Sensitivity of Technetium-99m-d,l-HMPAO to Radiolysis in Aqueous Solutions

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The sensitivity of technetium-99m (99mTc) d,l-HMPAO to radiolytically induced dissociation in aqueous solutions was investigated. It was found that cobalt-60 (60Co) gamma irradiation of solutions containing 99mTc-d,l-HMPAO with only 1600 cGy reduced the lipophilic chelates’ radiochemical purity (RCP) to 50%-60%. The radiolytic sensitivity of 99mTc-meso-HMPAO is significantly lower. The results indicate that radiolytically produced intermediates limit the in vitro stability of 99mTc-d,l-HMPAO.


Technetium-99m (99mTc) complexes of tetramethylpropyleneamine oxime (TMPAO) and its derivatives have limited stability in aqueous solutions (1—4). Technetium-99m-d,l-hexamethylpropyleneamine oxime (99mTc-d,l-HMPAO), a 99mTc-TMPAO derivative (1—3), is used to image cerebral perfusion (5—7) but requires administration within 30 min of formulation due to its in vitro conversion from a hydrophobic chelate to hydrophilic 99mTc-species (2—4). In contrast, 99mTc-complexes with the propyleneamine oxime (PmAO) class of ligands are far more stable than the respective 99mTc-TMPAO chelates (3,8—11). The principal differences between these two classes of compounds is that PmAO-based ligands have two methyl groups attached to each of the two carbon atoms, alpha to the two secondary amines and beta to the two oxime N-atoms on the ligand backbone, whereas TMPAO-based ligands have a single methyl group attached to these same carbon atoms (J). Both TMPAO and PmAO ligands form neutral-lipophilic technetium chelates where the technetium is present as the Tc(V) mono-oxo core (12). The precise reasons for their differential stability is not understood.

Other factors, both chemical and structural, appear to influence the conversion rate of the lipophilic 99mTc-TMPAO chelates to hydrophilic species. Studies with 99mTc-HMPAO have demonstrated major stereochemical effects on its in vitro stability where the d,l form is less stable than the meso form in aqueous solutions (2, 4,13). In the presence of various buffers or excess reducing agents, the rate of conversion of 99mTc-d,l-HMPAO is increased (4). We have reported that gentisic acid, 2,5-dihydroxybenzoic acid (GA), reduces the rate of dissociation of the lipophilic chelate (LC) substantially (14). GA is a free radical scavenger and its stabilizing effect may result from its ability to intercept radiolytically produced free radicals preventing them or their products from reacting with the 99mTc-HMPAO chelates. The purpose of this study was to investigate the effects of irradiation on the stability of 99mTc-HMPAO chelates in aqueous solution.

MATERIALS AND METHODS

Technetium-99m-d,l-HMPAO was prepared from a commercial kit (Ceretece, Amersham Intl., Arlington Heights, IL) containing 0.5 mg of d,l-4,8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime (d,l-HMPAO), 7.6 µg stannous chloride dihydrate and 4.5 mg sodium chloride, freeze-dried and stoppered under nitrogen. Pertechnetate in 0.9% aqueous NaCl was eluted from a commercial Mo/mTc generator (Medi-Physics, Inc., Paramus, NJ) that had been eluted exactly 24 hr earlier and was immediately used to initiate each experiment. This ensured that the 99mTc/99mCratio in the eluate was always the same at the beginning of each experiment. Between 5—30 mCi (185—1110 MBq) in 5 ml of 99mTcO4- in 0.9% saline were injected into the vial. Technetium-99m-meso-HMPAO was prepared by adding 1—6 mCi (37—222 MBq) of 99mTc— in 1 ml saline containing 1 mg meso-HMPAO (obtained from Amersham Intl.) and 50 µl of a saturated solution of stannous tartrate. Samples of 99mTc-d,l-HMPAO used to isolate the LC by ether extraction were also prepared by the same method used for 99mTc-meso-HMPAO preparations. The pH of all solutions was measured with a calibrated glass electrode.

