A CONVENIENT SYNTHESIS OF SODIUM ACETATE-$^{18}O_2$

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SUMMARY

Sodium acetate-$^{18}O_2$ is synthesized by the hydrolysis of triethyl orthoacetate with water-^{18}O in 89% chemical yield with a 1.1 to 1.2-fold dilution of the isotopic label contained in water-^{18}O.

Key Words: Sodium acetate, Oxygen-18, Triethyl orthoacetate hydrolysis

INTRODUCTION

We report the synthesis of sodium acetate-$^{18}O_2$ by a convenient and high yield procedure from the hydrolysis of triethyl orthoacetate with water-^{18}O. Others have reported the synthesis of ^{18}O-labeled sodium acetate by the hydrolysis of acetyl chloride[1] and acetonitrile[2] with water-^{18}O. Hydrolysis of acetyl chloride, although facile, at maximum gives labeled product of only half the ^{18}O-enrichment of the water. Hydrolysis of acetonitrile, while theoretically yielding enrichment equal to that of the water, requires more vigorous reaction conditions and the reported yield[2] (66%) is not high. The hydrolysis of triethyl orthoacetat with water, first with acid catalysis, then with base, can be carried out in one flask using mild, convenient reaction conditions, and sodium acetate-$^{18}O_2$ of isotopic enrichment equivalent to that of the water used is obtainable theoretically.

$$CH_3C(OCH_2CH_3)_3 + H_2{}^{18}O \xrightarrow[(cat.)]{p\text{-}TsOH} CH_3{}^{18}COCH_2CH_3 + 2CH_3CH_2OH \quad (1)$$

$$CH_3{}^{18}COCH_2CH_3 + H_2{}^{18}O + NaOCH_3 \xrightarrow[THF]{CH_3OH} CH_3C^{18}O_2Na + CH_3CH_2OH + CH_3OH \quad (2)$$

The synthesis according to equations (1) and (2) was carried out twice: labeled material of the composition shown in the Table and having a 91% chemical purity was obtained in two separate runs. The lower isotopic enrichment obtained in run (a) was probably due to

Table of the Percentage Isotopic Enrichment of Sodium Acetate-$^{18}O_2$.

Experiment	Water (mol%) [1]	Sodium Acetate (mol%) [2]
a	^{18}O(95.08), ^{17}O(1.96), ^{16}O(2.96)	$^{18}O_2$(77), ^{18}O-^{16}O(17)
b	^{18}O(96.6), ^{17}O(1.8), ^{16}O(1.6)	$^{18}O_2$(90), ^{18}O-^{16}O(10)

1. Analysis supplied by Monsanto Research Corporation.
2. Analyzed as described in the Experimental.

moisture on the glassware because the glassware was not dried as rigorously in this experiment as in experiment (b). Since these results were satisfactory for our purposes, we made no additional attempts to further minimize the isotopic dilution of ^{18}O or to maximize the purity of the resulting labeled sodium acetate.

EXPERIMENTAL

Sodium Acetate-$^{18}O_2$. Water-^{18}O (566.6 mg., 28.2 mmol)[3] was stirred together with 40 ml of dry triethyl orthoacetate[4] and 2 mg of p-toluenesulfonic acid monohydrate until only one liquid phase remained (ca. 1 min). An equivalent amount of 2.63 N sodium methoxide in methanol (prepared from super-dry methanol and freshly-cut sodium metal) was added to the resulting labeled ethyl acetate followed with a second equivalent of water (577.3 mg., 29.1 mmol) in 1-2 ml anhydrous THF. The reaction mixture

deposited white crystals of sodium acetate in a few minutes, solidifying tc a fluffy white, crystalline mass mixed with solvent shortly thereafter. This mixture was heated in a water bath for 20 hr. at 70°C, then the alcohols and unreacted triethyl orthoformate were removed by distillation first with a water aspirator and second with an oil pump at 70°C.[5] The crystalline residue of sodium acetate-$^{18}O_2$ weighed 2.39 g (89% yield, based on 91% purity determined as indicated below).

p-Phenylphenacyl Acetate-$^{18}O_2$. The preparation of the p-phenylphenacy acetate-$^{18}O_2$ was carried out by a modification of the procedure of Durst, et al.[6] Sodium acetate-$^{18}O_2$ (10.3 mg., 0.125 mmol) was reacted with 69 mg. (0.25 mmol,) of p-phenylphenacyl bromide (Aldrich Chemical Co.) and 4 mg of 18-crown-6-acetonitrile complex in 2 ml of acetonitrile-benzene (1:1) at reflux for 2 hr. The mixture was evaporated to an oil with a stream of nitrogen, dissolved with 2 ml of chloroform and 2 ml of water, and extracte with two more 3 ml volumes of chloroform. The combined organic extract was washed with water, brine, and dried over anhydrous sodium sulfate. Evaporation of the extract yielded 92 mg of crystalline residue which was purified by preparative tlc on silica gel (benzene) to yield 60 mg of the acetate-$^{18}O_2$ derivative. The sample was crystallized from 95% alcohol and its ^{18}O content determined by mass spectroscopic analysis[7]. Isotopic dilution assay[8] with the p-phenylphenacyl derivative of sodium acetate-1-^{14}C indicated the sample was 91% pure.

REFERENCES

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4. Triethyl orthoacetate (Aldrich Chemical Company) was stirred over anhydrous potassium carbonate at ambient temperature for 20 hr. then distilled.
5. The sample should be dried as much as possible or the crystals become brown on standing.

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