

Synthesis and NMR Spectra of ^{17}O Oxygen Enriched Phenols

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Summary

An efficient and convenient method of preparing ^{17}O enriched phenols is described. Aryl boronic acids are oxidized with ^{17}O enriched potassium hydroperoxide. The ^{17}O labeled potassium hydroperoxide is prepared from the autoxidation reaction of benzhydrol with ^{17}O enriched oxygen gas in the presence of potassium t-butoxide. [0- ^{17}O]Phenol, p-bromo[0- ^{17}O]phenol and p-methoxy[0- ^{17}O]phenol were prepared in good to modest overall chemical yields (40-60%) and high isotopic retention (82-90% from 16.8 atom % $^{17}\text{O}_2$ starting material). ^{17}O NMR spectra of the three enriched phenols demonstrate the benefits of using enriched samples in reducing the total experiment time and greatly improving the signal-to-noise ratio compared to unenriched samples.

Key Words [0- ^{17}O]Phenol, [^{17}O]p-Bromophenol, [^{17}O]p-Methoxyphenol, ^{17}O NMR Spectra

Introduction

We report here a simple, convenient and efficient synthesis of ^{17}O enriched phenols from the reaction of ^{17}O enriched potassium hydroperoxide and aryl boronic acids. The ^{17}O NMR spectra of these compounds are obtained in remarkably short times. We were interested in obtaining phenols enriched in ^{17}O in order to investigate the substituent effects on the ^{17}O NMR chemical shifts and quadrupolar coupling constants of several phenols, their metal derivatives and surfaced adsorbed phenols.

A literature search revealed few syntheses giving high yields of ^{18}O enriched phenols and none in fact for ^{17}O enriched phenols. Furthermore, some procedures designed for ^{18}O enrichment are not suitable for the less available and more costly ^{17}O isotope.

Since oxygen-17 is a rare isotope, water and oxygen gas isotopically enriched at even low levels is difficult to obtain in large quantities and is relatively expensive. To minimize the quantities of these materials, a synthetic route to phenols was needed in which the labeled precursor is introduced only at the later stages of the synthesis and would not require a large excess of ^{17}O labeled reactants. Additionally, a high yield and good label incorporation are desirable for effective use of labeled reagents.

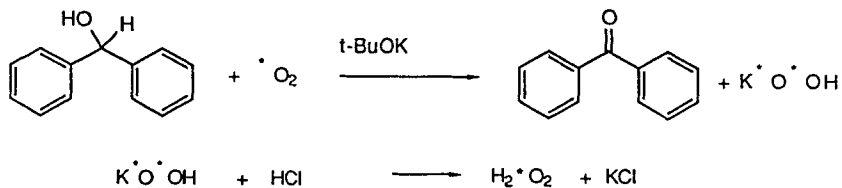
Walker and Goldblatt synthesized phenols enriched with oxygen-18 by reacting labeled molecular oxygen with aryl Grignard reagents.¹ Although the ^{18}O enrichment levels were high, the overall yields were only 20-30%. Cohen et al.² have reported that copper catalyzed hydrolysis of diazonium salts gave excellent yields of phenols, however the dilute conditions used by the reaction would make the cost of using ^{17}O isotopically labeled water prohibitive. A modification which minimizes the amount of water was reported by Pinchas and coworkers³ who isolated the diazonium salt and performed the hydrolysis in an ether/ H_2^{18}O emulsion; however the yield of o-18 phenol was only 36% based on aniline and 20% based on moles of labeled water. Risley and Van Etten subsequently used this procedure to obtain labelled phenol but obtained only a 24% incorporation of the ^{18}O label.⁴

We were encouraged by the fact that Hawthorne found that phenyl boronic acids reacted with hydrogen peroxide to give much higher yields of the corresponding phenols than oxidation of the Grignard reagents.⁵ In our planned approach, the aryl boronic

acids prepared from the appropriate Grignard reagents and methyl borate, would be reacted with labelled hydrogen peroxide. By isolating the arylboronic acids, the yield from the oxidation step could be optimized and thereby minimize the use of labeled oxidizing agent.

