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Ultrasound and Microwaves in Chemistry: A Relay Race or a Tandem?

The Combined Use of Microwaves and Ultrasound: Improved Tools in Process Chemistry and Organic Synthesis

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Abstract: Microwave heating and ultrasonic waves are among the most simple, inexpensive, and valuable tools in applied chemistry. Besides saving energy, these green techniques promote faster and more selective transformations. Could they be combined to enhance their effects still further? As they are of a basically different nature (quantum and non-quantum fields), each must be fine-tuned by its specific parameters; a combined device will often be subject to additional hazard limitations. However, recent developments evidence that such a combination is certainly possible and safe, ranging from simple modifications to flow systems that are well suited for automation and scaling-up. By using selected examples, this concept article gives an overview of apparatus currently available for simultaneous or tandem irradiation and explains how it can be utilized in organic synthesis and analysis.

Keywords: flow reactors · green chemistry · microwaves · synthetic methods · ultrasound

Introduction

Chemists have always looked for synergism, that is, a combination of tools, reagents, or processes producing a larger effect than the sum of their individual effects. Medicinal chemists know well that drug synergism often provides great therapeutic advantages. Combined analytical technologies are now indispensable to achieve efficient separations and purifications. It is expected that in the future organic synthesis will undergo increased automation and require the construction of continuous-flow systems capable of rapid, efficient and scalable automated processes.[1] However, the design and development of routes for manufacturing fine chemicals or pharmaceuticals (collectively denoted as process chemistry) impose strict criteria concerning not only efficiency and selectivity, but also time frame, safety, cost, robustness, and environmental impact.[2]

In this context, our aim is to show how two of the most important, green activation techniques (microwaves and ultrasound), so far regarded in a Janus-like fashion, may be combined to provide a reliable and cost-effective strategy for an increasing number of synthetic transformations. Emerging from its early stage of development, such a combination may soon become another household package in conducting chemical synthesis.

At the outset it is helpful to highlight the physical uniqueness of microwaves (MW) and power ultrasound (US), the better to overcome conceptual and technical hurdles standing in our way.

Combining Two Ways of Energy Transfer

Nowadays many scientists are familiarized with MW irradiation, some with US, but few with both. Their nature and effects are intrinsically different, although the effects are often interpreted in terms of similar activation processes. Table 1 summarizes a series of conceptual differences between MW and power US.[3,4]

Electromagnetic radiation with a frequency in the range 0.3 to 300 GHz (most applications being restricted to 2.45 GHz), heats matter through a dielectric mechanism that may involve dipolar polarization and ionic conduction. It is the ability of a material to absorb MW energy and convert it into heat that causes bulk heating; the temperature of the whole sample rises simultaneously, in stark contrast with conventional conductive heating.[5] Although non-thermal

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Table 1. US versus MW: a matter of striking differences.

Application	Ultrasound	Microwaves
reaction media	aqueous and organic solvents	MW-absorbing liquids; solvent-free protocols
use of bulk metals	favorite domain	forbidden practice
acceleration	variable (from min to h)	large (min, even seconds!)
activation	cavitation (thermal effects) (electric?, plasma-like?)	Thermal effects (specific non-thermal)
scaling up	possible but still a challenge	possible
chemical effects	selectivity changes, mechanistic switching, waste reductions	selectivity changes, waste reductions
other effects	light emission, cleaning, microstreaming	heating above boiling points, change in solvent properties

effects have been invoked for reactions in which the transition state is more polar than the ground state,[6] it is generally accepted that rate enhancements largely stem from thermal effects. In fact, the average energy of a photon in the microwave region is even lower than the energy imparted by Brownian motion.

