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Perspective

Sonochemistry of carbohydrate compounds

Nathalie Kardos,* Jean-Louis Luche

Laboratoire de Chimie Moléculaire et Environnement[†], *Université de Savoie-ESIGEC, Technolac, F-73376 Le Bourget du Lac, France*

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Dedicated to Professor Ralf Miethchen on the occasion of his 60th birthday

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Abstract

A literature survey of carbohydrate sonochemistry is presented. The basic physical principles are discussed qualitatively before the main applications are reviewed. Along with other non-classical activation methods developed in accordance with 'Green Chemistry' requirements, ultrasonic irradiation offers important potential for the conversion of biomass raw materials such as polymeric carbohydrates to useful lower weight molecules. A number of reactions involving mono- or disaccharides, considered as a renewable source of fine chemicals, can also be performed with ultrasonic activation. This is the case for glycosylation, acetalization, oxidation, C–D, C-heteroatom, and C–C bond formations, which are improved in terms of reaction rates and yields and, in some instances, in their chemo-, regio- and stereoselectivities. The equipment available is briefly described, and practical considerations are given.

Keywords: Ultrasound; Carbohydrates; Physical principles; Homogeneous and heterogeneous media; Synthetic methods; Practical references

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* Corresponding author. Tel.: +33-479-758602; fax: +33-479-758885.

E-mail address: nathalie.kardos@univ-savoie.fr (N. Kardos).

[†] Web page for this laboratory: http://www.univ-savoie.fr/labos/lcme/lcme-gb.htm.

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1. Introduction

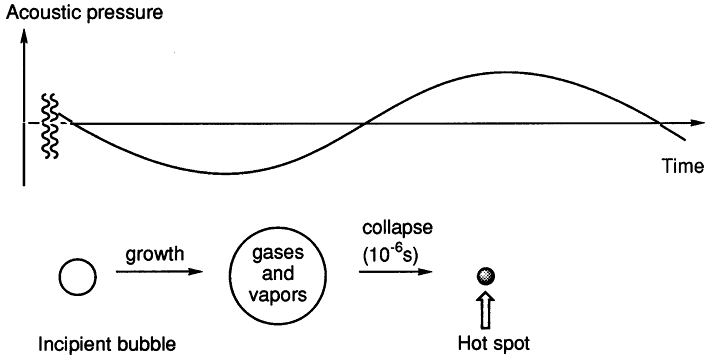
1.1. Scope and intent.—In their continuous search for improved synthetic pathways, chemists have developed a vast array of activation methods, the most popular being chemical catalysis. Recent emphasis has been given to 'unconventional' physical agents, for instance, high pressures, microwaves, supercritical fluids, and ultrasound.[1a–d] The respective advantages and limitations of each of these techniques can be found in reviews[2a–d] and in a book.[3]

Non-conventional chemistry appears to offer important possibilities in the arsenal of environmentally friendly synthetic methods,[4] especially in connection with the emerging concept of 'Green Chemistry'.[5] The objectives are the reduction of wastes, the design of non-polluting products and processes, and an optimal use of materials, especially renewable resources from biomass.

Based on the above, it is reasonable to envisage, for example, the combination of carbohydrates as the source of starting materials, with sonochemistry as a tool, in the design of original synthetic pathways.[6] This approach was sketched as early as 1933,[7] i.e., only a few years after the first paper by Richards and Loomis devoted to the chemical effects of ultrasound.[8] This relatively small-time gap demonstrates that the potential of this activation method, in years where this notion was not yet timely, was recognized very soon, especially for biphasic systems. A ready access to valuable compounds, as pharmaceuticals, drugs, food additives, and now, fine chemicals, is indeed made easier by using sonochemical methods.

The purpose of this review is to collect the papers scattered in the chemical literature between publications of general interest (organic synthesis, polymers) and more specialized journals related to carbohydrate chemistry and sonochemistry. However, before reaching this stage, a few basic principles which govern the chemical action of acoustic waves will be discussed.

1.2. Principles of sonochemistry.—At the very beginning, an important point must be emphasized: acoustic waves, of purely mechanical nature, should not be confused (as it is still found in the literature) with the electromagnetic microwaves. Since the acoustic energy cannot be absorbed by molecules, it must be transformed to a chemically usable form via the indirect, complex phenomenon known as cavitation. Beyond an intensity threshold, acoustic waves can break the cohesion of a liquid and create microcavities.[9] From an initial submicron size, gas bubbles trapped in the liquid or on solid surfaces grow to a few tens of microns and become unstable. Collapse occurs on a very short time scale (estimated to 1/5 cycle). In the 20–50 kHz range, used in many applications (the 'low' frequency domain reaches to 100 kHz), this corresponds to ca. 10^{-6} s, short enough to lead to intense heating in the residual bubble, i.e., a 'hot spot' (Scheme 1).



Scheme 1.

Transient temperatures of at least 5000 K,[10,11] and pressures up to 1200 bars have been calculated. Consequently, under these extreme conditions, sufficiently volatile molecules vaporized into the gas phase are thermolyzed to free radicals, followed by very fast cooling (> 10^{10} K/s).[12] An extensively studied reaction is the sonolysis of water, which produces hydroxyl radicals and hydrogen atoms (Scheme 2).[13,14] This initial reaction can be followed by the formation of hydrogen peroxide and, in the presence of oxygen, hydroperoxyl radicals. These species are responsible for the oxidative properties of sonicated aqueous solutions, as illustrated below (see Sections 2.1.2 and 2.2). The efficiency of this homolytic cleavage appears to be improved by increasing the frequency,[15] from 100 kHz up to 1.7 MHz (the 'high' frequency domain).

The collapse also generates shock waves[16] which induce mechanical effects, even in homogeneous media. If this phenomenon is too fast to alter small molecules, it is likely to increase the splitting of less mobile polymers to smaller fragments, including radicals, by the resulting shear forces (see Section 2.1.1). Combined with the propagation of the waves, these pressure peaks produce intense mixing[17] and some heating (see Section 3.2).

Next to the interface of biphasic systems the collapse occurs dissymmetrically, with a liquid jet crossing the cavity at a velocity reaching several hundreds of m/s. Small particles, solid or liquid, are ejected by the impact (Scheme 3).

In a liquid–liquid system, emulsions are produced, generally more stable than those formed conventionally.[1d] Solids undergo fragmentation and/or erosion, enlarging the activated areas.[18] Cavitation also accelerates mass transport[19] and diminishes repassivation by the reaction products.[20,21] The overall result, of interest to chemists who attempt heterogeneous reactions, is the much easier contact between immiscible or poorly soluble reactants. These mechanical effects usually predominate over free radical production, with the consequence that the potentially competitive sonolyzes in the liquid phase can usually be neglected.

