JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2002; **45**: 715–746.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.593

Review Article

Microwave applications in radiolabelling with short-lived positron-emitting radionuclides

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Summary

The use of microwave dielectric heating to reduce reaction times in organic transformations is rapidly increasing worldwide. Besides the time gains from simply performing reactions faster, other advantages have been noted, e.g. cleaner reaction mixtures due to decreased sample decomposition and altered product distributions as well as improved chemical flexibility due to the ability to accelerate typically sluggish reactions of less activated substrates. Microwave applications in radiolabelling tracers for positron emission tomography, paralleling and sometimes preceding developments in other areas of microwave-enhanced chemistry, are reviewed here. Copyright © 2002 John Wiley & Sons, Ltd.

Key Words: microwaves; positron emission tomography; carbon-11; fluorine-18; radiolabelling

Introduction/background

In the mid-1980s, two papers published nearly simultaneously[1,2] reported that dramatic reductions in reaction times for organic transformations could be achieved by heating the samples in a

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Received 20 November 2001
Revised 20 February 2002
Accepted 28 February 2002

household microwave oven. The potential for changing the way we do chemistry, which was suggested by these reports, was easy to imagine by all of us who grew up experiencing the impact microwave techniques has had on the way food is prepared at home. A rash of attempts (published as well as unpublished) at performing chemistry with the aid of microwaves ensued. Many of the early enthusiasts were, however, discouraged by unexpected rampant reactions, which led to exploding microwave ovens and hours of cleaning contaminated fume hoods. A lack of appropriate monitoring devices, which could be used in electromagnetic fields, was the major reason why it was so difficult to predict the appropriate conditions and to avoid these runaway reactions. The impetus for developing application-optimized microwave equipment[3] was thus provided not only by the exciting reports of the accelerations attainable but also by the discouraging problems with unpredictability, unreliability and irreproducibility. The improved availability of appropriate microwave devices and of process monitoring devices, whether or not they are integrated into the microwave power control, appears to be an important reason for the rapidly expanding use of microwaves in chemistry.[4–6]

Multi-step, remote-controlled methods for radiolabelling with the radioisotopes of positron emission tomography (PET) have always integrated the latest developments in chemical and apparatus techniques in order to achieve the most rapid and efficient incorporation of radioactivity into the desired tracer molecules. Since the starting materials, the radionuclides, are so short lived ($t_{1/2} = 2$, 10, 20, 110 min for ^{15}O, ^{13}N, ^{11}C, and ^{18}F, respectively), this field of chemistry is dependent on the creativity with which radiochemists can find new synthetic strategies and/or shave minutes off total synthesis times. The implementation of microwave techniques into PET radiochemistry illustrates how cross-fertilization between disciplines is important. Early studies of the states of organic carbon formed in microwave plasma decompositions[7] and of the use of microwave discharges for labelling with tritium,[8] were followed by the use of discharge cavities to produce small molecule labelling precursors for PET.[9–11] Shortly after the 1986 papers on using microwaves in organic transformations,[1,2] the first successful microwave-accelerated radiopharmaceutical syntheses in solution were reported.[12] Knowledge, gained from atomic and molecular spectroscopy about the importance of and means for generating an intense microwave field in samples, led to the first use of a single-mode microwave cavity to perform these transformations in

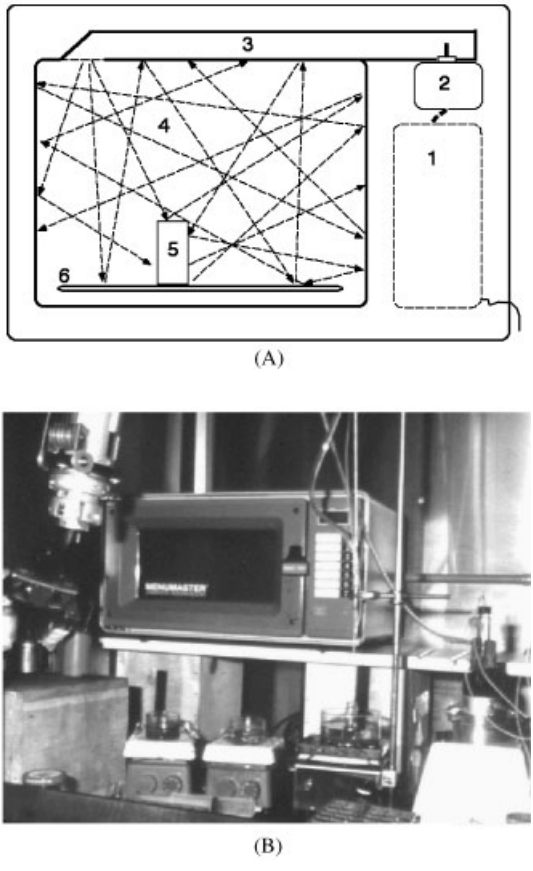

Figure 1. (A) Schematic illustrating operation of a domestic microwave oven. A high voltage power supply (1) drives a magnetron (2) generating microwaves which are brought through a waveguide (3) into the oven (4), where they are randomly reflected and eventually hit the sample (5) placed on a rotating carousel/plate; and (B) The microwave oven placed inside a lead-shielded working area of the Kettering Medical Center's PET laboratory. The door could be opened and closed for insertion and removal of the vessel by a remote manipulator (provided by D-R Hwang)

solution.[13] Devices for process optimization and monitoring have been utilized.[14–17] Household devices were promptly incorporated in set-ups with manipulators to remotely move vessels and open and close the door (Figure 1) and for inclusion in robot-based automation.[18] Monomodal devices designed for the space limitations of radiolabelling environments were also constructed,[15,19,20] some of which have subsequently become commercially available. In this paper we will

attempt to review these developments and their applications in the syntheses of PET radiopharmaceuticals.

Mechanisms underlying microwave dielectric heating

Microwaves are defined as electromagnetic waves with vacuum wavelengths ranging between 0.1 and 100 cm or, equivalently, with frequencies between 0.3 and 300 GHz. The heating properties of microwaves were observed shortly after the invention of radar technology during World War II.[21] Since microwaves are used in telecommunication, the frequency ranges allowed for other applications are limited to a few bands, of which the most common are the 2.45 GHz (2.400–2.500 GHz) and the 0.915 GHz (0.902–0.928 GHz) bands.[22] The corresponding wavelengths in air and in most organic liquids are about 1–30 cm, which are also the dimensions of the microwave applicators and vessels used in radiolabelling chemistry.