The ease and success of this method depended on obtaining ^{17}O labeled hydrogen peroxide. An exchange reaction with labeled water is a not an attractive candidate.⁶ Fluorosulfonic acid catalyzed exchange requires highly concentrated and highly enriched H_2^{18}O and leads to moderate exchange.⁷ Modena et al catalyzed the exchange between labeled hydrogen peroxide and water under dilute conditions using vanadium (V) or molybdenum (IV) compounds to effect a 50% label exchange.⁸ We found that neither a vanadium nor molybdenum compounds catalyzed the exchange with 30% H_2O_2 . Thus labelled oxygen gas is the precursor of choice.

Labeled hydrogen peroxide has been synthesized by multiple-step routes^{6,9} involving specialized laboratory equipment and long reaction times. A more convenient method, proposed by Sawaki and Foote,¹⁰ for preparing small quantities of labeled hydrogen peroxide uses the base catalyzed autoxidation of benzhydrol:



The isolated solid hydroperoxide is then treated with HCl to give labeled hydrogen peroxide. Unfortunately, the concentrations of the labeled H_2O_2 solutions obtained by this procedure are very dilute (0.5 molar or 2%). Baude et al improved on this method by concentrating the solution of labeled H_2O_2 by careful microdistillation.¹¹

A key finding which obviated the need for hydrogen peroxide was our discovery that the oxidation of phenylboronic acids to phenols can be accomplished more efficiently with solid potassium hydroperoxide (K^*O^*OH) rather than the derived hydrogen peroxide. We found that the acidification of potassium hydroperoxide gave poor yields and weak and/or uncertain strengths of hydrogen peroxide solutions. Thus, the inefficient second step of the reaction could be eliminated. This finding is consistent with Kuivila's finding that the rate of the reaction is dependent upon the concentration of the hydroperoxide ion.¹² Therefore, it seems reasonable that $KOOH$, a more concentrated source of hydroperoxide ion than hydrogen peroxide, would be a more effective oxidizing agent.

Results

Labeled potassium hydroperoxide was synthesized from benzhydrol and ^{17}O labeled gas in good to excellent yield (70-100%). Because potassium hydroperoxide is highly reactive, the solid was not completely dried. The ^{17}O labeled solid was then used as the oxidizing agent to prepare three isotopically enriched phenols: [0- 17]phenol, p-bromo[0- 17]phenol and p-methoxy[0- 17]phenol. In view of the expense of labeled starting materials, the synthetic procedures used to prepare ^{17}O enriched phenols were worked out in essentially three stages. First, each step of the procedure was optimized using unlabeled starting materials. Next, the less costly ^{18}O labeled materials were used to calibrate the extent of enrichment. Oxygen-18 gas (28 atom %) was used to synthesize $KOOH$ which was in turn used to make ^{18}O labeled phenol. The product of this reaction was then analyzed and determined to be enriched by 23%. Once the success of the labeled $KOOH$ synthetic route to enriched phenols was established, oxygen-17 gas (16.8 atom %) was used to synthesize three phenols which were isotopically enriched in ^{17}O .

Table I. Reactions of Arylboronic Acids with Labelled Potassium Hydroperoxide^a

Arylboronic Acids	Yield ^b	Enrichment ^c
Phenyl ^d	60(96)	23.0 ^e
	53(86)	13.8 ^f
p-Bromophenyl ^d	39(60)	15.2 ^f
p-Methoxyphenyl ^g	41(66)	15.1 ^f

a. In diethyl ether at room temperature see Experimental for details. b. Overall isolated yields in percent based on oxygen. The numbers in parentheses are based on the arylboronic acid. c. Enrichment in percent as determined by mass spectrometry see Experimental for details. d. Commercially available. e. ^{18}O enriched using O-18 gas (28.0 atom %). f. ^{17}O enriched using O-17 gas (16.8% atom %) g. Prepared from p-methoxy phenyl magnesium bromide and methyl borate.

