Behavior of Reaction Mixtures under Microwave Conditions: Use of Sodium Salts in Microwave-Induced N-[^{18}F]Fluoroalkylations of Aporphine and Tetralin Derivatives

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Summary: Microwave treatment combined with manipulation of the ionic strength of the reaction mixture increases the radiochemical yield dramatically of *N*-[^{18}F]-fluoroalkylations of secondary amines as compared to thermal heating.

Microwave ovens have been used in many laboratory procedures including biological sample preparation[1] and organic chemistry.[2] It has been shown that the electromagnetic field generated in microwave ovens induces alterations in chemical reactivity of substrates.[2,3] The applicability of this technique is determined by several parameters such as sample geometry, microwave intensity, polarity of the medium, and ionic strength of the sample solution.[2,4] Recently, it has been shown that microwave treatment is a powerful technique for accelerating production rates for carbon-11- and fluorine-18-labeled radiopharmaceuticals.[5]

In the present study, we have examined the behavior of reaction mixtures in a microwave field and the use of sodium salts to manipulate reaction rates. Three potential dopamine D_2 agonists 2-[*N*-(3-[^{18}F]fluoropropyl)-*N*-[(4-fluorophenyl)ethyl]amino]-5-methoxytetralin (**2**), 6-(2-[^{18}F]fluoroethyl)-10,11-diacetylnoraporphine (**4a**), and 6-(3-[^{18}F]fluoropropyl)-10,11-diacetylnoraporphine (**4b**) were synthesized in a commercial Miele M 686 microwave oven.[6] The radiochemical yield based on [^{18}F]fluoroalkyl iodide and corrected for decay was determined by HPLC analysis.[7] The identity of the labeled products was established by comparison with the HPLC elution profiles of reference material. The reference materials were identified by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and mass spectroscopy.[8] Compounds **2**, **4a**, and **4b** were also synthesized in a reaction medium heated on an oil bath for comparison with microwave treatment.

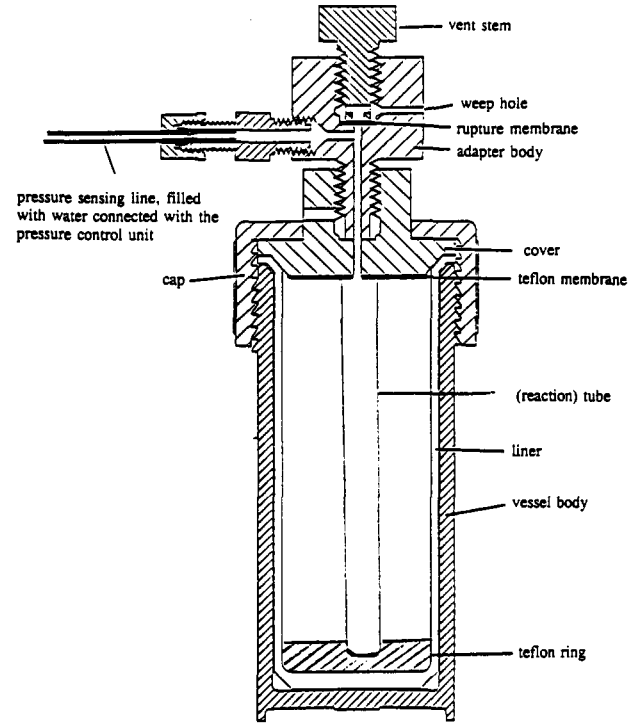

Figure 1. Lined digestion vessel with pressure control adaptor.

Microwave energy transfer to a sample is determined by two mechanisms: ionic conduction and dipole rotation.[9] The presence of an electrolyte in a medium strongly facilitates microwave energy absorption.[2,9] Ions are forced into motion by the oscillating electric field and immediately share their kinetic energy through collisions with the medium. These effects are dependent on the concentration of the ions in the solution, ion radius, ionic charge, and the solvation capacity of the medium.[4,9] The energy absorption during the microwave experiments can be tested through the development of pressure in a closed tube during microwave exposure. Pressure measurement experiments were carried out in a CEM MDS-81D microwave oven.[10] Pressure tubes were placed in a lined digestion

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(6) In a typical Miele microwave experiment, the acetonitrile (1 mL) reaction mixture was transferred to a borosilicate pressure tube (11 mL), sealed tightly by a Schott GL 14 cap. To ensure an optimum antenna function of the reaction tubes during microwave heating, the diameter of the reaction tubes was 1.0 cm. The tube was placed in a Parr microwave acid digestion bomb. The digestion bomb was put in a fixed position in the microwave oven. After a typical run of 2 min of microwave energy (600 W), the bomb was cooled to room temperature. After each run of 2 min, the cap was renewed.

