising as sonochemistry has proven during the past two decades to be an invaluable and unique tool for, to name a few, the fabrication of nanomaterials,[1] the formation of polymers[2] as well as their controlled degradation,[3] in green technologies,[4] and more recently for promoting supramolecular aggregation.[5]

These remarkable effects can be reasonably interpreted in terms of the physical phenomenon called acoustic cavitation, that is, formation, growth, and collapse of micrometer-sized bubbles when a pressure wave of enough intensity propagates through a liquid. Such a collapse is actually a quasi-adiabatic process resulting in the generation of high temperatures and pressures within the nanosecond scale and with extreme cooling rates ($>10^{10}\,\mathrm{K\,s^{-1}}$). Acoustic cavitation is also accompanied by the emission of light (sonoluminescence) and mechanical effects.

However, the pluses of sonication observed with macromolecular entities and nanoparticles often represent its Achilles' heel at a discrete molecular level. One may certainly state that cavitation generates sufficient kinetic energy to break chemical bonds, but unlike light, heat, or electromagnetic radiation, ultrasound is a nonquantum energy and cavitation is a complex, nonlinear phenomenon. Although a series of empirical rules have been proposed to rationalize reactivity in an acoustic field, they should be used with caution.[6]

However, in some cases, application of ultrasound may completely change the distribution of products or even cause the formation of new substances. The first example in which ultrasound induced a divergent pathway relative to thermal conditions was reported by Ando et al. more than two decades ago.[7] By using alumina-supported potassium cyanide as a catalyst in toluene suspension, benzyl bromide gave, with stirring at 50°C, the regioisomeric diphenylmethanes, whereas sonication (45 kHz) of the same reagents under identical conditions produced benzyl cyanide (Scheme 1). Thus, ultrasound completely switched the mechanism from an aromatic electrophilic substitution (Friedel–Crafts reaction) to an aliphatic nucleophilic substitution.



Scheme 1. The original sonochemical switching.

The origin of this switch is not yet fully understood; early studies with poisoning agents suggested that ultrasound modifies the structure of catalytic sites, thereby inhibiting the aromatic substitution. However, benzyl cyanide might also be formed by a single-electron-transfer pathway as ultrasound often enhances a radical component when simultaneously competitive polar and electron-transfer mechanisms emerge.[6] Since then, other examples of sonochemical switching have been reported and analyzed,[8] although the role of ultrasound is not always unambiguously determined to be either a truly chemical or a purely physical activation.

It is in the latter physical context that mechanical shocks resulting from the cavitational collapse could provide chemical consequences as well. In a brilliant piece of work, Moore and coworkers have initiated an electrocyclic ring opening by ripping bonds apart with ultrasound.[9] The authors first computed the effects of molecular deformation on *cis*- and *trans*-1,2-dimethoxybenzocyclobutenes by pulling the methoxy groups in opposite directions, which would cleave the four-membered ring. Although stress-induced bond cleavage has been employed in organic chemistry,[10] these processes have only found synthetic application with polymers.

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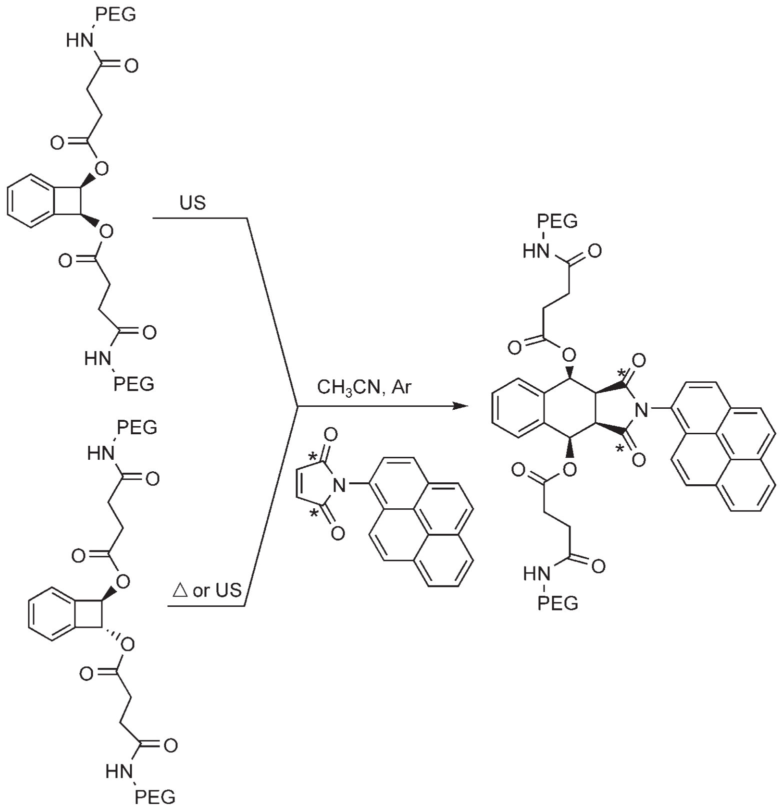
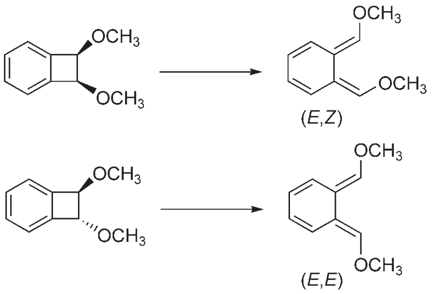
Accordingly, Moore and co-workers rightly reasoned that a small benzocyclobutene would be rather inert to mechanical activation, but that this activation could be amplified by incorporating two functionalized polymer chains attached at either side of the cyclobutene unit, thus leading to bond cleavage.[9] In other words, the polymers could channel ultrasound-induced stress into a target bond. To this end, *cis*- and *trans*-benzocyclobutene derivatives bearing terminal carboxylic acid groups were coupled to an amino-functionalized poly(ethylene glycol) to afford functionalized polymers that were then subjected to ultrasonic irradiation (probe system with pulsed sonication: 20 kHz, 8.7 $\mathrm{W\,cm^{-2}}$, 6–9 °C, CH_3CN solutions). In principle, this transformation could be synthetically useful, but is not particularly relevant because, after all, the same benzocyclobutene derivative can be fragmented by either heat or light through a well-known electrocyclic ring cleavage. However, experimental verification by using ultrasonic waves gave surprising and quite unexpected results as both *cis* and *trans* isomers yielded the same isomeric diene ((*E*,*E*)-*ortho*-quinodimethide diene) as could be deduced from the isolated quenching products (Scheme 2).

