

Effect of Oxygen on the Reduction of Pertechnetate by Stannous Ion

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The effect of oxygen on the reduction of sodium pertechnetate by stannous chloride has been investigated using a paper electrophoresis method. It has been shown that oxygen interferes with the reduction process by oxidizing stannous ion, Sn(II), to stannic, Sn(IV), thereby leaving less Sn(II) available for the reduction of pertechnetate ion. In a solution of $1.66 \times 10^{-3} \text{M TcO}_4^-$ saturated with oxygen, a 3.4 molar ratio of Sn(II) to TcO_4^- was required for complete reduction of TcO_4^- , whereas in a nitrogen atmosphere, a 2.4 molar ratio was required for the same purpose. The oxygen interference increases as the concentration of TcO_4^- decreases. In a nitrogen atmosphere, 1.40 and 10.05 molar ratios of Sn(II) to TcO_4^- were required for the complete reduction of $1.66 \times 10^{-3} \text{M}$ and $1.66 \times 10^{-5} \text{M TcO}_4^-$ respectively. Once the reduction is accomplished, however, it is not easily reversible. Bubbling with oxygen for 1 hr had no effect on the quantity of reduced technetium.

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Technetium-99m sodium pertechnetate is reduced during the preparation of various radiopharmaceuticals (1-5). Many different reducing agents have been used—such as ferrous ion (6), ferric ion with ascorbic acid (7), and D-penicillamine (8)—but the most popular agent continues to be stannous ion. The concentration of stannous ion normally used is very large when compared with the almost carrier-free concentration of the pertechnetate present. This excess has usually been assumed to be necessary to maintain the stability of the reduced Tc species, probably Tc(IV). However, the influence of oxygen present in the solution, and the potential for reaction between it and the stannous ion may, in part, explain the necessity for excess reducing agent.

The present study concerns the effect of oxygen on the reduction of pertechnetate in acidic solutions by stannous ion. The stoichiometric relationship between the TcO_4^- and Sn(II) in oxygen-rich and oxygen-free solutions has been determined in order to study possible oxidation of either the reduced technetium species and/or the Sn(II). This work is aimed at a more complete understanding of the rou-

tine chemical reaction commonly used to produce radiopharmaceuticals containing Tc-99m.

METHODS AND MATERIALS

Chemicals and their preparation for use. The radionuclide Tc-99m in the form of TcO_4^- ion in a saline solution was used.* The "carrier-free" $^{99\text{m}}\text{TcO}_4^-$ was extracted from Mo-99 in 5 N sodium hydroxide solution using a modified version of the methyl-ethyl-ketone extraction method of Lathrop and co-workers (9).

Carrier Tc-99 as ammonium pertechnetate† was also used. Various concentrations of carrier $^{99}\text{TcO}_4^-$ were prepared by diluting this solution with water previously bubbled with either nitrogen or oxygen.

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A known amount of the "carrier-free" Tc-99m solution was added to each dilution.

Phosphate buffer (0.05 M; pH 6.80) was prepared by dissolving 6.32 g of disodium hydrogen phosphate and 0.76 g of sodium dihydrogen phosphate in 1 liter of distilled water. The buffer solution was bubbled with either nitrogen or oxygen depending on the nature of the experiment to be done. Fresh solutions of the buffer were prepared as required.

Stannous chloride[‡] dissolved in concentrated HCl was diluted with either oxygen- or nitrogen-bubbled water to give the desired Sn(II) concentration, and the pH adjusted to 2.0. Fresh stannous chloride solutions were prepared for each series of experiments. In general the diluting water was prepared by bubbling distilled water with nitrogen or oxygen overnight.

Experimental procedure. Different concentrations of TcO_4^- (1.66×10^{-2} – $1.66 \times 10^{-5}M$) were reduced with various concentrations of SnCl_2 in order to determine the molar ratio of Sn^{2+} to TcO_4^- necessary for complete reduction of TcO_4^- . The normal experimental procedure was to mix 0.3 ml of the appropriate concentration of TcO_4^- with 5 ml of the stannous chloride solution. After 10 min, the extent of TcO_4^- reduction at any one concentration did not change with standing from 10 min to 12 hr.

A 5- μl aliquot of each experimentally reduced solution was placed at midpoint on a paper strip and 350 V DC was applied for 1 hr at ambient temperature. The electrolyte was 0.05 M phosphate buffer at pH 6.8. After drying, each strip was cut into 60 equal lengths and the Tc-99m activity assayed with a sodium iodide well counter. To ensure that no Tc-99m was lost during analysis, the sum of the activity on each strip was compared with a 5- μl aliquot of a suitably diluted standard.