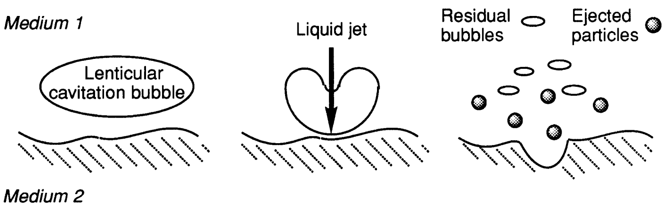
Due to these highly energetic conditions, it was anticipated that many chemical reactions should be activated by sonication. However, numerous attempts failed, making necessary a careful screening of the application domain. A decisive finding, 'sonochemical switching'

$$H_2O \xrightarrow{))))} H^\bullet + HO^\bullet$$

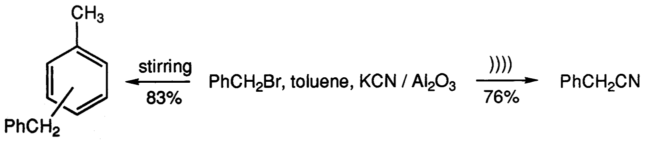
$$HO^\bullet + HO^\bullet \longrightarrow H_2O_2$$

$$H^\bullet + O_2 \longrightarrow HO_2^\bullet$$

Scheme 2.



Scheme 3.



Scheme 4.

(Scheme 4),[22] established that sonication can change the nature of reaction products, in homogeneous[23a–c] and heterogeneous systems as well.[24a–d]

Such qualitative changes cannot result only from improved mixing. Cavitation, then, must induce a specific chemical reactivity, rationalized by empirical rules.[25] In general, sonication of solutions enhances free radical processes, leaving polar ones mostly unaffected. In biphasic systems, in which reactions can follow either a polar or a monoelectronic mechanism, ultrasound favors the second one, but the mechanical component still present adds to the chemical activation. This synergetic effect occurs in the presence of metals, at least in some instances.[26] If only a polar pathway can exist, the net effect will be limited to the mechanical effects of cavitation with rate and yield improvements, but no sonochemical switching.

2. Sonochemistry of carbohydrates and derivatives

In line with the preceding principles, sonochemical methods are potentially useful in carbohydrate chemistry. First, the mechanical effect of the acoustic waves improves heterogeneous reactions, e.g., of simple or polymeric sugars, in terms of smoother experimental conditions reducing the need of expensive or polluting solvents. Second, due to the easy formation of transient reactive species (radicals), new transformations can be designed.

Most of the initial work was dedicated to phenomenology, i.e., what occurs when a given compound is irradiated by acoustic waves. However, some authors indicated clearly the potential applications, in particular for the ultrasound-induced partial or total depolymerization of natural polysaccharides. These aspects will be presented first, before the discussion of recently developed synthetic applications, using the simpler, better-defined mono- or disaccharides.

2.1. Hydrolysis and cleavage of di- and polysaccharides.—Polysaccharides, as a quantitatively and qualitatively important source of useful carbohydrates, cannot be used as such for many chemical or biological applications. A treatment aimed at depolymerization (partial or total) is therefore a prerequisite, and hydrolytic procedures have been extensively studied to achieve this goal.

2.1.1. Polysaccharides

2.1.1.1. Starch: The first notes dealing with ultrasound-assisted carbohydrate chemistry, published in 1933, describe qualitatively, the hydrolysis of aqueous starch, gum arabic, and agar. At a frequency of 722 kHz shorter chain molecules are produced as indicated by viscosity measurements.[27,28] When audible sounds (1–15 kHz) are used, some reducing sugar(s) are also formed.[7] On the other hand, starch is totally depolymerized to glucose under ultrasonic assistance with sulfuric acid as the catalyst,[29] even at 23 °C.[30,31] Most recently, a reliable and rapid dosage method of total carbohydrates in environmental (seawater and marine mucilage) and food (cereals) samples was proposed.[32] Standard procedures require prolonged contact of starch and several complex polysaccharides with strong acids frequently under heating, or difficult enzymatic pre-treatment. Common oxidation side-reactions can be avoided by employing an ultrasonic cleaning bath (35 kHz) operated at room temperature in a first step. Oligosaccharides, rapidly obtained in neutral medium, are then quantitatively hydrolyzed to monosaccharides (based on the Dubois colorimetric technique) at 25–30 °C in 90 min.

The ultrasound-mediated enzymatic depolymerization of starch has been studied, constituting one of the rare examples of using enzymes in sonochemistry.[33] Unexpectedly, at low acoustic power, some enzymes are not deactivated, whether supported on porous silica gel[34] or free [alpha-amylase (EC 3.2.1.1), glucoamylase (EC 3.2.1.3)].[35] Sonication in a cleaning bath increases the hydrolysis rate (1.2–2 times), even at high substrate concentration (50 g/L), probably because of better mixing and diffusion of the components.

2.1.1.2. Dextran: Partially depolymerized dextrans, of great interest in medicine as plasma expander adjuvants, can be produced, among other methods (extrusion, jet-cook-ing),[36] from the sonochemical degradation of native dextrans. It is believed that hydrodynamic shear forces, generated by low-frequency cavitation, are able to split, homolytically or heterolytically, macromolecules mid-chain in a non-random way.[37] Statistical recombinations of the fragments lead to a narrower mass distribution, resulting from the easier cleavage of the larger molecules and the relative inertness of the smaller ones. Several investigations have provided a better understanding to this reaction, demonstrating the influence of the solvent,[38,39] the initial molecular size (10^4–10^7 D),[40–42] the acidic catalysis,[42] the reaction temperature (30–70 °C),[43], the concentration of polysaccharide (2–10%),[39,43] the acoustic power (20–60 W),[43] and the frequency (35 kHz–1.6 MHz).[41] In short, these results illustrate the advantages of using low frequencies at room temperature for the degradation of relatively dilute polymer solutions.