The Lorentz force describes the interaction between the electromagnetic field and matter. It is easily shown[4h,23] that the magnetic component does not contribute to the energy transfer. Therefore, we only have to consider the Coulomb interaction of the field with electric dipoles and charges. It is assumed that electric dipoles are responsible for the major part of the coupling. The common understanding of the absorption process is that the oscillating microwave field causes hindered rotations of the solute and solvent molecules, which, through friction, induce heat in the reaction sample. Free or semi-free charges also present as the ionic pairs of dissolved salts or, more recently, in ionic liquids used as solvents will intensify the coupling with the field. The energy absorbed per unit time and volume is proportional to (a) the radial frequency, (b) the square of the electric field in the sample, and (c) the imaginary part of the complex valued electric susceptibility of the load (i.e. the sample and the vessel in which the sample is contained).

Design considerations

The common household multimodal microwave ovens that have been frequently used in microwave-enhanced chemistry give electric fields (*E*-fields) that are highly unstable with regard to variations in the sample geometry and electric susceptibility. More efficient, controllable, and consequently more reproducible devices have instead been sought,

which led to the development of single-mode microwave cavities, in which the electromagnetic waves are given a definite structure through well-defined resonance or standing wave conditions.

Efficient microwave applicators for chemistry should be designed so that strong coupling with the electric field component can be achieved. Consequently, the electric field in the reacting sample should be as strong and as homogeneous as possible. This is not, however, entirely easy to accomplish since the geometrical as well as the dynamical properties of the microwave field are affected by the different electric properties of the samples to be treated.

The sharpness of the resonance condition in a cavity is described by its so-called quality or Q-value,[23] which is defined as the average applied angular frequency times the stored energy divided by the power loss. Resonance conditions vary with the electric susceptibility. Since a compound's electric susceptibility varies with temperature, either an easily variable driving frequency is required or the applicator must be able to maintain a high E-field in the sample when the resonance frequency of the combined sample and applicator system varies during the heating process. Even moderately high power microwave generators with variable frequencies[24] are much more expensive than the commonly used, fixed frequency magnetrons. We are therefore limited to using fixed frequency systems with cavities which can efficiently couple the electric field to the sample and at the same time maintain a strong electric field when the resonance conditions vary slightly. The design of applicators therefore always involves finding a compromise between strong coupling capability and field stability.

The use of microwave devices in PET radiolabelling chemistry places other constraints on the design. The lead-shielded hot cells in which labellings are performed are filled with various, often automated equipment and measuring devices. These restrict the available working space and the accessibility. The part of the microwave device in which the sample is placed should therefore be small.

Most microwave-enhanced chemistry has been performed using domestic microwave ovens. These ovens are multimodal in the sense that no standing waves are present. All objects inside the oven randomly reflect the microwaves (Figure 1(A)). A slight change in the geometry, caused by altered positions of a vessel or by using a slightly different vessel, may considerably change the field intensity inside the sample. The producers of domestic microwave ovens have in fact recognized this

problem. Food is now usually placed on a rotating bottom plate for more even heating averaged over time. Similar, but far more sophisticated laboratory devices with vessels fixed on special rotating carousels have been constructed primarily for microwave-assisted sample preparations via acid digestions.[3]

Multimodal ovens have the obvious advantages of being relatively inexpensive and readily available. The first[12] and majority of the PET radiolabellings have been performed using domestic microwave ovens. Carefully optimizing the conditions have made considerable reductions in reaction times possible, even when treating the very small sample sizes typically used in PET radiochemistry. A hot cell set-up with a multimodal oven is shown in Figure 1(B).

The first single-mode microwave device used for radiolabelling by the Karolinska PET group[13] had a driving power unit, which could be placed outside the hot cell. A coaxial cable supplied the so-called coaxial cavity with the microwave power (Figure 2(A)). This device had a relatively high *Q*-value, which also meant that its performance was sensitive to the geometry of the reaction vessel as well as the vessels used. These experiences led this group to construct a second device with a lower *Q*-value (Figure 2(B)), which was found to be less efficient than the first prototype, but more stable with respect to variations in geometry as well as the electric properties of the reacting sample.[15] These designs were commercially developed to the Microwell 10 (Figure 2(C)), which was marketed by Labwell AB (currently Personal Chemistry AB, Uppsala, Sweden).

A microwave cavity with a flat characteristic (i.e. relatively wide peaks around the resonance frequency) was constructed by the Brussels group and briefly described in preliminary contributions.[19] This cavity has been successfully used in the routine preparation of a number of radiopharmaceuticals.

Monomodal cavity applicators have been constructed for the St Louis PET group[20] (Figures 2(D) and 2(E)). The design is based on a so-called foreshorted 3/4 wave radial microwave cavity as described previously.[25] Both of these have flat characteristics and the Model 520A is commercially developed by Resonance Instruments Inc. (Skokie, IL).

Even with the much more focused and optimized fields of the single-mode devices, the reaction times and power input required for a reaction vary for the different devices. This illustrates how difficult it is to achieve comparably intense and homogeneous fields. The advantages of the single-mode devices over multimodal ovens are clearly evident

