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NEW SYNTHESES OF FLUORO-COMPOUNDS BY FLUORINATION IN WATER

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Summary: The formation of a C-F bond by reaction of F_2 with organic compounds in aqueous media is described. The feasibility of the reaction was tested by preparing 4-fluoroantipyrine 4-FAP, ^{18}F-labelled 4-FAP, 5-fluorouracil 5-FU, and ^{18}F-labelled 5-FU by reacting F_2 or ^{18}F-labelled F_2 with the appropriate starting material in water. The reactions carried out at pH 13 did not involve any detectible side reactions. Radiochemical (chemical) yields were 15% (36%) for ^{18}F-4-FAP and 30% (68%) for ^{18}F-5-FU expressed relative to ^{18}F-labelled F_2 in a 30 and 20 min synthesis, respectively.

The use of ^{18}F-labelled radiopharmaceuticals in in vivo studies of the human brain with positron emission tomography (PET)[1-4] has prompted considerable interest in new and more convenient syntheses of these substances. We report here the fluorination and synthesis of ^{18}F-labelled biological tracers in an aqueous media that results in the formation of a C-F chemical bond and with this a fluorinated compound. We also describe the synthesis of two ^{18}F-labelled compounds that have previously been suggested as tracers for in vivo measurement of physiological variables with multitracer autoradiography[5] and PET[6]. The same general approach can be used for the synthesis of other ^{18}F-labelled radiopharmaceuticals for PET studies, where the speed of synthesis is more important than the chemical yield.

Fluorinating species of fluorine formed in water (e.g. hypofluorous acid and/or F_2O)[7] were reacted in situ with the appropriate starting materials. Although hypofluorous acid has been used as a reagent for hydroxylation of aromatic compounds[8], oxidation of porphyrin[9], and synthesis of N-fluoro-carbamates[10], to our knowledge it has not been shown to be a fluorinating agent for formation of the C-F bond. Hypofluorous acid has been prepared in the past by reacting fluorine with ice at a temperature of -40°C or with water in a liquid form[8 - 11].

We prepared these fluorinating species by bubbling fluorine (5% F_2 in N_2 or 0.5% ^{18}F-F_2 in Ne) into 8 ml of water in a plastic reaction vessel at a flow rate of about 50 ml/min. At the end of the introduction of the gas mixture, antipyrine or uracil (0.3 mmol) was added and the reaction mixture stirred by bubbling helium at the same rate for about one minute. (Prolonged mixing did not increase the yield of the reaction.) Alternatively, the reactions were carried out by bubbling the fluorine mixture through an aqueous solution of the starting material. These reactions were done at two different pH values (7 and 13) and at two different water temperatures (room temperature and ice bath temperature). At the end of bubbling, the pH of the solution was adjusted to between 6 and 7 and the fluorinated products extracted with ethyl acetate or methylene chloride. High performance liquid chromatography (HPLC) of the organic phase was done on a Partisil-10 silica column with ethyl acetate-hexane (95:5) as an elution solvent .

HPLC analysis of the organic phase in the antipyrine reaction done at pH 7 revealed the presence of three compounds with elution volumes Ve(1) = 0.4 ml, Ve(2) = 1.4 ml, and Ve(3) = 2.5 ml and relative ratios of 11:1:10. Thin layer radiochromatography (TLRC) of the same organic phase done on silica gel using ethyl