(7) HPLC was performed on a Chrompack microporasil column (25- × 7.8-mm i.d.), equipped with an UV absorption detector (280 nm) and a radioactivity detector. For the purification of **2** the column was eluted with a mixture of chloroform–hexane (2/3 v/v, 3 mL/min; retention time 8.5 min). For purification of **4a** and **4b** the column was eluted with a mixture of chloroform–hexane (4/1 v/v, 4 mL/min; retention times 17 and 15 min, respectively).

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(10) In a typical CEM microwave experiment the acetonitrile (1 mL) solutions were transferred to a borosilicate pressure tube (11 mL). To ensure an optimum antenna function of the tubes during microwave treatment, the diameter of the pressure tubes was 1.0 cm. Microwave treatment was performed for a variable period of time, after which the tube was cooled to room temperature.

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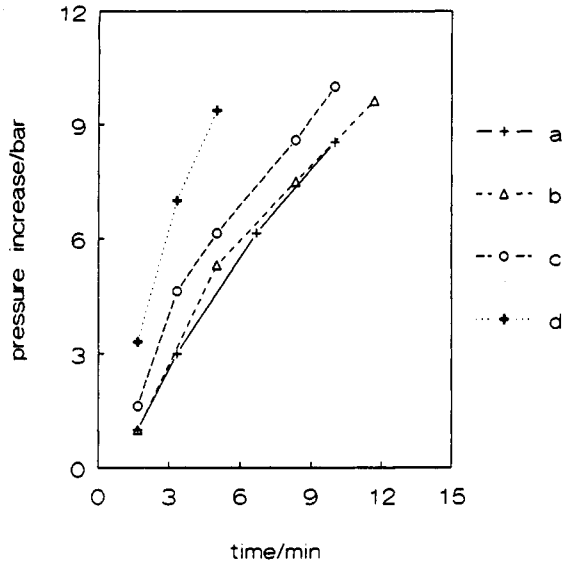


Figure 2. Pressure development versus time, measured during microwave heating (600 W, 2.45 GHz) in a pressure tube filled with CH_3CN (1 mL) and (a) no salt; (b) 10 mg of K_2CO_3; (c) 30 mg of K_{222}; and (d) 10 mg of K_2CO_3 and 30 mg of K_{222}.

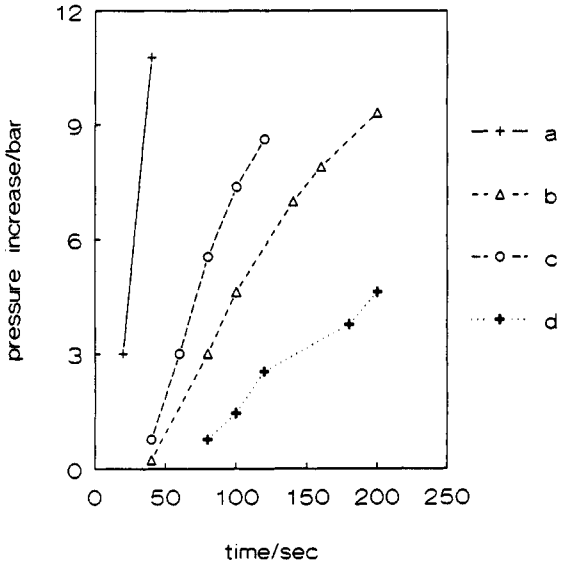


Figure 3. Pressure development versus time, measured during microwave heating (600 W, 2.45 GHz) in a pressure tube filled with CH_3CN (1 mL) and (a) 10 mg of NaI; (b) 1 mg of NaI; (c) 75 mg of NaBr; and (d) 145 mg of NaCl.

vessel (CEM P/N 600267; Figure 1), fixed on an alternating turntable. The digestion vessel was attached via a Teflon tube, filled with water, to an external pressure control unit, which controlled the microwave oven.