The ^{17}O NMR spectra for the enriched phenols were recorded as described in the Experimental section. For comparison the spectrum for phenol in natural abundance was recorded. Vast improvement in signal-to-noise ratio is obtained by using ^{17}O enriched samples as illustrated in Figure 1. Natural abundance phenol shows a ^{17}O signal with a S/N ratio of approximately sixteen whereas ^{17}O enriched phenol has a signal with an S/N ratio of approximately 1500 under the same conditions. Thus, the spectral sensitivity is enhanced by approximately 94-fold by enrichment. With a natural abundance of ^{17}O of 0.037 the ratio of concentrations is 373. Accordingly, most, but not all of the anticipated factor is observed experimentally. Obviously the total experiment time for the enriched material could be substantially reduced to obtain an excellent signal.

Table II records the ^{17}O chemical shifts of the three enriched phenols as well as the ^{13}C chemical shifts of the C-1 carbon atom. Iwamura and coworkers have noted a relationship between the ^{17}O chemical shifts and the ^{13}C shifts of the ipso or C-1 carbon of a series of substituted anisoles.¹³ In Table II we

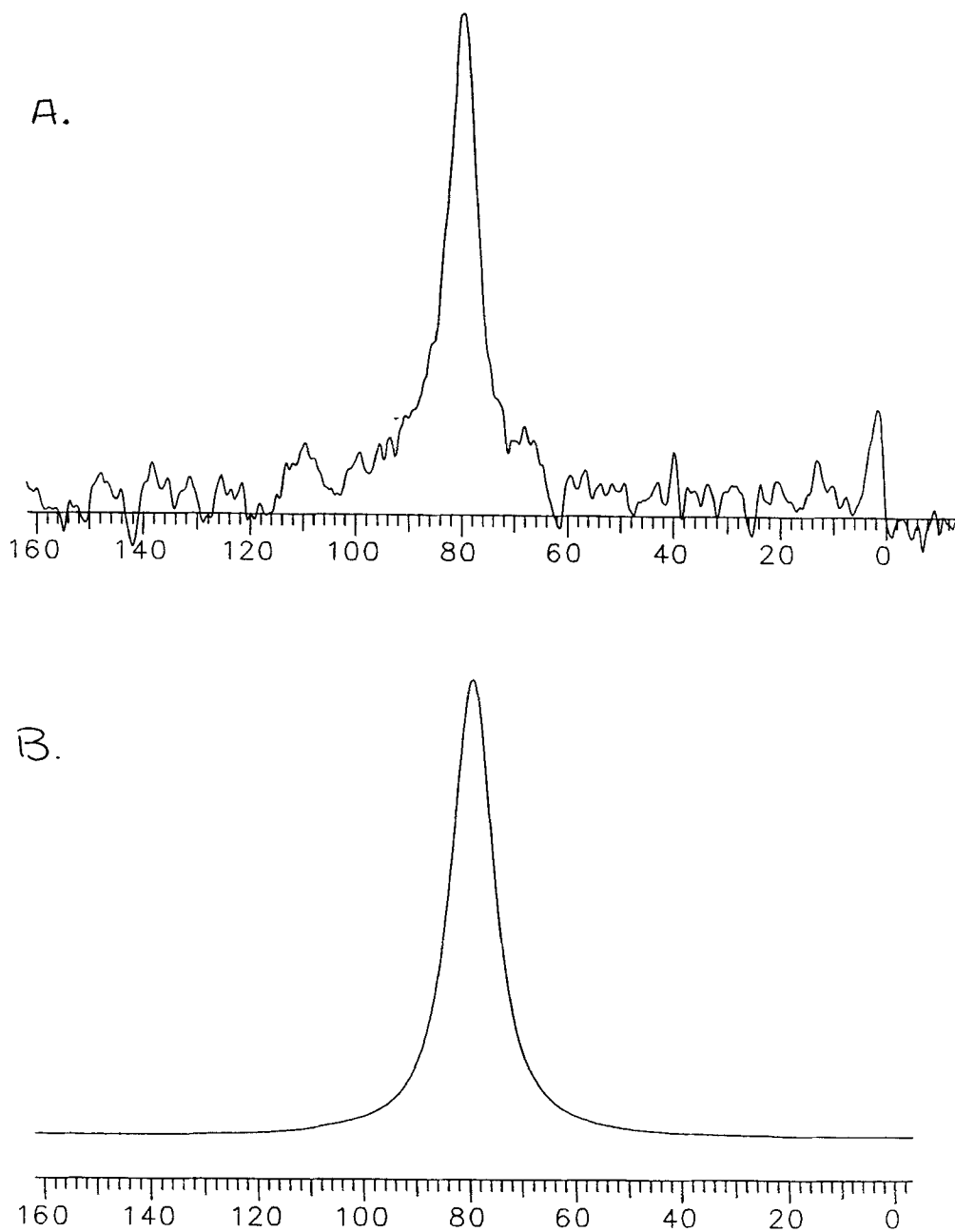


Figure 1. ^{17}O NMR spectra for phenols at 40.660 MHz. There were 29000 transients and 300 Hz line broadening was applied. A) Natural abundance. B) ^{17}O Enriched phenol.

compare this relationship for the phenols and the corresponding anisoles. When there is a small perturbation of the pi electronic system, e.g. a para-bromo group, there is no particular trend in either the ^{17}O or the ^{13}C NMR shift values. However, when there is a large perturbation of the pi electronic system, e.g. a para-methoxy group, there is a trend. Moreover, the substituent effect on chemical shifts is greater for ^{17}O NMR than for ^{13}C NMR in both phenols and anisoles. This is depicted graphically in Figure 2. For p-methoxy phenol the C-1 carbon is shifted 5.4 ppm by ^{13}C NMR (relative to phenol) while the ^{17}O shift of phenolic oxygen is 7.8 ppm. Likewise, for p-methoxy anisole the carbon-13 C-1 shift relative to unsubstituted anisole is 7.7 ppm compared to 14 ppm for oxygen. In both cases the ^{17}O NMR chemical shift is nearly twice that of the C-13 shift.

