

## SYNTHESIS OF SODIUM [<sup>11</sup>C]THIOCYANATE USING [<sup>11</sup>C]CYANOGEN BROMIDE

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A method for the preparation of sodium [<sup>11</sup>C]thiocyanate from [<sup>11</sup>C]cyanogen bromide and sodium sulfide is described. Sodium [<sup>11</sup>C]thiocyanate was obtained in 94% decay-corrected radiochemical yield with a specific radioactivity of 122 GBq μmol<sup>-1</sup> (3.3 Ci μmol<sup>-1</sup>) in a synthesis time of 21 minutes. The sodium [<sup>11</sup>C]thiocyanate was used in the synthesis of ethyl-, isopropyl-, and benzyl [<sup>11</sup>C]thiocyanate in 78, 71 and 84% radiochemical yields, respectively.

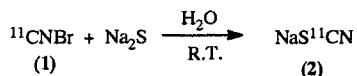
**Key words:** [<sup>11</sup>C]cyanogen bromide, sodium [<sup>11</sup>C]thiocyanate, alkyl [<sup>11</sup>C]thiocyanates.

### Introduction

In the course of an investigation into the synthetic usefulness of the electrophilic labelling precursor [<sup>11</sup>C]cyanogen bromide, we have investigated the possibility of producing [<sup>11</sup>C]thiocyanate ion as a synthetic intermediate. The pseudohalogenide thiocyanate ion mimics the behaviour of chloride ion *in vivo*,<sup>1</sup> and has been suggested useful in tracing anion kinetics in the human brain using positron emission tomography, (PET).<sup>2</sup> Sodium [<sup>11</sup>C]thiocyanate has previously been prepared in moderate yield and low specific radioactivity by treating sodium [<sup>11</sup>C]cyanide with elemental sulfur.<sup>2,3</sup> Herein, we report a simple procedure for the preparation of sodium [<sup>11</sup>C]thiocyanate in high radiochemical yield and high specific radioactivity, Scheme 1. The sodium [<sup>11</sup>C]thiocyanate was used in the synthesis of ethyl [<sup>11</sup>C]thiocyanate (**3**), isopropyl [<sup>11</sup>C]thiocyanate (**4**) and benzyl [<sup>11</sup>C]thiocyanate (**5**).

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Scheme 1

Benzyl [ $^{11}\text{C}$ ]thiocyanate has previously been prepared from [ $^{11}\text{C}$ ]cyanogen bromide by another method.<sup>4</sup>

## Experimental

### General

[ $^{11}\text{C}$ ]Carbon dioxide was produced by the  $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$  reaction using a nitrogen gas target containing 0.1 % oxygen and 17 MeV protons produced by the Scanditronix MC-17 cyclotron at the Uppsala University PET Centre. The [ $^{11}\text{C}$ ]carbon dioxide was converted to hydrogen cyanide using the Scanditronix RNP-17 radionuclide production system. Analytical and semi-preparative HPLC was performed using a Beckman 126 gradient pump and a Beckman 168 diode array detector in series with a  $\beta^+$ -flow detector. Ion-chromatography was performed using a Dionex DX-300 with a conductivity detector in series with a  $\beta^+$ -flow detector. [ $^{11}\text{C}$ ]Cyanogen bromide was prepared as described elsewhere.<sup>4</sup>

### Synthesis of sodium [ $^{11}\text{C}$ ]thiocyanate

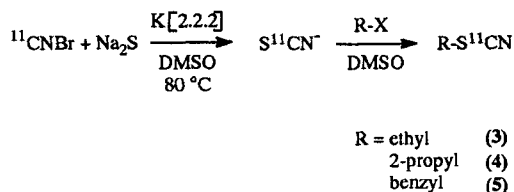
[ $^{11}\text{C}$ ]Cyanogen bromide was trapped at room temperature in 300  $\mu\text{L}$  water containing 2.0 mg (8.3  $\mu\text{mol}$ ) sodium sulfide nonahydrate (Janssen Chimica, p.a.). After transfer of the radioactivity, 1.0 mL normal saline (9 mg/mL) was added and the crude product injected into the semi-preparative HPLC column (Spherisorb ODS1 C18, 5  $\mu\text{m}$ , 250 $\times$ 10 mm i.d.), eluted at ambient temperature with saline, flow 4 mL/min. The fraction containing sodium [ $^{11}\text{C}$ ]thiocyanate eluted at 4.8 min. After addition of 1 mL sterile 0.1 M phosphate buffer, the product fraction was passed through a 0.22  $\mu\text{m}$  sterile filter (Dynagard ME) to provide a solution ready for i.v. injection. Samples were analyzed on a Supelcosil LC-SAX (5  $\mu\text{m}$ , 250 $\times$ 4.6 mm i.d.) eluted at 2 mL/min with 50 mM ammonium formate, pH 3.5/methanol, 80/20 (v/v), UV-detection at 254 nm, or on a Dionex IonPac A64A-SC, (250 $\times$ 4 mm i.d.) eluted at 1 mL/min with 90/10 (v/v) water/50 mM NaOH. Retention times were 4.1 and 8.1 min, respectively.