RESULTS AND DISCUSSION

Electrophoresis. During the electrophoresis the reduced technetium tended to stay at the original placement site, while the TcO_4^- migrated towards the anode. The extent of TcO_4^- migration was independent of TcO_4^- concentration. The failure of the reduced species to migrate suggests that, under the analytical conditions of pH 7, either a complex of higher molecular weight, a neutral species, or a precipitate is formed. It could also mean that the reduced species is bound to the paper strip.

While the electrophoretic analysis does little to reveal the charge, the oxidation state, or the extent of hydration of the reduced technetium species, the fraction of TcO_4^- reduced under a given set of conditions can be accurately determined. Typical patterns of Tc-99m migration under conditions of zero,

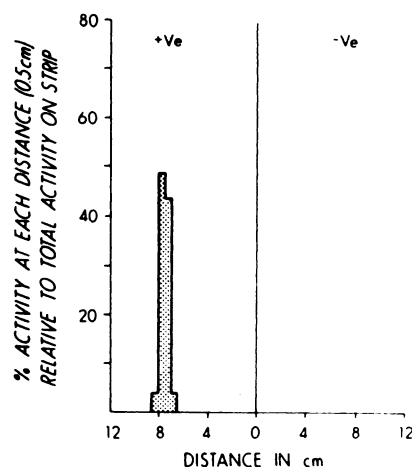


FIG. 1. Electrophoretogram of unreduced $^{99m}\text{TcO}_4^-$.

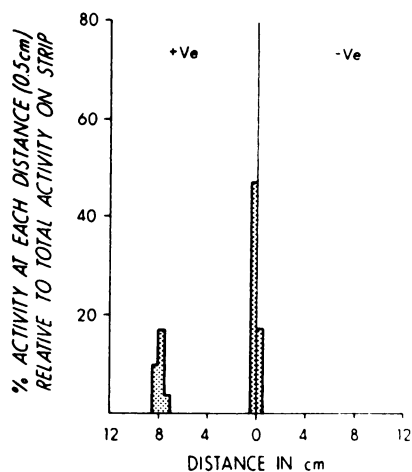


FIG. 2. Electrophoretogram of partially reduced $^{99m}\text{TcO}_4^-$.

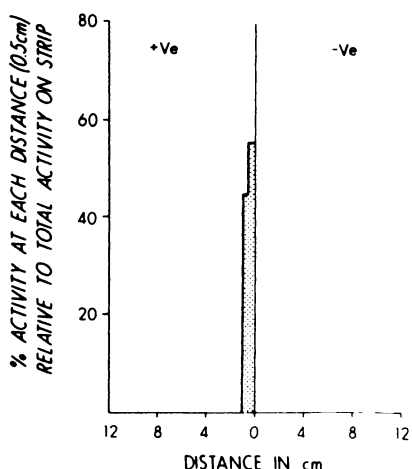
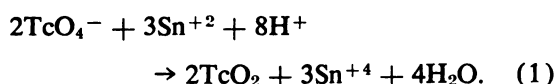


FIG. 3. Electrophoretogram of completely reduced $^{99m}\text{TcO}_4^-$.

partial, and complete reduction are shown in Figs. 1-3, respectively.

Stoichiometry studies. Under oxygen-free conditions (in a nitrogen atmosphere) various concentrations of stannous chloride and pertechnetate ion were reacted. In Fig. 4 the fraction of reduced technetium is shown as a function of the Sn(II) to TcO₄⁻ molar ratio at various TcO₄⁻ concentrations. It can be seen that the reaction goes to completion (100% TcO₄⁻ reduction) at a molar ratio approaching 1.5 only when the TcO₄⁻ concentration is at the highest value studied (1.66 × 10⁻²M). This limiting molar ratio for complete reduction is predicted by the commonly accepted redox reaction for TcO₄⁻ given in the following equation.



That the reduced species is Tc(IV) in various media has been substantiated by a number of workers (see Table 1). It is clear from Fig. 4 that in all but the highest concentrations, excess stannous chloride was required to drive the reaction to completion. This suggests that at lower TcO₄⁻ concentrations, another reaction is effectively competing for the stannous chloride, and explains in part why excess stannous chloride is required in the routine preparation of Tc-99m radiopharmaceuticals (2-4).

