Fluorine-18-*N*-Methylspiroperidol: Radiolytic Decomposition as a Consequence of High Specific Activity and High Dose Levels

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High specific activity [^{18}F]*N*-methylspiroperidol(8-[4-(4-[^{18}F]fluorophenyl)-4-oxobutyl]-3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, 5–10 mCi/ml, 4–8 Ci/μmol at EOB) in saline solution undergoes significant radiolytic decomposition resulting in a decrease in radiochemical purity of 10–25% during the first hour. The rate of decomposition is affected by the specific activity, total dose to and chemical composition of the solution. That radiolysis is responsible for the observed decomposition was verified by the observation that unlabeled *N*-methylspiroperidol is decomposed in the presence of [^{18}F]fluoride.

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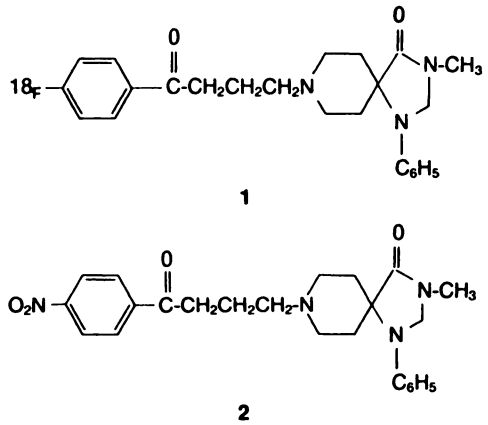
We recently reported a synthesis for no-carrier-added (NCA) [^{18}F]*N*-methylspiroperidol ([^{18}F]NMS), **1** (*1*). Based on studies in mice and baboons and comparison of the kinetic behavior of **1** to other structurally similar fluorine-18- (^{18}F) labeled butyrophenones (*2*), we suggested that this radiotracer had ideal properties for studying the dopamine receptor in humans (*3*) (Scheme 1). In pursuing these studies, we began to prepare [^{18}F]*N*-methylspiroperidol at the high specific activity levels required for positron emission tomography (PET) studies in humans where only a small percentage of the total receptor population is to be occupied by radioligand. Furthermore, through the use of high performance liquid chromatography (HPLC), a product which was relatively free of chemical contaminants was obtained. In these runs, typically 15–30 mCi of [^{18}F]*N*-methylspiroperidol was produced in an injection solution of 3 ml volume. The specific activity was typically in the range of 4 to 10 Ci/μmol (EOB) (^{19}F/^{18}F = 425–170) and the only chemical contaminant observed was a small amount of the "nitro-*N*-methylspiroperidol" (2) resulting from tailing during the HPLC purification. When samples of the injection solutions were analyzed immediately after preparation, radiochemical purities of 97–99% were measured. However, when samples of the injection solution were analyzed later in the day (EOS + 4–6 hr), the radiochemical purity was reduced by as much as 50% (Fig. 1) as determined by an analytical HPLC system which provided a base line separation between **1** and unidentified decomposition products. Since the [^{18}F]*N*-methylspiroperidol produced in low activity runs was stable through several hours and also thermally stable even at pH extremes, radiolytic decomposition appeared to be a plausible mechanism for the observed product instability at higher radiation levels. Because we and, to our knowledge, other groups had not previously observed or reported such decomposition in positron emitter labeled radiotracers for PET studies, and because of the



Scheme 1

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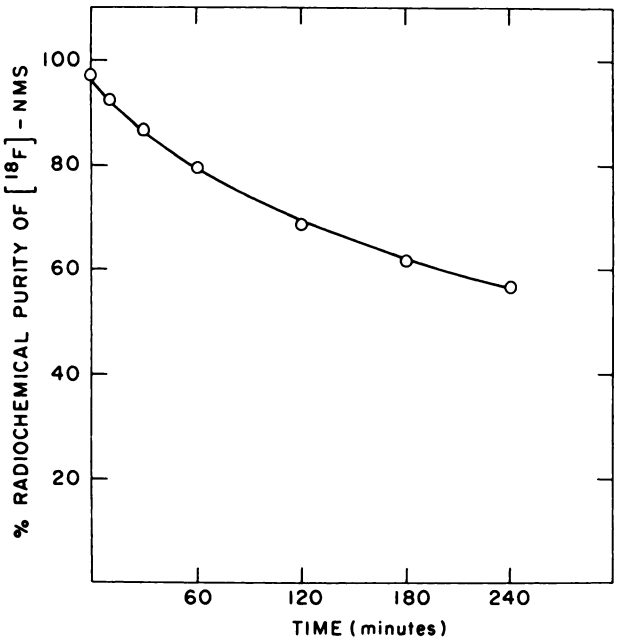

FIGURE 1
Percent radiochemical purity of [^{18}F]NMS at time of preparation for injection (15.2 mCi/3 ml) as measured at different times after its preparation. This solution contained 5.9 nmol of NMS and 0.48 nmol of "nitro-N-methylspiroperidol."

potential impact of such a radiolytic decomposition on the ability to transport or even store a batch of high-activity, high specific activity radiotracer for multiple PET studies during the day, we set out to study this phenomenon in more detail.