2.1.1.3. Cellulose derivatives and other polysaccharides: Shear degradation of rayon,[44] and hydroxyalkyl cellulose derivatives[45,46] has been conducted under low frequency sonication, varying the other parameters as for dextran.[46] Similar behavior is observed leading to lower weight polymers and oligomers, with conservation of the primary structure. NMR spectroscopy of the sonochemical hydrolyzate of carboxymethylcellulose permits characterization of the structure of the polymeric chain. If the acidic and enzymatic hydrolyzes provide data on the regularity of the substitution,[47] by using ultrasound, a partial degree of substitution could be attained quantitatively for the first time without oligomers formation and side group cleavages.[48]

A comparative study of the progressive depolymerization of sodium hyaluronate under acoustic and enzymatic activation has shown the potential advantage of the former for generating controlled lower molecular weight polysaccharides with retained general chemical structure.[49] The characterization of ι- and κ-carageenans has also been carried out on ultrasonically pre-treated samples,[50] leading in the latter case to a novel liquid crystalline phase.[51]

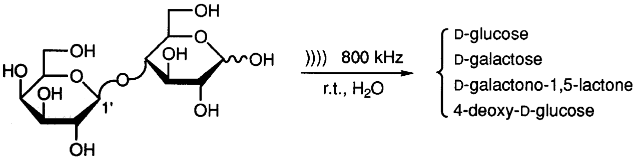
The effect of ultrasound has also been studied on chitosan under various experimental conditions,[52] on xanthan,[53] chitin,[54] native cinerean,[55] carboxymethyl derivative of β-(1 → 3)-D-glucan,[56] carboxymethylated chitin-glucan,[57,58] seemingly with the purpose of structural elucidation,[53,55,56,58] and lower weight molecules production.[52,54,57] From the latter perspective, sonolysis of heparin at 800 kHz leads to potentially useful antithrombotic agents.[59]

2.1.2. Disaccharides

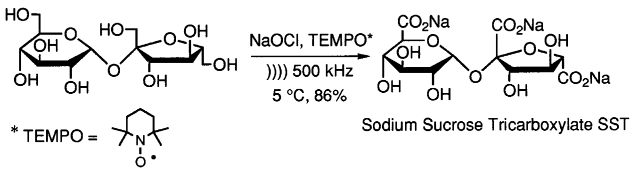
2.1.2.1. Sucrose: In the case of disaccharides, the first studies were performed in 1933 on sucrose.[7,27,28] Under neutral conditions, sonolytic cleavage occurs faster and more smoothly than under conventional reflux, and the addition of a trace of acid leads to almost instantaneous hydrolysis. Similar observations were again made in 1970[60] during investigations of the influences of several parameters. The rate increases in line with the acoustic power and frequency (to 1 MHz), and the yield of glucose reaches 95% (the amount of fructose is not mentioned). From comparative experiments, conducted with added formic acid, it can be concluded that the breakage of the glycosidic linkage is not a direct effect of sonication but proceeds via the in situ formation of a small amount of this acid. The latter probably results from the oxidation of the organic solutes by the hydroxyl radicals generated by water sonolysis (see Scheme 2), accounting for the missing 5% of glucose. This explanation is consistent with the higher reaction rate when the solution is saturated by oxygen.

Other kinetic studies show that sonication increases by 130–150% the activity of the enzyme invertase (EC 3.2.1.26) in buffered acidic solutions of sucrose (0.1 M at 815 kHz[61] to 0.7 M in a cleaning bath[35]). Besides the possible dispersion of the hydrogen-bonded clusters, the larger mechanical effect at low frequency can account for the rate enhancement in more viscous solutions.

2.1.2.2. Lactose and other disaccharides: Lactose-hydrolyzed milk products are essential for people who cannot tolerate lactose. Dur-



Scheme 5.



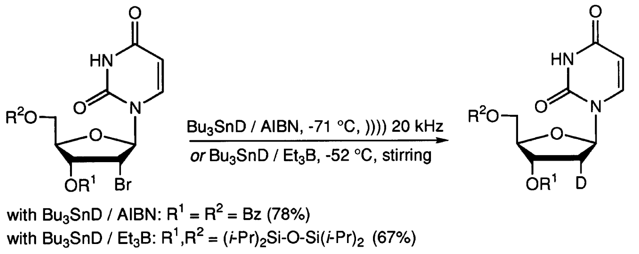
Scheme 6.

ing the milk fermentation process using lactic acid bacteria, the efficiency of a 200 kHz transducer has been proved.[62] It appears that intracellular β-galactosidase is released from the cells by ultrasound, thus decreasing by 60% the lactose content (compared with 35% in the control experiment). The scission of the glycosidic linkage can occur also, purely sonochemically in addition to enzymatically. Indeed, from a mechanistic viewpoint, the radical at C-1′ seems to be a key intermediate in both the sonolysis at 800 kHz and the γ-radiolysis of several disaccharides, like lactose in aerated aqueous solutions.[63,64] This first-generated and predominant intermediate undergoes mainly hydrolysis, with fragmentations remaining of minor importance, as judged from the GC analyses and the reported energetic yields (hydrolysis/fragmentation *G*-value ratios: 8.2 for sonolysis, and 4.2 for radiolysis) (Scheme 5).

2.2. Oxidative reactions.—In line with the work discussed above, glucose in aerated solutions irradiated under the same conditions[63,64] reacts with hydroperoxyl radicals (Scheme 2).[65,66] This oxidative reaction leads essentially to glyceric acid, ribonic acid γ-lactone, xylose and tartaric monoaldehyde. In contrast, cleavage of the carbon skeleton is minimized when sonolysis (800 kHz, 5 °C, 2 days) is performed on deoxygenated aqueous solutions. Gluconic acid, hexosuloses, hexodialdoses and deoxy sugars were identified as the major products.[67]

These processes cast light on some undesired oxidations, whose synthetic applications appear difficult, due to their low selectivity. However, useful reactions can be designed by alternate sonochemical methods. For example, hexoses are oxidized to the corresponding uronic acids, glucose being chemoselectively oxidized to glucuronic acid in aerated aqueous solution at 100 kHz with a catalytic amount of $FeSO_4$ in 6 h. This reaction does not take place without oxygen or acoustic activation.[68] Another efficient system has recently received attention. It consists of the TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy radical)-catalyzed oxidation of primary hydroxyl groups by bleach.[69] The role of cavitation in this homogeneous system is essential, most probably for the formation of the actual oxidizer, the nitrosonium ion, directly from TEMPO with excess sodium hypochlorite in the presence of sodium bromide. The first case studied was methyl α-D-glucopyranoside as a model, which is transformed to the uronate in 87% yield at 20 kHz. The reaction was further extended to sucrose leading to the corresponding tricarboxylate (SST), expected to display complexing properties for alkali earth cations, in 59% yield. Significantly, the glycosidic linkage of sucrose remains stable in this process. The yield is increased to 80% by irradiation at 500 kHz. The next optimization step aimed to omit sodium bromide. Experiments proved to be successful, especially at 500 kHz.[70] The best yield (86%) was obtained by continuous sonication of the oxidizing mixture before and after addition of sucrose (Scheme 6). This result, together with the enhanced efficiency of the high frequency (known to generate radicals in higher amounts[15]), led the authors to propose the existence of transient species (e.g., atomic or molecular chlorine). In any case, this procedure has significant synthetic value.

