PREPARATION OF N.C.A. [^{18}F]-CH_2BrF VIA AMINOPOLYETHER SUPPORTED NUCLEOPHILIC SUBSTITUTION

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SUMMARY

A complex of the macrocyclic aminopolyether Kryptofix® 2.2.2. and potassium carbonate was used to synthesize [^{18}F]-CH_2BrF from dibromomethane. At the no-carrier-added level the nucleophilic ^{18}F-for-Br exchange gives rise to a corrected radiochemical yield up to 62%.

Key words: ^{18}F-bromofluoromethane, nucleophilic fluorination, Kryptofix® 2.2.2., aminopolyether

INTRODUCTION

The ideal nuclear properties of fluorine-18 ($T_{1/2}$ = 110 min, 97% β^+, E_{β^+} = 0.635 MeV) are most useful for positron emission tomography (PET). Unfortunately, the methods available for no-carrier-added (n.c.a.) radiofluorination which are often needed are limited and mainly restricted to nucleophilic substitution. Fluorination via small prosthetic groups is an

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alternative route for labelling complex, multisubstituted, or nonactivated substrates.

Several attempts have been made to prepare [^{18}F]-halofluoromethanes (1-6) as fluoromethylating agents. They appear promising for replacing the compounds labelled via [^{11}C]-CH_3I by the corresponding longer lived [^{18}F]-labelled pharmaceuticals R-Z-$CH_2{}^{18}F$ (eq. I), where Z is an oxygen-, sulfur-, nitrogen-, or carbon-containing function.

$$CH_2X^{18}F + R\text{-}Z\text{-}H \longrightarrow R\text{-}Z\text{-}CH_2{}^{18}F + XH \qquad (I)$$

X = Cl, Br, and I

So far, only poorly reproducible results were reported (2) on functionalized fluoromethanes with little information on chemical and radiochemical purity (4-6). Since it has recently been shown (7-10) that mild and effective nucleophilic substitution with n.c.a. ^{18}F-fluoride ions can be accomplished in the presence of potassium ions cryptated by the macrocyclic aminopolyether Kryptofix® 2.2.2., we have extended the applications of this method, and present here the synthesis of n.c.a. [^{18}F]-bromofluoromethane and inactive CH_2BrF via nucleophilic F-for-Br exchange in CH_2Br_2.

EXPERIMENTAL

Chemicals. The aminopolyether Kryptofix® 2.2.2. (4,7,13,16,21,24-hexaoxa-1,10-diazobicyclo-8,8,8-hexacosan) (APE 2.2.2.), the reagents and solvents were purchased from Merck (Darmstadt, FRG). The acetonitrile used as reaction solvent was Uvasol grade and was additionally distilled and dried over 5A molecular sieve. Also dibromomethane was purified by distillation over molecular sieve and had a final purity of 99.96%, as determined by GLC analysis.

Helium, neon, and hydrogen had a stated purity of 99.996 and 99.998%, respectively.

Accelerator production of ^{18}F-fluoride. For the production of ^{18}F-fluoride via the $^{20}Ne(d,\alpha)^{18}F$ process (for a review cf. 11) a cylindrical gas target (Inconel 600) filled with Ne gas containing 15% H_2 (total pressure 18 bar) was bombarded with 14 MeV deuterons at the Jülich CV 28 compact cyclotron. Irradiations were carried out at 25 µA and the [^{18}F]-HF was collected by rinsing the target wall with bidistilled water.

Reactive [^{18}F]-fluoride labelling system. The reproducible conversion of the n.c.a. ^{18}F radioactivity into the reactive form was carried out as reported previously (9,10). The aqueous solution of n.c.a. ^{18}F-fluoride (0.5-5 mCi) was added to 0.250 ml of an aqueous solution of 4.6 mg (0.03 mmol) potassium carbonate and 26 mg (0.06 mmol) APE 2.2.2. in a cylindrical vessel of pyrolytic glassy carbon (Sigradur®-G, 18x70 mm, from Sigri, Meitingen, FRG). At an oil bath temperature of about 115 °C the solution was purged with helium (10 ml min^{-1}) to dryness. Purging went on while cooling the vessel to room temperature.