We report here the results of a study of the decomposition of [^{18}F]*N*-methylspiroperidol as a function of specific activity, total dose and pH. The decomposition of unlabeled *N*-methylspiroperidol (NMS) by [^{18}F]fluoride was also studied. The impact of these results on radiotracer development for PET will be discussed.

MATERIALS AND METHODS

[^{18}F]*N*-Methylspiroperidol Preparation

Fluorine-18 is produced using a small volume water target as described previously (*4*). The dose on target ranged from 1 μA hr to 26 μA hr, depending on the activity level of product which was required. [^{18}F]*N*-Methylspiroperidol was prepared from 4-nitrophenyl cyclopropyl ketone as described previously (*1*). Preparative HPLC purification of the crude reaction product after alkylation was accomplished using a 10 mm × 250 mm reversed phase column* (ODS-1) using a methanol: 0.02 N ammonium formate solution (75:25) with a flow rate of 5 ml/min. Retention times for **1** and **2** are 12 and 8 min, respectively, using this system. The effluent of the HPLC column was passed through a uv detector at 254 nm and into a fraction collection system set up in an ionization chamber. The product fraction was taken at ~12 min when the uv trace had returned to base line and when radioactivity eluted from the column. Collection was continued for ~3 min. After collection was complete, 0.6 ml of a 2% HCl (conc)/ethanol solution was added to the HPLC eluent and the solution evaporated to dryness. To the residue was added 5 ml of ethanol which was also evaporated to dryness in order to remove traces of formic acid. A stream of dry N_2 was applied to the residue for ~1 min to ensure removal of all traces of solvent. To the residue was added 2.9 ml of a sterile solution of saline:water (3:1) and the resulting solution was filtered through a 0.22 μm millipore filter into a multi-injection vial containing 0.1 ml of sterile $NaHCO_3$ solution (1 Meq/ml). A sample of (10 μl) was taken immediately after filtering and added to 1 ml of methanol (as a quench) for HPLC analysis of radiochemical purity. A second sample (50 μl) was injected into an analytical HPLC column [4.6 × 250 mm ODS-1 column*] using the solvent system described above at a flow rate of 2.0 ml/min. Radioactivity was determined using a calibrated ion chamber† and a sodium iodide well counter.‡ (Picker). Ultraviolet absorbance at 254 nm was recorded and from this and calibration curves obtained with standard solutions of **1** and **2**, the specific activity and chemical purity was obtained. The retention times for **1** and **2** were 10.7 min and 8.3 min, respectively. The injection solution was used as a stock solution for the experiments described below. The total injection solution typically contained 3 to 12 nmol of NMS and 2 to 5 nmol of "nitrospiroperidol."

Kinetic Analysis of [^{18}F]*N*-Methylspiroperidol (1) Solutions

All solutions for analysis were made up from the stock solution (15–30 mCi/3 ml) described above. All reaction volumes were 1.5 ml unless otherwise stated with isotonic saline being added as a diluent. Reactions were run in standard 10 ml multi-injection vials at ambient temperature. Solutions for analysis for each run were prepared within 1 min of millipore filtration. A "zero" time was noted and the total radioactivity was measured. Aliquots (10 μl) taken for HPLC analysis were quenched by addition to 1 ml of methanol (*5*, *6*) and analyzed within 1 hr postsampling. Sampling times were typically 10, 30, 60, 120, 180, and 240 min. HPLC analysis of the methanol solution immediately after quenching and through several hours verified that no further reaction occurred after sampling and that methanol effectively quenched the decomposition. The HPLC system used for analysis was the same as described above except that the solvent system was methanol:0.05 N NH_4HCO_2 (80:20) and the flow rate was 1.6 ml/min. [^{18}F]*N*-Methylspiroperidol has a retention time of 8 min in this solvent. Authentic unlabeled **1** was added to each sample before analysis to determine the percent of total radioactivity associated with the carrier peak. For each sample, an injection standard was retained and counted and the effluent from the HPLC column was collected in 0.5-min fractions and counted in an automated gamma counter. In each analysis, the fraction in which the carrier eluted was noted and the total activity eluting from the column was compared with the injection standard. The activity injected was quantitatively recovered from the column using this system, and thus the fraction of unchanged **1** was taken as the activity eluting with the carrier divided by the total activity injected. Comparison of the injection standard with the total sample showed that >98% of the activity was accounted for throughout the course of the study, excluding the possibility of loss of activity due to [^{18}F]fluoride binding to glass surfaces.