2.3. Formation of carbon–deuterium bonds.—Deuterium labeled sugars and glycolipids, useful for the elucidation of cellular metabolism, are conventionally prepared in refluxing D_2O in the presence of Raney–Nickel. The high temperature and the long incubation times are responsible for low regioselectivities and racemization. The desired H → D exchange takes place with complete retention of configuration in (5:1) THF–D_2O at 40 °C using the same catalyst and a direct



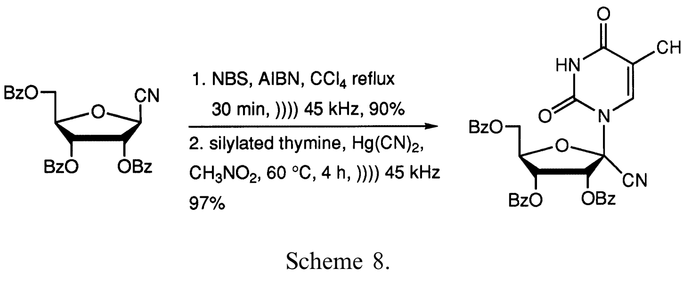
Scheme 7.

20 kHz immersion probe.[71,72] When the reaction is conducted on methyl β-D-galactopyranoside, the regioselectivity of deuterium incorporation is improved under these very mild conditions (low temperature, short contact times), affording exchange at the C-2 (27%), C-3 (73%), and C-4 (89%) positions only.[72] In an immiscible pair of solvents (*n*-heptane–D_2O), the selectivity is slightly increased at C-3 (90%).[72] The advantages of this method rely on its applicability to a broad range of substrates (saccharides, glycolipids) without any isomerizations or rearranged byproducts, and the easy catalyst activation by sonophysical effects.

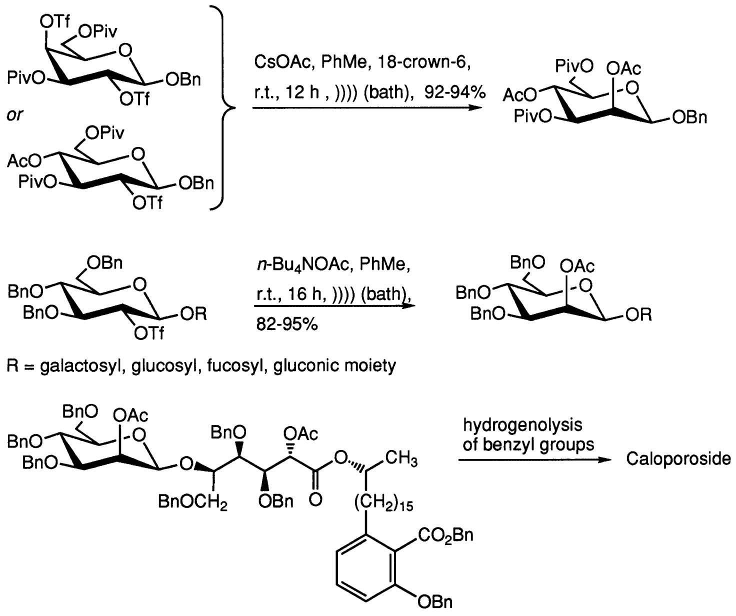
Sonication also improves the selectivity of homogeneous free radical substitutions, made feasible at lower temperatures. For example, labeling with deuterium can be achieved by Bu_3SnD–AIBN-reduction of 3′,5′-di-*O*-benzoyl-2′-bromo-2′-deoxy-ribonucleosides.[73] 2′-Deoxy-2′-deutero-ribonucleosides are obtained at 20 kHz and − 71 °C in 78% yield and with an excellent 24:1 diastereoselectivity in favor of the isomer (2′R). The silent reaction is successful (23:2 diastereoselectivity) at − 52 °C if Et_3B replaces AIBN (90% yield), but no direct comparison was given with the equivalent sonicated experiment. Better stereoselectivity is obtained under these conditions (> 99:1, 67% yield) when the benzoyl groups are changed for a disiloxan-1,3-diyl ring (Scheme 7). Thus, the objective of preparing specifically labeled compounds can be fulfilled either sonochemically or conventionally, but the latter method is less straightforward.

2.4. Formation of carbon–heteroatom bonds.— In particular cases, bromine-containing sugar derivatives can be readily synthesized under sonication via radical substitution at a C–H center. For example, sonobromination of penta-*O*-acetyl-β-D-glucopyranose was claimed to occur at C-5 more selectively than photobromination.[74] Such a conclusion can also be drawn in the case of the bromination of 2,3,5-tri-*O*-benzoyl-β-D-ribosyl cyanide at C-1, but neither of these two methods seems to offer a clear advantage [tungsten lamp or)))), 85 °C, 30–35 min, 90%].[6,75] However, when the 1-bromo-1-cyano derivatives are engaged in nucleophilic substitution reaction with a silylated pyrimidine, the sonochemical effect is beneficial. The 1′-cyanoribonucleosides are thus obtained in 97% yield after 4 h at 60 °C, instead of 80% with an excess of reagents in 3 days at room temperature (Scheme 8).[76] Likewise, the $HgBr_2$-catalyzed substitution of the bromide in 2,3,5-*O*-tribenzoyl-4-bromo-β-D-ribofuranosyl acetate by the same activated pyrimidine in acetonitrile gave the expected 4-(1′-thyminyl)-α-L-lyxofuranose in 55% yield.[77]

Epimerization at C-2 (and C-4) by S_N2 processes in various saccharides is strongly disfavored by electrostatic repulsion between the oxygen atoms of the sugar and the nucleophile. Conventionally, indirect strategies must be developed, but a successful direct substitution process became possible, probably by sonophysical activation.[78,79] A 2-azido-2-deoxy-β-D-mannopyranoside derivative was formed from a protected 2-*O*-triflylglucopyranoside by reaction with tetra-*n*-butylammo-



Scheme 8.