The lipophilic 99mTc-d,l-HMPAO or 99mTc-meso-HMPAO chelates were separated from their respective formulation solutions leaving hydrophilic materials (including Sn(2+)) behind by extracting 1 ml of the solutions with 1 ml of diethyl ether vortexed for 1 min. The use of ether containing peroxides must be avoided since peroxides will induce chelate dissociation. One hundred fifty microliters of the ether layer contain-

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ing the LC were pipetted into a fresh test tube. The ether was evaporated to dryness using a stream of N₂ and 0.5 ml 0.9% aqueous NaCl containing either no excess ligand or 3.7 × 10⁻⁴ M d,l- or meso-HMPAO was added to redissolve the residue (the concentration of the ligand present in the commercial kits reformulated with 5 ml generator eluate). Since some uncomplexed HMPAO is extracted by ether (partition coefficient 0.25 [17]), the concentration of HMPAO in the no-excess ligand formulations is ~ 2.8 × 10⁻⁵ M. The pH of these solutions ranged from 6.5 to 7.8. The specific concentration of ⁹⁹ᵐTc in the resulting 0.5 ml solutions contained either 5.7 ± 1.0 mCi/ml (211 ± 37 MBq/ml) or 0.88 ± 0.21 mCi/ml (32.5 ± 7.8 MBq/ml). The radiochemical purity (RCP) of the saline solutions containing ⁹⁹ᵐTc-d,l-HMPAO or ⁹⁹ᵐTc-meso-HMPAO were measured as a function of time at room temperature (22°C—23°C) using 5–20 µl aliquots for chromatographic analysis at 2, 15, 30, 60, 120, 180, and 240 min after dissolving the residue (Table 1).

Radiation doses using ⁶⁰Co gamma rays in a Gamma G-12 irradiator were delivered to 0.5 ml ether-extracted aqueous solutions containing ⁹⁹ᵐTc-d,l-HMPAO or ⁹⁹ᵐTc-meso-HMPAO with low-specific concentrations (0.88 ± 0.11 mCi/ml or an average of 32.5 ± 6.9 MBq/ml). The radiation doses delivered to the solutions were measured with an ionization irradiator were delivered to 0.5 ml ether-extracted aqueous solutions containing ⁹⁹ᵐTc-d,l-HMPAO or ⁹⁹ᵐTc-meso-HMPAO obtained directly from reconstituted freeze-dried kits (i.e., not ether extracted). RCP in each of these samples was measured at 2 min (initial conditions prior to gamma irradiation) and after the gamma-irradiation (see Fig. 2). Control samples (0 cGy of ⁶⁰Co-gamma-irradiation) accompanied each set of irradiated samples.

The percent of ⁹⁹ᵐTc present as the LC was measured using the three-strip method (2,4,16) and the one-strip paper chromatographic method developed in our laboratory (4,14). Briefly, the three-strip method involves developing one instant thin-layer chromatography (ITLC-SG) strip with MEK, one ITLC-SG strip with saline and one paper chromatography strip with 50% acetonitrile/50% H₂O. The RCP of the LC and the percentage of each of the non-lipophilic products (including ⁹⁹ᵐTcO₂, Hyd-Red-⁹⁹ᵐTc and secondary ⁹⁹ᵐTc species) were calculated by the method previously described (2, 4,16).

In the one strip method, a 2¾-inch × ⅛-inch strip of solvent saturation pads (Gelman Sciences, Inc., Ann Arbor, MI) was spotted one-half inch from the bottom and developed with either 100% diethyl ether or 100% ethyl acetate (4,14). All of the non-lipophilic ⁹⁹ᵐTc-species remain at the origin with either eluting solvent while only the lipophilic ⁹⁹ᵐTc-HMPAO chelate (LC) migrates to the top of the strip (Rf = 0.9–1.0). The strips were then sectioned 0.50-inch to 0.75-inch from the origin with the percentage of ⁹⁹ᵐTc on the top portion of the strip representing the RCP.

High-pressure liquid chromatography (HPLC) was used to determine the percentage of secondary ⁹⁹ᵐTc-species that were formed in these samples. The gradient elution system previously described was employed using water and acetonitrile as mobile phase solvents with a Hamilton PRP-1 reversed-phase column that had never been exposed to samples containing stannous or stannic ions (4).