Decomposition of 1 at Different Doses

From stock situations of **1** (20.1 mCi/3 ml) different volumes (0.010–3.00 ml) were used to give a 300-fold range of activities. To reduce the variable of injection solution volume a "simulated" injection solution was added to each of the above volumes of **1** so that the total volume of injection solution was constant at 3.0 ml. For example, to the 0.010 ml of **1** was added 2.99 ml of "simulated" injection solution. The "simulated" injection solution was prepared by evaporating 15 ml of HPLC solvent in the presence of 1 ml of 2% HCl/EtOH, dissolving the residue in 3 ml of saline:H_2O (3:1) and filtering (millipore) the resulting solution into 0.1 ml of $NaHCO_3$ (1*M*). Unlabeled N-methylspiroperidol (*7*) (9 nmol) was added to each of the solutions to give a constant mass. Sampling, quenching and HPLC analysis were carried out as described above.

Decomposition of 1 at Constant Dose and Different Specific Activity

A stock solution (0.2 nmol/1 μl) of unlabeled **1** in isotonic saline was prepared and premixed with appropriate volumes of saline solution to give two solutions having 20 nmol and 100 nmol of carrier, respectively, to which equal volumes (0.5 ml) of the stock [^{18}F] solution were added. A third NCA sample was used as a control. The total volume of each solution was adjusted to 1.5 ml with saline and total activity was 3.5 mCi at time of study. Sampling, quenching, and HPLC analysis were carried out as described above.

Decomposition of 1 in Presence or Absence of Oxygen

Oxygen rich and oxygen depleted saline were prepared by bubbling pure oxygen or nitrogen through 5 ml volumes of saline in sealed, vented multiinjection vials for 5 min. The stock solution was prepared with 2 ml of deoxygenated saline:water. To 1 ml of oxygenated saline and to 1 ml deoxygenated saline was added 0.7 ml of stock solution. Aliquots of each were analyzed over a 3-hr period.

Decomposition of 1 in HPLC Solvent

HPLC solvent containing **1** (1.5 ml, 0.3 mCi) was analyzed for unchanged **1** over a time course of 3 hr and no decomposition was observed.

Decomposition of 1 at Different pHs

Solutions which contained equal activities of 1 were prepared as usual and pH was adjusted by adding 2 N HCl. pH was measured at the end of the study using a calibrated pH meter.

Decomposition of Unlabeled *N*-Methylspiroperidol in Presence of [^{18}F]Fluoride

To a solution of 23.3 nmol of *N*-methylspiroperidol in 1.5 cc of saline was added 1 cc of irradiated $H_2{}^{18}O^{\S}$ (95–99%, Monsanto Research Corporation) containing 239 mCi (t_o) of $^{18}F^-$. Aliquots (40 μl) were taken at different times and analyzed by HPLC for unreacted NMS using uv detection at 254 nm. In addition to the mass peak corresponding to NMS (retention time = 8 min) new mass peaks at 6.7, 4.4, 4.0, and 3.1 min were present in the solution which had been incubated with [^{18}F]fluoride. Absolute peak areas for NMS on the chart recorder traces were determined by the cut and weigh method.

Calculation of Rate Constant Data

The rate constants presented here were derived by plotting the natural logarithm of the ratio of percent [^{18}F]NMS at zero time to the percent [^{18}F]NMS at some later time versus the fraction of the total dose as a function of time. The slope was then divided by the total dose to the system to normalize and give a pseudo first order rate constant for the decomposition.

The total dose to the system was calculated assuming the total energy of the positron was deposited in the solution (see Appendix 1).

RESULTS AND DISCUSSION

That compounds labeled with long-lived radioisotopes can undergo radiolytic self-decomposition over time has long been known. When the labeled compound is diluted by solvent, primary external decomposition, where an emitted particle strikes and alters another labeled molecule, is unlikely. In solution, secondary decomposition is commonly the most damaging mode and results from the interaction of labeled molecules with reactive species produced from solvent molecules by ionizing radiation (*5*). The radiolysis of water has been studied extensively (*8,9*) and involves the formation of primary radicals e^-_{aq}, H·, and OH· which can react either with labeled molecules causing their destruction or with other constituents of the solution to produce secondary reactive species. The amount of these species produced is dependent on the radiation energy absorbed by the solution, or dose, usually expressed in rads, where 1 rad deposits 100 ergs per gram of material. A common quantitative measure of the efficiency of a radiation-chemical effect, the G value, is the number of molecules created or destroyed for each 100 eV of energy absorbed. The calculation of total dose and G value is given in Appendix 1.