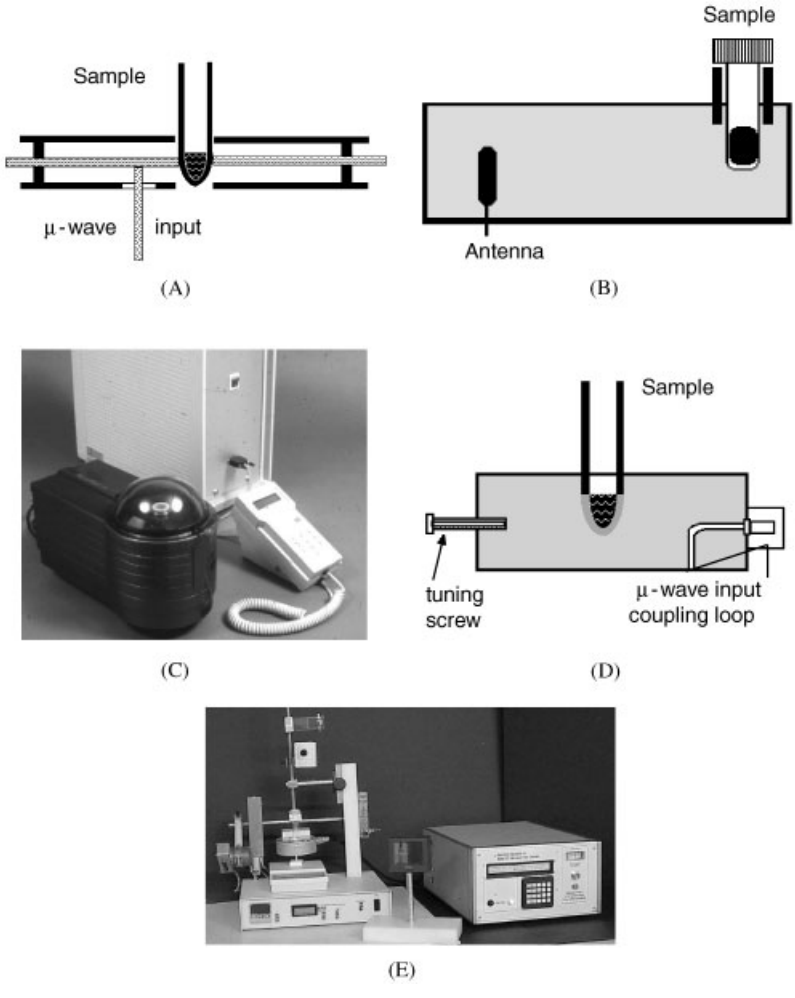

Figure 2. (A) Schematic diagram of the first prototype single-mode cavity used in PET radiosyntheses;[13] (B) Schematic of the second Karolinska prototype cavity[15] designed for the special conditions of PET radiolabellings; (C) Series-produced cavities (MicroWell 10) based on the concepts in Figures 2(A) and 2(B) have been used in a number of PET-related procedures (see Tables 1–9) (Labwell AB, Uppsala, Sweden); (D) Schematic of the St Louis resonance-type prototype cavity,[20] Model 420 BX custom-built by Micro-Now Instruments to improve their results with household microwave ovens; and (E) Laboratory microwave heater, Model 520A, built by Resonance Instruments Inc. (Skokie, IL) for rapidly heating ml volume samples (provided by C. Dence and C. Arnow).

from the results presented in the tables, as are the time gains for both multimodal and single-mode devices compared with conventional heating.

Microwave conditions

Monitoring

In electromagnetic fields, polar organic solvents and reactants can be heated to 'nucleation-limited boiling points' (NLBPt)[6k,26] which can be $\geqslant 20^{\circ}C$ higher than their conventional reflux temperatures. If appropriate vessels which can sustain 10–40 atm. over-pressure are available, boiling point elevations of 50–100°C can be achieved. For every 10°C increase in reaction temperature, the reaction rate should increase by a factor of two, all other factors being constant. In PET radiochemistry, the rapidity with which the samples arrive at these high temperatures can also be a significant factor, since losses due to decay of the radionuclide are further reduced.

Monitoring the effect of the microwave treatment on the sample is the most direct route to understanding the operative physicochemical mechanisms, attaining reproducibility and for building a knowledge base for future predictability. Unfortunately, most conventional monitoring probes are affected by or even incompatible with the electromagnetic field and the first 10 years of microwave-induced chemistry suffered from the lack of or affordability of appropriate devices.

Apart from 'yield'-driven trial-and-error optimization in PET applications, some studies have also used monitoring devices of varying sophistication to quantify effects and optimize conditions. With the open construction of the first monomodal device,[13] visual inspection of the samples allowed relative observations of the effect of condition changes, as reflected in the 'time to start boiling'. Even with this crude method, the importance of geometry, solvent microwave susceptibility and of salt additions could be seen. More direct measurements of sample temperature have been attempted. A thermocouple inserted immediately after the microwave treatment gave a means of following relative changes in conditions.[17] Fiberoptic probes have been placed directly in the sample for more accurately monitoring the temperature during treatment.[16,27] Although the price of these devices is not as prohibitive as 5–10 yr ago, it is still more practical to

use them during process optimization than in routine radiopharmaceutical productions. Calibrated infrared (IR) monitoring of the outside temperature of vessels is now becoming a standard feature of many laboratory synthetic units, but has not, as yet, been used in PET microwave devices.

Measuring the pressure in closed vessels can help maximize the heating of volatile solvents and may also be necessary to avoid exceeding the pressure tolerances of the vessel. Devices used vary from pressure gauges simply connected via tubing through septum-capped Pyrex vessels[15] to those connected to acid digestion bombs capable of withstanding many atmospheres over-pressure.[14] This latter device was used to accurately quantify the effects of adding different amounts of different salts in order to maximize the sample's dielectric coupling with the field.

Reflected power has been used to trim the microwave field for different sample loads in a monomodal device.[19,20] An attempt to use the reflected power for process monitoring was not successful, due to difficulties in calibrating the temperature variations in the sample microwave absorptions.[17] In the same study, however, the monitoring advantage of highly energetic radioactivity was utilized when scintillators were tightly collimated to the bottom (2 cm) reaction zone of the vessel and conditions for achieving controllable heating could thereby be rapidly identified.

Vessels

In microwave dielectric heating, vessels should be chosen with respect to their (1) microwave transparency, (2) chemical inertness, (3) dimensions (allowing for suitable head space and for optimal sample placement in the highest field intensity), and (4) if the vessels are to be closed during heating, they should be able to sustain the pressures generated and be equipped with pressure-releasing safety features. In PET radiochemistry, the usual requirements for accessing the sample for other remote manipulations must also be met.

Microwave chemistry is typically performed in vessels made of Pyrex or quartz or in transparent plastics such as Teflon. However, the latter are not designed for repeated use with very high boiling solvents and are susceptible to explosive failure at high temperatures and/or pressures. Problems with irreproducibility can also be caused sometimes by irregularities in glassware and it is recommended that the vessels either be precisely designed or that other measures are taken to ensure that the

vessels are as homogeneous as possible. Metal vessels are inappropriate, since they are not transparent to microwaves.

