On the Mechanism of Hydrolysis of Sulfinate Esters: Oxygen Isotope Exchange and Theoretical Studies

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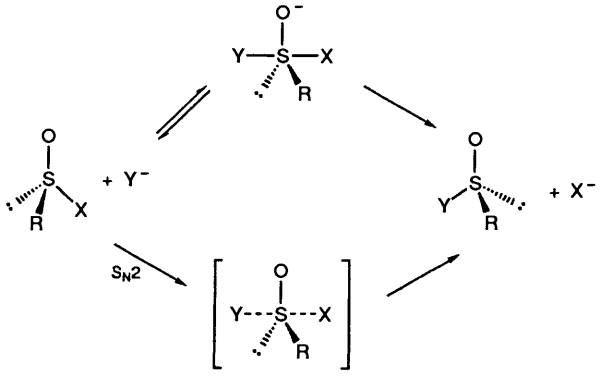
A small but detectable amount of ^{18}O loss at the sulfinyl oxygen was observed during acid hydrolysis of ^{18}O-labelled methyl benzenesulfinate, while no detectable loss of the label was found during alkaline hydrolysis. The relative rates of the acid-catalysed isotope exchange and hydrolysis were evaluated to be about 1/200. This large difference in the rates seems to be incompatible with the reaction of water with the conjugate acid of the substrate protonated at the sulfinyl oxygen. A mechanism involving an S_N2-like reaction at the sulfur through the protonation at the alkoxy oxygen of the substrate is proposed on the basis of theoretical calculations.

Nucleophilic substitution at sulfur can occur through an addition–elimination mechanism with a trigonal bipyramidal intermediate (sulfurane) or a concerted S_N2-like mechanism (Scheme 1).[1] Sulfurane can be isolated if it is stabilized enough



Scheme 1

by certain structural factors.[2] However, it is still to be clarified whether simple nucleophilic substitution at sulfur takes place through a sulfurane intermediate. One measure of the existence of such an intermediate may be oxygen isotope exchange during hydrolysis of sulfinate ester. This situation is quite similar to that for the tetrahedral intermediate formed during the hydrolysis of carboxylate esters.[3] Previous efforts along these lines in the alkaline hydrolysis of cyclic sulfinates[4,5] and a sulfinamide[6] were unsuccessful. We have now found that ^{18}O-labelled methyl benzenesulfinate does undergo oxygen exchange during acid hydrolysis, but the difference in rates between the hydrolysis and exchange is very large (a factor of 200). These results argue *against* a sulfurane intermediate, and an S_N2-like mechanism is proposed.

Results and Discussion

Preparation of the ^{18}O-Labelled Sulfinate.—Few efficient methods for the ^{18}O-labelling of sulfinic acid derivatives seem to have been reported previously.[7] We have recently found that cyclic sulfinate esters are stable in aqueous acids but undergo ^{18}O exchange with the ^{18}O-enriched water.[5,8] Acyclic sulfinate esters undergo acid-catalysed transesterification in alcoholic solution[9] while they undergo hydrolysis in aqueous acids.[10,11] Since the transesterification is reversible, the sulfinate ester should be in equilibrium with sulfinic acid in acidic aqueous alcoholic solution and isotope incorporation be attained by using ^{18}O-enriched water as a cosolvent, eqn. (1).

$$RS(O)OR' + H_2{}^{18}O \overset{H^+}{\rightleftharpoons} RS(O)^{18}OH + R'OH \overset{H^+}{\rightleftharpoons} RS(^{18}O)OR' + H_2O \quad (1)$$

Methyl benzenesulfinate labelled at the sulfinyl oxygen (**1**–^{18}O) was obtained by this method, eqn. (2). The ^{18}O exchange of

$$2\underset{\mathbf{1}}{PhS(O)OMe} + H_2{}^{18}O \xrightarrow{H^+,\,Br^-} PhS(^{18}O)OMe + PhS(O)OH + MeOH \quad (2)$$
$$\mathbf{1}\text{–}^{18}O$$

the sulfinate **1** was carried out in a 20:1 (v/v) mixed solvent of methanol and ^{18}O-enriched water (95 atom %) using trifluoroacetic acid as a catalyst. Sodium bromide was also added to accelerate the exchange since the acid-catalysed isotope exchange of cyclic sulfinates was found to undergo nucleophilic catalysis by bromide ion.[5] About 65% of the sulfinate was recovered after a few days of reaction at room temperature and enriched with ^{18}O by *ca.* 45 atom %.[8] The side products were the sulfinic acid and a small amount of *S*-phenyl benzenethiosulfonate, eqn. (3). Although it has been stated that sulfinic acids

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

do not undergo acid-catalysed esterification with alcohols because of the prevalent disproportionation of eqn. (3),[12] this is not always the case. The esterification leading to the isotope incorporation can well compete with the disproportionation.