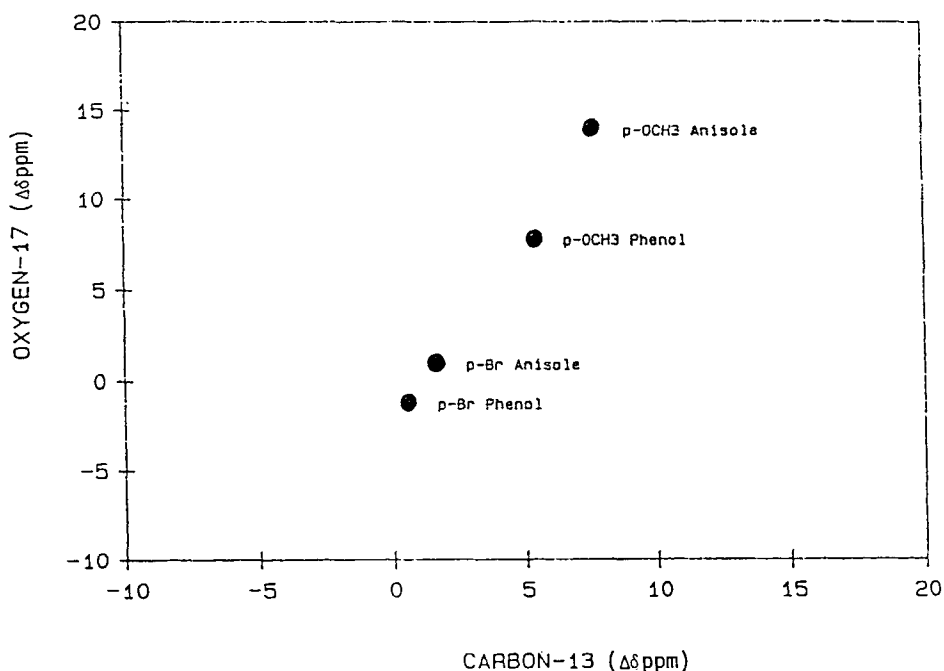


Figure 2. Comparison of ^{17}O and ^{13}C chemical shift values for anisoles and phenols.

Table II. Comparison of ^{17}O and ^{13}C NMR Chemical Shifts of para Substituted Phenols and Anisoles

	$\delta^{17}\text{O}$	$\Delta\delta^{17}\text{O}$	$\delta^{13}\text{C}$ (C-1)	$\Delta\delta^{13}\text{C}$ (C-1)
<u>Phenols</u>				
X = H	80.6	--	155.1	--
X = Br	81.8	-1.2	154.5	0.6
X = OCH ₃	72.8	7.8	149.7	5.4
<u>Anisoles⁸</u>				
X = H	155	--	159.2	--
X = Br	154	1	157.6	1.6
X = OCH ₃	141	14	151.5	7.7

Experimental

General Methods. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Electron impact mass spectra were recorded on a MAT 731 mass spectrometer operating at 70 eV. Carbon-13 NMR spectra were obtained on a Varian XL300 instrument operating at 75.5 MHz.

^{17}O NMR Spectra. The ^{17}O NMR spectra were recorded on a Bruker WH400 operating at 54.244 MHz and a Varian XL300 operating at 40.660 MHz. A spectral width of 10000 Hz was employed with a 90° pulse corresponding to 16 microsec. There was no pulse delay and an acquisition time of 0.819 sec for the WH400 and 0.058 sec for the XL300 was used. Between 3000 and 3200 transients were accumulated for each ^{17}O enriched sample (10 mm sample tube width). The concentration of the samples was approximately 100 mg in 2 mL of methanol. Chemical shifts are reported relative to an external H₂O, D₂O standard.

Materials. Phenylboronic acid, p-bromophenylboronic acid potassium tert-butoxide, p-bromoanisole and trimethyl borate were

purchased from Aldrich. Benzhydrol was purchased from Eastman. Water (^{18}O , 20 atom %) was purchased from Cambridge Isotope Laboratories. Water (^{18}O , 50 atom % and ^{17}O , 35.8 atom %) and oxygen gas (^{18}O , 28 atom % and ^{17}O , 16.8 atom %) were obtained from Icon Services, Inc.

[0-17]Potassium Hydroperoxide. A 100 mL four-neck flask was equipped as follows: three tubing adapters with Teflon stopcocks were connected separately to a nitrogen source, a vacuum source and a cylinder of ^{17}O gas (16.8 atom % enriched). Another neck was fitted with a rubber septum with an 18", 16 gauge needle on a 50 mL syringe attached to syringe pump. A balloon was wired securely on the final neck.

Potassium tert-butoxide (3.33 g, 30 mmole) was placed in the flask with a magnetic stirrer. The flask was evacuated and filled with nitrogen several times. After a final evacuation, $^{17}\text{O}_2$ was introduced until a slightly positive pressure was reached (as indicated by expansion of the balloon). Benzhydrol (5.52 g, 30 mmoles) was dissolved in dry ethyl ether (40 mL) and charged to the syringe. The benzhydrol solution was slowly added to the potassium t-butoxide over a period of about twenty minutes. As oxygen was consumed by the reaction (indicated by the balloon deflating), addition of the gas was continued until no more was consumed (about 1.5 h). The potassium hydroperoxide which precipitated as a yellow solid during the reaction was collected on a cooled fritted glass filter (Porosity M) and washed with a small amount (10 mL) of cold ethyl ether. The pale yellow solid (1.55 g, 71 % yield based on benzhydrol and 62% yield based on oxygen) was stored at 0°C.