The last remark also applies to US in its practical range extending from 20 to 100 kHz, as ultrasonic frequencies (up to a few MHz for imaging applications) do not even alter rotational or vibrational molecular states. US (consisting of pressure waves that are not quantized) is not absorbed by single molecules, though it is partially converted into heat. Accordingly, frequency effects that are sometimes observed cannot be easily rationalized. Ultrasound effects derive from the unique, nonlinear phenomenon of cavitation, that is, the creation, growth, and collapse of micrometer-sized bubbles that are generated when a pressure wave of sufficient intensity propagates through a liquid. Bubble implosion creates local conditions of thousands of Kelvin degrees and hundreds of atmospheres accompanied by shock waves of extremely short duration.[4,7] In other words, cavitation can be regarded as a quasi-adiabatic process that releases enough kinetic energy to drive chemical reactions. Although it is still poorly understood, a current theory (usually referred to as the hot-spot theory) accounts for most experimental observations, such as particle fragmentation, radical scission, and/or formation of excited species resulting from pyrolitic cleavage of solvent or substrate molecules.[8] In fact, cavitation is more dependent (and can be fine-tuned) on physical properties such as vapor pressure, viscosity and surface tension, than on chemical characteristics normally assessed (acidity, basicity, or polarity).

Although microwave practitioners often refer to the existence of hot spots, it is still uncertain whether these actually represent cavitation-like environments. In MW chemistry, hot spots are to be understood as hot domains approaching molecular dimensions that arise from nonhomogenities of the electromagnetic field. They cause a nonlinear dependence of thermal and electromagnetic properties of the material being heated on temperature. In catalytic systems, hot spots could be created as a temperature gradient between solid particles.[9]

While popular wisdom just associates MW with a superior heating and US with an efficient agitation, these techniques are capable of doing much more, which provides additional impulse to their expansion in synthesis and processing. Both also share the inherent advantage of being green technologies, as by reducing reaction times and increasing yields they lead to an overall energy saving. Reproducibility, however, still requires further attention, especially because some design parameters are sometimes overlooked.

Simultaneous irradiation with MW and US sources involves technical and safety considerations. The ultrasonic energy generated by a transducer (i.e., a device capable of converting either mechanical or electrical energy into US) is delivered to the reaction vessel by means of a sonic horn, usually made of titanium alloy. Evidently, a piece of metal placed inside a microwave chamber will lead to arcing that could result in vessel rupture or perhaps an explosion, if flammable compounds are involved. Electric arcs in the cavity can also be formed by an excess input of microwave energy (efficiency of MW absorption decreasing as temperature rises); therefore temperature, pressure, stirring, and power input among other variables, should be monitored and controlled.[10] From the sonochemical side, although several types of transducer exist, the commonest uses a piezoelectric ceramic material that is sintered under high pressure and temperature. Its crystallites are then aligned by cooling it in a magnetic field from a temperature above the ferroelectric transition.[11] In general, piezoelectric devices are not suitable for continuous use at high temperatures and perform optimally at a fixed frequency.

To overcome these limitations, ultrasonic irradiation in a single reaction vessel can be achieved inside a modified MW oven by inserting in it a horn made of quartz, even though quartz is not the ideal piezoelectric material because of its fragility. Pyrex also shares the same drawback, while ceramic horns are more expensive. The most recent development patented by Cravotto and associates[12] introduces horns made from engineered plastics, such as PEEK (polyether ether ketone) or PTFE (polytetrafluoroethylene), materials that are much more resistant to shock and can be more firmly jointed to the booster (Figure 1).

As domestic ovens (Figure 2) lack reproducibility and do not allow an accurate control of reaction parameters, the same solution for tandem or simultaneous MW/US irradiation should be adopted with professional multimode systems currently available on the market (Figure 3). As we shall see later, other combinations of MW and US reactors are used for sequential irradiation. These systems, tailored for flow processes, may be more versatile and should be well-suited for automated syntheses.

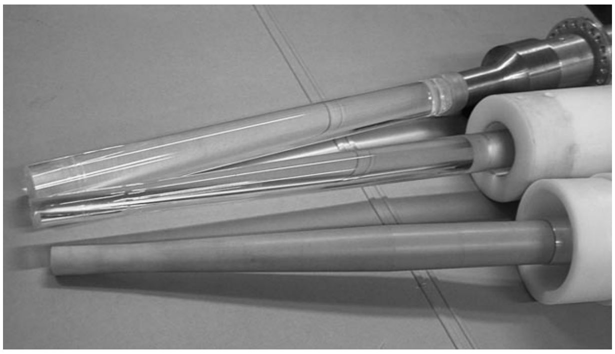


Figure 1. Different types of MW-inert horns made in quartz, pyrex, and PEEK.