The internal radiation dose (D) delivered to each 0.5 ml solution from the decay of ⁹⁹ᵐTc in the 0.5 ml sample was calculated using the following MIRD equation (17):

\[ D = \lambda \left( \Delta \phi_0 + \left( \Delta \phi_k \right) \right) \]

where \( \Delta \phi_0 \) and \( \Delta \phi_k \) are the respective equilibrium dose rate constants for particulate emissions and electromagnetic radiation emissions from ⁹⁹ᵐTc. \( \Delta \phi_k \) is the summation of \( \Delta \phi_k \) for each type of particulate emission (18). It was assumed that the absorbed fraction, \( \phi_0 \) was 1. \( \Delta \phi_k \) was calculated using \( \Delta \phi_k \) from the MIRD Nuclear Decay Table for ⁹⁹ᵐTc (18) assuming that \( \phi_0 \) for the 140-keV gamma-ray from ⁹⁹ᵐTc is 0.02. The \( \phi_k \) estimation for 0.5 ml samples was based on the absorption parameter method (19).

### RESULTS

The RCP of the ether-extracted LC in the 0.5 ml of 0.9% aqueous NaCl solutions after redissolving the residues was consistently high. The RCP measured at 2 min in the high-specific concentration samples (i.e., 5.7 ± 1.0 mCi/ml or 211 ± 37 MBq/ml) ranged from 84%–96% while the RCP measured at 2 min in low-specific concentration samples (i.e., 0.88 ± 0.21 mCi/ml or 32.5 ± 6.9 MBq/ml) ranged from 86%–96% (Table 1). The RCPs determined by the three-strip method and the one-strip paper chromatography methods were comparable.

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**TABLE 1**

Effects of Specific Concentration on the Radiochemical Purity* of Ether-Extracted [⁹⁹ᵐTc-d,l-HMPAO]

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>%LC*</th>
<th>%⁹⁹ᵐTcO₂*</th>
<th>% Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03</td>
<td>88.4±5.1</td>
<td>4.3±2.6</td>
<td>4.3±1.9</td>
</tr>
<tr>
<td>0.25</td>
<td>91.3±1.9</td>
<td>0.7±0.4</td>
<td>2.0±1.0</td>
</tr>
<tr>
<td>0.50</td>
<td>84.5±6.9</td>
<td>8.7±3.5</td>
<td>6.3±3.7</td>
</tr>
<tr>
<td>1.00</td>
<td>91.8±2.7</td>
<td>0.9±0.4</td>
<td>1.5±1.8</td>
</tr>
<tr>
<td>2.00</td>
<td>82.9±3.5</td>
<td>11.0±2.8</td>
<td>5.3±0.3</td>
</tr>
<tr>
<td>3.00</td>
<td>91.7±2.1</td>
<td>1.0±0.1</td>
<td>1.3±1.3</td>
</tr>
<tr>
<td>4.00</td>
<td>81.9±2.7</td>
<td>12.5±2.5</td>
<td>4.7±0.4</td>
</tr>
<tr>
<td>6.00</td>
<td>91.6±0.4</td>
<td>2.2±1.0</td>
<td>0.7±1.2</td>
</tr>
<tr>
<td>8.00</td>
<td>75.4±4.7</td>
<td>19.2±1.0</td>
<td>4.5±1.5</td>
</tr>
<tr>
<td>10.00</td>
<td>88.4±0.8</td>
<td>4.2±1.0</td>
<td>0.4±0.7</td>
</tr>
<tr>
<td>15.00</td>
<td>69.8±1.8</td>
<td>23.7±3.4</td>
<td>2.0±1.8</td>
</tr>
<tr>
<td>20.00</td>
<td>88.5±3.6</td>
<td>4.8±2.2</td>
<td>0.6±0.5</td>
</tr>
<tr>
<td>24.00</td>
<td>64.7±7.4</td>
<td>29.8±7.4</td>
<td>3.0±1.6</td>
</tr>
</tbody>
</table>

* Yields were measured by the three-stripe chromatography method. LC = Lipophilic ⁹⁹ᵐTc-d,l-HMPAO chelate.

The average specific concentration of ⁹⁹ᵐTc in these solutions was 5.7 ± 1.0 mCi/ml (211 ± 37 MBq/ml). The data are presented as the mean ± s.d. (n = 4).

The average specific concentration of ⁹⁹ᵐTc on these solutions was 0.88 ± 0.21 mCi/ml (32.5 ± 6.8 MBq/ml). The data are presented as the mean ± s.d. (n = 3).
percentage of Hyd-Red-99mTc in all samples was <2%. The percentage of secondary hydrophilic 99mTc products (2,4) present at 5 min was <6% in both the low- and high-specific concentration samples (Table 1). The percentage of secondary hydrophilic 99mTc products measured by HPLC or the three-strip method in the 60Co irradiated solutions was <5% and demonstrated that 99mTcO₄⁻ was the principal radiolytically produced hydrophilic 99mTc product. Pertechnetate was also the major radiolytic product produced in 60Co gamma-irradiated samples obtained directly from the reconstituted vials with the percentage of secondary hydrophilic 99mTc products <6.5%.