For compounds labeled with carbon-14 or tritium, the time frame in which radiolytic self-decomposition is observed is usually months or years. In contrast, in order for measurable decomposition to be observed with the short-lived positron emitters, the rate of decomposition would have to be comparable to the radioactive half-life. This indeed appeared to be the case for high purity [^{18}F]*N*-methylspiroperidol of high specific activity in an injection solution intended for PET studies. An investigation of this process was undertaken in the hope of both learning how to prevent it and something of its general features.

HPLC analyses of **1** at various time points after its preparation showed at least three radioactive decomposition products in addition to unreacted [^{18}F]NMS, although those with short retention time were not cleanly resolved (Fig. 2). The ratio of the two well separated product peaks remained constant over the time course, suggesting that the products are formed from primary reactions with [^{18}F]NMS and are not the result of sequential reactions where one product is further decomposed to another. The product ratios were quite similar over the pH range of 8–9, but shifted at lower pH (data not shown).

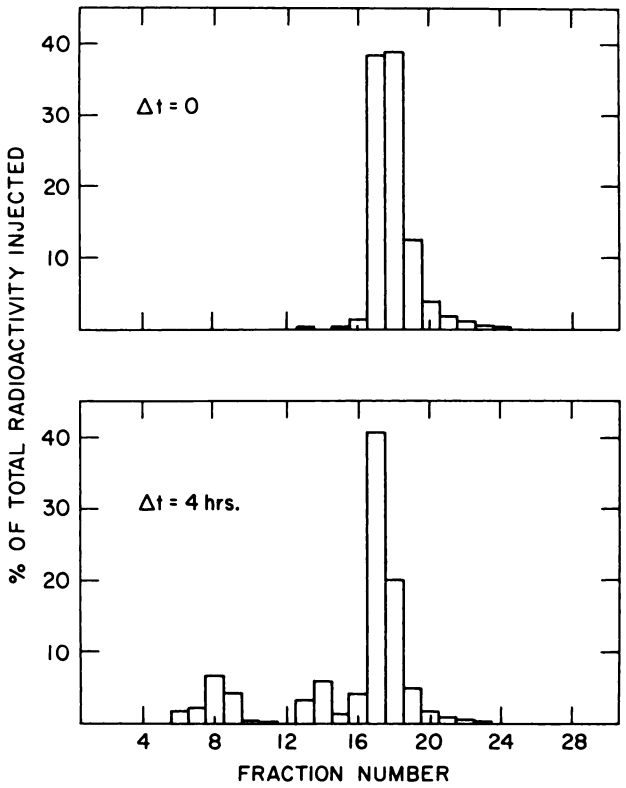

FIGURE 2
Comparative profiles of radioactivity eluting from the HPLC at $\Delta t = 0$ (within 1 min after preparation for injection) and at $\Delta t = 4$ hr. The radioactivity in fractions 16–23 corresponded to the ultraviolet trace for authentic carrier N-methylspiroperidol added to the samples.

In addition to the relatively clearly defined parameters of total dose, specific activity, and pH, it was suspected that in the [^{18}F]NMS product solution there existed one or more unknown scavenger species which effectively competed with [^{18}F]NMS for the reactive products from the radiolysis of water (i.e., they exert a "protective" effect). Thus the phenomena might be represented by an equation of the nature (see Appendix 2):

$$\frac{\text{Rate of Decomposition}}{\text{Total Dose}} = k_i[1] = \frac{k_i' k_2[1]}{k_2[\text{NMS}] + k_3[2] + \ldots \sum_i k_i[I_i]},$$

where $\sum k_i[I_i]$ is a sum over other scavenger reactions. Since the denominator in this equation is considerably more complex than the numerator, we chose to examine the variables in terms of the reciprocal of the pseudo first order rate constant

$$1/k = \frac{k_2[\text{NMS}]}{k_i' k_2} + \frac{k_3[2]}{k_i' k_2} + \frac{\sum_i k_i[I_i]}{k_i' k_2}.$$

Decomposition as a Function of Specific Activity

It would be expected that unlabeled NMS would compete effectively with [^{18}F]NMS for the reactive species generated from the radiolysis of water. As the amount of NMS present increased, fewer of the species would react with [^{18}F]NMS because more would be consumed by reaction with NMS. As is shown in Fig. 3, the reciprocal of the rate increases linearly with the amount of carrier NMS. It might be mentioned thatwith the addition of a few more NMS concentration points, a plot such as this could serve as a calibration curve and provide a new, independent, method for the estimation of specific activity that should allow the determination of carrier to within a nanomole or two.

