Application of Microwave Technology to the Synthesis of Short-lived Radiopharmaceuticals

D.-R. Hwang, S. M. Moerlein, L. Lang, and M. J. Welch*

The Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, 510 S. Kingshighway, St. Louis, MO 63110, U.S.A.

Using the rapid heating capability of microwave ovens, short-lived radiopharmaceuticals can be prepared with decreased reaction times and hence higher radiochemical yields.

Microwave ovens have been used in many laboratory procedures, including organic synthesis,[1] metallurgical processing,[2] biological sample preparation,[3] and gas-phase reactions leading to radiolabelled precursors.[4] When they were applied to organic syntheses a substantial rate increase was observed, which was attributed to the effect of higher pressure and superheating of the solvent.[1]

It has always been a challenging task to prepare radiopharmaceuticals labelled with short-lived radionuclides rapidly and in high radiochemical yield, particularly with the positron-

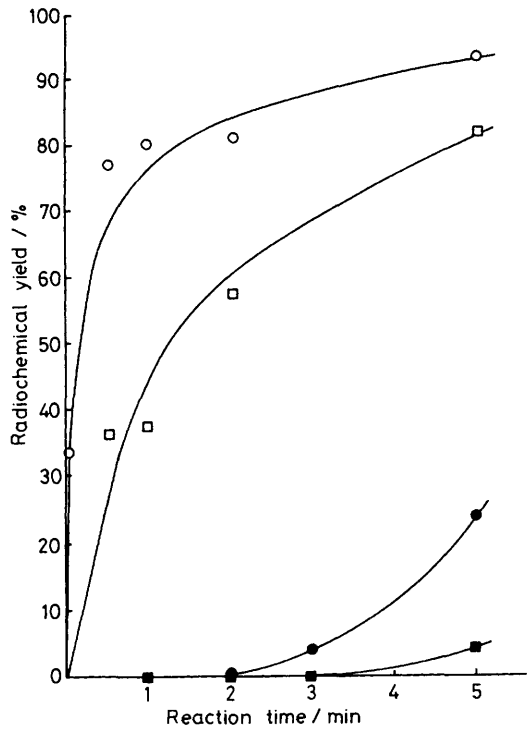

Figure 1. Effect of microwave pre-treatment of reaction vessel on the isotopic exchange reaction $^{131}I^- + p\text{-}I\text{-}C_6H_4\text{-}X \rightarrow p\text{-}^{131}I\text{-}C_6H_4\text{-}X$. Filled symbols, no pre-treatment of vessel; empty symbols, vessel pre-treated 30 min. ● and ○, X = NO_2; ■ and □, X = OMe. Reaction conditions: 25—50 μCi $^{131}I^-$/ 5 μl 0.1 M NaOH, 0.5 mg IC_6H_4X, 0.25 mg CuCl, 0.1 ml DMSO. Each data point represents the mean from 2—3 expts.

emitting nuclides iodine-122 ($t_{\frac{1}{2}}$ = 3.6 min), carbon-11 ($t_{\frac{1}{2}}$ = 20 min), and fluorine-18 ($t_{\frac{1}{2}}$ = 110 min).[5] The increased rates reported using microwave technology provide a means of decreasing reaction time, and thus increasing the final radiochemical yield of radiopharmaceuticals. We report here the results of the application of microwave heating technology to the synthesis of a variety of labelled organic compounds that are representative of radiopharmaceuticals. This technique has led to a dramatic increase in isolated radiochemical yields, since reaction time is the most critical factor in the synthesis of rapidly-decaying radiopharmaceuticals.