The rate of conversion of 99mTc-d,l-HMPAO to hydrophilic 99mTc species in saline depends upon the 99mTc specific concentration. Regression analysis of the RCPs as a function of time demonstrates that the pseudo-first order rate constant (kₐ) for the conversion reaction(s) are 0.03 h⁻¹ and 0.089 h⁻¹ for the low- and high-specific concentration samples, respectively (Table 2). The latter value is similar to that reported by Hung et al. (4) using samples with the same high-specific concentrations. In contrast, the kₐ for the conversion of 99mTc-meso-HMPAO at a specific concentration of 0.50 ± 0.10 mCi/ml (18.5 MBq/ml) was only 0.009 ± 0.001 h⁻¹ (Table 3).

The results of RCP analysis of the lipophilic 99mTc-d,l-HMPAO chelate in low-specific concentration solutions after irradiation with doses of 0, 200, 800, 1600, and 3200 cGy are summarized in Table 3. The rate of radiolytically-induced dissociation in the absence or presence of excess HMPAO ligand was not significantly different (Table 4). RCP decreases progressively with increasing doses of gamma irradiation. The rate constant (kₐ) for radiolytically-induced dissociation of the 99mTc-d,l-HMPAO chelate, obtained from the plot of natural log RCP versus irradiation dose (Fig. 1), is (2.8 ± 0.76) x 10⁻⁶ cGy⁻¹ (Table 4). The rate of decrease in RCP plotted as a function of internal radiation dose (self-irradiation) to the high-specific concentration samples is shown in Figure 1 with kₐ calculated to be (4.3 ± 0.2) x 10⁻⁴ cGy⁻¹. The RCP of 99mTc-meso-HMPAO as a function of dose decreased at a much slower rate than the d,l-isomer (Fig. 1, Table 4).

The conversion of 99mTc-d,l-HMPAO in the solutions from reconstituted vials as a function of gamma irradiation dose does not follow first order kinetics (Fig. 2). The plot shown in Figure 2 demonstrates that the rate of chelate dissociation is slower in the low dose region (i.e., doses <800 cGy) but accelerates at higher doses. The normalized percentage of RCP at 1600 and 3200 cGy in these were 46.9 ± 10.7% and 16.7 ± 4.7%, figures which are both significantly lower than observed at these doses in the ether-extracted samples.

### TABLE 2

<table>
<thead>
<tr>
<th>Specific concentration</th>
<th>99mTc-d,l-HMPAO at pH 7–7.8 at 22°–24°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>mCi/ml</td>
<td>MBq/ml</td>
</tr>
<tr>
<td>0.88 ± 0.21</td>
<td>32.5 ± 7</td>
</tr>
<tr>
<td>5.7 ± 1.0</td>
<td>211 ± 37</td>
</tr>
<tr>
<td>0.96 ± 0.24</td>
<td>35.5 ± 8.9</td>
</tr>
</tbody>
</table>

* All samples were "ether-extracted" and the radiochemical purity was determined as a function of time using the one-strip chromatography method using ether as the mobil phase. The correlation coefficient for all least-square regression analyses was ≥0.97.

### TABLE 3

<table>
<thead>
<tr>
<th>Dose (cGy)</th>
<th>99mTc%</th>
<th>99mTcO₄⁻%</th>
<th>Secondary %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>86.4 ± 2.9</td>
<td>9.8 ± 3.2</td>
<td>2.9 ± 0.0</td>
</tr>
<tr>
<td>200</td>
<td>85.0 ± 5.1</td>
<td>10.4 ± 2.3</td>
<td>3.8 ± 2.9</td>
</tr>
<tr>
<td>800</td>
<td>76.2 ± 8.4</td>
<td>20.1 ± 8.1</td>
<td>2.6 ± 0.1</td>
</tr>
<tr>
<td>1600</td>
<td>53.7 ± 4.5</td>
<td>42.2 ± 4.1</td>
<td>2.9 ± 0.1</td>
</tr>
<tr>
<td>3200</td>
<td>31.6 ± 5.3</td>
<td>64.2 ± 5.6</td>
<td>3.8 ± 1.4</td>
</tr>
</tbody>
</table>

* Radiochemical purity of the LC was measured by the three-strip chromatography method and is presented as the mean ± s.d. (n = 3). Data obtained 1.5 hr after initial complexation using low-specific activity 99mTc-d,l-HMPAO samples.