Decomposition as a Function of Hydrogen Ion Concentration

The inverse relationship of the rate of decomposition and the hydrogen ion concentration is shown in Figure 4. It was found that the rate had a linear relationship to the pH in the range 8–9 which could be expressed by the equation $pH = 0.906k + 7.67$. While the linearity is probably a coincidence since it predicts that the rate will go to zero at pH 7.67 which it does not, this linear relationship made it possible to normalize rates to a common pH for comparison of other variables over the pH range used in these studies.

Although a linear pH dependence was observed in the bicarbonate buffer system used in all of these studies, the rate of decomposition of **1** in the absence of bicarbonate was much faster. For example in a single experiment at pH 7.3 where no bicarbonate was used in the preparation of a solution of **1**, the rate of decomposition was significantly greater than that of a bicarbonate containing solution of **1** at the same pH. Furthermore, when pH adjustment was made with phos-

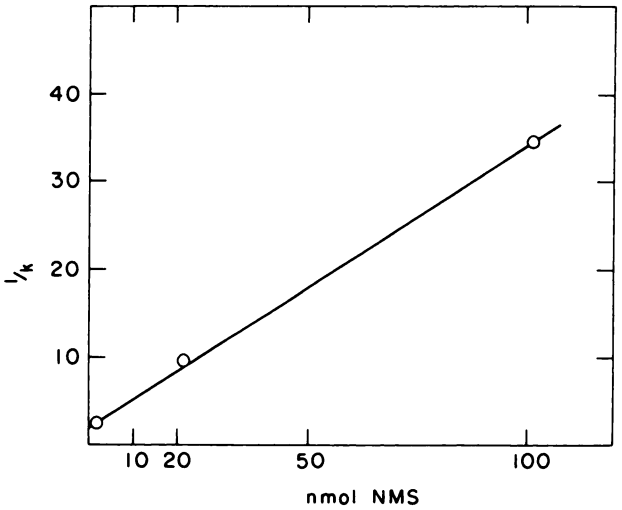

FIGURE 3
Plot of the reciprocal of the observed rate constant (k in krad) for the decomposition of 1 at three different specific activities. The total dose in each solution was 3.5 mCi at zero time and pH = 8.4.

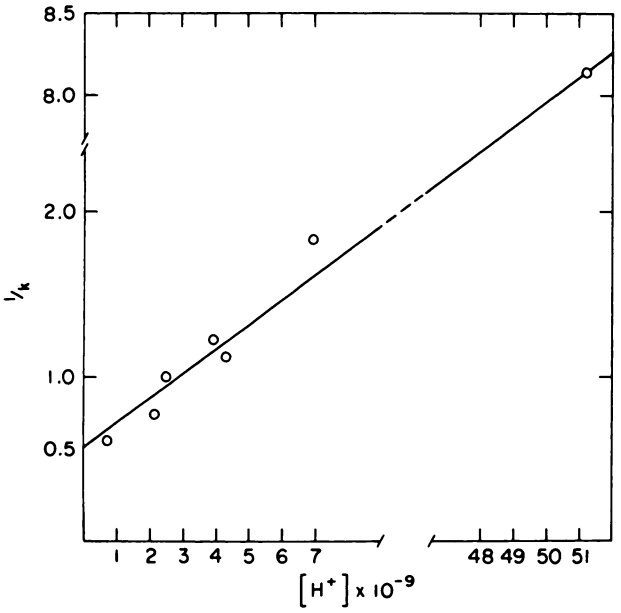

FIGURE 4
Plot of the reciprocal of the rate constant (k in krad) for 1 at different hydrogen ion concentrations. Values are normalized to 5 mCi.

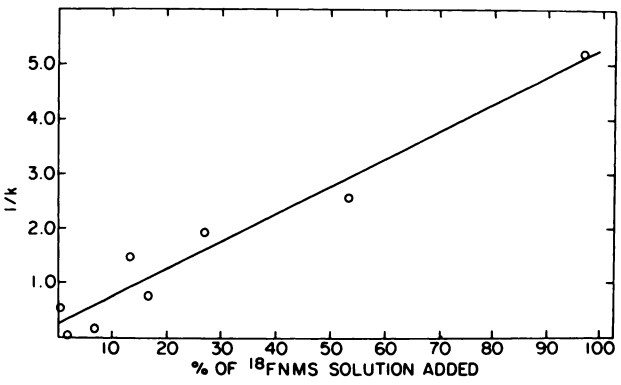

FIGURE 5
Relationship between the reciprocal of the observed rate constant (k in krad) of decomposition of 1 and the volume of [^{18}F]NMS stock solution used in that particular run.

phate buffers rather than bicarbonate buffers, decomposition was even faster and a pH dependence was not observed (data not shown).

Although it is premature to speculate on the mechanism of the observed pH dependence of the rate of decomposition and the influence of bicarbonate, these preliminary data are consistent with destruction of NMS by an unspecified radical (Rad·) which could possibly be CO_3^- or OH··.