[0-17]Phenol. Phenylboronic acid (1.0 g, 8 mmoles) and ethyl ether (10 mL) were charged to a 25 mL two-neck flask fitted with

a reflux condenser, magnetic stirring bar and a nitrogen blanket. About 1 mL of ethanol was added to dissolve the phenylboronic acid. ^{17}O labeled potassium hydroperoxide (1.1 g, 15 mmoles) was added to the reaction in small quantities (5-6 additions), and after each addition reflux occurred for 2-5 minutes. When all of the potassium hydroperoxide had been added, the solution was allowed to stir for 1 hour at room temperature. A gray suspension of boronic salts formed during the reaction. The mixture was extracted twice with 10% sodium hydroxide (10-15 mL). The aqueous phases were combined and acidified with 10% HCl (10-15 mL). The phenol was extracted with ethyl ether. The combined ether extracts were dried (MgSO_4), filtered and evaporated to give a gold colored oil. Distillation of the oil in a Kugelrohr apparatus gave 0.65 g of colorless crystals (86% yield). ^{13}C NMR (CDCl_3): δ 115.331(d), 120.778(d), 129.641(d), 155.136(s); high resolution mass spectrum calcd for $\text{C}_6\text{H}_6^{17}\text{O}$ 95.0461, found 95.0462.

p-Bromo[0- ^{17}O]phenol. A corresponding preparation from p-Bromophenylboronic acid (1.0 g, 4.6 mmoles) and ^{17}O -labelled potassium hydroxide (0.7 g, 9 mmoles) gave 0.70 g of an orange oil. Distillation of the oil in a Kugelrohr apparatus gave 0.48 g (60% yield) of the product as a light orange oil. ^{13}C NMR (CDCl_3): δ 112.753(s), 117.184(d), 132.398(d), 154.467(s); high resolution mass spectrum calc for $\text{C}_6\text{H}_5\text{Br}^{17}\text{O}$ 172.9566, found 172.9569.

p-Methoxyphenylboronic acid. To a solution of the Grignard reagent prepared from a solution of p-bromoanisole (18.7 g, 0.1 mole) in 57 mL of ethyl ether and 2.64 g (0.11 mole) of magnesium turnings was added (1h) trimethyl borate (10.4 g, 0.1 mole) in 125 mL of ethyl ether which had been cooled to -60°C with a dry

ice/acetone bath. The mixture was stirred overnight at -60 , warmed to 0°C and poured over 100 mL of 10% cold(0°C) sulfuric acid. The layers were separated and the ether was evaporated to leave 9.81 g (65% yield) of a gray solid. The crude product was recrystallized from water (150mL) and dried under a stream of moist air to prevent formation of the anhydride to give 3.50 g (23% yield) of p-methoxyphenyl boronic acid (melting point $201-203^\circ\text{C}$). ^{13}C NMR (DMSO - d_6): $\delta 54.872, 112.978, 135.120, 135.930, 161.050$.

p-Methoxy[0-17]phenol. Reaction of p-methoxyphenyl boronic acid (1.0 g, 6.6 mmoles) with ^{17}O labeled potassium hydroperoxide (1.0 g, 13.9 mmoles) gave 0.87 g of an orange oil. Distillation of the oil in a Kugelrohr apparatus gave the product p-methoxy[0-17]phenol (0.46 g, 65.5% yield) as light pinkish crystals. ^{13}C NMR (CDCl_3): $\delta 55.129(\text{q}), 114.451(\text{d}), 115.552(\text{d}), 149.675(\text{s}), 152.621(\text{s})$; high resolution mass spectrum calc for $\text{C}_7\text{H}_8\text{16O}^{17}\text{O}$ 125.0566, found 125.0566.

Acknowledgment. The authors gratefully acknowledge financial support from the General Electric Company.

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