Isotope Exchange.—The labelled sulfinate **1**–^{18}O was subjected to both alkaline and acid hydrolysis at 25 °C. After two to four half-lives of reaction,[11] the unchanged ester was recovered by extraction with dichloromethane and analysed for the ^{18}O content by mass spectrometry. As summarized in Table 1, a small but definite amount of the label was lost during the acid hydrolysis in perchloric acid as well as in hydrochloric and hydrobromic acids, the loss increasing with reaction time. The relative rate of the exchange and the hydrolysis is evaluated to be roughly 1/200 from about 1% of the exchange observed during three half-lives of the acid hydrolysis. To confirm that the

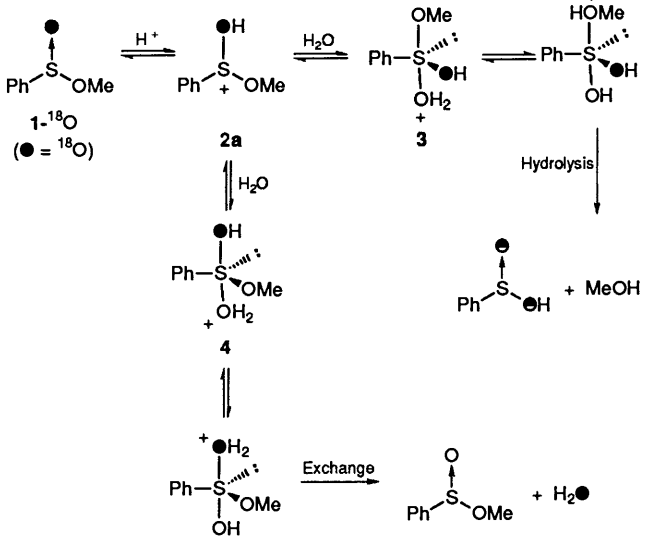
Table 1 Remaining ^{18}O in the recovered substrate during hydrolysis of labelled methyl benzenesulfinate 1–^{18}O[a]

Conditions (pH)	$t_{\frac{1}{2}}$	Reaction time	MS intensity[b]	% Excess ^{18}O
Unchanged		0	88.82, 88.83, 88.35	45.40
NaOH (10.6)[c]		15 min	88.71	45.51
borate (9.25)[d]	43 min	1 h	88.34	45.40
carbonate (10.08)[e]	5.5 min	10 min	88.23	45.37
		15 min	88.62	45.48
$HClO_4$	2 h	4 h	87.86, 87.58	45.22
(2 mol dm^{-3})		4 h[f]	87.65	45.19
		4 h[g]	87.67	45.20
		6 h	87.00, 87.37	45.06
		8 h	86.11	44.73
HCl (1 mol dm^{-3})	25 min	50 min	87.89	45.27
HBr (1 mol dm^{-3})	10 min	20 min	87.60	45.18

[a] Reactions were carried out at 25 °C with an initial substrate concentration of 0.9–1.4 mmol dm^{-3}. [b] % Intensity of a peak $m/z = 158$ relative to that of $m/z = 156$. Values on the same line indicate results of independent analyses of the same sample. [c] $[S]_0 = 5 \times 10^{-4}$ mol dm^{-3}. [d] Buffer concn = 0.2 mol dm^{-3}. [e] Buffer concn = 0.01 mol dm^{-3}. [f] In the presence of methanol at 0.012 mol dm^{-3}. [g] In the presence of methanol at 0.12 mol dm^{-3}.

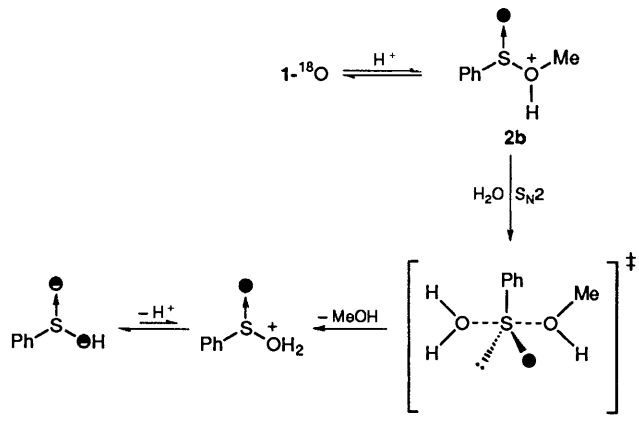
exchange is not due to the reversibility of the hydrolysis (return from the products, sulfinic acid and methanol), effects of added methanol was examined. Any influence of 0.12 mol dm^{-3} methanol was not observed. Alkaline hydrolysis of 1–^{18}O was carried out in aqueous NaOH and in buffer solutions, but the recovered ester retained the original label at the same level of ^{18}O content to within experimental error (Table 1). No isotope loss was detected during the alkaline hydrolysis as was previously found with cyclic sulfinates.[4,5]