We have compared conventional heating with microwave treatment for the nucleophilic substitution reactions of activated nitrobenzenes with ^{18}F-fluoride, and isotopic exchange reactions of activated and deactivated halogenoarenes using ^{18}F-fluoride and ^{131}I-iodide. These reactions are commonly used in procedures for radiopharmaceutical production. No-carrier-added (NCA) ^{18}F-fluoride was produced by the $^{18}O(p,n)\,^{18}F$ nuclear reaction on enriched ^{18}O-water using the Washington University CS-15 cyclotron, and was used for fluorination reactions following resolubilization into dimethyl sulphoxide (DMSO) with tetrabutylammonium hydroxide.[6] For the iodination reactions, 5 μl of a solution of ^{131}I-iodide in 1 nM NaOH (prepared from $Na^{131}I$, 1641 Ci/mmol in 0.1 M NaOH from New England Nuclear) was used. The isotopic exchange reactions of ^{131}I-iodide were catalysed with 0.05 ml of CuCl solution (5 mg/ml DMSO).[7] All reactions were carried out in sealed 3 ml Reacti-vials (Alltech Associates Deerfield, IL) and heated by either a Kenmore microwave oven (model 565.8728611, 500 W), or by an aluminium

Table 1. Fluorination yields for the aromatic substitution reaction

$$^{18}F^- + p\text{-}X\text{-}C_6H_4\text{-}G \rightarrow p\text{-}^{18}F\text{-}C_6H_4\text{-}G$$

		Radiochemical yield[a]			
		Microwave	135 °C		
X	G	5 min	5 min	30 min	Lit.
NO_2	CN	68 ± 5	52 ± 2	82 ± 2	81,[10] 50[11]
NO_2	COMe	25 ± 3	10 ± 5	22 ± 1	31[10]
NO_2	$CO[CH_2]_2CH_2$	77 ± 5	24 ± 7	80 ± 1	65[10]
F	COMe	70 ± 1	12 ± 2	73 ± 2	34[11]

[a] Reaction conditions: 0.7—3.5 mCi $^{18}F^-$, 0.25 μmol Bu^t_4NOH, 0.5 mg XC_6H_4G, 0.1 ml DMSO. Data represent the mean from 2—4 expts.

heating block. Reaction conditions were identical for each set of experiments. A total volume of 0.1 ml was employed, with substrate concentrations of 5 mg/ml DMSO. Radiochemical yields were determined by either aqueous–organic (CH_2Cl_2) extraction followed by h.p.l.c. analysis of the organic phase (for the ^{18}F expts.), or by direct h.p.l.c. analysis of the reaction vessel contents (for the ^{131}I reactions).

Although there have been recent advances in the regioselective introduction of low specific activity ^{18}F onto aromatic rings *via* fluorodemetallation reactions with elemental fluorine or acetyl hypofluorite,[8] in many cases high specific activity ^{18}F-labelled products are required, as in the preparation of spiperone analogues.[9] High-specific activity ^{18}F-labelled radiopharmaceuticals can be produced only with nucleophilic reactions of NCA ^{18}F fluoride. Table 1 shows examples of NCA nucleophilic aromatic fluorination (^{18}F-for-NO_2 or -^{19}F) reactions[10,11] in which the speed of radiofluorination was enhanced by the application of microwaves. These aromatic systems had intermediate reactivity toward nucleophilic substitution; rings of greater activation (G = *o,m,p*-NO_2) underwent rapid fluorination with both microwave treatment or conventional heating, while aromatic systems deactivated toward nucleophilic attack (G = H, F, Me, OMe) had poor labelling yields using either treatment. As seen in Table 1, NCA fluorination yields after 5 min of microwave heating significantly exceeded those from conventional heating for the same interval, and in most cases were approximately equal to those obtained after 30 min at 135 °C. The shorter microwave treatment relative to conventional heating not only leads to less decay of the radio-labelled product during synthetic procedures, but may also cause less degradation of reagents and generation of side-products which make isolation of the desired labelled compound difficult.

Radioiodinated compounds have been employed in biomedical research for many years.[12] When microwave heating was applied to isotopic exchange reactions of ^{131}I-iodide, a substantial increase in the rate of the labelling reaction took place. Within minutes all absorbed microwave energy apparently warmed both the Reacti-vial and the reagents: when the Reacti-vial was preheated in the microwave oven for 30 min, isotopic exchange of ^{131}I iodide reached completion within 5 min in substrates both activated and deactivated toward nucleophilic substitution (see Figure 1). Aromatic iodination yields exceeding 80% were obtained within 60 s, indicating the utility of this technique for syntheses with positron-emitting I^{122} ($t_{\frac{1}{2}}$ = 3.6 min) as well as with γ-emitting ^{123}I ($t_{\frac{1}{2}}$ = 13.2 h).