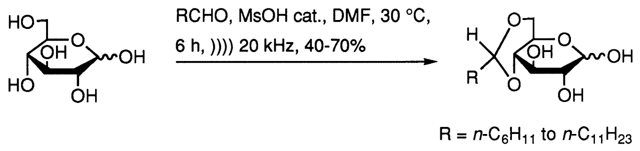
Scheme 9.

nium azide in benzene (91% yield).[78] The acetate nucleophile was also introduced stereospecifically using CsOAc in the presence of 18-crown-6, from either a 2-triflyl glucopyranoside or directly from a 2,4-ditriflyl galactopyranoside in excellent yields (Scheme 9). Similar reactions have been examined with the more reactive n-Bu_4NOAc and several disaccharides.[79] The authors emphasize the unsatisfactory outcome of these reactions conducted just under heating. The sonochemical process proved its efficiency in the key-step of the total synthesis of caloporoside, a potent inhibitor of phospholipase C.[80]

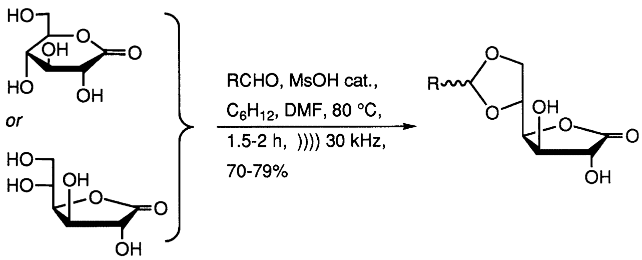
2.5. Acetalization.—This particularly important reaction, a frequent preliminary transformation in multistep syntheses from sugars, requires a simple, mild protocol with high yields. The heterogeneity of the initial medium, in most cases, contributes to making the usual reactions slow, which stimulated interest in improving the rate sonochemically.

The first paper reports the acid-catalyzed preparation of di-*O*-isopropylidene-D-glucose, although in low (25%) yield.[30] In a subsequent patent, the procedure (500 kHz, room temperature) was applied to L-sorbose with an improved (70%) yield.[81] This was extended to making di-*O*-cyclohexylidene monosaccharides, even on multigram scales.[82] For example, 2,3:5,6-di-*O*-cyclohexylidene-D-mannose was made in 66% yield in 60 min in a cyclohexanone–ethyl acetate system under catalysis by sulfuric acid at room temperature in a cleaning bath, and the di-*O*-isopropylidene analogue in 92% in only 15 min in acetone.

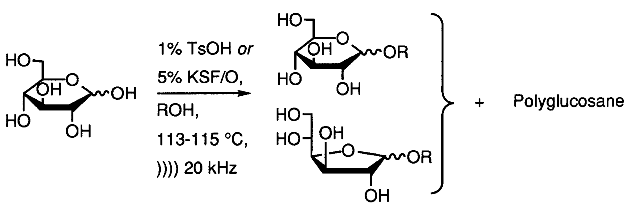
Benzylidenation at the C-4- and C-6-hydroxyl groups of alkyl α-D-glycopyranosides was efficiently achieved by sonicating the benzaldehyde–zinc chloride mixture prior to addition of the substrate.[83] This procedure avoids the undesired crystallization of the complex, and the overall reaction is finished in less than 1 h (77% yield). Based on these



Scheme 10.

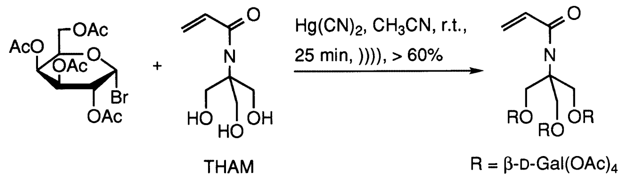


Scheme 11.

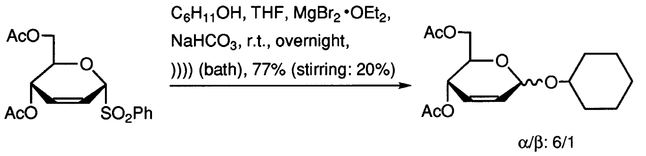


% Yields	))))	(stirring)	))))	(stirring)
ROH = *n*-butanol	75-83	(67-85)	7-11	(8-10)
ROH = *n*-dodecanol	15-21	(16-43)	70-75	(31-34)

Scheme 12.



Scheme 13.



Scheme 14.

methods, fatty-chain 4,6-*O*-(*n*-alkylidene)-D-glucose were selectively obtained in a biphasic liquid–liquid medium in 40–70% yields (Scheme 10).[84] The interest in this new type of acetal with biodegradable surfactant properties led to the developments given below.

The same reaction applied to D-gluconolactone and C_{12} and C_{14} aldehydes provides acetals, which can undergo a ring opening to introduce a second fatty chain.[85] The advantage of this method relies on the reduced amount of the expensive DMF solvent required for the solubilization of the starting lactone. Only the unexpected 5,6-acetalated product is obtained in high yield, in contrast with a previously proposed structure[86] (Scheme 11). Moreover, the product is the same starting from either the 1,5- or the 1,4-lactone. Sonochemical activation slightly accelerates this transformation.

Transacetalization of unprotected sucrose by 2,2-dimethoxyalkanes (C_6–C_{12} fatty chains) was reported to give the 4,6-*O*-acetal in 30% yield (after acetylation) in 120 min without sonication. An improved 45% yield is reached in only 10 min under ultrasound, due to a faster solubilization of sucrose.[87] In both cases, the composition of the final reaction mixture remains unknown.

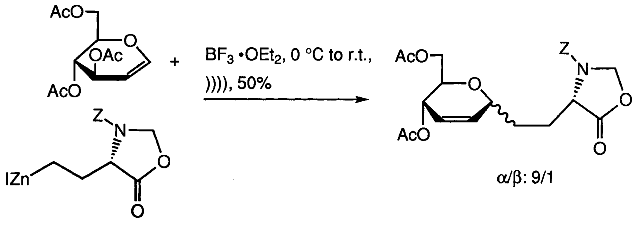
2.6. Glycosylation.—Glycosylation as a particular case of acetalization could also benefit from sonocatalysis. For industrial applications, a procedure allowing the direct use of unprotected sugars would be highly advantageous. This proved to be possible as shown in the next example, in which the starting materials are poorly soluble in the solvent chosen (THF). For this reason, octanol with D-mannose and *N*-acetyl-D-glucosamine were sonicated in the presence of $BF_3 \cdot OEt_2$.[88] The α-pyranosides were obtained with a high stereoselectivity ($>90\%$) in shorter times without the need of additives (barium or calcium chloride).