Radiolabelling procedures in multimodal microwave devices have typically e.g.[12,28] used the Reacti-vials (2–5 ml) common in conventional heating procedures. A notable exception is the combined glass tube/Parr microwave digestion bomb in the Groningen study of the effect of salt additions on *N*- and *O*-alkylations.[14] In monomodal devices, Pyrex tubes with screw caps and septa and dimensions suited to the geometry of the apparatus have been described.[13,15] A septum can function as a pressure-releasing device and allows for connections to the synthetic set-up by lines or needles inserted prior to and/or after the treatment.

Most procedures are performed with closed vessels either to avoid loss of volatile reactants and radiolabelled products or to utilize the pressure build-up to further increase the sample temperature. Open vessels have, however, been successfully used in the nucleophilic substitutions of [^{18}F]fluoride with non-volatile substrates.[17,20,29,30] In one case,[17] the open vessel was also equipped with a reflux column and a device to monitor for microwave leaks.

Sample compositions

Properties determining the degree to which solvents interact with the electromagnetic field have been discussed in depth elsewhere.[4f,6g] Briefly, polar solvents such as DMSO, DMF, CH_3CN, alcohols, amines, H_2O are microwave-susceptible and heated rapidly while solvents such as ethers, chlorinated hydrocarbons, hydrocarbons are only slightly or not at all heated. The addition of reacting or non-reacting salts changes the dielectric properties of the sample and can be used to improve the microwave heating[13,14,31] and the radiochemical yields as well. Similar to the experiences in microwave digestion procedures,[3] it has been noted that particular caution should be exercised when performing difficult reactions with mineral acids and/or bases.[32] Without process monitoring and careful control of the conditions (e.g. by intermittent cooling between microwave cycles or by using low input powers with open vessels), runaway heating and explosions can be a problem.

Diffusion-dependent reactions utilizing immobilized reagents have been remarkably accelerated with microwave techniques.[5] A preliminary study[33] has indicated that product distributions obtained with these reagents in PET radiochemistry can be different from those obtained in solution. The differences may be due to unfavorable competition

between the nanomolar amounts of the labelling agent and the huge excesses of other counter ions in the resin. The solvent-free techniques so successfully used in other areas of microwave chemistry[5] have only recently been explored in PET radiolabelling problem areas.[27,34a] However, application of these techniques must take into account the difficulty of efficiently mixing the small amounts of radiolabelled reactants with excesses of other, usually solid reagents.

Review of the reported microwave-assisted PET radiolabellings

Microwave techniques in radiolabellings for PET are tabulated in Tables 1–9, according to types of reactions. Both microwave-assisted radiolabelling precursor preparations and their use in the productions of radiopharmaceuticals are given. Since the input power and irradiation times depend on the equipment used, the equipment is designated here as 'mmo' for the multimodal commercially available microwave ovens (see references for model and supplier) while the specially designed single-mode (sm) devices are individually specified (see abbreviations). Since the reagents used contribute to the sample's microwave susceptibility, these components are also given. Comparisons with conventionally heated reactions, when made in the individual references, are also included here. Preliminary abstracts are only included when they have not, to our knowledge, been published as a full paper.

Special observations

Ever since the early reports that reacting samples could be highly accelerated by microwave irradiation, so-called 'special microwave effects' due to sample interactions with the rapidly reversing electromagnetic field have been sought, but difficult to prove. Instead, most of the observations have been explained by the highly elevated solvent boiling temperatures, to the extremely rapid rate of heating, to the increased mobility of the reactants, to local 'hot spots' in the sample, etc.[6] However, several consequences of heating with microwave irradiation have had 'special' ramifications for PET radiolabelling applications. First, simply being able to speed up the reactions presented in the tables meant more product obtained at end of synthesis, due to the short half-lives of the reactants. Saving 5 min in a synthesis with

Table 1. Gas phase/discharge labelling precursor syntheses

Reactants	Product	Reference	Microwave equipment	Microwave			Conventional		
				Power (W)	Time (min)	Yield (%)	Temp (°C)	Time (min)	Yield (%)
$^{13}N_2 + H_2$	[^{13}N]NH_3	9	Evenson discharge cavity	100	10	65			
$H^{18}F + F_2$	[^{18}F]F_2	10	Discharge cavity	100	5	3			
$^{11}CO_2 + H_2 + N_2$	[^{11}C]HCN	11	Raytheon PGM-10	50	15	37			
$^{11}CO_2 + H_2S + Ar$	[^{11}C]CS_2	11	Raytheon PGM-10	<20	15	10			

Table 2. Nucleophilic aromatic substitutions with [^{18}F]fluoride: $^{18}F^- + R\text{-}Ph\text{-}X \rightarrow R\text{-}Ph\text{-}^{18}F$[a]

Reaction product	R	X	Use	Reference	Equipment/ solvent/ reagents	Microwave			Conventional		
						Power (W)	Time (min)	Yield (%)	Temp (°C)	Time (min)	Yield (%)
4-[^{18}F]-benzonitrile	1-CN	4-NO_2	Precursor	12	mmo/A/II	500	5	68	135	5	52
										30	82
				36	sm1/A/I	20	0.5	65	150	10	40–70
				33	sm2/B/resin	20	0.5	40–50			
				20	sm4/A/ns	150	0.15	46	135	5	52
					mmo/A/ns	500	5	68			
		4-NMe_3^+	Label oligo-nucleotides	35	sm3/A/I	100	1	95	180	20	80–85
2-[^{18}F]-benzonitrile	1-CN	2-NO_2	Precursor	36	sm1/A/I	20	0.5	74	150	15	65
4-[^{18}F]-benzaldehyde	1-CHO	4-NO_2	4-[^{18}F]-dexetimide	37	mmo/B/I	500	4	50–60			
			Precursor	36	sm1/A/I	20	0.5	75	85–110	20	70
			[^{18}F]fluoro-bepridil	38	ns/B/I	ns	5	ns			
			Nonactivated aromatics	39	mmo/A/I	300	2	65	145	20	65
		4-Br	Precursor	36	sm1/A/I	20	1.5	13	85–110	20	3
		4-Cl	Precursor	36	sm1/A/I	20	0.5	6	85–110	20	1
		4-NMe_3^+	Precursor	36	sm1/A/I	20	0.25	74	120	10	70
2-[^{18}F]-benzaldehyde	2-CHO	2-NO_2	2-[^{18}F]-dexetimide	37	mmo/B/I	500	4	50–60			
			Nonactivated aromatics	39	mmo/A/I	300	2	65	145	20	65
			Precursor	36	sm1/A/I	20	0.25	76	120	10	78
			Precursor	20	sm4/A/ns	150	0.1	67	135	5	55
				20	mmo/A/ns	500	5	65			