Synthesis of n.c.a. [^{18}F]-CH_2BrF. 1 ml of 10% v/v solution of CH_2Br_2 (1.43 mmol) in anhydrous CH_3CN was added to the reactive [^{18}F]-fluoride labelling system, and the mixture was refluxed under a stream of helium (10 ml min^{-1}) with an oil bath temperature of about 115 °C. The volatile compounds were collected in a trap cooled with liquid nitrogen. After the desired reaction time the oil bath temperature was lowered to 40 °C, while cooling in the reflux condenser discontinued, and He flushing went on for further 15 minutes. Then, the apparatus was allowed to reach room temperature, and the

reaction vessel and trap were rinsed each with 20 ml carbon tetrachloride. The resulting solutions were resolved by GLC and fractions at 1 or 0.5 minute intervals were absorbed discontinuously on active charcoal tubes, which subsequently underwent scintillation gamma-counting.

Synthesis of CH_2BrF. The same equipment and procedure as in the n.c.a. synthesis was used. 4.6 mg K_2CO_3 (0.03 mmol), 100 mg APE 2.2.2. (0.23 mmol), and 46.2 mg KF (0.80 mmol) were dissolved in 2 ml H_2O in the glassy carbon vessel. The solution was dried under helium stream (50 ml min^{-1}) as previously described, and 0.3 ml CH_2Br_2 (4.3 mmol) dissolved in 2.7 ml anhydrous CH_3CN were added to the solid residue. The resulting mixture was refluxed and the vapours collected as in the n.c.a. synthesis; in this case the reaction time was 30 minutes. The content of the trap underwent preparative

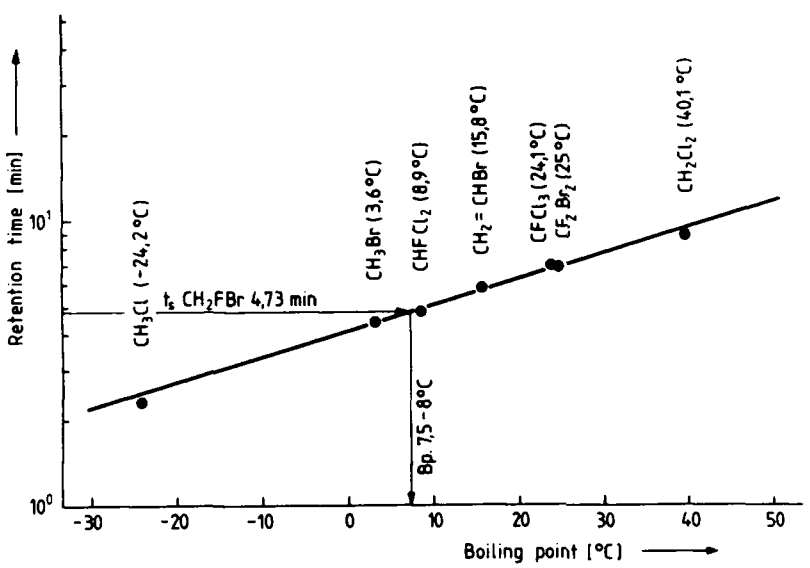

Fig. 1 Semi-logarithmic plot of retention time vs. boiling point of selected halogenocompounds (for conditions see experimental).

GLC purification and the unknown peaks were collected and analyzed by MS.

Analysis. A gas chromatograph (Intersmat IGC-16), equipped with a 12 m x 5 mm I.D. glass column, filled with 20% SF-96 on Chromosorb W-AW-DMCS 60-80 mesh, and TCD detector was used for GLC purification and analysis of [^{18}F]-CH_2BrF and inactive CH_2BrF. The experimental conditions were as follows: helium flow 100 ml min^{-1}; linear temperature programming was used from 60 to 140 ^{o}C at a rate of 2 ^{o}C min^{-1}. The identification of the products was achieved by comparison of the retention volumes with those of authentic samples. In Fig. 1 the plot of the retention time in logarithmic scale vs. the boiling point is shown for a number of halogenomethanes and vinylbromide, a by-product of the synthesis. CH_2BrF showed a retention time of 4.73 min.

The identification of CH_2BrF was achieved by recording its MS spectrum at 70 eV bombarding electron energy with a VG Micromass 3001 instrument. Radioactive measurements were carried out in a Packard Auto-gamma scintillation counter. The radiochemical yield of [^{18}F]-CH_2BrF was calculated in percent of ^{18}F activity found in [^{18}F]-bromofluoromethane relative to the sum of the ^{18}F activity in the collecting trap and the reaction vessel.