Oxygen effects. Figure 5 shows the influence of using oxygen-bubbled water on the reduction. It is clear that more stannous chloride is required to achieve a complete reduction when the solution is saturated with oxygen. Oxygen could influence the reaction in two ways:

TABLE 1. REDUCTION OF PERTECHNETATE ION BY STANNOUS CHLORIDE IN VARIOUS MEDIA

Medium	Method of study	Oxidation state	Reference
Hydrochloric acid	Potentiometric titration	IV	(14)
	Spectrophotometry	IV	(15)
Potassium thiocyanate	Colorimetry	IV	(16)
Dimethylglyoxime-picolinic acid	Colorimetry	IV	(16)
	Spectrophotometry	IV, V	(17)
Sodium citrate	Polarography	IV	(13)
	Potentiometric titration	IV	

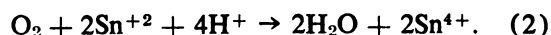
1. It may oxidize the stannous ion to stannic ion, thereby leaving less stannous ion available to reduce the TcO₄⁻ ion.
2. It may reoxidize either an intermediate or the final reduced species back to TcO₄⁻ ion.

To determine which of the preceding possibilities is dominant, the reduction reaction was studied by adding oxygen in one case and nitrogen in the other to the TcO₄⁻ ion and stannous chloride solutions before and after mixing. The extent of TcO₄⁻ reduction in each situation was studied as a function of the length of oxygen or nitrogen bubbling time at a constant flow rate. Figure 6 clearly shows that with oxygen less TcO₄⁻ is reduced, which suggests that the oxygen competes with TcO₄⁻ for the stannous chloride.

However, it is also possible that the reduced technetium species is reoxidized to TcO₄⁻ by the excess oxygen present in solution. To test this possibility, nitrogen and oxygen were bubbled into two identical solutions after the reactants had been mixed. As seen in Fig. 7, the yield of reduced technetium remained constant as a function of bubbling time for both oxygen and nitrogen experiments.

These experiments suggest that the effect of oxygen is to compete for the stannous chloride in the reduction of the TcO₄⁻ ion. The postmixing experiment shows that the Tc(IV) is not reoxidized by oxygen. However, Lavrukhina and Pozdnyakov (10) and Boyd (11) have reported that technetium dioxide is readily oxidized by oxygen to technetium heptoxide (Tc₂O₇).

When oxygen is dissolved in water, its equilibrium concentration is 1.23 × 10⁻³M at 25°C and 1 atm (12). It most probably reacts with stannous ion as shown in Eq. 2:



The concentration of stannous ion required for com-

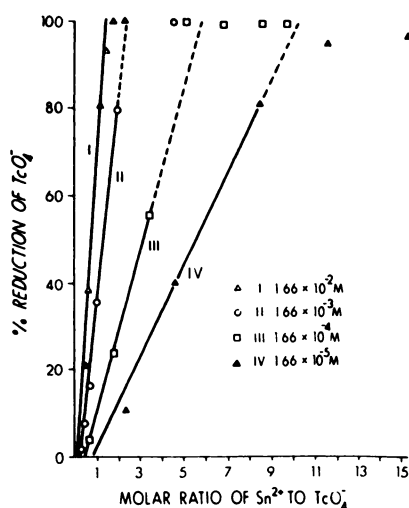


FIG. 4. Reduction of various concentrations of TcO₄⁻ by Sn²⁺. As the concentrations decrease (curve IV vs. curve I) a larger excess of Sn²⁺ is required to achieve same reduction.

plete reaction with oxygen in a saturated aqueous solution is $2.46 \times 10^{-3}M$. According to Eq. 1, for $1.66 \times 10^{-3}M$ TcO_4^- , $2.49 \times 10^{-3}M$ stannous ion is required for complete reaction. For the combined reactions the molar ratio of Sn(II) to Tc(VII) for complete reduction of $1.66 \times 10^{-3}M$ TcO_4^- in O_2 solution is calculated below as 2.98:

$$\begin{aligned} [Sn^{2+}] &= 1.5 [TcO_4^-] + 2[O_2] \\ &= (1.5 (1.66) + 2 (1.23)) \times 10^{-3}M \\ &= 4.95 \times 10^{-3}M \\ \frac{[Sn^{2+}]}{[TcO_4^-]} &= \frac{4.95 \times 10^{-3}}{1.66 \times 10^{-3}} \\ &= 2.98. \end{aligned}$$

When oxygen is bubbled into the solutions before mixing, the experimentally observed value of the molar ratio for complete reduction of $1.66 \times 10^{-3}M$ TcO_4^- is 3.40 (Fig. 5). This ratio of 3.40 is somewhat larger than the computed value of 2.98, but some oxidation of Sn(II) can take place during storage of the solid reagent.

