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Oxygen-18 Labeling of Cyclic and Acyclic Sulfinate Esters

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ABSTRACT

Both cyclic and acyclic sulfinate esters were labeled with ^{18}O at the sulfinyl oxygen by acid-catalyzed isotope exchange with $H_2{}^{18}O$ or alkaline hydrolysis in $H_2{}^{18}O$ followed by re-esterification. Long-range ^{18}O isotope effects on the ^{13}C NMR chemical shifts were observed.

Isotopically labeled substrates are useful in investigations of reaction mechanisms as well as structure elucidations. The oxygen of sulfinic acid derivatives is a key atom of the functional group of this class of compounds, and ^{18}O-labeled sulfinate esters were previously prepared from labeled sulfinic acids or sulfinyl chlorides [1]. All these procedures are not efficient either in terms of isotopic or chemical yield. We now present in this article simple procedures for obtaining ^{18}O-labeled sulfinate esters of both cyclic and acyclic structures by isotope exchange. These procedures are based on the mechanisms of reactions of the esters.

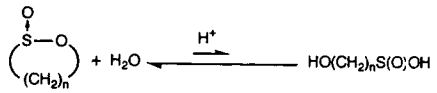
A sulfinate ester undergoes acid-catalyzed transesterification in an alcoholic solution (Equation 1) [2] and hydrolysis in an acidic aqueous solution [3]. Since the transesterification is reversible,

$$RS(O)OR' + R''OH \overset{H+}{\rightleftharpoons} RS(O)OR'' + R'OH \quad (1)$$

we thought that the sulfinate ester would be in an equilibrium with sulfinic acid in an acidic aqueous alcoholic solution and that the isotope would be incorporated in the ester as well as in the acid if we used ^{18}O-enriched water as a cosolvent (Equation 2). This was successfully achieved with methyl benzenesulfinate.

$$RS(O)OR' + H_2{}^{18}O \overset{H+}{\rightleftharpoons} RS(O)\,{}^{18}OH + R'OH \overset{H+}{\rightleftharpoons} RS({}^{18}O)OR' + H_2O \quad (2)$$

It was found that a cyclic sulfinate ester (sultine) undergoes ring opening in an aqueous alkaline solution, while the corresponding hydroxy sulfinic acid cyclizes in acid [4]. The cyclic sulfinate is stable in an acidic aqueous solution. An equilibrium of the intramolecular hydrolysis-esterification shown in Equation 3 is largely on the side of the ester, even in aqueous solution. Although the apparent reaction cannot be seen, the sultine must be in a dynamic equilibrium (Equation 3) in aqueous acid. Therefore, the isotope should be incorporated into the sultine in a solution containing ^{18}O-enriched water.



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RESULTS AND DISCUSSION

Preparation of Benz-Fused Sultines

Sulfinate esters used in this article are summarized in Scheme 1. Acyclic sulfinate esters are prepared by nucleophilic substitution of sulfinyl derivatives by alcohols, while cyclic sulfinates

This paper is dedicated to Prof. James Cullen Martin on the occasion of his sixty-fifth birthday.

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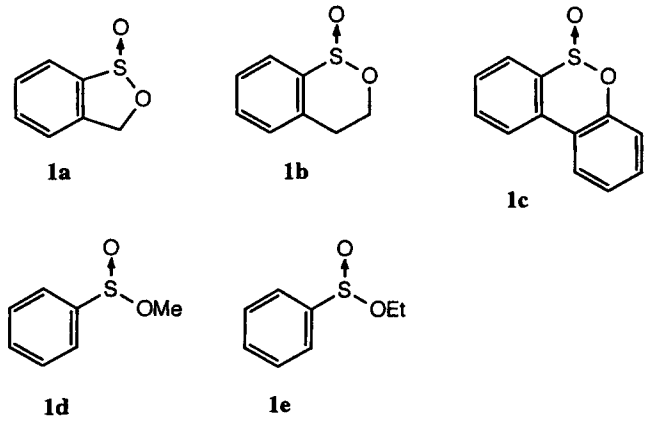
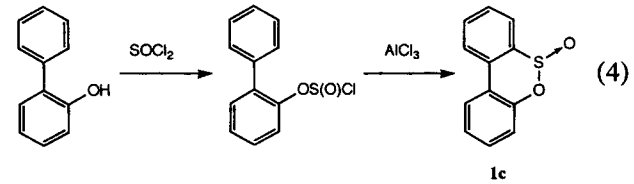


SCHEME 1

(sultines) are usually prepared by cyclization involving hydroxyl and sulfur functions [5,6]. Methyl and ethyl benzenesulfinates (**1d** and **1e**) as well as the benzo-γ-sultine **1a** were prepared according to the literature [6,7]. However, it is not always easy to get appropriate precursors for sultines. The dibenzo-δ-sultine **1c** was prepared by an $AlCl_3$-promoted cyclization of a sulfite derived from *o*-hydroxybiphenyl (Equation 4) according to the reported method [8]. A similar procedure was successfully applied to the preparation of the benzo-δ-sultine **1b** (Equation 5) which has never been reported in the literature.