This goes against a tenet of theoretical chemistry: the principles of conservation of orbital symmetry.[11] A *trans* isomer should undergo a conrotatory motion to yield the *E*,*E* diene, whereas the *cis*-cyclobutene gives only the *E*,*Z* diene, both of which are consistent with the atomic motions for thermally allowed pathways (Scheme 3). In contrast, the photochemically allowed cyclobutene–1,3-diene rearrangement is disrotatory in either direction according to the Woodward–Hoffmann rules.



Scheme 2. Unusual cyclobutene fragmentation induced by ultrasound (PEG denotes a poly(ethylene glycol) polymer and the stars mark positions isotopically labeled with ^{13}C atoms). US = ultrasound.



Scheme 3. Thermally allowed conrotatory electrocyclic ring openings.

Activation by ultrasound apparently induces a disrotatory motion in the *cis* isomer and a conrotatory opening in the *trans* isomer, leading to the same (*E*,*E*)-*o*-quinodimethide intermediate. However, it was difficult to prove by conventional analytical methods that bond cleavage had occurred at the small benzocyclobutene fragment as the larger polymer chains with typical M_w = 40 kDa will overshadow the tiny signals from the reactive site. In a clever choice, these reactions were performed in the presence of the dienophile *N*-(1-pyrenyl)maleimide as a trap, which was further labeled with ^{13}C atoms at the carbonyl positions (see Scheme 2). The pyrene label allowed the reaction to be monitored by gel permeation chromatography with ultraviolet detection, and the ^{13}C enrichment also enabled detection by NMR spectroscopy. Both benzocyclobutene stereoisomers showed the same single peak, that is, the maleimide trapped the same product irrespective of which stereoisomer was used.

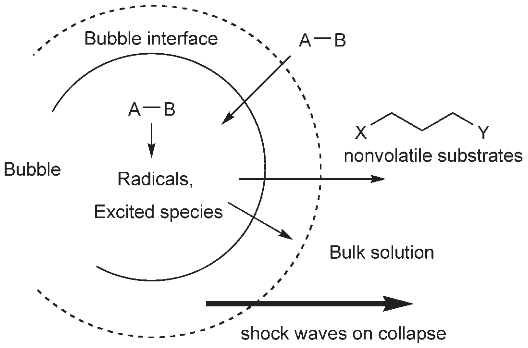
How does ultrasound induce this distinctive, formally forbidden pathway? In their conclusive statements, Moore and co-workers suggest that mechanical forces are capable of altering the shape of the potential energy surfaces, thereby biasing the reaction pathway towards products that would otherwise be disfavored under other physical influences.[9a]

The relationship between sonochemistry and tribochemistry (the study of chemical transformations arising from mechanical stresses) is not new, although the picture is complex and most studies have been focused on solids.[12] Shock waves produced upon microbubble collapse, both at the interface and in bulk medium induce shear forces as violent as those of other mechanical shocks. Likewise, collapse near a solid causes microjets to hit its surface. Although shocks will ultimately produce heat, physicochemical transformations may take place at a molecular level if mechanical energy is transferred faster than heat is evolved. Other explanations suggest that tribochemical effects can be attributed to accumulation of energy in lattice defects, which can relax either by emission of heat or by the ejection of atoms, electrons, formation of excited species, or bond breakages.

Sonochemistry in solution can often be rationalized in terms of the hot-spot theory: solutes with enough volatility can be vaporized into the bubble where they undergo pyrolytic cleavage with the formation of radical or excited species. These species may induce subsequent reactions with less-volatile substrates at the bubble shell or in the bulk medium, not mentioning the intense shock waves that form upon collapse (Scheme 4).[13]

In a few cycloadditions in which the diene might be oxidized to its radical cation, a positive sonochemical effect has been observed.[14] In the present case however, given the low volatility of the substrates, the reactions should not be occurring in the microreactor bubble and a purely thermal interpretation seems inadequate, whereas the mechanochemical hypothesis appears to be plausible. In fact, Moore and co-workers demonstrated by ^{13}C NMR spectroscopic analysis that the Diels–Alder adduct was present in the uncleaved polymers, thus revealing that activation occurs without fragmentation. However, this need not be the last word; the orbital-symmetry rules apply only to concerted reactions, and this fascinating result might be consistent with paths other than violation of the Woodward–Hoffmann rules.

It seems that in answering one important question, Moore and co-workers have raised many more. This model study should, however, motivate further work aimed to uncover the intimate link between ultrasound and mechanochemistry.



Scheme 4. The cavitational bubble as a chemical microreactor.

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