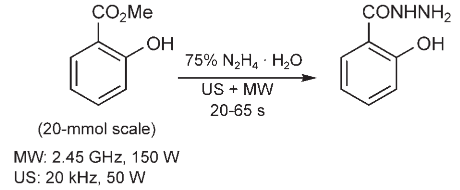
Figure 2. A modified domestic oven for simultaneous US and MW irradiation with a quartz horn.

Figure 3. Simultaneous irradiation in a multimode MW oven (Milestone®) equipped with a pyrex horn.

Applications in Synthesis and Catalysis

Early examples documenting the acceleration of chemical reactions by simultaneous MW and US irradiation concerned a few esterification and condensation reactions, reluctant by nature, and remained until recently an academic curiosity.[13] Pioneers of the method avoided subjecting the horn to the electromagnetic field. Since cavitation depends on the viscosity of the solvent, decaline (a low-viscosity apolar liquid)[14] could be exposed to ultrasound outside the microwave oven and employed as an energy-transfer medium to convey US inside the oven to the reaction mixture placed in a double-jacketed pyrex vessel.

Chinese authors employed a simple, home-made, yet efficient, device by inserting a detachable horn (the material of which was not specified) into a modified domestic oven. Potentially hazardous MW leakage was prevented by a copper mesh screen tightly fastened onto the horn.[15] This set-up was applied to the hydrazinolysis of esters with hydrazine monohydrate under solventless conditions (Scheme 1). This process may be tedious with less reactive esters, although it circumvents the nongreen use of acyl anhydrides or halides for the synthesis of hydrazides. Data gathered in Table 2 show that simultaneous MW and US irradiation overcomes

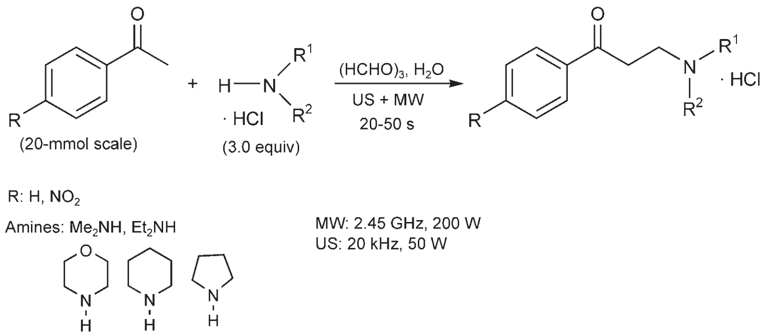


Scheme 1. Formation of hydrazides under simultaneous MW/US irradiation.[15]

Table 2. Hydrazinolysis of methyl salicylate.

Method	Time	Yield [%]
reflux	9 h	73
US (50 W) + reflux	1.5 h	79
MW (200 W)	18 min	80
MW + US	40 s	84

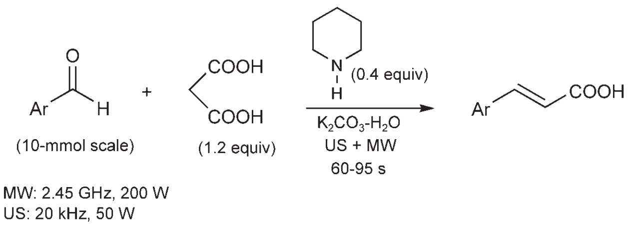
the inertness of most esters and dramatically reduces reaction times (13 examples: 79–94% yield within 20–65 seconds). As of these transformations occur under heterogeneous conditions, acceleration was interpreted in terms of enhanced heat and mass transfer. Cavitation causes liquid jets to hit the interface and the mutual injection of droplets results in fine emulsions.



Scheme 3. Enhanced Mannich reactions under green conditions: simultaneous US and MW irradiation in an aqueous environment.

The same strategy was successfully applied to the classical Williamson ether synthesis involving phenols with aryl or benzyl chlorides.[16] While reflux was unpractical (16 h to achieve but modest yields), either sonication or microwave alone improved results (1–2 h); excellent yields and reaction times were obtained when the two techniques were employed simultaneously (80% on average within 1–2 min). As expected from an efficient mass transport, no phase-transfer catalysts were required.