In the Fischer reaction between glucose and butanol, using homogeneous or heterogeneous catalysts, the sonochemical effect is complex.[89] In the presence of *p*-TsOH, the substrate conversion (95%) remained unchanged under sonication or stirring. However, a slight increase was observed with the montmorillonite KSF/O ['silent': 75%;)))): 82%]. In this case, the cavitation-accelerated release of acidity from the solid clay to the alcoholic phase may account for the observations. The latter effect may play a role when dodecanol is the alcohol used. Oligomerization becomes the favored pathway at the expense of glycosylation and the product is a semi-solid hydrated carbohydrate phase (Scheme 12). MALDI-TOF mass spectrometric analysis indicates a polymerization degree of up to 24 for the sonochemically prepared samples.[69b,90]

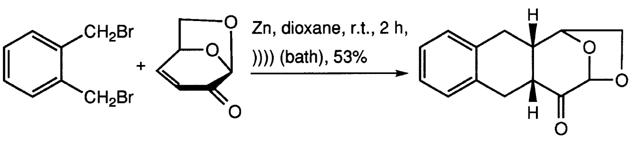
Acoustic waves demonstrate their applicability in the glycosylation of *O*-protected glucosyl donors. The trisubstitution of the triol shown in Scheme 13 (THAM) is sterically disfavored, and conventionally, mixtures of mono-, di-, and tri-*O*-glycosyl derivatives were produced on reaction with tetra-*O*-acetyl-α-D-galactopyranosyl bromide in low yield ($<40\%$). Fortunately, the tri-β-(galactoside) was formed as the sole stereoisomer ($>60\%$), after 25 min of sonication.[91] Further transformations provided detergents effective in extracting and purifying membrane proteins.

5-Hydroxynaphtoquinone β-D-glucopyranoside tetraacetate has been used in an asymmetric Diels–Alder reaction as an enantiomerically pure dienophile. It was isolated in 82% from a heterogeneous Ag_2O-mediated O-glycosylation between juglone and acetobromoglucose subjected to ultrasonic waves (cleaning bath) for 3 h in dry acetonitrile.[92] This procedure gave the best and reproducible results as compared with conventional methods. The *O*-protected glucosyl bromide was also used for α-glycosylation reactions. The influences of ultrasonic activation, heterogeneous catalysts (e.g., silver zeolite), solvent, and nature of the alcohol were reported.[93] The rates, yields and stereoselectivities are slightly improved by sonication.

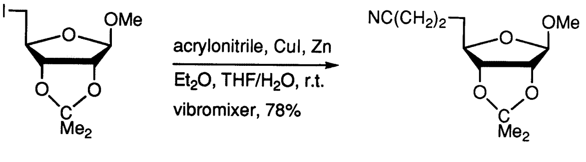
A mild and versatile glycosylation method starting from an activated glycosyl sulfone is based on the use of $MgBr_2{\cdot}OEt_2$ and solid $NaHCO_3$ at room temperature overnight (Scheme 14).[94] Ultrasonic assistance substantially accelerates the S_N2-like substitution, and increases the yield from a low 20% up to a satisfactory 77%.



Scheme 15.



Scheme 16.



Scheme 17.

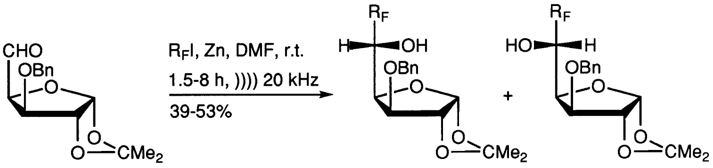
2.7. Formation of carbon–carbon bonds.—It has been reported that 2,3-unsaturated *C*-glycosyl compounds can be made by the carbon–Ferrier type reaction (via a S_N2'-like mechanism) between electrophilic glycals and organometallic nucleophiles.[95–97]

The bromomagnesium salt of 4-*tert*-butylphenol reacts sluggishly in 56 h with 3,4,6-tri-*O*-acetyl-D-glucal in dichloromethane at room temperature to give the 2,3-unsaturated α-*C*-glycosyl derivative, with the sugar linked to C-2 of the phenol, but in only 12% yield due to the heterogeneity of the medium. Undesirable aggregation phenomena of the phenoxide salts in the apolar solvent are minimized by using an ultrasonic cleaner in which case the α anomer was obtained in 6 h in 71% yield.[95] This improved procedure was successfully applied to variously substituted bromomagnesium phenolates and glycals.

The same ultrasonic effect was observed when the $BF_3{\cdot}OEt_2$-promoted reaction was carried out with the 3,4,6-tri-*O*-acetyl-D-glucal in the presence of the insoluble 3-cyanopropylzinc iodide. The coupling, inefficient without ultrasonic activation (3–8 h in dichloromethane at room temperature), gave 63% of the 2,3-unsaturated 3-cyanopropyl-*C*-glycosyl compounds with a 5:1 stereoselectivity in favor of the α-isomer.[96] Consistent with these results, the synthesis of a *C*-linked glycosyl amino acid derivative has been achieved. The acetate displacement in the same glycal by an iodohomoalanine-derived zinc nucleophile, compatible with a large variety of functionalities, led to the expected *C*-glycosyl compounds in 50% yield with high α-stereoselectivity (Scheme 15).[97]

Carbon–carbon bond formation at other positions of sugar compounds has also been studied. The first example deals with the preparation of a synthetic precursor of pyranonaphthoquinones, which exhibit several biological activities.[98] The reported strategy involves the annelation of levoglucosenone, obtained by the pyrolysis of cellulose, with α,α′-dibromo-*o*-xylene over zinc powder. Irradiation of this mixture at room temperature smoothly afforded the desired cycloadduct as the major product (Scheme 16).

In order to prepare sinefungin analogues, the addition of a protected ribose-5-yl moiety



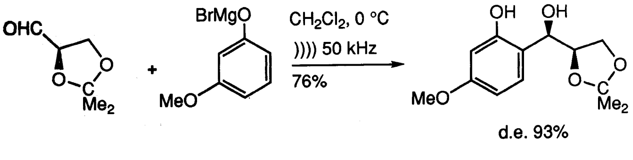
Scheme 18.

to the electron deficient olefin acrylonitrile, promoted by the zinc/copper couple, was investigated.[99] Sonication allowed the desired adduct to be obtained in modest yield. Better stirring of the heterogeneous medium with a vibromixer was more successful. The effects of hydrodynamic cavitation, which exhibit some parallel with acoustic cavitation,[100] can be invoked in this case (Scheme 17).