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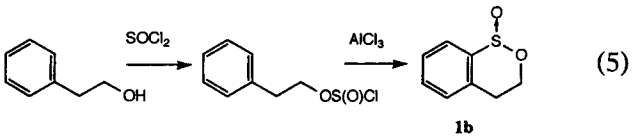


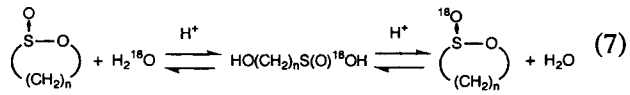
(5)

A considerable amount of resinous products, which arose probably from intermolecular reactions and could have been suppressed by high dilution, were formed as by-products. An attempt to prepare a 7-membered sultine from 3-phenylpropanol resulted in a very low yield of the desired product and mostly in resinous products. However, this method may have some generality for preparation of aromatic sulfinate esters involving acyclic ones, e.g., as shown in Equation 6.

$$\text{ROH} \xrightarrow{\text{SOCl}_2} \text{ROS(O)Cl} \xrightarrow{\text{ArH, AlCl}_3} \text{Ar-S(O)OR} \quad (6)$$

^{18}O-Labeling of Sultines

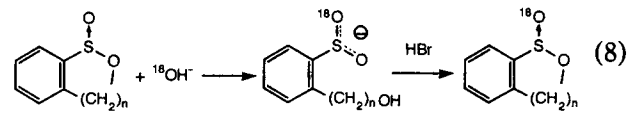
Sultines are apparently stable in acidic solutions, but acyclic esters undergo hydrolysis in aqueous acids. This implies that sultines are in a dynamic equilibrium of ring opening (hydrolysis) and closure in aqueous acids, as shown in Equation 3. These reversible reactions lead to ^{18}O incorporation in ^{18}O-enriched water, as shown in Equation 7. This was, in fact, achieved with **1a** and **1c**, although the ^{18}O incorporation was quite slow [9].



(7)

In aqueous dioxane (about 10% of water containing roughly 50 at. % excess of ^{18}O), 33.5 and 24.6% excesses of ^{18}O were incorporated into **1a** and **1c**, respectively, with use of about 0.5 M $HClO_4$ and at 25°C after 1 month of reaction. The site of labeling was confirmed solely at the exocyclic sulfinyl oxygen by the isotope shift of the ^{13}C resonance (discussed subsequently). Since we have found that the exchange was accelerated by bromide ion [4], addition of bromide salt, such as NaBr, to the reaction mixture would have accelerated the isotope incorporation by some 10 times.

Since the acid-catalyzed ^{18}O exchange was very slow, an alternative procedure was adopted for the preparation of ^{18}O-labeled **1b** as well as **1a**. Since the ring-opening reaction was found to be rapid in an alkaline solution and the reverse ring closure was effected by acid [4], ring opening was carried out in an ^{18}O-enriched alkaline medium and recyclization was subsequently attained by addition of a strong acid. Hydrobromic acid was used for acidification, because the ring closure was found to be faster in HBr than in HCl or $HClO_4$ [4]. Incorporation of more than 40 at. % excess of ^{18}O at the sulfinyl oxygen was attained within a day by using 95 at. % enriched water. The position of the ^{18}O label was determined by the ^{13}C NMR spectra, and the internal oxygen has never been labeled. This implies that the nucleophilic reaction occurs solely at the sulfur but not at the carbon which would have led to C–O bond cleavage and the internal labeling.