*Synthesis of alkyl [ $^{11}\text{C}$ ]thiocyanates.*

[ $^{11}\text{C}$ ]Cyanogen bromide was trapped at room temperature in 300  $\mu\text{L}$  DMSO (Aldrich, +99%) containing 2.0 mg (8.3  $\mu\text{mol}$ ) sodium sulfide nonahydrate and 2.8 mg (8.4  $\mu\text{mol}$ ) Kryptofix [2.2.2] (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane, Merck, zur Synthese). The reaction mixture was heated at 80  $^{\circ}\text{C}$  for 1 min, after which a solution of the alkyl halide (10  $\mu\text{mol}$  of ethyl iodide, isopropyl iodide or benzyl chloride) in DMSO (100  $\mu\text{L}$ ) was added, and the reaction mixture heated for 2 - 5 min at 80 - 120  $^{\circ}\text{C}$ . The reaction mixture was then diluted with 1 mL ammonium formate/methanol, 70/30 (v/v), and injected into the semi-preparative HPLC column (Beckman Ultrasphere ODS, 5  $\mu\text{m}$ , 250 $\times$ 10 mm i.d.), eluted at ambient temperature with ammonium formate/methanol 40/60, flow 5 mL/min, UV-detection at 254 nm. The appropriate fractions were collected and analyzed using a Beckman Ultrasphere ODS, (5  $\mu\text{m}$ , 250 $\times$ 4.6 mm i.d.) eluted with ammonium formate, pH 3.5/methanol, 55/45 (v/v), linear gradient 20/80 over 4 - 8 min, flow 1.5 mL/min, column temperature 25  $^{\circ}\text{C}$ , UV-detection at 254 nm.

**Results and Discussion**

Sodium [ $^{11}\text{C}$ ]thiocyanate suitable for intravenous injection was obtained in near-quantitative radiochemical yield in 21 min synthesis time by treatment of [ $^{11}\text{C}$ ]cyanogen bromide with sodium sulfide in aqueous solution, Scheme 1. The product had a radiochemical purity higher than 98% as analyzed by two independent chromatographic systems, and was found to be sterile and free from pyrogens. The specific radioactivity of the product at the end of synthesis was 122 GBq  $\mu\text{mol}^{-1}$  (3.3 Ci  $\mu\text{mol}^{-1}$ ) as analyzed by anion exchange HPLC.

*Scheme 2*

Treating [ $^{11}\text{C}$ ]cyanogen bromide with sodium sulfide in DMSO and the anion-activating agent Kryptofix<sup>®</sup> allowed the sodium [ $^{11}\text{C}$ ]thiocyanate to be obtained in 91 % radiochemical yield under anhydrous conditions for use in substitution reactions, Scheme 2. The radiochemical

yields of the alkyl [ $^{11}\text{C}$ ]thiocyanates prepared are summarised in Table 1. The primary, secondary and benzyl halides used gave comparable radiochemical yields of labelled product, and were obtained in higher than 98 % radiochemical purities.

Table 1. Radiochemical yields of [ $^{11}\text{C}$ ]thiocyanates<sup>a</sup>

Product	Radiochemical yield (%)	Synthesis time (min)
2 Sodium [ $^{11}\text{C}$ ]thiocyanate	94 <sup>b</sup>	21
3 Ethyl [ $^{11}\text{C}$ ]thiocyanate	78	27
4 Isopropyl [ $^{11}\text{C}$ ]thiocyanate	71	28
5 Benzyl [ $^{11}\text{C}$ ]thiocyanate	88	25

<sup>a</sup> Isolated and decay-corrected radiochemical yield, based on sodium [ $^{11}\text{C}$ ]thiocyanate. <sup>b</sup> Based on [ $^{11}\text{C}$ ]cyanogen bromide.

Work is now in progress to develop methods for the conversion of organic [ $^{11}\text{C}$ ]thiocyanates to [ $^{11}\text{C}$ ]thiocarbamates. The sodium [ $^{11}\text{C}$ ]thiocyanate itself may become interesting as a tracer for small anion kinetics in various organs. The tubular transport of anions in the kidneys provides an example where this tracer might be potentially useful. Conditions like edema, where disturbances of the cellular fluid balance play a role is yet another field of interest.

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