Aqueous and heterogeneous Knoevenagel-like reactions leading to cinnamic acids were completed in no more than one minute when simultaneous irradiation was used (Scheme 2, Table 3). This acceleration was approximately 30-fold faster than that seen under MW alone, or 140-fold faster than that seen under US alone. No need for aqueous workup or chromatographic purification, and an easy catalyst recovery were extra advantages.[17]



Scheme 2. Formation of cinnamic acids (10 examples) under MW and US irradiation. Adapted from reference [17].

Table 3. Synthesis of 3-aryl acrylic acids by means of a MW/US-activated Knoevenagel–Doebner reaction.

Ar	Time [s]	Yield [%]
C_6H_5	65	87
4-ClC_6H_4	60	92
4-$MeOC_6H_4$	95	85
4-$NO_2C_6H_4$	70	91
furyl	60	73

A series of β-amino ketones can be easily obtained through an aqueous Mannich reaction as shown in Scheme 3.[18] Simultaneous US/MW irradiation achieved good yields (60–84%) in less than one minute, an acceleration ranging from 10 to 30-fold faster than under either MW or US alone. This heterogeneous process benefits from rapid dielectric heating, acoustically enhanced mass transfer, and microemulsification. The authors noted that the same microwave-assisted reactions, when conducted under homogeneous conditions microwave, only gave comparable or even inferior results. This could be verified by a control experiment in which ethylene glycol monomethyl ether used as co-solvent afforded a homogeneous solution. It was hypothesized that the resulting Mannich salts acted as hydrotropes,[19] that is, as low-molecular water-soluble organics that increase the solubility of certain hydrophobic substrates, such as the parent acetophenones. The reaction mixture gradually becomes a homogeneous solution and this also accounts for the synergic effect of microemulsification when an extra acoustic field is present.

Given the positive effects that microwaves and ultrasound often exhibit on catalyst activation and heterogeneous reactions in general,[20] combined irradiation applied to some synthetically useful catalytic reactions could result in improved results and additional benefits. We envisaged the design of flow reactors for sequential MW/US irradiation that would allow the use of commercially available metal horns. A pump circulates the reacting mixture through two separate reaction cells (Figures 4 and 5.).

Aryl–aryl couplings are among the most versatile protocols in modern synthesis, enabling the construction of biaryls in natural or modified skeletons. Pd-catalyzed homo- and cross-couplings of boronic acids and aryl halides can be successfully performed in aqueous media under high-intensity ultrasound and microwave, either alone or in a combined fashion.[21] Such Suzuki reactions have been activated by microwaves in water with a ligand-free palladium catalyst within a few minutes.[5,22] Ultrasound equally promoted Suzuki homocoupling of aryl boronic acids with an inexpensive, air-stable Pd/C catalyst, cutting reaction times down to 90 min or less and increasing isolated yields. Bubbled oxygen or, better still, air, is a simple means to oxidize Pd^0 to Pd^{II} species in the catalytic cycle.[23]

Combined US (20.5 kHz, 40 $W\,cm^{-2}$) and MW (2.45 GHz, 700 W) irradiation was carried out in the flow reactor for

Figure 4. Overall picture of a flow reactor combining MW and US irradiation in a sequential mode.

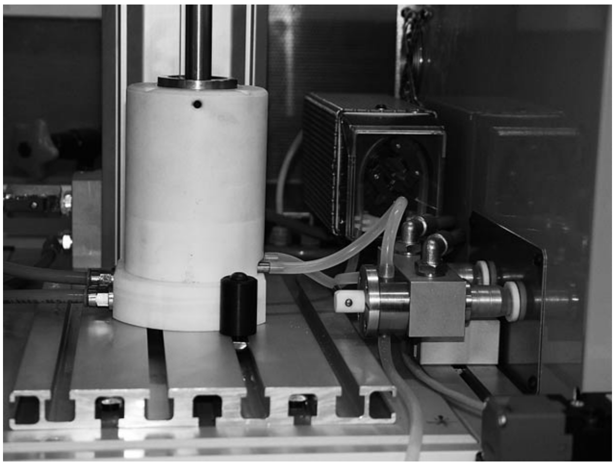
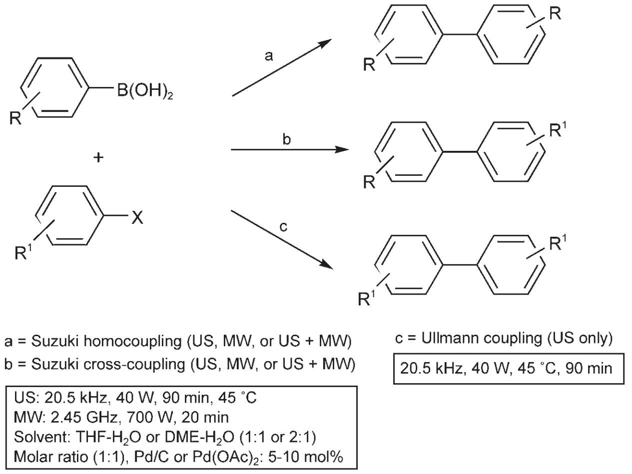