Decomposition as Function of Volume of 1

In the studies mentioned above, where equal volumes of the [^{18}F]NMS stock solution could be used, it was possible to isolate a single factor and see the change in rate as a function of this factor. These results were quite easily interpreted, as the other terms dropped out cleanly. When unequal volumes of the stock solution were used results were more complicated. For example, in the study of decomposition at different total dose, as described in the materials and methods section, while the dose was varied, so was the volume of stock solution of **1**, even though an attempt to control for this was made by adjusting to constant volume using a "simulated" injection solution. It was noticed in the early stages of this work that decompositions at low dose and small volumes were disproportionately fast. Figure 5 shows the relationship between the inverse of the rates of decomposition (normalized to a common pH) and the volume of [^{18}F]NMS stock solution that was used in that particular run. The data for this figure was taken from eight runs prepared from three different batches of **1**. There also appeared to be a nonlinear dependence of rate on volume within a single stock solution. This was the most variable and difficult to quantitate factor in these studies. One possible candidate for the unknown scavenger was the small but detectable amount of the contaminant "nitro-N-methylspiroperidol" **2**. Nitro compounds are known as good radical scavengers. The amount of this contaminant varied slightly from synthesis to synthesis (i.e., 2–5 nmol) and this could represent a significant variable when different volumes were used from a single batch of **1**.

Decomposition as Function of Dose

As was pointed out in the preceding discussion, it was not possible to measure the rates of decomposition at different doses without introducing other variables associated with sampling different volumes from a batch of **1**. Even though the intercomparison of different batches of **1** prepared by using varying amounts of $^{18}F^-$ in the synthesis may appear to eliminate all variables except for total dose, it also suffers the difficulty of requiring that each batch be identical with respect to trace chemical impurities, specific activity, pH, etc. Since the demonstration that the rate of decomposition was proportional to total dose was an important one, a series of six solutions varying in total activity over a 300-fold range was studied. Equal volumes from a batch of **1** for each of these solutions was simulated by balancing the smallest volume of **1** used with a "simulated" injection solution (see Experimental Section). Furthermore, unlabeled NMS was added to give a constant mass of 9 nmol per solution. A plot of percent **1** decomposed at 120 min vs total **1** (mCi) in solution at start of the run shows a striking, although nonlinear, dependence on total dose (Fig. 6).

Decomposition of 1 in Presence and Absence of Oxygen

The rates of decomposition of **1** in oxygen rich saline and in oxygen depleted saline were similar, showing little, if any, dependence on the presence of oxygen.

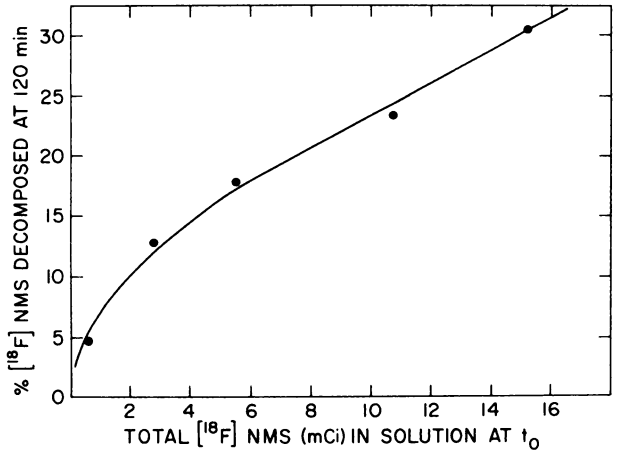

FIGURE 6
Percent of [^{18}F]NMS decomposed at 120 min versus total mCi of [^{18}F]NMS at $\Delta t = 0$. Each solution contained 9 nmole of added NMS.

Decomposition of *N*-Methylspiroperidol in Presence of [^{18}F]Fluoride

To demonstrate independently that NMS was unstable in the presence of the products of the radiolysis of water, unlabeled NMS, in quantities which could be accurately assayed by conventional HPLC/uv analysis, was dissolved in an aqueous solution containing 239 mCi of $^{18}F^-$. For this study a ratio of $^{18}F^-$/nmol of NMS was chosen to approximate that of the [^{18}F]NMS studies (i.e., 239 mCi/23.3 nmol and 30 mCi/3 nmol, respectively). The decomposition of this solution as a function of time is shown in Figure 7. Decomposition under these conditions appears similar to the self-decomposition shown in Figure 1. As further support of the similarity of the two decompositions, a week after the described experiment, a portion of the solution was coinjected with a sample from a current conventional decomposition experiment. When the ultraviolet absorbance at 254 nm and radiochromatogram were superimposed there was a correspondence between the retention times of the products of decomposition of unlabeled NMS and the radioactivity of the self-decomposed [^{18}F]NMS.