Table 2. (*continued*)

Reaction product	R	X	Use	Reference	Equipment/ solvent/ reagents	Microwave			Conventional		
						Power (W)	Time (min)	Yield (%)	Temp (°C)	Time (min)	Yield (%)
4-[^{18}F]-3-OMe-benzaldehyde	1-CHO 3-OMe	4-NO_2	Nonactivated aromatics	39	mmo/A/I	300	2	55	145	20	55
2-[^{18}F]-4-OMe-benzaldehyde	1-CHO 4-OMe	2-NMe_3^+	2-[^{18}F]-tyrosine	19	sm5/ns	ns	ns	70			
		2-NO_2	Nonactivated aromatics	39	mmo/A/I	300	2	75	145	20	75
2-[^{18}F]-4,5-OMe_2-benz-aldehyde	1-CHO 3,4-OMe_2	2-NO_2	Nonactivated aromatics	39	mmo/A/I	300	2	50	145	20	50
			Precursor	36	sm1/A/I	20	0.5	53	120	10	23
		2-NMe_3^+	6-[^{18}F]-DOPA	19	sm5/ns	ns	ns	60			
6-[^{18}F]-piperonal	1-CHO 3,4-OCH_2O	6-NO_2	Precursor	36	sm1/A/I	20	0.25	51	120	10	51
3-[^{18}F]-6- CF_3-benzaldehyde	6-CF_3 1-CHO	3-NO_2	Precursor	40	mmo/A/I	800	2.5	65			
			[^{18}F]-FTP	41	mmo/A/I	800	2.5	65			
1-[^{18}F]-3-nitro-5-CF_3-toluene	5-CF_3, 3-NO_2	1-NO_2^-	[^{18}F]TFMPP	42	mmo/A/I	800	2.5	70	150	45	79
			^{18}F-labelled EFGR-TK inhibitors	43	mmo/A/I	750	2.5–3.5	ns			
3-[^{18}F]-6-CF_3-benzaldehyde, *i*-propylimine	6-CF_3, 1-CH = N-*i*Pr	3-NO_2	Model reaction	40	mmo/A/I	800	2.5	20			
4-[^{18}F]-aceto-phenone	1-C(O)-CH_3	4-NO_2	Precursor	12	mmo/A/II	500	5	25	135	5	10
										30	22
			Fluoroalkyl-benzenes	44	mmo/A/I	500	5	40–50			

		4-[^{18}F]-phenacyl bromide	45	mmo/A/I	500	5	55–60				
		4-[^{18}F]-phenacyl bromide -> proteins	46	mmo/A/I	500	5	55–60				
		4-[^{18}F]-fentanyl	47	mmo/A/I	ns	5	50				
		Precursor	48	mmo/A/I	700	5	44				
	4-F	Precursor	12	mmo/A/II	500	5	70	135	5	12	
									30	73	
	4-I	Precursor	48	mmo/A/I	700	5	4				
	4-NMe_3^+	Precursor	48	mmo/A/I	700	2.5	55				
2-[^{18}F]-aceto-phenone	2-NO_2	Precursor	36	sm1/A/I	20	0.4	11				
	1-C(O)-CH_3	Precursor	48	mmo/A/I	700	5	44				
	2-I	Precursor	48	mmo/A/I	700	5	4				
	2-NMe_3^+	Precursor	48	mmo/A/I	700	2.5	55				
4-[^{18}F]-Ph-CO_2-t-Bu	4-NMe_3^+ 1-CO_2-tBu	Fluorobenzyl-octreotide	49	sm4/A/II	ns	0.5	50				
4-[^{18}F]-Ph-CO_2Et	4-NMe_3^+ 1-CO_2Et	^{18}F-labelled peptides	50	sm, ns/A/ns	ns	ns	ns				
4-[^{18}F]-Ph-C(O)cprop	4-NO_2 1-C(O)-cprop	Precursor	12	mmo/A/II	500	5	77	135	5	24	
									30	80	
		[^{18}F]spip-erone	51	mmo/A/II	500	5	81	140	25	80	
		Fluoroalkyl-benzenes	44	mmo/A/I	500	5	70				
		[^{18}F] (3-N-methyl)-benperidol	52	mmo/A/II	500	8	87				

Table 2. (*continued*)

Reaction product	R	X	Use	Reference	Equipment/ solvent/ reagents	Microwave			Conventional		
						Power (W)	Time (min)	Yield (%)	Temp (°C)	Time (min)	Yield (%)
			[^{18}F]butyro-phenones	53	mmo/A/I	700	5	60			
		4-NMe_3^+	[^{18}F]butyro-phenones	53	mmo/A/I	700	5	67			
4-[^{18}F]-4-fluoro-benzophenone	1-C(O)-PhF	4-NO_2	Model reaction	13	sm1/A/I	35	1	30	160	25	40
4-[^{18}F]-4'-nitrobenzo-phenone	1-C(O)-$PhNO_2$	4-F	Model reaction	13	sm1/A/I	35	2.5	20	80	25	42
4-[^{18}F]-benzo-phenone	1-C(O)-Ph	4-NO_2	Precursor	36	sm1/A/I	20	0.5	81	160	10	66
2-[^{18}F]-anisole	1-OCH_3	2-NO_2	Model reaction	36	sm1/A/I	20	0.5	8			
3-[^{18}F]-anisole	1-OCH_3	3-NO_2	Model reaction	36	sm1/A/I	20	0.5	12			
4-[^{18}F]-anisole	1-OCH_3	4-NO_2	Model reaction	36	sm1/A/I	20	0.5	4			
4-[^{18}F]-1-CF_3-benzene	1-CF_3	4-NO_2	Model reaction	20	sm4/A, ns	150	0.15	20	135	20	20
				20	mmo/A/ns	500	3	16			
2-[^{18}F]pyridine	PyrN	2-NO_2	Model reaction	54	sm3/A/I	100	2	88	180	10	88
		2-Br	Model reaction	54	sm3/A/I	100	2	71	180	20	87
		2-I	Model reaction	54	sm3/A/I	100	2	14	180	20	19
		2-NMe_3^+	Model reaction	54	sm3/A/I	100	1	96	150	5	89
[^{18}F]cinnamic acid deriv	HC=CR	2-NO_2	GBR-12783	55	mmo, ns	ns	5	25–40	ns	5	0 *dec*