(8)

^{18}O-Labeling of Methyl Sulfinate

Reversible transesterification can be effected by acid. Incorporation of ^{18}O into **1d** could be achieved in methanol containing 5 vol % of $H_2{}^{18}O$ (95 at. % of ^{18}O) using trifluoroacetic acid as a catalyst. Partial hydrolysis accompanied the isotope exchange. Although the equilibrium of Equation 2 should be attained in due time, a side reaction of the sulfinic

acid (Equation 9) leads to a decreasing yield of the desired labeled **1d** in a prolonged reaction period [10]. The compromise reached for the reaction time is given in the experimental section, and the 40–60 at. % incorporation of ^{18}O could be attained in ca. 50% chemical yield.

$$3\ PhS(O)OH \rightarrow PhS(O)_2SPh + PhSO_3H + H_2O \quad (9)$$

^{18}O-Labeled Ethyl Sulfinate

Although the labeling at the sulfinyl oxygen of the ethyl sulfinate **1e** could be attained in the same way in ethanol as that of **1d**, labeling at both the sulfinyl and alcoholic oxygens was carried out by ethylation with a triethyloxonium salt [12] of the ^{18}O-sulfinate ion obtained from alkaline hydrolysis of the ester in $H_2{}^{18}O$. Sulfinate ion is an ambident nucleophile which gives, in general, both sulfone and sulfinate ester on alkylation [13], but the oxonium salt, a hard electrophile, is known to give mostly the ester [12]. In the present results, the alkylation product is solely the sulfinate ester and the ^{18}O distributes equally at the sulfinyl and alcoholic positions as found by the ^{13}C NMR (Equation 10).

$$PhSOR + {}^{18}OH^- \longrightarrow PhS({}^{18}O)O^- \xrightarrow{Et_3OBF_4} PhS({}^{18}O)OEt + PhSOEt \quad (10)$$

^{18}O Isotope Shift of ^{13}C Resonance

It is known that ^{13}C NMR chemical shifts are affected by adjacent isotopic atoms and the ^{18}O substitution for ^{16}O induces a 0.02–0.05 ppm shift of the α carbon [14]. In order to confirm the position of the label in our exchanged products, ^{13}C NMR spectra were carefully measured, and the signals of expanded spectra are shown in Figure 1.

The ethyl sulfinate **1e** we obtained as a 1:1:1 mixture of the unlabeled and the labeled ones at the alcoholic (internal) and sulfinyl (exo) oxygens (65% ^{18}O in total). Three peaks for the α-carbon of the ethyl group are recognized at about δ 61. The high-field peak (δ 61.035) must be due to the one labeled at the alcoholic oxygen (0.029 ppm upfield shift), while the other two are resonances of the unlabeled and the sulfinyl-^{18}O compounds, the lowest field peak (δ 61.069) being probably due to the long-range shift caused by the ^{18}O separated by three bonds (0.005 ppm downfield shift). The resonance of the ipso carbon of the phenyl group (δ 145) is also composed of two closely separated peaks. The smaller high-field peak (δ 145.039) is assigned to the *alcoholic*-^{18}O compound, with an 0.005 ppm upfield shift compared with the other peak at δ 145.044, because the *sulfinyl* ^{18}O does not affect the ipso carbon resonance of the methyl sulfinate **1d**. These results are summarized in Scheme 2.

Since the spectrum of **1d**-^{18}O did not show any large shift corresponding to the one-bond ^{18}O shift (~0.03 ppm), the labeling must occur solely at the sulfinyl oxygen. We can recognize the two closely separated peaks for the methyl group (δ 49.811 and 49.816) and the single peak for the ipso carbon (δ 143.961). Since the sample of **1d**-^{18}O contained 60 at. % excess of ^{18}O, the smaller high-field peak of the methyl carbon may be due to the unlabeled compound, and the sulfinyl ^{18}O (separated by three bonds) induces a downfield shift by about 0.005 ppm.

The cyclic sulfinates examined do not seem to show any separation of the carbon signals owing to the isotope shift. The peaks for the methylene and ipso carbons of **1a**-^{18}O are singlets, but the former peak seems to be broader. The ipso carbon signals for **1c**-^{18}O are also singlets, the phenolic one (δ 137.2) being broader. The signal for the 3-carbon of **1b**-^{18}O has a shoulder, probably owing to the small shift induced by the sulfinyl ^{18}O.