acetate as developing solvent also revealed the presence of three compounds with R_f-values 0.88, 0.75, and 0.65 and relative intensities similar to those obtained from HPLC chromatograms. The compound with R_f = 0.65 and Ve = 2.5 ml was identified by ^{1}H- and ^{19}F-NMR[12] as 4-fluoroantipyrine (4-fluoro-2, 3-dimethyl-1-phenyl-3-pyrazolin-5-one) (4-FAP) (1) in the "cold" synthesis and as ^{18}F-labelled fluoroantipyrine in the radioactive synthesis. The NMR spectra and melting point were the same as those of an authentic sample prepared by a published procedure[12] (($\phi(CDCl_3)$ -180.9 ppm, singlet), $\delta(CDCl_3)$, 2.25 (3H, doublet, $^3J_{HF}$ = 2.01 Hz, C-CH_3), 2.94 (3H, doublet, $^4J_{HF}$ = 1.02 Hz, N-CH_3), 7.2 (5H, singlet, C_6H_5), M.P = 132-134°). The second major peak (Ve = 0.4 ml and R_f = 0.88) was a mixture of two compounds, giving two multiplets in the ^{19}F-NMR spectrum with ϕ = -163.3 ppm, ϕ = -137.30 ppm, J_{HF} = 7.27 Hz and 5.82 Hz assigned by ^{19}F-NMR as cis and trans 3-fluoro-4-hydroxy-2,3-dimethyl -1-phenyl pyrazolin-5-one (2). Support for this structure was also found in the ^{19}F-NMR spectra where irradiation at C-CH_3 frequency reduced multiplet to singlet. Both of these compounds lost fluorine from the molecule about ten minutes after $NaOCH_3$ was added to a solution of these compounds in CH_3CN. These compounds were not observed when the fluorination reaction was done at pH = 13. A third small peak, Ve = 1.4 ml, which was also not formed at pH = 13, was not identified. The amount formed at pH = 7 was so small that not even an NMR spectrum was possible; it did not affect purification of ^{18}F-4-FAP. The ratio between different compounds found in the reaction mixture was the same in both "cold" and radioactive preparations. When the reaction was done at pH=13, although the radiochemical yield of ^{18}F-4-FAP did not increase, only ^{18}F-4-FAP was obtained. This pH therefore proved optimum for the synthesis of ^{18}F-labelled 4-FAP.

$[^{18}F]F_2$ used in the synthesis of labelled compounds was produced by irradiating a mixture of 0.5% F_2 in research purity neon. ^{18}F-fluorine was produced via a ^{20}Ne(d, α) nuclear reaction[13]. Fluorine was bubbled through an aqueous solution of antipyrine in water where it was reacted with antipyrine. ^{18}F-labelled 4-FAP was separated as described above for "cold" material. The synthesis takes only 30 minutes and produces ^{18}F-fluoroantipyrine in a radiochemical yield of about 15% (not corrected for decay). The chemical and radiochemical purity of purified ^{18}F-labelled-4-FAP as assessed by HPLC with UV (λ = 270 nm) and radioactivity detectors was greater than 99%.

A second model reaction using uracil as substrate produced ^{18}F -5-fluorouracil in a radiochemical yield of about 30% after a 20-minute synthesis. A simple purification of ^{18}F-5-fluorouracil by Sep-Pak column gave ^{18}F-5-fluorouracil with chemical "purity" of about 30% and a radiochemical purity greater than 98%. (The chemical impurity is attributed to the starting material.) HPLC purification yielded a product with a chemical and radiochemical purity of over 99%. The overall radiochemical yield after HPLC purification was about 30%. ^{1}H and ^{19}F-NMR spectra, melting point, and mass spectrum were identical to those of an authentic sample obtained commercially (Aldrich Chem. Co.): (ϕ= -172.7 ppm in d_6-DMSO, 1F, doublet, $^3J_{HF}$ = 6.1 Hz, δ (d_6-DMSO) 7.76 (1H, doublet $^3J_{HF}$ = 6.1 Hz), MP = 281-283°C, M^+ = 130). The elution volume for ^{18}F-5-fluorouracil on HPLC and the R_f on TLRC were also identical to an authentic sample and to ^{18}F-5-FU prepared by another synthetic method[14].