Cholesteryl-*p*-[^{18}F]-benzoate	C(O)OR	4-NO_2	Adrenyl agent	56	sm4/A/II	100/250	0.25/0.75	70–83	148	40	75
				56	mmo/A/II	800	5	0			
[^{18}F]F-A85380	1-PyrN 3-OR	2-NO_2	nAChR ligand	29	sm3/A/I	100	1	57–71	150	20	55–70
[^{18}F]norchloro-fluoroepi-batidine	1-PyrN 5-R	2-Br	nAChR ligand	57	sm3/A/I	100	2.5	72	180	10	ns
		2-NO_2	nAChR ligand	57	sm3/A/I	100	1	49	150	10	ns
[^{18}F]altanserin	C(O)Ar	4-NO_2	5-HT_2 antagonist	28	mmo/A/I	150	5	40	135	30	5–10
[^{18}F]altanserin	C(O)Ar	4-NO_2	5-HT_{2A} antagonist	58	mmo/B/I	50%	3.5	53			
[^{18}F]-Deut-altanserin	C(O)Ar	4-NO_2	5-HT_{2A} antagonist	58	mmo/B/I	50%	3	48			
[^{18}F]-MPPF	1-C(O)-NAr	4-NO_2	5-HT_{1A} antagonist	59	mmo/A/I	500	3	40	150	20	16
[^{18}F]Org13063	1-C(O)-NHR	4-NO_2	5-HT_{1A} antagonist	60	mmo/A/I	700	5	20			
^{18}F-labelled nitrophenyl carbamate	1-RO_2C-NH 3-NO_2	4-NO_2	DA uptake inhibitor	61	mmo/C/I	500	5	55	150	30	65

[a] Equipment: mmo = commercial multi-modal microwave oven. sm = single mode: 1: Karolinska prototype 1;[13] 2: Karolinska protype 2;[15] 3: Microwell 10; 4: St Louis protoype, Micro-Now 420-BX;[20] 5: Brussels cavity;[19] 6: Hammersmith cavity.[16]
Solvents = A: DMSO; B: DMF; C: CH_3CN; D: ROH; E: H_2O.
Reagents = I: K_2CO_3, Kryptofix 222; II: R_4NOH.
ns = not specified, * = with intermittent cooling.

Table 3. Nucleophilic aliphatic substitutions with [^{18}F]fluoride: $^{18}F^- + RX \rightarrow R^{18}F$[a]

Reaction product	X	Use	Reference	Equipment/ solvent/ reagents	Microwave			Conventional		
					Power (W)	Time (min)	Yield (%)	Temp (°C)	Time (min)	Yield (%)
Epi-[^{18}F]-fluorohydrin	OTs	[^{18}F]-fluoro-misonidazole	62	mmo/A/I	500	3	70–80	100	12	
$CH_3^{18}F$	NMe_2R	Blood flow agent	63	mmo/A/I	700	3	67	120	ns	25
[^{18}F]Fluoroethylamine	OTs	[^{18}F]FEMTU	64	mmo/C/I	650	5	56			
2-[^{18}F]-2-CF_3-4,4-dimethyl-2-oxazoline	Br	Radiolabelling precursor	65	sm2/B/I	50	0.25	59	110	20	9
$^{18}F(CH_2)_3Br$	Br	Radiolabelling precursor	33	sm2/B/resin	20	0.5	30–40			
			33	sm2/I	20	0.5	30–40			
^{18}FDG-Ac_4	OTf	[^{18}F]FDG	66	mmo/C/I	90	0.5	77	60	2	80
			19	sm5/C/I	ns	ns	ns			
			17	sm3/C/I	80	0.67	95	95	3	85
			33	sm2/C/resin	20	1	60–75			

[a] For abbreviations see Table 2 footnote.

Table 4. Nucleophilic aliphatic substitutions with [^{11}C]cyanide: $^{11}CN^- + RX \rightarrow R^{11}CN$[a]

Reaction Product	X	Use	Reference	Equipment/ solvent/reagents	Microwave			Conventional		
					Power (W)	Time (min)	Yield (%)	Temp (°C)	Time (min)	Yield (%)
nca [1-^{11}C]-4-hydroxy-butyronitrile	Br	Precursor for busulfan	31	sm1/D	50	0.5	60	90	7	60
ca [1-^{11}C]-4-hydroxy-butyronitrile	Cl	Precursor for busulfan	31	sm1/D/CN	70	0.5	42	90	7	18
nca PivCO$_2$-CH$_2^{11}$CN	Cl	Difunctional precursor	67	sm2/D	100	0.25	91	80	2	91
			33	sm2/D/resin	ns	ns	70			

[a] For abbreviations see Table 2 footnote.

Table 5. N-,O-,S- alkylations with [^{11}C]alkylhalides: $^{11}RX + R_nYH \rightarrow R_nY^{11}R + HX$[a]

^{11}RX	Y	Reaction product	Reference	Equipment/ solvent/reagents	Microwave			Conventional		
					Power (W)	Time (min)	Yield (%)	Temp (°C)	Time (min)	Yield (%)
$^{11}C_2H_5I$	S	Thioureas; NOS inhibitors	68	mmo/B	500	4	>80			
$^{11}CH_3I$	N	Carbamoyl cocaine analogs	69	mmo/A,B,C	500	10	17	135	10	9
$^{11}CH_3I$	N	CGP 20712A, β_1-adrenoceptor ligand	70	mmo/C/KOtBu	600	1.5	5	110	20	5
$^{11}CH_3I$	N *amide*	Flumazenil, BzD antagonist	15	sm2/B/NaOH	50	0.5	80	70	5	45
$^{11}CH_3I$	N	[^{11}C]HYMAP, 5-HT$_{1A}$ agonist	71	sm2/B/K_2CO_3	60	1 + *	30–40			
^{11}C-*n*-PrI	N	[^{11}C]PHNO, D2 agonist	16	sm6/B/$NaHCO_3$	ns	10	20–25	130	10	7–10
^{11}C-*n*-PrI	N	[^{11}C]8-OH-DPAT, 5-HT$_{1A}$ agonist	72	sm2/B/TMP, K_2CO_3	100	0.6	50–60			
^{11}C-*i*-PrI	O *acid*	Nimodipine, Ca antagonist	15	sm2/B/K_2CO_3	30	1	>95	120	10	60–80

[a]For abbreviations see Table 2 footnote.