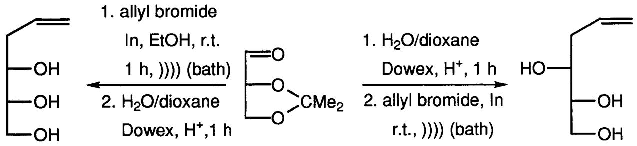
In contrast, sonochemical methods proved to be highly efficient for promoting the formation of carbon–carbon bonds by reaction of aldehydic function(s) of carbohydrates and organometallic nucleophiles. Thus, effective C-trifluoromethylation was carried out by ultrasonic mixing of various protected dialdoses with in situ generated trifluoromethylzinc iodide in DMF (47–70%).[101] *C*-Perfluoroalkylated sugars are expected to exhibit surfactant and pharmacological properties. The influence of the acoustic frequency (20, 35, and 850 kHz) has been studied for the introduction of fatty perfluoroalkyl chains (C_4–C_8) into the furanose derivative shown in Scheme 18.[102] The direct immersion 20 kHz probe provided the best activation of the metal.

The example in Scheme 19 represents the condensation of a magnesium phenolate with homochiral 2,3-isopropylidene glyceraldehyde.[103] Ultrasound greatly accelerates this transformation, which yields the syn-product with a diastereomeric excess of 93%, instead of 70% under 'silent' conditions (in a poor 25% yield). In contrast, the use of a titanium phenolate leads to the anti-addition with similar high diastereoselectivity.

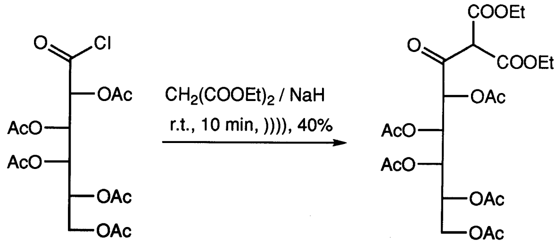
An application of C-allylation in organic–aqueous media[104] permits the direct use of unprotected sugars.[105] The carbonyl group of, e.g., D-mannose reacts with allyl bromide and tin powder (probably through an organotin intermediate[106]), with high diastereoselectivity (6:1) in favor of the threo isomer (relationship between the newly formed hydroxyl group and the vicinal one) in 90% overall yield. The environmentally undesirable tin metal was compared to the safer and more reactive indium. Although indium-mediated allylation does not require ultrasonic assistance,[106] a convenient sonicated preparation of synthetic precursors of 2-deoxy and 2,6-dideoxy unprotected sugars was reported.[107] The advantage of this method lies in its versatility. From a homochiral protected aldehyde, each of the two epimeric products (Scheme 20) can be obtained with good diastereoselectivity by a simple reversal of the steps. Whereas the allylation of the protected substrate leads to the major Cram product, the same process conducted with the deprotected aldehyde follows the chelation-control model.



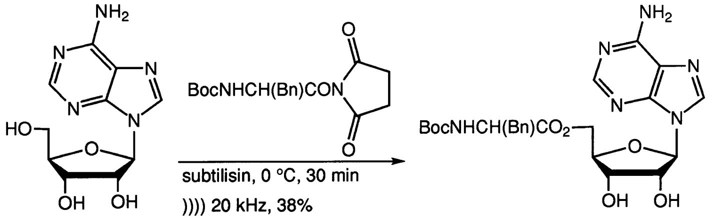
Scheme 19.



Scheme 20.



Scheme 21.



Scheme 22.

Malonic ester synthesis, which has not received much attention in sonochemistry, has been applied with 2,3,4,5,6-penta-*O*-acetyl-D-galactonyl chloride.[108] A slight yield increase and shorter reaction time were noted under sonication (Scheme 21).

2.8. Miscellaneous.—A case of using sonoactivation of an enzyme in a synthetic pathway to nucleopeptidic bioconjugates has been reported.[109] It consists of coupling adenosine with the succinimidic amide of Boc-phenylalanine in the presence of subtilisin. This procedure afforded the sole 5′-amino ester in 38% yield after only 30 min at 0 °C (Scheme 22). The same chemospecificity was observed under Mitsunobu's conditions in 24 h, but the tedious separation of the desired compound from the phosphorus by-products is required.

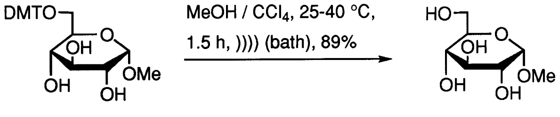
It can be envisaged that sonication helps in the removal of protecting groups with improved chemoselectivity (Scheme 23) for the cleavage of the 4,4′-dimethoxytrityl ether (DMT) without affecting the anomeric methoxy group. Usually this is achieved under acidic conditions (80% AcOH or 3% CCl_3COOH) with the risk of a poor chemoselectivity. The only reagent used here is CCl_4 in methanol,[110] the sonication of which yields hydrogen chloride in sufficiently small amounts to cause preferential removal of the sensitive DMT ether and afford the methyl glucoside in 89% yield.

3. Practical aspects of sonochemistry

Success in sonochemistry relies both on the quality of the equipment and expertise with its use. To keep this review within an acceptable size, we have not gone into experimental details, preferring to cite diverse information sources. However, a brief outlook at this complex topic can be sketched here; this should be complemented by consulting recent books.[111,112]

3.1. Sources of information about sonochemistry and ultrasonic instrumentation.—Ultrasonic emitters can be purchased from a number of companies, and the related information is easily available via the Internet. Although electronic addresses change without notice, 'ultrasonic (or sonochemical) equipment' can be used as keywords on a variety of search engines. A few data banks provide interesting entries, including the European Society of Sonochemistry[113] and DECHEMA.[114] They offer listings of academic and industrial laboratories, and a number of links. More directly, a few Web pages deserve a visit for general technical descriptions. Among these, some sites provide data for common low frequency bath and probe systems with suggested applications.[115a–g] Other pages illustrate less straightforward conceptions of different types of sonicators, including high frequency and special double frequency emitters and resonating tubes adapted to industrial flow techniques.[116a–c]

3.2. A general overview for the practitioner.—Three types of commercial equipment can be distinguished: the monofrequency emitters with a fixed or tunable electrical input, and the multifrequency generators with adjustable input. In every case, in order to ensure reproducibility and optimization, a few important



Scheme 23.

parameters (the type of the vessel, and its geometrical configuration, the bulk temperature, the frequency, etc.), and particularly the acoustic energy, must be considered.

3.2.1. Energy. The easiest way to quantify the acoustic energy is by calorimetry.[117] Since ultrasonic irradiation of a liquid produces heat, recording the temperature as a function of time leads to the acoustic power estimation (in W) by the equation:

$$P = m \cdot C_p \cdot (\mathrm{d}T/\mathrm{d}t)$$

where m (in g) is the mass of sonicated liquid, C_p its specific heat at constant pressure (J/g·K), and $\mathrm{d}T/\mathrm{d}t$ the slope at the origin of the curve. The calculated value is always lower than the electrical consumption. Most of the time it is expressed in watts per unit area of the emitting surface (W/cm^2), or in watts per unit volume of the sonicated solution (W/cm^3). For a given energy, a more even distribution can be obtained by increasing the emitting surface.