Since there was no difference in the ratio between compounds formed when the starting material was added before or after bubbling of F_2 or $[^{18}F]F_2$, we concluded that both reactions go through the same intermediate, i.e. F_2O and/or hypofluorous acid. This hypothesis is supported by the rate of the reaction

between F_2 and H_2O ($t_{1/2}=7\times10^{-6}$ sec)[15] as well as by the concentration of water relative to the starting material. To examine the possibility of radical mechanism, we have repeated the reactions outlined above in water saturated by oxygen and in the absence of light without any resultant change in the ratio between different compounds or any change in the chemical or radiochemical yield. Although our results did not indicate a radical mechanism, it could not be excluded, because radical mechanisms have been observed in the reaction of CF_3OF with many unsaturated compounds[16].

Since the fluorination reactions described here could be done in an aqueous media, they would prove convenient for the synthesis of labelled compounds. Because the physical half-life of ^{18}F ($t_{1/2}=110$ min) is relatively short, in situ fluorination with these fluorinating species might prove to be an important route in the synthesis of ^{18}F-labelled radiopharmaceuticals where the time required for the synthesis is of the utmost importance. Since protecting groups need not be removed, fluorination in an aqueous solution reduces manipulation of the labelled material, thereby minimizing unnecessary losses of labelled compound and exposure to ionized radiation. Since the reaction of F_2 with water is very fast, making it highly unlikely that F_2 is present in water 10 min after the end of bubbling[7], we think that the fluorinating species, is fluoroxy compound (s) possibly hypoflourous acid. If fluorinating agent is hypofluorous acid, our results would indicate that the reaction of hypofluorous acid is solvent-dependent because in the work of Appelman et al[8] reaction of hypofluorous acid with aromatic systems in nonpolar organic solvents resulted in epoxides and phenols but not fluoro compounds.

If the reactions do indeed go through hypofluorous acid and the polarization of hypofluorous acid is as expected from relative electronegativity[8,15], the mechanism shown in Fig. 1 can also explain the synthesis of these fluoro compounds. However, in other halogenation reactions of these two compounds it was observed that position 4 and 5 in antipyrine and uracil, respectively, are electrophilic positions[12,14,17,18]. Since the existence of F^+ in fluoroxy compounds is controversial[19], we would refrain from explaining of our results on the basis of electrophilic fluorine. The radical mechanism observed earlier for CF_3OF could also explain products obtained in this study. Because of the electrophilic nature of these positions[12,14,17,18] in antipyrine and uracil, the radical mechanism is the most probable mode of reaction. Our results in the synthesis of fluorinated sugars by the reaction of fluorine with triacetylglucal in water also indicate lack of regio- and stereo-specificity, since the reaction always produces a mixture of manno- and glucos-fluoro-pyranosides as well as gluco- and manno-pyranosyl fluorides. This also supports the radical mechanism theory.

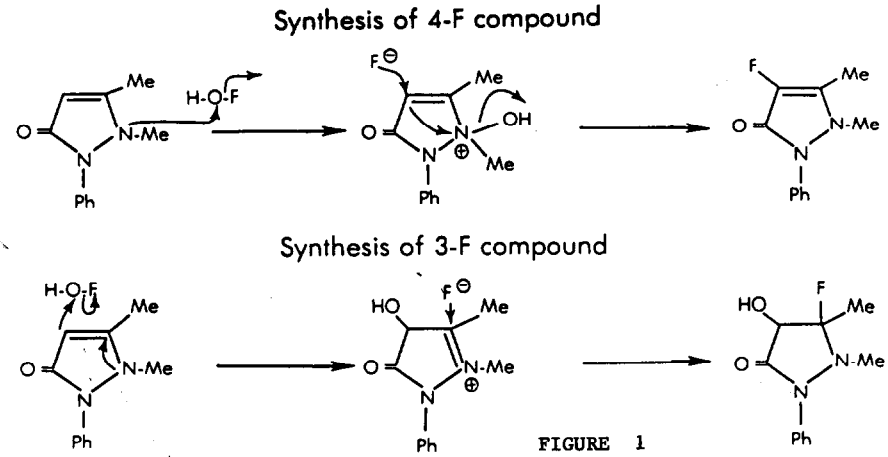

FIGURE 1

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