### TABLE 4

<table>
<thead>
<tr>
<th>Irradiation source</th>
<th>Stereochemical form</th>
<th>kₐ (cGy⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60Co meso</td>
<td>(4.3 ± 0.2) x 10⁻⁶</td>
<td></td>
</tr>
<tr>
<td>60Co d,l</td>
<td>(2.8 ± 0.76) x 10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>60Co d,l</td>
<td>(2.7 ± 0.85) x 10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>Self-Irradiation d,l</td>
<td>(4.3 ± 0.2) x 10⁻⁴</td>
<td></td>
</tr>
</tbody>
</table>

* Average doses to solutions from the 99mTc-decay in high specific concentration (5.7 ± 1.0 mCi/ml or 211 ± 37 MBq/ml) samples, in cGy, was calculated using MIRD formulation (18).

† The specific concentration of 99mTc in samples irradiated with 60Co-irradiation averaged between 0.85–1.0 mCi/ml (31.5–37 MBq/ml) in each group. The correlation coefficient for all least-square's regression analysis was ≥0.98.

‡ The 0.9% aqueous NaCl reconstitution solution contained 3.7 x 10⁻⁶ M excess d,l-HMPAO.
HMPAO is more sensitive to radiolysis than other $^{99m}$Tc radiopharmaceuticals. This radiolytic sensitivity may be the major factor limiting the total amount of $^{99m}$Tc activity that is recommended to be added to the Ceretec™ kit (i.e., a maximum of 30 mCi [1 110 MBq] in 5 ml is recommended in package insert) to ensure that the rate of LC conversion to a hydrophilic $^{99m}$Tc species remains within acceptable limits (2). The greater resistance of $^{99m}$Tc-meso-HMPAO to gamma-radiolysis parallels the higher in vitro stability of $^{99m}$Tc-meso-HMPAO relative to the d,l-isomer in aqueous solutions previously reported (2,4).

The rate of $^{99m}$Tc-d,l-HMPAO dissociation in ether-extracted samples induced by $^{60}$Co gamma irradiation of $^{99m}$Tc-meso-HMPAO (A) or $^{99m}$Tc-d,l-HMPAO (B). The radiation dose delivered to solutions containing 5.5 mCi/ml $^{99m}$Tc-d,l-HMPAO from self-irradiation (c) was calculated using the MIRD approach (17).

**DISCUSSION**

The rate of dissociation of $^{99m}$Tc-d,l-HMPAO over time depends upon the concentration of radioactivity with the $k_4$ for the high-specific concentration samples averaging of 3.1 times higher than the low specific concentration samples (Table 3). Since solution conditions in the samples were similar (pH and ligand concentrations) and the ligand/Tc ratios were high (0.9–5.3 x 10$^4$ for low-specific concentration and high-specific concentration solutions, respectively), it can be inferred that self-irradiation effects play an important role in the dissociative mechanism(s).

The relationship of RCP with gamma irradiation dose demonstrates that the stability of $^{99m}$Tc-d,l-HMPAO is more sensitive to radiolysis than other $^{99m}$Tc radiopharmaceuticals. This radiolytic sensitivity may be the major factor limiting the total amount of $^{99m}$Tc activity that is recommended to be added to the Ceretec™ kit (i.e., a maximum of 30 mCi [1 110 MBq] in 5 ml is recommended in package insert) to ensure that the rate of LC conversion to a hydrophilic $^{99m}$Tc species remains within acceptable limits (2). The greater resistance of $^{99m}$Tc-meso-HMPAO to gamma-radiolysis parallels the higher in vitro stability of $^{99m}$Tc-meso-HMPAO relative to the d,l-isomer in aqueous solutions previously reported (2,4).