RESULTS AND DISCUSSION

Formation of CH_2BrF. To provide unambiguous evidence for the formation of [^{18}F]-CH_2BrF it was necessary to investigate the GLC behaviour of an authentic sample of bromofluoromethane. Considering the possible applications to radiotracer studies, the synthetic methods described in the literature (12-14) were regarded as unsuitable. Therefore, the reaction conditions of the APE 2.2.2. supported nucleophilic fluorination (7-10) were adapted to the preparative scale. No attempt, however, was

made to optimize the yields; this aspect being at present beyond the scope of this work. Besides other products CH_2BrF was isolated and identified by comparison of its MS spectrum with that reported in the literature (15). An interesting aspect of the GLC studies is the observed relationship between retention time and boiling point. The derived boiling point for bromofluoromethane of 8 $\pm$ 1 ^{o}C is rather different from those reported in the literature (18-20 ^{o}C (12) or 17.5 ^{o}C (13)).

Finally, the described method appears simpler and more reliable than the previous ones (12-14) and promising for optimization and application to the synthesis of related compounds.

Formation of n.c.a. [^{18}F]-CH_2BrF. Test runs showed that a 10% v/v solution of CH_2Br_2 in acetonitrile provides the best

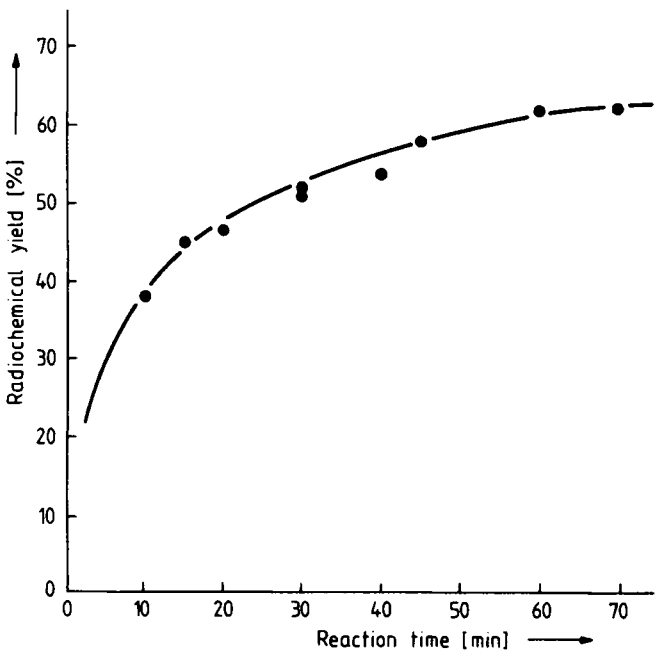

Fig. 2 Dependence of the radiochemical yield of n.c.a. [^{18}F]-CH_2BrF on reaction time in a 10% v/v solution of CH_2Br_2 in CH_3CN of the APE 2.2.2. assisted ^{18}F-for-Br nucleophilic substitution.

radiochemical yields of [^{18}F]-CH_2BrF at the n.c.a. level. At this concentration the plot of the radiochemical yield vs. the reaction time is presented in Fig. 2. Even at a reaction time as short as 10 minutes the ^{18}F-for-Br substitution process (eq. II) proceeds to a good extent with a radiochemical yield of about 40%. The saturation value of 62% (corrected for decay), reached after 45 minutes, is of lesser importance for labelling purposes, because of the radioactive decay.

$$CH_2Br_2 + \text{n.c.a.}\,^{18}F^- \xrightarrow[CH_3CN,\ 82\ ^oC]{[2.2.2./K]^+} CH_2Br^{18}F + Br^- \qquad \text{(II)}$$

The dipolar aprotic character of the reaction medium and the nature of the reactants are typical for nucleophilic reactions. Our previous attempts to prepare n.c.a. [^{18}F]-bromofluoromethane from CH_2Br_2 with several nucleophilic systems, including those analogous to the preparation of [^{18}F]-CH_3F from CH_3I (16), failed. Also, negative reports have been given by other groups which attempted geminal halogen substitution, mainly in CH_2I_2 (1-3). These observations extend the findings on the scarce propensity of geminal halogen displacement under the conditions usually employed in nucleophilic substitution to n.c.a. syntheses (17). Therefore, the efficient occurrence of the reaction (eq. II) is due to the enhanced reactivity of [^{18}F]-fluoride ion towards dibromomethane under the assistance of the potassium ion APE 2.2.2. complex. At present the utilization of [^{18}F]-CH_2BrF in n.c.a. fluoromethylation reactions (eq. I) is under investigation, as well as the comparison of its reactivity with that of other newly synthesized fluoroalkylating agents (18). Information on the stability of the expected fluorinated

compounds is scarce and limited to particular chemical conditions (19,20).

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