

An Improved Method for the Synthesis of Potassium Thiocyanate Labeled with Radioactive Sulphur

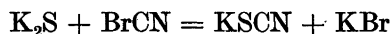
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Potassium thiocyanate is a normal constituent of saliva. It is formed from cyanide and thiosulphate through the action of rhodanese, an enzyme found in a variety of organs. Because of its pharmacological action potassium thiocyanate is used in the treatment of essential hypertension. The labeling of the compound with radioactive sulphur, therefore, warrants some interest as a tool for the study of its metabolism. However, labeled potassium thiocyanate may also be used for the introduction of radioactive sulphur into other organic molecules, for instance in the preparation of sulphur labeled mercaptoethylamine and taurine as described by this author ¹.

Potassium thiocyanate labeled with S³⁵ has previously been prepared by Wood ². The method was modified by Tabern *et al* ³. These procedures are based on the well known reaction between elementary sulphur and potassium cyanide. Because of the relatively low yield obtained by these investigators (49 per cent) and the difficulties involved in the handling of small amounts of elementary sulphur, the synthesis described below was developed. This method is well suited for isotopic work, the yield being high (86 per cent) on micro scale runs (30-40 mg of potassium thiocyanate).

The reaction employed was first used by Gutman ⁴ and can be written as:



The best yield was obtained by dissolving one equivalent of potassium sulphide together with two equivalents of potassium hydroxide in water, and adding in portions two equivalents of dry cyanogen bromide to the solution, kept at 80° C on a water bath. The reaction apparently starts with the reduction of the sulphide to colloidal elementary sulphur, as the reaction mixture turns faintly turbid for a few seconds immediately after the addition of cyano-

gen bromide. At lower temperatures the greater part of the elementary sulphur precipitates out. In a series of check runs, the thiocyanate formed was determined as the iron complex according to Snell ⁵, the extinction being read in a Uvispec spectrophotometer at 4 700 Å against a freshly prepared standard. Yields from 79 to 86 per cent were found. It was suspected that precipitation of small amounts of the intermediary colloidal sulphur might represent a limitation for the synthetic yield. Other solvents (dioxane, acetone, xylene) were therefore tried, but without success.

Since labeled sulphur is available as sulphuric acid at one tenth the price of labeled sulphide, sulphate was used as starting material. In the conversion of barium sulphate to barium sulphide as described by Kamen ⁶, hydrogen gas at 900—1 000° C is used as reducing agent. Apart from the explosion hazard, this method also suffers from the disadvantage that some of the sulphur is reduced to hydrogen sulphide. We have therefore worked out a different procedure, in which carbon monoxide at 850—900° C is used for the reduction. According to Houben ⁷ the reduction of calcium sulphate with carbon monoxide at this temperature gives carbon disulphide in quantitative yield. This is, however, incorrect, and seems to be due to a misinterpretation of the original Polish paper ⁸. Calcium sulphate as well as barium sulphate are reduced to the corresponding sulphides under these conditions. In check runs with reduction times from 20—30 minutes yields of barium sulphide of 99.5—100 per cent of the theoretical were found.

The conversion of barium sulphide to potassium sulphide was performed in the diffusion apparatus shown on Fig. 1. The barium sulphide was transferred to the small cup A and acidified with sulphuric acid through the syringe needle. A one hundred per cent excess of potassium hydroxide dissolved in water was placed in the outer compartment. Yields of 97—98 per cent of potassium sulphide were obtained. Using porcelain equipment, approximately 1 mg of barium sulphide was lost in the transfer from the reduction ship to the cup A in the diffusion apparatus. The same amount of barium sulphate was lost in the transfer from the ashing crucible to the reduction ship.

According to the results cited above, one can expect an overall yield of approximately 75 per cent of thiocyanate from sulphate as starting material. In a check run, a yield of 72 per cent was found.