In summary, the ^{13}C NMR spectra of the labeled sulfinates show that the labeling by isotope exchange occurred solely at the sulfinyl oxygen but not at the alcoholic (internal) oxygen. However, ethylation of the sulfinate ion by the oxonium salt took place indiscriminately at both of the oxygens leading to an equal amount of the sulfinyl and alcoholic ^{18}O labeling. Although the alcoholic ^{18}O induces about 0.03 ppm upfield shift of the α-carbon, it was also found that the ^{18}O can induce a small but detectable shift of about 0.005 ppm on some carbon two or three bonds apart. These long-range shifts were detected clearly with acyclic sulfinates, but only the broadening of the corresponding peaks was recognized with cyclic analogs. The further interesting feature of the long-range shift is that the sulfinyl ^{18}O induced the shift of the three-bond separated alcoholic carbon but not the two-bond separated ipso sulfinyl carbon. Furthermore, the ipso carbon shift can be induced by the alcoholic ^{18}O having a two-bond separation. These long-range shifts may be closely related to the conformation and electronic structure of the compounds, and more examples and theoretical considerations are awaited. The long-range isotope shifts induced by a deuteron have been observed, but those induced by heavier atoms do not seem to have been reported previously [14].

EXPERIMENTAL

The oxygen isotope contents of the products were determined by mass spectra recorded on a spectrometer JMS DX303. The NMR spectra were recorded by use of a solution in $CDCl_3$ with TMS as an internal standard on a spectrometer JNM GX500 or JNM GSX270. The ^{13}C NMR spectra were mea-

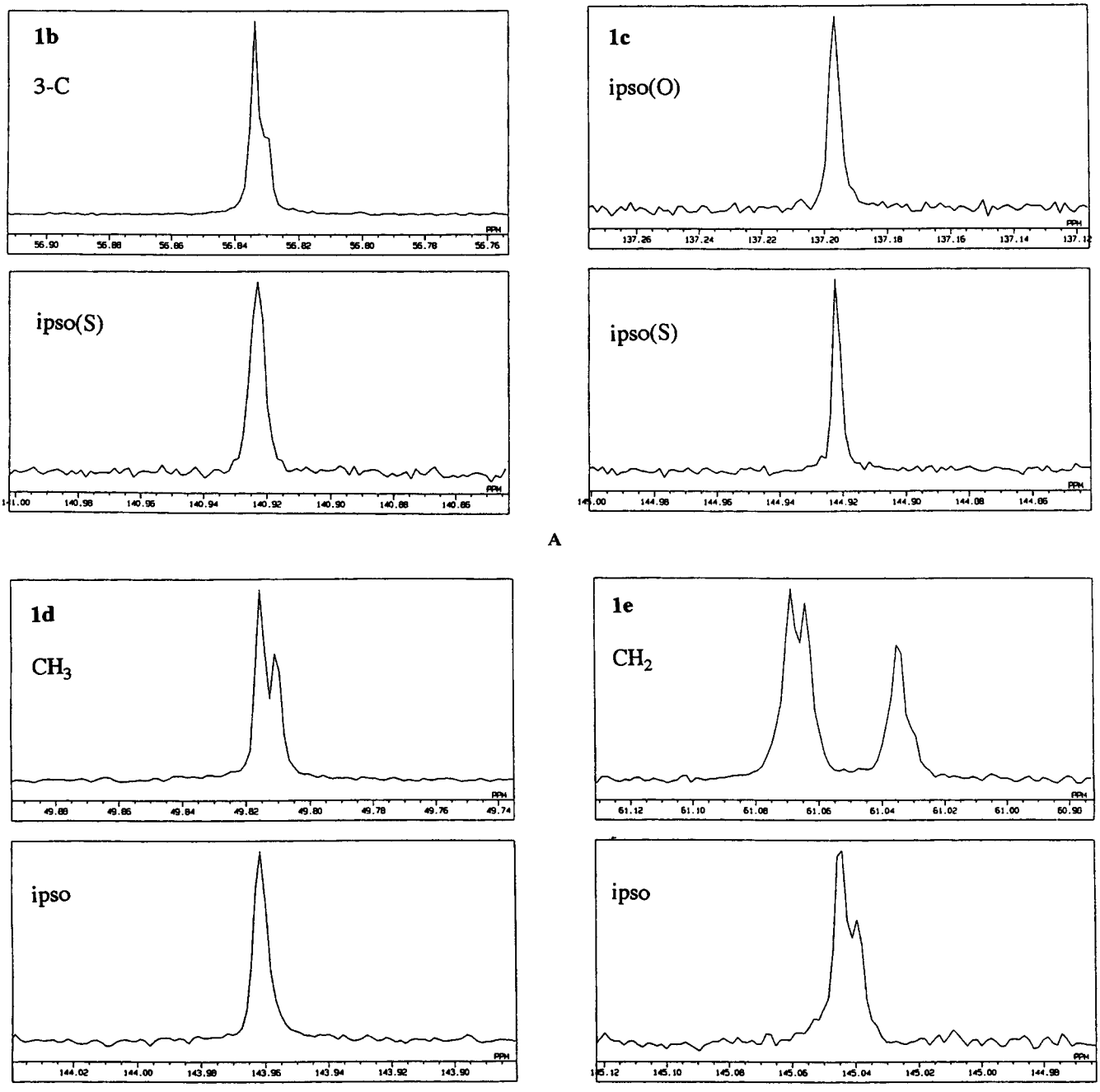
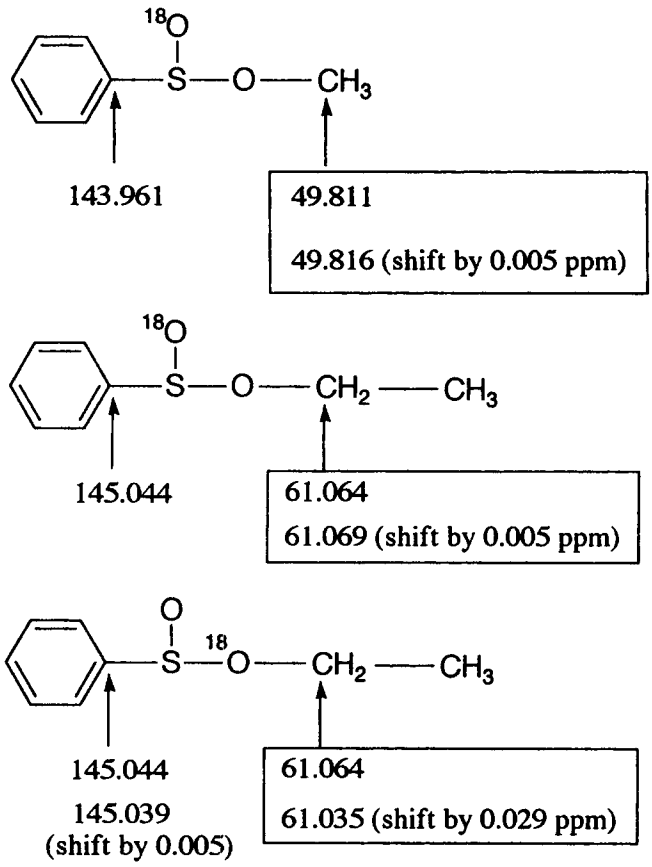