Figure 5. Details of the peristaltic pump and connecting tubing in a flow reactor combining MW and US irradiation.



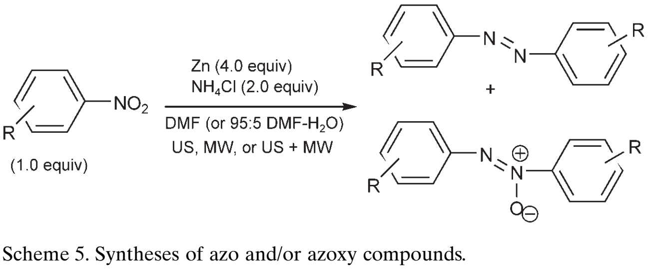
Scheme 4. Different types of Pd/C-catalyzed aryl-aryl couplings under US or MW individually, or combining both.

Table 4. Suzuki-type couplings under US or MW alone, or under both fields.

Aryl halide	Boronic acid	US [%]	MW [%]	MW/US [%]
3-bromoanisole	$PhB(OH)_2$	54	64	88
2-iodothiophene	$PhB(OH)_2$	40	37	59
4-chloronitrobenzene	$PhB(OH)_2$	22	30	57
none	thianthrene-1-boronic	48	55	69
none	4-*tert*-butylboronic	68	74	86

both Suzuki homocoupling and cross-coupling reactions involving boronic acids and aryl halides (Scheme 4, Table 4) in DME or DME/H_2O mixtures at 45 °C, using 10 % Pd/C as catalyst. Under such conditions the expected biaryls were obtained after 1 h irradiation as the sole products and in higher yields than using sonication or microwaves separately.[21]

Catalytic coupling was also extended to the Zn-mediated Ullmann reaction (Scheme 4). Remarkably, this transformation did not proceed under microwaves, which reflected the reluctance of most MW-promoted Ullmann condensations: high reaction temperatures (close to 200 °C) and long irradiation times (2–22 h) are typical of copper-mediated C–N, C–O, and C–S bond-forming hetero-Ullmann reactions.[5] It is worth noting that ultrasound alone promoted this Zn-mediated coupling under mild conditions (20.5 kHz, 45 °C, 90 min) and CO_2 bubbling. Although yields were rather modest, this finding evidences the positive effect of ultrasonic waves on heterogeneous reactions. 3-Bromonitrobenzene gave the expected 3,3′-dinitrobiphenyl along with 3,3′-dibromo azoxybenzene resulting from reductive N–N coupling.



Scheme 5. Syntheses of azo and/or azoxy compounds.

In this context, aromatic azo and/or azoxy compounds could be obtained by reduction of nitroarenes by using the simple Zn/NH_4Cl reagent under US or MW, or the simultaneous application of both (Scheme 5, Table 5).[24] The latter could easily be performed with a professional multimode MW oven in which a pyrex horn was inserted directly (Figure 2). The process worked well in anhydrous DMF, al-

Table 5. Reductive coupling of nitroarenes under non-conventional energy sources.[a]

Nitrocompound	US [60 °C]		MW [120 °C]		US/MW [95 °C]	
	azo	azoxy	azo	azoxy	azo	azoxy
4-$ClC_6H_4NO_2$	26	40	46	25	57	13
4-$NO_2C_6H_4COOH$	18	49	9	62	27	–
3-nitropyridine	22	73	18	70	69	23
1-nitronaphthalene[b]	30	45	33	57	40	45
chloramphenicol[b]	–	83	–	78	traces	85