Considerable effort has been invested by research groups in the development of rapid synthetic methods for the incorpora-

tion of ^{11}C into organic radiopharmaceuticals.[5] We chose the reductive amination of *N*-methylaniline with acetone as a model reaction because it has been used for the synthesis of ^{11}C-pindolol.[13] Using 0.03 equiv. of acetone, yields (based on acetone) of *N*-isopropyl-*N*-methylaniline as high as 64% could be achieved within 90 s using microwave heating. Under conventional heating at 110 °C for 10 min, the yield was 67%. This clearly illustrates the applicability of this technique to the synthesis of ^{11}C-labelled radiopharmaceuticals, as the decrease in reaction time, 8.5 min, corresponds to 25% less decay and higher yield of the 20 min half-life compound.

For multi-step syntheses microwave technology should shorten the overall reaction time even more than for these single-step reactions. As a practical example, microwave heating was applied in the 3-step synthesis of ^{18}F-spiperone. With microwaves, the overall time needed for the synthesis was 45 min, 12 min for the three-step reaction, 8 min for extraction and evaporation of pentane, and 25 min for h.p.l.c. purification. This represents 50% less time than the 90 min required using conventional heating.[14]

These results indicate that the rapid heating capability of microwave ovens is useful for decreasing reaction times with short-lived radionuclides, and that this technique can be conveniently applied in the synthesis of a wide variety of radiopharmaceuticals or other radiolabelled compounds.

This work was supported by NIH grants HL13851 and NSO6833. The authors thank the members of the Washington University Cyclotron team for the production of ^{18}F.

Received, 7th July 1987; Com. 959

References

1 R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, and J. Rousell, *Tetrahedron Lett.*, 1986, **27**, 279.
2 F. Smith, B. Cousins, J. Bozic, and W. Flora, *Anal. Chim. Acta*, 1985, **177**, 243.
3 T. R. White and G. E. Douthit, *J. Assoc. Off. Anal. Chem.*, 1985, **68**, 766.
4 R. A. Ferrieri, D. J. Schlyer, B. W. Wieland, and A. P. Wolf, *Int. J. Appl. Radiat. Isot.*, 1983, **34**, 897.
5 J. S. Fowler and A. P. Wolf, 'The Synthesis of Carbon-11, Fluorine-18 and Nitrogen-13 Labeled Radiotracers for Biomedical Applications,' Technical Information Center, U.S. Department of Energy, Oak Ridge, TN, 1982 (NAS-NS-3201).
6 J. W. Brodack, M. R. Kilbourn, M. J. Welch, and J. A. Katzenellenbogen, *Int. J. Appl. Radiat. Isot.*, 1986, **37**, 217.
7 V. I. Stanko, N. G. Iroshnikova, A. F. Volkov, and A. I. Klimova, *Int. J. Appl. Radiat. Isot.*, 1984, **35**, 1129.
8 H. H. Coenen and S. M. Moerlein, *J. Fluorine Chem.*, 1987, **36**, 63.
9 D. Y. Chi, M. R. Kilbourn, J. A. Katzenellenbogen, and M. J. Welch, *J. Org. Chem.*, 1987, **52**, 658.
10 M. Attina, F. Cacace, and A. P. Wolf, *J. Labelled Comp. Radiopharm.*, 1983, **20**, 501.
11 C.-Y. Shiue, M. Watanabe, A. P. Wolf, J. S. Fowler, and P. Salvadori, *J. Labelled Comp. Radiopharm.*, 1984, **21**, 533.
12 Radiopharmaceuticals Labelled with Halogen Isotopes, Proceedings of the International Symposium on Radiohalogens, Banff, Alberta, 1985. *Appl. Rad. Isot., Int. J. Radiat. Appl. Instrum. Part A*, 1986, **37**, No. 8.
13 C. Prenant, J. Sastre, C. Crouzel, and A. Syrota, *J. Labelled Comp. Radiopharm.*, 1987, **24**, 227.
14 C-Y. Shiue, J. S. Fowler, A. P. Wolf, D. M. McPherson, C. D. Arnett, and L. Zecca, *J. Nucl. Med.*, 1986, **27**, 226.