FIGURE 1 The ^{13}C NMR signals of the carbons adjacent to the sulfinate function of some ^{18}O-labeled sulfinate esters. Spectra were measured at 125.65 MHz with resolution of 0.19 Hz, and the full scale of the abscissa is 20 Hz (ca. 0.16 ppm).



SCHEME 2

sured at 125.65 MHz and 35°C, and resolution was as precise as 0.19 Hz or 0.0015 ppm.

Oxygen-18 enriched water (95 at. %) was obtained from Sigma Chemical Co., Inc. (St. Louis, MO). Methyl and ethyl benzenesulfinates were prepared from *N*-phenylsulfinylphthalimide [7].

3*H*-2,1-Benzoxathiole 1-oxide (**1a**) was obtained by chlorination-hydrolysis [6] of 2-hydoxymethylbenzenethiol [15]. ^{1}H NMR ($CDCl_3$), δ 5.54 (d, 1H), 5.98 (d, 1H), 7.6–7.8 (m, 4H). ^{13}C NMR ($CDCl_3$), δ 78.32, 123.33, 129.12, 132.12, 138.07, 146.98.

Dibenzo-2,1-oxathiin 1-oxide (**1c**) was prepared by reaction of *o*-hydroxybiphenyl with thionyl chloride followed by an $AlCl_3$-promoted cyclization [8]. ^{13}C NMR ($CDCl_3$), δ 120.55 (quaternary C), 121.42, 124.45, 124.55, 125.46, 125.67, 126.55 (quaternary C), 128.38, 130.68, 132.95, 137.20 (quaternary C), 144.92 (quaternary C).