[a] Yields refer to isolated products. [b] MW and US/MW reactions were conducted at 80 °C; higher temperatures caused partial decomposition.

though with some sterically hindered nitrocompounds, such as the drug chloramphenicol or 1-nitro-2,4-di(pentan-3-yl)-benzene, the presence of water was also required. Conventional heating required harsh conditions (130 °C) for several hours and was less selective. It is worth noting that optimum, though different, temperatures and intensities were found for ultrasound (60 °C, 50 W), microwaves (120 °C, 80 W), and combined US/MW (95 °C at 40 W and 50 W, respectively). US or MW led to completion in approximately 1 h, whereas a combination of both radiations decreased reaction times to 25–40 min.

This study also shows that a meaningful comparison of these non-conventional energy sources requires an appropriate power adjustment, a fact usually overlooked in most green chemistry assessments. For instance, reduction at 80 °C implies that the power has to be cut down to 45 W for MW alone and to 25 W and 30 W, respectively, for the coupled US/MW irradiation.

Extraction and Analysis

Sample preparation, selective extraction from synthetic and biological matrices, and accurate determinations are recognized as the fundamental steps of modern instrumental analysis. High throughputs, low consumption of reagents, total automation, and increased safety are essential goals.[25] Microwaves and ultrasound, along with solid-phase extraction and supercritical extraction have been widely employed for digestion, dissolution, and extraction processes,[26] although both MW and US may cause chemical transformations (e.g., isomerization) or degradation of labile components.[27]

As observed in synthetic work, the association of efficient heat transfer and mass transport leads to enhanced effects in analytical procedures as well. In a pioneering study Chemat and associates showed that simultaneous MW/US irradiation enabled digestion and dissolution of solid and liquid samples to be carried out rapidly at atmospheric pressure, as exemplified in the determination of copper in olive oil and the dissolution of refractory oxides in ceramics.[28] No sample pretreatment was required and the protocol could be coupled to plasma atomic emission spectroscopy ICP-AES. Under combined irradiation (US: 20 kHz, 150 W; MW: 2.45 GHz, 150 W), the total amount of copper(II) in olive oil was digested in 30 min and dissolution of Co_3O_4 took only 60 min (figures for MW alone were 40 and 180 min, respectively). The advantages were observed even though the samples were not directly subjected to both MW and US,[13] which detracted from maximal efficiency. In subsequent work, the same modified US/MW reactor was applied to nitrogen analysis for a wide variety of foods as well as to the determination of metal traces in edible oils.[29] US/MW Kjeldahl analysis gives reproducible results, can be applied to liquid, solid, and viscous samples, and takes only 10 min for completion. This is a third of the time required with MW heating and considerably less than with the classical thermal treatment (3 h).

Conclusions and Outlook

The above examples clearly show that combined US/MW irradiation, being practically hazard-free, represents an emerging technological innovation that deserves widespread attention in fine-chemical and pharmaceutical research. Although the mechanisms of cavitation and microwave effects are not fully understood, processes requiring enhanced heat transfer and mass transport (especially heterogeneous reactions) will no doubt benefit from this green technique. Combinations of both energies may be simultaneous or sequential, and conditions can be tailored for the analytical and preparative modes.

Ultrasound and microwaves can be applied in a straightforward manner to numerous, but certainly not all, chemical reactions. Identification of optimal parameters and hindrances concerning both techniques will allow us to get matched expectations. So far, only a limited number of studies have described experiments carried out in parallel under MW and US; more shall be needed in order to identify pros and cons and could to achieve optimization of combined effects.[30]

Of particular importance will be the use of room-temperature ionic liquids as green and recyclable media. These neoteric solvents can themselves be advantageously prepared under ultrasound or microwaves, that also offer an efficient way to speed up synthetic applications in these media.[31] On the one hand ionic liquids, because of their high polarity and conductivity, absorb MW irradiation strongly. On the other, their negligible vapor pressure and viscosity make them ideal candidates as cavitational media, because they cannot easily enter the microbubbles, therefore cannot interfere with reactions of volatile substrates.

This innovation needs of course further study and increased safety. Possibilities of continuous flow, ready scale-up, as well as miniaturization,[32] represent the next challenges.

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