EXPERIMENTAL

The "carrier free" labeled sulphuric acid was obtained from the Isotope Division, Atomic Energy Research Establishment, Harwell, England in a vial containing 10 mc S³⁵ in approximately 0.5 ml of solution. By means of a curved Pasteur pipette inserted to the bottom of the opened and inverted vial, the solution and the subsequent washings were

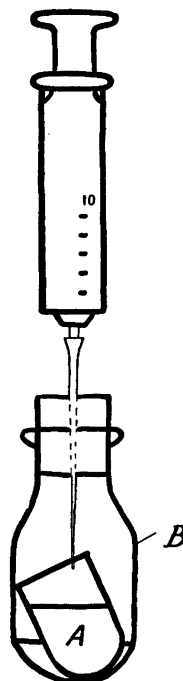


Fig. 1. Diffusion apparatus for the conversion of barium sulfide to sodium sulfide.

blown into a carrier sulphate solution containing 64.2 mg of sodium sulphate. After precipitation and ignition according to Kolthoff⁹, a quantitative yield of 105.5 mg barium sulphate was achieved. The barium sulphate was transferred to a porcelain ship and carefully spread to give a greater surface. In this step 1.5 mg of barium sulphate was lost, being burned into the crucible. The carbon monoxide for the reduction was evolved as described by Vogel¹⁰ and passed through a tower filled with potassium hydroxide and a washing bottle containing concentrated sulphuric acid. The silica reduction tube was preheated to 850–900° C and preflushed with carbon monoxide before insertion of the barium sulphate. After passing carbon monoxide at a slow, constant rate through the tube for 30 minutes at 850–900° C, a quantitative yield of 75.5 mg of barium sulphide was found. The reduction ship was cooled in a desiccator over phosphorus pentoxide at atmospheric pressure. Because of the instability of the barium sulphide, the next synthetic step was carried out as soon as possible. The compound was transferred to the small cup A, of the diffusion apparatus, Fig. 1, 0.7 mg being lost in the reduction ship. Into the outer vessel B was introduced 105 mg of potassium hydroxide dissolved in 2 ml of water. Through the rubber stopper was inserted a new, chromium plated injection needle, through which 1.5 ml of 10 per cent sulphuric acid was slowly added to the barium sulphide by means of a glass syringe. The needle was immediately withdrawn to avoid reaction with the metal. Because of the slightly increased pressure inside the diffusion apparatus, the syringe was kept attached with the plunger pressed against the bottom, while withdrawing the needle. The vessel was left for 48 hours with external cooling. The next step was now performed in the diffusion vessel B (Fig. 1). The cup A was removed after

washing the outside walls with 1 ml of water. The alkaline potassium sulphide solution was heated to 80° C on a water bath and cyanogen bromide added in three portions of 43 mg, 22 mg and 22 mg with 10 minute intervals. The cyanogen bromide was freshly prepared according to Hartman and Drager¹¹.

No attempt was made to isolate undiluted potassium thiocyanate from the above reaction mixture, although this could be done if the highest possible specific activity of the compound were desired. In order to insure a good recovery, 300 mg unlabeled thiocyanate was added as carrier. The solution was neutralized with 1 N hydrochloric acid, and evaporated to dryness under reduced pressure. The residue was then extracted with three portions of boiling ethanol (9 ml, 4.5 ml, and 4.5 ml) and filtered. After evaporation of the ethanol, the residue was extracted in the cold with three 50 ml portions of ethyl acetate, and again filtered. The ethyl acetate was then removed under reduced pressure. After four crystallizations of the final residue from absolute ethanol, 266 mg of potassium thiocyanate, with m.p. 172° C (uncorr.), was recovered.

For the preparation of labeled mercaptoethylamine and taurine¹ the isolation of potassium thiocyanate proved to be unnecessary. In this case the reaction mixture containing the radioactive thiocyanate could, after neutralization, be directly utilized for the next step in the synthesis.

SUMMARY

A procedure is described for the preparation of labeled potassium thiocyanate from sulphate S³⁵. The sulphate is reduced by carbon monoxide to sulphide, which is subsequently converted to thiocyanate through the reaction with cyanogen bromide.

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