The results of the pressure experiments are shown in Figures 2 and 3. The pressure increase of a solution of K_2CO_3 in CH_3CN during microwave treatment was comparable to the pressure development of pure acetonitrile, due to the low solubility of K_2CO_3 in CH_3CN. This small effect on the pressure increase was also found for Kryptofix (K_{222}). Although K_{222} is easily soluble in CH_3CN, it does not increase the ionic strength of the solution. However, by dissolving K_2CO_3 and K_{222} simultaneously in acetonitrile, the pressure increase during microwave treatment was considerable. In solution this Kryptofix–potassium carbonate complex contributes to the increased ionic strenth of the reaction medium, although we did not

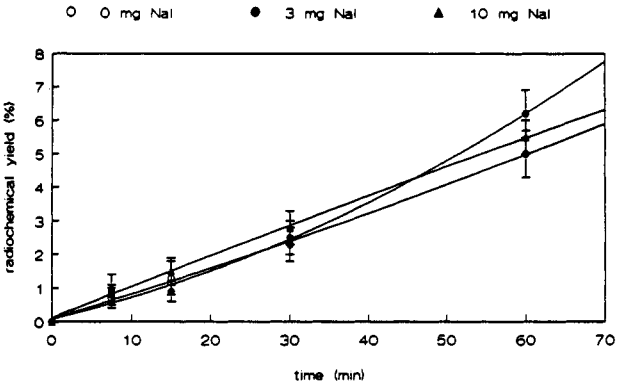
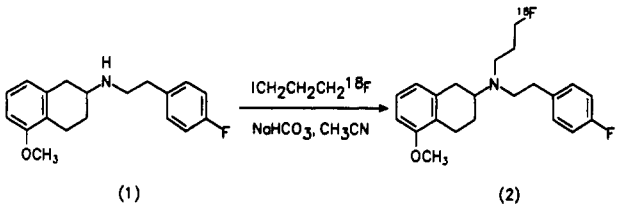


Figure 4. Effect of NaI on the radiochemical yield of 2 synthesized in an oil bath ($n = 5$, mean values ± SEM). Reaction conditions: 5 mg of precursor 1, 2 mg of $NaHCO_3$, 1 mL of CH_3CN at 120 °C.

Scheme I. N-3-[^{18}F]Fluoropropylation of 2-[*N*-[(4-Fluorophenyl)ethyl]amino]-5-methoxytetralin



examine which part of the organic salt contributes most substantially to the ionic migration effect. The same effect is found upon dissolving sodium salts in CH_3CN (Figure 3). Although the ionic radius of iodide is larger than that of chloride, a dramatic effect is observed due to the solubility difference of these two sodium salts in CH_3CN. Figure 3 demonstrates the dependence of pressure development inside the pressure tube on the amount of dissolved salt in the reaction medium. After dissolving 10 mg of NaI, the pressure development inside the pressure tube is almost out of control.

Manipulation of the ionic strength of the reaction medium during microwave treatment seems a very useful tool in radiolabeling reactions as is demonstrated in the N-[^{18}F]fluoropropylation reaction of 2-[*N*-[(4-methylphenyl)ethyl]amino]-5-methoxytetralin ((1), Scheme I).[11] Under thermal heating conditions (refluxing in an oil bath), the radiochemical yield (based on $^{18}FCH_2CH_2CH_2I$) was independent of the amount of sodium iodide added to the reaction mixture, as is shown in Figure 4. However, during microwave treatment (Miele M 686), the radiochemical yield could be improved by a factor of 20 by adding 4 mg of sodium iodide to the reaction medium (Figure 5). This increase of the radiochemical yield can be explained by the extra microwave energy absorption of the reaction medium due to dissolved NaI.

The improvement of radiochemical yields by manipulation of the ionic strength of the reaction medium is also demonstrated by the N-[^{18}F]fluoroalkylation of norapor-

(11) To a solution of 3-[^{18}F]fluoropropyliodide in CH_3CN (1 mL) were added 2-[*N*-[(4-fluorophenyl)ethyl]amino]-4-methoxytetralin (5 mg, 0.016 mmol), NaI (x mg), and $NaHCO_3$ (2 mg, 0.023 mmol). The reaction tube was sealed and transferred to the Miele microwave oven (600 W, 5 times 90 s) or placed in an oil bath (120 °C). After the reaction mixture was cooled to room temperature the acetonitrile and nonreacted 3-[^{18}F]-fluoropropyliodide were evaporated under reduced pressure at 40 °C. The residue was redissolved in $CHCl_3$ and passed through a Millipore SR-filter. The product was purified by HPLC.