The chemical efficiency can also be estimated by dosimetry of the radicals formed in aqueous or organic solutions. In sonolyzed water, the OH radicals oxidize iodide ions to I_3^-,[118] which can be determined chemically or spectrometrically. In organic media, the radicals generated can be quantified by quenching with the deep blue stable free radical DPPH (2,2-diphenyl-1-picryl-hydrazyl) transformed to the corresponding yellow hydrazine.[119]

When tunable emitters are used, it is important to note that at low energies, below the cavitation threshold, practically no reaction occurs. On the other hand, too high an energy also leads to poor results. A dense cloud of bubbles acts as a screen for the transmission of ultrasound to the medium,[120] much like suspended dust inhibits photochemical reactions. Rate and/or yield improvements as a function of acoustic power can be found in many papers discussed above, inter alia references.[43,60,62,69,102]

3.2.2. Temperature. When the vapor pressure of the solvent increases, it penetrates in larger amounts into the bubble and weakens the collapse energy by the so-called ‘cushioning effect’. This phenomenon has a paradoxical consequence: sonochemical reactions can be accelerated by decreasing the temperature,[43] potentially with higher selectivity.[73] But this statement should be tempered by two elements: first, a limit exists when the agitation becomes less efficacious due to the viscosity increase despite the micromixing effect, and second, the optimal temperature depends on each particular chemical system under study. For instance, hydrolysis of sucrose is faster at 75 °C than at 50 °C.[60]

3.2.3. Frequency. Two domains can be distinguished, the low range at 20–100 kHz, and the high range above 100 kHz. The waves are emitted generally by ceramics, which convert the electrical current to mechanical vibrations via the inverse piezoelectric effect. Since the wavelength is equal to two times the thickness of the transducer, varying the frequency requires changing the emitting device, even with multifrequency generators.

As an empirical rule, mechanical effects are much higher in the lower range which should be preferred for biphasic reactions as shown in the partial depolymerization of dextran.[41] The production of radicals is reported to be larger at higher frequencies (see Section 1.2). For instance, some radical reactions occur efficiently at ca. 200–300 kHz,[121] although most of the studies were done at 500 kHz for reasons of equipment availability. An illustrative case is the TEMPO-mediated oxidation of sucrose.[69,70]

3.2.4. The sonicators. Commercial ultrasonic emitters are suitable for chemical applications despite the fact that they were not always initially designed for this purpose, e.g., cleaning baths or cell disruptors (immersed ‘probes’ or ‘horns’).

In the first case, ultrasonic cleaners deliver a low energy (1–2 W/cm^2) at frequencies of 30–50 kHz.[122] The transducers are fixed to the underside of the tank filled with a fluid, almost always water. The reaction flask should be placed at a position of maximum energy,[35] visualized by the strong agitation at the water surface. Quiet places receive only low (or even no) energy. Optimization of the energy transmission is achieved by adjusting the depth of the water in the tank. With a level below λ ($\lambda = 75$ mm at 40 kHz in water), high intensities are not obtainable.[123] It is generally preferable to run the reactions in flat bottom vessels, in which the waves are transmitted much more efficiently (up to ten times) rather than round-bottomed flasks.[122] Heat is produced, requiring a temperature control by circulating cold water in a coil placed in the bath, with the inconvenience of an imprecise adjustment. However, many unproductive conventional reactions become successful using this simple equipment. Illustrative studies include nucleophilic substitution,[79,80] acetalization,[82,83] and several carbon-Ferrier type alkylations.[95–97]

Energy and temperature are more easily controlled with immersion horn emitters. With these devices, the acoustic wave is produced directly in the reaction mixture, at the tip (possibly exchangeable) of a titanium rod. The temperature can be adjusted by dipping the vessel into a thermostatized bath (down to − 71 °C[73]), or by circulating a cooling fluid in a double walled glass cell. Typical models can be found in the literature.[1d,124]

High frequency generators are less commonly commercialized, and most investigators design their own equipment. In this domain,[125] the accessible temperature range is narrower than at low frequency, and the set-up should be studied case by case.[61–63]

Other systems are less frequently used. The ‘cup-horn’ set-up has less synthetic applicability due to generally small processing volumes,[1d,122] despite the advantage of high-energy density. It consists of a probe operated upside down with emission directly into the sonicated mixture or indirectly via a transmitting fluid. The latter technique represents a compromise between the cleaning bath and the probe.

Less useful in the laboratory, but better fitted for industrial extrapolations, several emitters can be mentioned. These include resonating cavities excited by a vibrating blade (‘whistle’)[126] and plates or tubes driven by a piezoceramic.[127]

4. Conclusions and perspectives

As has been shown in this review, ultrasound can be a versatile tool in carbohydrate chemistry. Sonication generally displays a beneficial role in terms of better rates, yields and chemo-, regio- and stereoselectivities for common depolymerization, glycosylation, and acetalization processes and the more sophisticated oxidations and C−heteroatom or C–C bond formations as well. Performing such reactions is made possible through multiple techniques, from the common cleaning bath to the immersion probe and high frequency emitters.

A kind of matrix could then be defined, with chemical entries reflecting the multiple transformations allowed, and technical ones representing the various means to achieve them. The optimal conditions can be selected with regard to the desired outcome, although generally initial attempts will be run in ultrasonic cleaners. Their relatively low acoustic energy is not a drawback for many synthetic reactions, and even permits a synergetic effect with sensitive reagents, e.g., enzymes.[35] This choice is especially reasonable when only mechanical effects are expected in heterogeneous systems. In the case of unsatisfactory results, sonication should be undertaken by probe, whose larger acoustic energy domain broadens the field of accessible reactions, e.g., those involving shear forces.[43] The latter effect is virtually absent under high frequency activation, which will favor homolytic cleavages and therefore free radical processes, e.g., oxidation of sucrose.[69,70] This last example, together with the allylation coupling,[107] illustrates the potential offered by the use of aqueous media in synthesis, a breakthrough that needs to be further exploited.

Even if really large-scale applications are still in the future, experiments starting from several tens of grams have already been reported.[82,83] Recent progress in sonochemical engineering[17] and in ultrasound generators with improved energetic yields should be applicable to industrialization. All these developments lead to the creation of environmentally friendly processes and compounds, emphasizing the role of ultrasound and carbohydrates in ‘Green Chemistry’.

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