Reaction Mechanisms.—Possible mechanisms for the acid hydrolysis of 1–^{18}O with accompanying isotope exchange are presented in Schemes 2 and 3. The reactions may start from the



Scheme 2

protonated sulfinate **2a** (protonation at the sulfinyl oxygen), which can be taken as a hydroxymethoxysulfonium ion, or **2b** (protonation at the alkoxy oxygen). Although participation of acid can be of a general-acid type without a conjugate acid of the substrate as a discrete intermediate, the mechanisms are described with its intermediary formation for simplicity and for the purpose of specifying the site of protonation.



Scheme 3

The mechanism in Scheme 2 involves the trigonal bipyramidal (sulfurane) intermediate **3** (with the methoxy group in an apical position) leading to hydrolysis and the intermediate **4** (with the labelled hydroxy group in an apical position) leading to exchange. Since the methoxy and the hydroxy groups of the protonated substrate **2a** are similar in nature, both can equally be directed at one of the apical positions of a trigonal bipyramidal intermediate, leading to **3** or **4**. Furthermore, the two sulfuranes **3** and **4** may readily be interconvertible with each other through pseudo-rotations.* These considerations lead to the conclusion that the exchange and the hydrolysis may occur with similar ease† contrary to the experimental results. The S_N2-like mechanism with **2a** is also unlikely. It is hard to rationalize that a poor nucleofuge like methoxide or hydroxide ion can be expelled by a weak nucleophile, such as water, and that the methoxy group (in hydrolysis) is much more readily expelled as compared with the hydroxy group (in the exchange).

An alternative mechanism shown in Scheme 3 involves the conjugate acid **2b** with protonation at the alkoxy oxygen that may readily undergo an S_N2-like hydrolysis. Although the basicity of the alkoxy oxygen is weaker than the sulfinyl oxygen, the protonated substrate **2b** would be unstable to undergo facile hydrolysis (or more probably the reaction may be general-acid catalysed).‡ The ^{18}O exchange cannot accompany this hydrolysis but the observed exchange may be incorporated by some other contaminating pathway like one shown in Scheme 2.

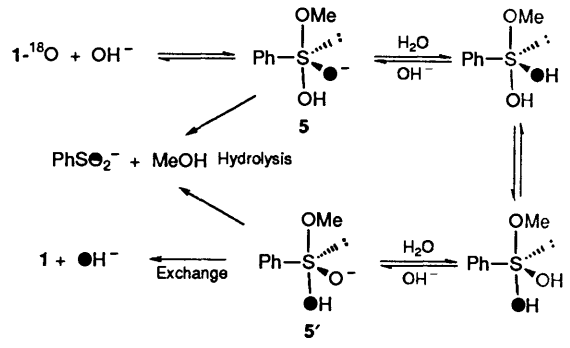
Possibilities of these mechanisms are also considered on the basis of theoretical calculations.

The lack of ^{18}O exchange during alkaline hydrolysis may also be due to the S_N2-like mechanism. If there existed a sulfurane intermediate **5**, rapid protonation and pseudo-rotations would have led to the isotope exchange (Scheme 4). In view of the rapid pseudo-rotations observed with tetraphenylsulfurane at low temperature,[13] it is hard to account for the lack of rearrangement of a putative sulfurane intermediate.

* Since the rearrangement of tetraphenylsulfurane was found to be very rapid even at −105 °C,[13] possible sulfurane intermediates of the hydrolysis could readily undergo rearrangement, if they existed.

† Relative rates of hydrolysis and ^{18}O exchange in the acid hydrolysis of ethyl benzoate (expulsion of HOH and HOEt) were found to be 5.2.[3b] Expulsion of HOMe from the intermediate leading to the hydrolysis could be faster than that of HOH (exchange), but the difference of 200 times seems to be too large if not impossible. In this sense, Scheme 2 as a probable mechanism cannot strictly be excluded at the present stage.

‡ The conjugate acid **2b** would not be a discrete intermediate, but the proton transfer might be concerted with the nucleophilic reaction of water at the sulfur. However, it is difficult to confirm experimentally the possible general acid catalysis of this reaction, since strongly acidic conditions are needed owing to the low reactivity of sulfinate ester.