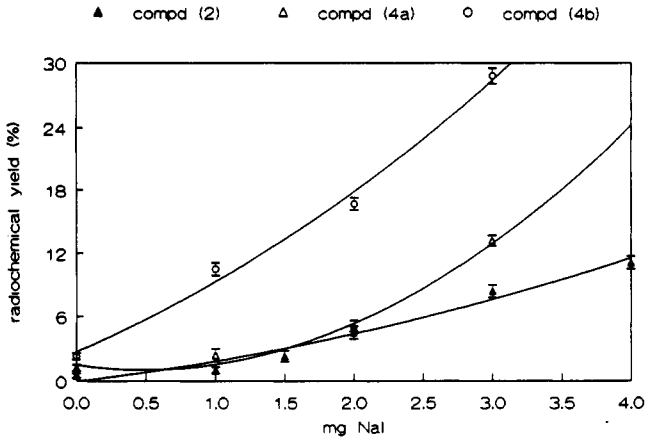
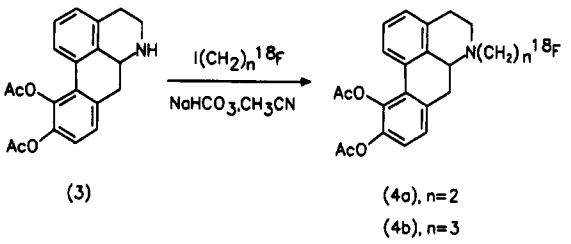


Figure 5. Effect of NaI on the radiochemical yield of **2**, **4a**, and **4b** using a Miele M 686 microwave oven (600 W, 2.45 GHz; n = 5, mean values ± SEM). Reaction conditions: 5 mg of precursor, 2 mg of $NaHCO_3$, 1 mL of CH_3CN, reaction time 5 times 90 s.

Scheme II. N-[^{18}F]Fluoroalkylation of Acylated Noraporphine



(3) (4a), n=2 (4b), n=3

phine derivatives (**3**, Scheme II).[12] Under thermal heating conditions (refluxing in an oil bath), fluoroalkylation of the compounds **4a** and **4b** was not successful. During the alkylation process under basic conditions ($NaHCO_3$) considerable loss of the acetyl protective groups was observed (more than 10% after refluxing in oil bath for 2 h), resulting in a mixture of several products. Compounds **4a** or **4b** could not be isolated after HPLC separation. However, using microwave exposure (Miele M 686), we were able to synthesize the ([^{18}F]fluoroalkyl)-noraporphine derivatives **4a** and **4b** in 2% and 3% yield, respectively, with hardly any loss of acetyl groups. The radiochemical yield of the fluorine-18-labeled compounds **4a** and **4b** could be further improved by a factor of 10 after adding 3 mg of NaI to the reaction mixture (Figure 5).

Although the substantial increases of reaction rates in microwave ovens are generally considered as being a result of "superheating" or "microwave effect", little is known about the exact nature of this phenomenon. The increase of reaction rates is hard to explain just by the temperature dependency as described by the Arrhenius equation,[2,4] or by pressure buildup in a closed reaction vessel as described by Bram et al.[13] It has been suggested that the extra stimulus given to reactants by the microwave field causes an effective decrease in the potential energy barrier between the reactants and their surrounding molecules.[4] Taking into account that under conventional heating conditions in an oil bath the O-deacylation in the *N*-([^{18}F]-fluoroalkyl)noraporphine synthesis goes much faster than the N-[^{18}F]fluoroalkylation procedure, it is remarkable that under the same basic conditions employed in the microwave oven almost no deacylation could be observed. Other groups have also reported less degradation of reagents and generation of side products during microwave treatment.[3,14] The question arises whether this phenomenon of different reactivity might be explained by activation of rotational levels of different groups which as a consequence show more or less reactivity (site selectivity). The frequency used in our microwave experiments (2.45 GHz) does not conflict with this hypothesis. Although it is generally accepted that rotational vibrations are not quantified in solutions, the observed site selectivity under microwave conditions seems an interesting topic for future research.

In conclusion, we were able to improve the radiochemical yield of fluorine-18-labeled potential D_2 agonists by manipulating the ionic strength of the reaction mixture during microwave treatment. No improved radiochemical yield was observed when the reaction mixtures were heated in an oil bath. Due to the short half-lives, it is obvious that microwave exposure in combination with manipulation of the polarity of the medium is a powerful technique for accelerating reaction rates in the synthesis of carbon-11- and fluorine-18-labeled radiopharmaceuticals.

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(12) To a solution of n-[^{18}F]fluoroalkyl iodide in CH_3CN (1 mL) were added 10,11-diacetylnoraporphine (5 mg, 0.015 mmol), NaI (x mg), and $NaHCO_3$ (2 mg, 0.023 mmol). The reaction tube was sealed and transferred to the Miele microwave oven (600 W, 5 times 2 min) or placed in an oil bath (120 °C). After the reaction mixture was cooled to room temperature the acetonitrile and nonreacted n-[^{18}F]fluoroalkyl iodide were evaporated under reduced pressure at 40 °C. The residue was redissolved in $CHCl_3$ (0.5 mL) and filtered via a Millipore HV-filter. The product was purified and isolated by HPLC.

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