The rate of $^{99m}$Tc-d,l-HMPAO dissociation in ether-extracted samples induced by $^{60}$Co gamma irradiation [where $k_4 = (2.87 \pm 0.76) \times 10^{-4}$ cGy$^{-1}$] is ~65% as high as the dissociation rate that could be induced by self-irradiation [$k_4 = 4.3 \pm 0.2 \times 10^{-4}$ cGy$^{-1}$], assuming that radiolysis is the only factor responsible for causing dissociation (Table 4). On the other hand, the results may suggest that the rate of conversion of the LC in aqueous solutions is caused by more than one mechanism and that ~35% of the dissociative reactions involve nonradiolytic reactions. Since the chemical environments were similar in all ether-extracted samples, it can be assumed that nonradiation-induced dissociative reactions with $^{99m}$Tc-d,l-HMPAO in aqueous solutions to occur. However, since the radiation dose was delivered from $^{99m}$Tc decay products over a 4-hr period while the gamma-irradiation dose was delivered in less than 20 min, dependence of $k_4$ on dose rate cannot be excluded. Regardless of the amount of nonradiolytic reactions, the comparatively low rate of $^{99m}$Tc-d,l-HMPAO dissociation observed with the low-specific concentration samples in the absence of other solutes or excess uncomplexed ligand (Table 3) shows that this chelate is inherently more stable in aqueous solutions than previously realized (2,4). This suggests that simple hydrolysis or unimolecular conversion of the chelate to hydrophilic products does not play a prominent role in the conversion processes at higher specific concentrations.

Sensitivity of $^{99m}$Tc-d,l-HMPAO in the reconstituted vial to radiolysis was also demonstrated (Fig. 2). In contrast to the ether-extracted samples which follow pseudo-first order dissociation kinetics as a function of dose (cGy) (Fig. 1), $k_4$ in the kit solutions has a shoulder in the lower dose region. The decreased sensitivity at doses ≤800 cGy may be due to the presence of dissolved stannous or stannic ions in these solutions. Above 800 cGy, the sensitivity to radiolysis increases significantly (Fig. 2).

The reactive intermediates or free radicals initially produced in dilute aqueous solutions from the decay of $^{99m}$Tc (self-irradiation) will be identical to those produced by external beam irradiations (15). Since the concentrations of solutes in the solutions were low (i.e.,

![Figure 1](image1.png)

**FIGURE 1**

Effect of radiation dose (cGy) on radiochemical purity (RCP) of $^{99m}$Tc lipophilic chelates, normalized to RCP at 2 min post-reconstitution of ether-extracted samples. RCP was determined by paper chromatography using diethylether as the eluting solvent. Cobalt-60 gamma radiation was delivered to 0.9% aqueous NaCl solutions containing ~1 mCi/ml (37 MBq/ml) of $^{99m}$Tc-meso-HMPAO (A) or $^{99m}$Tc-d,l-HMPAO (B). The radiation dose delivered to solutions containing 5.5 mCi/ml (204 MBq/ml) $^{99m}$Tc-d,l-HMPAO from self-irradiation (c) was calculated using the MIRD approach (17).

![Figure 2](image2.png)

**FIGURE 2**

Effects of radiation dose (cGy) on radiochemical purity (RCP) of the lipophilic $^{99m}$Tc-d,l-HMPAO chelate following irradiation of solutions obtained directly from reconstituted Ceretec® vials using $^{60}$Co gamma radiation.
HMPAO \leq 3.7 \times 10^{-4} \, M and \text{Tc-d,l-HMPAO} \leq 5.5 \times 10^{-8} \, M, free radical products from radiolysis of H_2O will comprise essentially all of the initial reactive intermediates (15). The implication of free radical-mediated reactions or free radical-produced intermediates (e.g., peroxides) on promoting dissociation of \text{Tc-d,l-HMPAO} is consistent with the observation that the presence of gentisic acid in solutions substantially reduces the rate of \text{Tc-d,l-HMPAO} conversion to hydrophilic products (14). Gentisic acid, a free radical scavenger, may provide protection from free radical attack by intercepting radicals before they interact with other solutes.

In summary, this study demonstrates that \text{Tc-d,l-HMPAO} in aqueous solutions at or near neutral pH or in solutions in the reconstitution vials is sensitive to radiolysis with decomposition of the LC at radiation doses of only \leq 800 \, cGy. These results also indicate that a principal part of the decomposition occurs in samples that contain moderate to high specific concentration of \text{Tc} and that this decomposition arises from self-irradiation, with \text{TcO}_2 being the primary hydrophilic species.

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