Table 6. N-,O-,S- alkylations with [^{18}F]alkylhalides: $^{18}FRX + R_nYH \rightarrow R_nY^{18}FR + HX$[a]

^{18}FRX	Y	Reaction product	Reference	Equipment/ solvent/reagents	Microwave			Conventional		
					Power (W)	Time (min)	Yield (%)	Temp (°C)	Time (min)	Yield (%)
^{18}F-alkyl-Cl	N	[^{18}F]spiperone, DA antagonist	51	mmo/1-methyl 2-pyrrolidinone/KI	500	2.5	19	140	25	17
^{18}F-epoxide	N	[^{18}F]-fluoro-misonidazole	62	mmo/C/*N*,*N*-di-isopropylethylamine	500	12	65	100	50	
$^{18}F(CH_2)_2I$	N	*N*-fluoroalkyl aporphines	14,73, 74	mmo/C/KI, $NaHCO_3$	600	7.5 + *	13	110	h	0
$^{18}F(CH_2)_3I$	N	*N*-fluoroalkyl aporphines	14,73, 74	mmo/C/KI, $NaHCO_3$	600	10 + *	29	110	h	0
$^{18}F(CH_2)_3I$	N	5-Hydroxy-2-aminotetralins	14, 75	mmo/C/KI, $NaHCO_3$	600	7.5 + *	11	120	70	6

[a]For abbreviations see Table 2 footnote.

Table 7. Nucleophilic condensations with [^{11}C]cyanide/Addition reactions/Cyclization[a]

Type of reaction	Reaction product	Reference	Equipment/ solvent/reagents	Microwave			Conventional		
				Power (W)	Time (min)	Yield (%)	Temp (°C)	Time (min)	Yield (%)
$^{11}CN^-$ with aldehyde bisulfite adduct	Hydantoin for D,L-[1-^{11}C]-tyrosine	31	sm1/E/KCN, $(NH_4)_2CO_3$, NaOH	80	0.5	ns	170	10	ns
		76	sm/E/$(NH_4)_2CO_3$	50	0.3	81			
	Hydantoins for D,L-[1-^{11}C]amino acids	77	mmo/E/$(NH_4)_2CO_3$	600	0.5	ns			
Diels Alder	Antagonist at TCP site/ NMDA receptor	78	mmo/AcOH:TFE 1:99	500	6	20			
Amidation (peptide conjugation)	^{76}Br-PhC(O)NH-octreotide, somatostatin	79	sm3/CH_2Cl_2	10	30	70–90	All		Not > 20
Amidation (peptide conjugation)	^{76}Br-PyrC(O)NH-octreotide, somatostatin	79	sm3/CH_2Cl_2	10	30	50			

[a] For abbreviations see Table 2 footnote.

Table 8. Hydrolyses/alcoholysis[a]

Group	Reaction product	Reference	Microwave equipment/reagents	Microwave			Conventional		
				Power (W)	Time (min)	Yield (%)	Temp (°C)	Time (min)	Yield (%)
$R(OAc)_4$	[^{18}F]FDG	19	sm5/HCl	ns	ns	ns			
		33	sm2/E/resin	20	1	>80			
		17	sm3/HCl	80	6	97	95	9–15	95
Hydantoin	D,L-[1-^{11}C]tyrosine	31	sm1/E/NaOH	80	0.5	60 *tot*	170	10	40–60
		33	sm2/E/resin	ns	ns	15 *tot*			
		76	sm/NaOH	ns	0.1	ns			
Hydantoin	D,L-[1-^{11}C]-phenyl alanine, D,L-[1-^{11}C]-DOPA, D,L-[1-^{11}C]-methionine, D,L-[1-^{11}C]-leucine	77	mmo/NaOH	600	0.45	40–60 10 40–60 70–80			
[^{11}C]ethyl ester	$HO_2C^{11}CO_2H$ for [^{11}C]DHQX, [^{11}C]DCQX, [^{11}C]ACEA1021	32, 80, 81	sm1/E/HCl	70	0.25	100	150	2	100
[^{11}C]ethyl ester	Ro 15-3890, BzD metabolite	15	sm2/B/NaOH	50	0.5	>95	70	2	40
[^{11}C]ethyl ester	$HOCH_2\,^{11}CO_2H$, precursor	67	sm2/H_2SO_4	75	0.25	90	120	5	90
[^{11}C]nitrile, then cyclize to lactone	[1-^{11}C]-γ-butyrolactone	31	sm1/H_2SO_4	50	1	≥80	150	10	‡80
[^{11}C]nitrile	$EtOC(O)^{11}CO_2Et$, for [^{11}C]DHQX, [^{11}C]DCQX, [^{11}C]ACEA1021	32, 80, 81	sm2/EtOH/$HCl_{(g)}$	70	0.5	90	60	10	90
[^{11}C]nitrile, with protecting group removal	$HOCH_2\,^{11}CO_2Et$, precursor	67	sm2/EtOH/$HCl_{(g)}$	75	0.5	93	80	10	93
^{18}F-oxazoline, with protecting group removal	[^{18}F]CF_3CO_2Et, precursor	82	sm2/EtOH/H_2SO_4	30	0.3	60–80			

[a] For abbreviations see Table 2 footnote.