3,4-Dihydro-2,1-Benzoxathiin 1-Oxide (**1b**)

To a solution of thionyl chloride (13 g, 0.11 mol) in dichloromethane (50 mL) was added dropwise a solution of 2-phenylethanol (12.2 g, 0.1 mol) in dichloromethane (50 mL) at −20°C. Triethylamine (14 mL, 0.1 mol) was then added dropwise, and the mixture was stirred at 0°C for 30 minutes. The precipitates were filtered off by suction. The filtrate was added dropwise to a vigorously stirring suspension of aluminum chloride (27 g, 0.2 mol) in dichloromethane (100 mL) at −20°C under argon. After the addition, the mixture was further stirred at room temperature overnight. Water was added and some resins that had formed were removed by decantation. The organic layer was washed with aqueous hydrochloric acid and water. After drying with $MgSO_4$, the solvent was evaporated under vacuum and the residues were distilled. The fraction boiling at 105–110°C at 0.15 mmHg was collected, and it solidified on standing (3.6 g, 21% yield). The HPLC analysis showed contamination with an isomer, 2,3-dihydro-1-benzothiophene 1,1-dioxide (about 8%), which could not be removed by recrystallization from hexane-ethyl acetate or ethanol-water. Analytical and kinetic samples were purified by preparative HPLC. Mp 53.0–54.2°C. Anal. calcd for $C_8H_8SO_2$: C, 57.12; H, 4.79; S, 19.06. Found: C, 56.84; H, 4.79; S, 18.87. IR, 1125 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ 2.84 (d of broad peaks, 1H), 3.22 (ddd, 1H), 4.21 (ddd, 1H), 4.84 (ddd, 1H), 7.24 (d, 1H), 7.39 (t, 1H), 7.44 (dt, 1H), 7.54 (dd, 1H). ^{13}C NMR ($CDCl_3$), δ 26.99, 56.83, 127.56, 127.75, 130.06, 131.45, 132.13, 140.92.

Acid-Catalyzed Isotope Exchange of Sultines

A sultine (0.5 mmol) was dissolved in a solution prepared from 0.1 mL of $H_2{}^{18}O$, 0.1 mL of 70% perchloric acid, and 2 mL of dioxane and kept at 25°C. A 0.1 mL aliquot of the mixture was occasionally withdrawn, and the sultine was extracted with dichloromethane and analyzed by mass spectrometry. Finally, after 30–34 days of reaction, the whole reaction mixture was diluted by addition of water and the sultine was extracted with dichloromethane. Extents of excess ^{18}O were **1a**, 33.5% and **1c**, 24.6%.

Labeling by Ring Opening and Recyclization of Sultines

Sultine **1b** (84 mg, 0.5 mmol) was dissolved in a solution composed of 0.2 mL of $H_2{}^{18}O$, 20 mg of NaOH, and 2 mL of acetonitrile. The mixture was stirred vigorously (a phase separation occurred) at room temperature for 3 hours and 4 mL of 2 M HBr was added. After additional reaction for 30 minutes, the mixture was shaken with dichloromethane three times, and after having been washed with water, the organic layer was dried over $MgSO_4$. Removal of the solvent left the ^{18}O-labeled sultine essentially quantitatively (ca. 75 mg). Mass spectral analysis showed that ^{18}O was enriched by 31.6%. A similar reaction with **1a** resulted in a 41.5% labeling.

Labeled Methyl Benzenesulfinate

In a typical run, sulfinate **1d** (0.12 g) was dissolved in a solution prepared from 4 mL of methanol containing 0.38 M of trifluoroacetic acid, 0.2 mL of $H_2{}^{18}O$, and 0.2 g of sodium bromide (0.5 M) and kept at 25°C for 60 hours. The reaction was quenched by addition of 10 mL of water, and the sulfinate was extracted with dichloromethane. Evaporation of the solvent gave 65 mg of the residues composed mainly of **1d** contaminated with a small amount of *S*-phenyl benzenethiosulfonate (HPLC). Repeated runs gave rise to about 50% chemical yields and 45–60% of ^{18}O contents.

Labeled Ethyl Benzenesulfinate

Methyl sulfinate **1d** (0.16 g, 1 mmol) was dissolved in a solution composed of acetonitrile (4 mL), $H_2{}^{18}O$ (0.2 mL), and KOH (60 mg, 1 mmol) and stirred for 1 hour until all the **1d** had disappeared (by HPLC). The solvent was removed by evaporation under vacuum to dryness. A dichloromethane solution of 1 M triethyloxonium fluoroborate (1.1 mL) obtained from Aldrich Chemical Co., Inc. (Milwaukee, WI), was added to the residues and shaken for 10 minutes. Water (10 mL) and dichloromethane (10 mL) were added to the mixture. The organic layer was washed with water and dried over $MgSO_4$. Removal of the solvent gave 30 mg (18% yield) of the ethyl sulfinate containing 65.1 at. % of ^{18}O.

ACKNOWLEDGMENTS

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