Richards and Steigman (13) in their polarographic and potentiometric study of the reduction of $3.4 \times 10^{-4}M$ TcO_4^- by Sn^{2+} in various complexing media used a 6:1 molar ratio. This sixfold molar excess of Sn^{2+} is in agreement with the 5.56 molar ratio of Sn^{2+} to TcO_4^- needed for complete reduction in the present studies when $1.66 \times 10^{-4}M$ TcO_4^- is reduced with $SnCl_2$ (Fig. 4, curve III).

It has been shown that atmospheric oxygen interferes with the reduction of TcO_4^- ion by Sn(II).

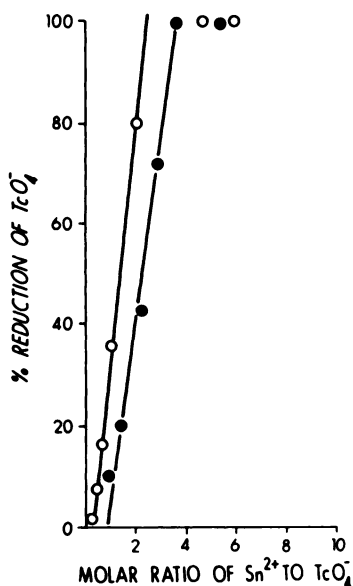


FIG. 5. Reduction of the same concentration of TcO_4^- ($1.66 \times 10^{-3}M$) by Sn^{2+} using water bubbled with N_2 (○) and O_2 (●).

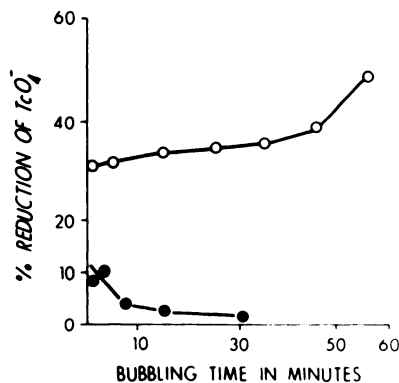


FIG. 6. Effect of bubbling reagent solutions with nitrogen or oxygen before reduction of $5.0 \times 10^{-3}N$ TcO_4^- by $3.3 \times 10^{-3}N$ Sn^{2+} . ○ = Nitrogen bubbled; ● = Oxygen bubbled.

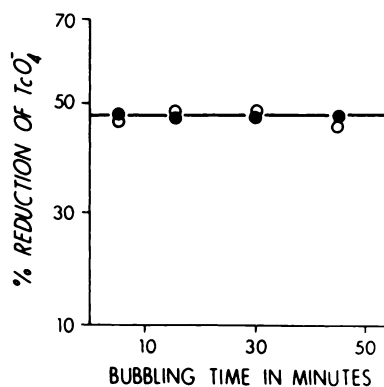


FIG. 7. Effect of bubbling nitrogen or oxygen after reduction of $5.0 \times 10^{-3}N$ TcO_4^- by $3.3 \times 10^{-3}N$ Sn^{2+} . ○ = Nitrogen-bubbled solution of reduced TcO_4^- ; ● = Oxygen-bubbled solution of reduced TcO_4^- .

Oxygen oxidizes Sn(II) to Sn(IV), thereby making less Sn(II) available for the reduction of TcO_4^- ion. Oxygen interference increases as the concentrations of TcO_4^- and Sn(II) decrease. In order to fully reduce carrier-free TcO_4^- ion with low concentrations of Sn(II), it is necessary to exclude oxygen as much as possible. The reduction of $^{99m}TcO_4^-$ can be driven to completion by the addition of excess Sn(II) as is the current practice in the routine preparation of Tc-99m radiopharmaceuticals. Alternatively innocuous antioxidants may be added.

The reduced technetium species (technetium dioxide) seems to be stable to oxygen and does not revert to pertechnetate under the conditions of this experiment. The extent to which this situation applies to Tc-99m radiopharmaceuticals is not known at this time.

FOOTNOTES

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