Table 9. Miscellaneous[a]

Reaction	Product	Reference	Equipment/ solvent/reagents	Microwave			Conventional		
				Power (W)	Time (min)	Yield (%)	Temp (°C)	Time (min)	Yield (%)
Reductive amination with acetone	Model reaction	12	mmo/A/II	500	1.5	64	110	10	67
Decarbonylation	4-^{18}F-PhCH = CH_2 Precursor	83	mmo/benzonitrile/ $RhCl(PPh_3)_3$	ns	2	70			
Di-amidation, hetero-cyclization	Quinoxaline-2,3-dione	27	sm3/*p*-TsOH	ns, 140°	2.5	94			
OMe deprotection	Phenol, Model reaction	34a	sm3/LiI, solid supports	ns	ns				
	Phenol	34b	CH_3SO_3H	100	0.2	75			
	Desmethyl PD153035	34b	CH_3SO_3H	75	0.6	85	200	10	70

[a]For abbreviations see Table 2 footnote.

carbon-11, for example, gives 15% more product. Furthermore, several reactions[14,55,65,79] could only be achievable in useful yields by using microwave heating. Less reactive substrates could be successfully used, thereby widening the range of potential starting materials.[31,36,57] Non-reacting salts were added to the media to increase the coupling with the electromagnetic field and consequently raise the temperature[13] and this phenomenon could be exploited to increase radiolabelling yields.[14,31] With microwave heating, the amount of starting material required for driving the pseudo first order labelling reaction could sometimes be reduced, which saved precious precursors and simplified clean-up procedures[28] and decreased the competing reactions with other reactive sites in the starting material.[65] The microwave susceptibility of ionic species, in particular aromatic ammonium salts, in the electromagnetic field has been cleverly employed as a route for synthesizing the labelled volatile decomposition product, $CH_3^{18}F$, to be used as a blood flow tracer.[63] Finally, by using a solvent with low microwave susceptibility and a low input power for a relatively long exposure (30 min), the prosthetic group labelling of the *N*-terminal of octreotide could be accomplished by microwave, but not by conventional heating at a range of different temperatures.[79] It is tempting to conjecture that in this reaction the radiolabelling precursor's access to the *N*-terminal had been facilitated by the oscillating electromagnetic field.

Reflections on microwaves in a wider perspective

Publications on the applications of microwaves span over fields as divergent as organic, inorganic, pharmaceutical, analytical, polymer and physical chemistry, ceramics, engineering, chemical physics and material sciences. It is impossible in the context of this paper to summarize all the many interesting findings, which can potentially be useful for the radiolabelling field in the future. A number of excellent reviews are available[4–6] which summarize the multitude of organic transformations which have been aided by microwave heating, provide relevant data of importance for performing chemistry in microwave fields and discuss the hypotheses proposed about the mechanisms at work. Only a few are therefore briefly commented on here.

Of current radiosynthetic interest? Microwaves have been used to accelerate an increasing number of metal catalyzed carbon–carbon bond formations.[4i] These reactions, a popular means of fine-tuning the

structures of lead compounds in pharmaceutical research, are relatively new PET radiolabelling strategies, which should likewise benefit from microwave heating. Ring-forming reactions (heterocyclizations, condensations, Diels Alder, etc.) that generally require high temperature and long reaction times have also been accelerated by microwave treatment.[4j] Implementing these experiences in PET chemistry could catalyze the development of new bifunctional precursors and provide new routes for introducing the radiolabel in more metabolically stable positions.

'*New*' *media?* At the very high temperatures achievable in pressurized vessels with microwave heating, the dielectric constant of water approaches that of acetone. So water can, under these conditions, essentially be considered a pseudo-organic solvent. This characteristic has been used for 'environmentally friendly' syntheses by avoiding organic solvents and for facilitating organic product isolations after the microwave treatment.[84] It would be interesting to see whether these 'pseudo-organic' characteristics of water could be exploited in radiolabelling. The potential utilization of ionic liquids in microwave treatments is also of interest. As extremely microwave-susceptible media, they should be instantaneously heated to very high temperatures. The synthesis of ionic liquids has been aided by microwave heating,[85] but temperature monitoring and controllable microwave conditions would be necessary for their safe and reproducible handling as solvents.

Equipment developments: As the application of microwaves in different areas is widening, the incentive for designing new equipment from down to multi-microliter and up to liter sample volumes is also increasing. On-line monitoring methods are becoming standard features of new microwave devices, since they have been proven to be invaluable in finding optimal reproducible reaction conditions. The volumes used in PET radiolabelling do not differ greatly from those used in high throughput, drug discovery, which is currently one of the most microwave-active areas of development. Just as the results with the single-mode devices of PET radiolabelling laid the foundation for further instrumental evolvement, that very evolution may someday solve the problems of finding the equipment most suitable for special synthetic circumstances.

Conclusion

When presenting the PET applications reviewed here for other microwaving specialists, we often hear that we must be the only ones

who do not ever have to justify why we want to do reactions faster. In spite of that, even in this field of performing chemistry against the clock, microwave devices are still not standard components in radiolabelling set-ups. Why not? There are of course many other methods which can be employed to reduce production times, e.g. by using more reactive precursors and substrates, new catalysts, new solvent systems, supercritical conditions, optimizing isolation procedures, etc. All of these are important parts of the arsenal of techniques used in radiolabellings with short-lived radionuclides. The cost and relative unavailability of appropriate microwave devices have certainly been factors that have hampered their more widespread implementation. And if an apparatus does become a dedicated part of a radiopharmaceutical production, then a second would be needed for new developmental work.

Why microwave then? *For one*, either by just forcing the reaction to go or by favorably tilting the balance between desired and undesired reactions, microwave heating allows us to sometimes do what cannot be achieved by other methods in the time frame we have available. The advantages of doing things faster in labellings with short-lived radionuclides are unique. With a more efficient synthesis, you can choose to work with less radioactivity (the shorter cyclotron bombardments will also reduce the total production times). Or you can keep the same amount of starting activity and instead take the pay-off in a higher specific radioactivity or in more product for the intended PET applications. *For another*, the way in which the electromagnetic field affects sample components compels us to rethink our solvent and catalyst choices, to revise our ingrained thinking about the implications of relative substrate reactivity, and to take a more macroscopic view of the dynamics of the physicochemical forces at work in these reactions. All of these aspects, when put to practical application in synthesis designs, can lead to new radiosynthetic strategies. *And finally*, microwave-assisted chemistry is still a very young field. The transformations that have been tested with microwave heating are relatively few. The reasons for the microwave effects are still intensely debated. For those of us who are mechanistically curious, working with a technique that surprises you and awakens your curiosity is undoubtedly an added plus over all the other advantages offered by the technique. We look forward to the day when access to application-optimized microwave devices in the chemical and radiochemical laboratory is as unquestioned as it is today for applications in the home.

Acknowledgements

Support from the Swedish National Board for Technical Research (210-1997-494) is gratefully acknowledged. This paper was, in part, initiated through the EU sponsored D10 COST program (Innovative Methods and Techniques for Chemical Transformations).

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