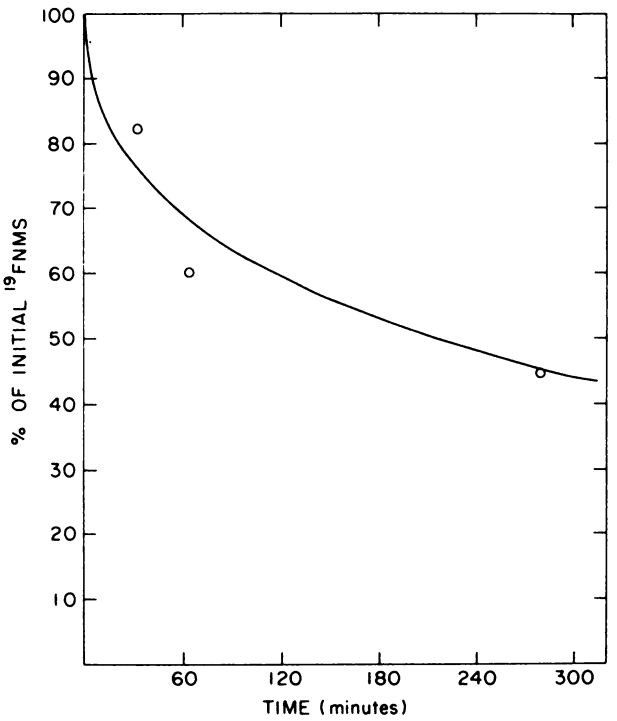

FIGURE 7
Decomposition of unlabeled N-methylspiroperidol (23.3 nmol) in the presence of ^{18}F-(239 mCi).

CONCLUSIONS

The half-life of ^{18}F has been shown to be compatible with multiple studies from a single radiotracer synthesis and with shipment to institutions hundreds of miles distant. The salient point of this report is the observation that the phenomena of radiolytic decomposition associated with compounds labeled with long-lived isotopes which "most investigators regard as an unmitigated nuisance" (*10*) can occur with high specific activity tracers labeled with short-lived positron emitters on a time scale comparable to the physical half-life of ^{18}F.

Recent advances in fields of targetry and radiotracer synthesis have resulted in significant increases in the specific activities of tracers for PET studies. In the present study, the rate of decomposition of [^{18}F]NMS is proportional to the specific activity of the radiotracer and this appears to be the single most important factor responsible for the observed decomposition. The addition of even relatively small amounts of carrier significantly retards the rate of decomposition. To put these observations in perspective, it is informative to compare the extent of radiolytic decomposition which one would expect for a low specific activity tracer such as 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}FDG). This tracer is commonly obtained via electrophilic fluorination in a specific activity of 10 mCi/μmol, a factor of $\sim 10^3$ lower than the [^{18}F]NMS produced for PET studies of the dopamine receptor. If ^{18}FDG at 10 mCi/μmol were to self-radiolyze at a rate comparable to [^{18}F]NMS, less than 0.1% of the labeled compound would have decomposed after 2 hr. It is highly likely that the decomposition rate of other high specific activity compounds will vary depending on chemical structure (with some functional groups being more vulnerable than others) as well as additives or impurities in the parent solution. What we have observed is that there appears to be a complex interplay of factors which are responsible for the observed rates and that variables are difficult to control in these preparations where small amounts of unidentified scavenger substances appear to have large effects on rate.

From the results of this study, it is clear that care must be exercised when chemically pure compounds of high specific activity are not used immediately after they are prepared for injection. In practical terms, we carry out PET studies with **1** by injecting the material within 5 min of its preparation. If a delay should occur between the projected preparation time and its use, the tracer is left in the HPLC solvent (where it is stable) until it is needed. Furthermore, shipment to collaborating institutions has been possible by shipping **1** in the HPLC solvent and removing the solvent and preparing the injection solution immediately prior to use.

Our continuing studies are addressing the identification of radiolysis products, the identification and study of scavenger substances in the injection solution itself, and the examination of this phenomenon for other high specific activity tracers. In addition the use of additives which both retard the decomposition of the injection solution and are safe for parenteral administration is being investigated. For example, during the course of these investigations we have observed that the addition of as little as 1 μmol of ammonium formate to solutions of **1** significantly retards the radiolytic decomposition (data not shown) in contrast to benzyl alcohol and sodium bisulfite which increase the rate at the same concentration.

We would caution other groups who are using high specific activity radiotracers to monitor the radiochemical purity of their tracer both immediately after preparation and for a significant portion of its usable shelf life thereafter using a high resolution analytical system.

NOTES

* (ODS-1) Phenomenex Inc., Ranchos Palos Verdes, CA.
† (CRC-4) Capintec, Inc., Ramsey, NJ.
‡ Picker Int'l., Highland Hghts., OH.
§ Monsanto Research Corp., Dayton, OH.

APPENDIX 1

Calculation of Total Absorbed Dose and G Value (*10*)

Total Absorbed Dose

The total absorbed dose to the solution from the positrons is obtained through the following calculation assuming:

1. All the energy from the positron is deposited in the solution.
2. The gamma dose will be small in comparison.

$$\text{dose(rad)} = \text{mCi} \times \frac{1 - e^{-\lambda t}}{\lambda}\,(\text{min}) \times 2.22 \times 10^9 \frac{\text{dis}}{\text{mCi}} \times$$

$$1.60 \times 10^{-12} \frac{\text{erg}}{\text{ev}} \times \frac{1\ \text{rad}}{100 \frac{\text{erg}}{\text{g}}} \times \bar{E}_{\beta^+}\text{ev} \times \frac{1}{\text{w (g)}}$$

$$\text{for F-18 } \lambda = 6.31 \times 10^{-3}\ \text{min}^{-1}$$

$$\bar{E}_{\beta^+} = 0.250\ \text{MeV}$$

$$\text{dose} = \text{mCi} \times \frac{1 - e^{-\lambda t}}{\lambda} = 1407 \times \text{mCi}\,(1 - e^{-\lambda t}) \times \frac{1}{\text{w (g)}}.$$

Calculation of G Value for Decomposition of NMS (F-19 + F-18)

Average energy per decomposition = 250 keV. Energy deposited in 1 hr for 5 mCi in 1.5 cc solution.

$$5\ \text{mCi} \times \frac{1 - e^{-\lambda t}}{\lambda}\,(\text{min}) \times 2.22 \times 10^9 \frac{\text{dis}}{\text{mCi} - \text{min}}$$

$$\times 250\ \text{keV} \times \frac{1000\ \text{eV}}{\text{keV}} = 1.38 \times 10^{17}\ \text{eV}.$$

Number of molecules decomposed $(1-0.815) \times 6.023 \times 10^{14}$ molecules/nmol $\times$ 2.1 nmole = 2.34×10^{14} molecules

$$G = \frac{2.34 \times 10^{14}}{1.38 \times 10^{15} \times 100\ \text{eV}} = \frac{0.17\ \text{molecules}}{100\ \text{eV}}.$$

APPENDIX 2

Kinetic Expressions for [^{18}F]NMS Decomposition

The decomposition of the [^{18}F]NMS (**1**) follows psuedo first-order kinetics when plotted as a function of the dose to the solution. This observation is consistent with a mechanism involving radicals produced from the radiolysis of water as the reactive species. One such plausible mechanism for the decomposition is given below, where Rad· could be OH· or CO_3^- (produced by reaction of OH· with HCO_3^-).

$$H_2O \xrightarrow{k_1'} \text{Rad.}$$
$$\text{Rad·} + 1 \xrightarrow{k_2} H_2O + P^*$$
$$\text{Rad·} + \text{NMS} \xrightarrow{k_2} H_2O + P$$
$$\text{Rad·} + 2 \xrightarrow{k_3} H_2O + R,$$

where k_1' is the rate of generation of radicals, P^* is a labeled decomposition product(s) from **1** and P and R are unlabeled decomposition products from NMS and **2**. If steady state is assumed for the Rad· radical then the rate equilibrium will have the form

$$\frac{-d(1)}{dt} = \frac{k_1'k_2[1]}{k_2[\text{NMS}] + k_3[2] + \sum_i k_i[I_i]},$$

where I refers to other unidentified scavengers. Thus when ln A_0/A (where A_0 = % [^{18}F]NMS at zero time and A = % [^{18}F] NMS at some later time) is plotted versus dose, an effective rate constant (k_{obs}) can be found. This pseudo first order rate constant will be a sum of the terms in the actual rate equation, i.e.,

$$k_{obs} = \frac{k_1'k_2}{k_2[\text{NMS}] + k_3[2] + \sum_i k_i[I_i]}.$$

By plotting $1/k_{obs}$ versus [NMS], for example, it is possible to separate out one of the terms

$$\frac{1}{k_{obs}} = \frac{k_2[\text{NMS}]}{k_1'k_2} + \frac{k_3[2]}{k_1'k_2} + \frac{\sum_i k_i[I_i]}{k_1'k_2}$$

plotted versus (NMS) the slope will be $1/k_1'$ and the intercept

$$\frac{k_3(2)}{k_1'k_2} + \cdots \frac{\sum_i k_i[I_i]}{k_1'k_2}.$$

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