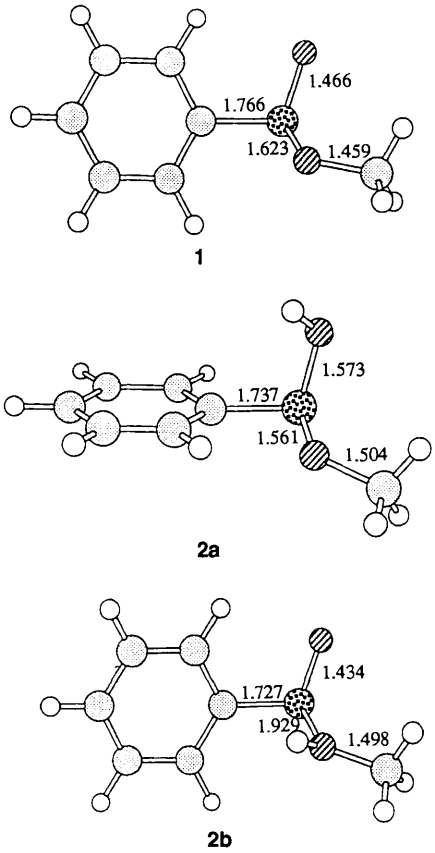


Fig. 1

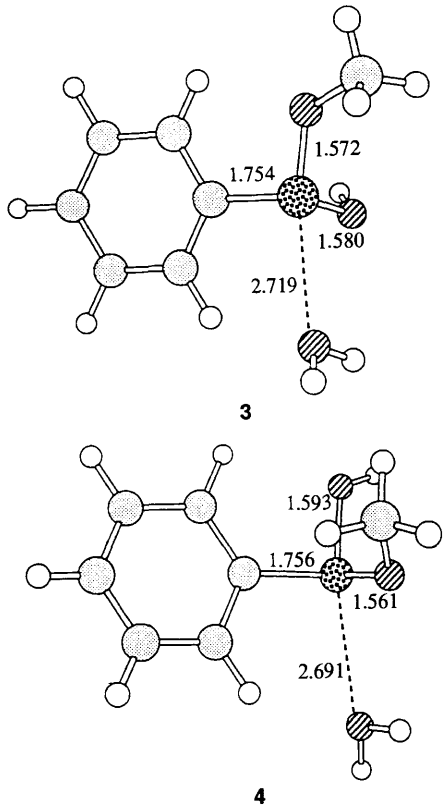


Fig. 2

$$1 + H_3O^+ \longrightarrow \underset{\text{2a}}{Ph\text{–}\overset{\overset{OH}{|}}{\overset{+}{S}}\text{–}OMe} + H_2O \qquad \Delta E^\circ = -110.5\ \text{kJ mol}^{-1} \quad (4)$$

$$1 + H_3O^+ \longrightarrow \underset{\text{2b}}{Ph\text{–}S\overset{\overset{O}{\uparrow}}{\underset{+}{O}}\text{–}Me} + H_2O \qquad \Delta E^\circ = -88.3\ \text{kJ mol}^{-1} \quad (5)$$

Theoretical Considerations.—Ab initio molecular orbital calculations were carried out to obtain the structure and energies of **1** and related species in the gas phase by full optimization at the HF/3-21G(*) level[14] using GAUSSIAN 92.[15] Single point calculations were also performed to obtain improved energies on the basis of the second-order Møller–Plesset perturbation (MP2) theory[16] with the larger basis set 6-31G*.[17]

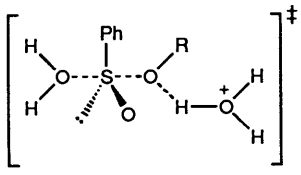
The optimized structures of **1** and its conjugate acids, **2a** and **2b**, are shown in Fig. 1. On protonation at the alkoxy oxygen O_a (**1** to **2b**), the S–O_a bond is considerably extended from 1.623 to 1.929 Å, while protonation at the sulfinyl oxygen O_s (**1** to **2a**) results in rather mild changes in the S–O bond lengths. It is also worth noting here that the sulfinyl S–O_s bond is essentially coplanar with the benzene ring in both **1** and **2b** (the twisting angles being about 10 and 3° for **1** and **2b**, respectively), while the S–O_sH bond is orthogonal (89.8°) to the benzene ring in **2a** (the coplanar structure seems to be about 20 kJ mol^{-1} less stable). Energies for protonation of **1**, summarized in eqns. (4) and (5), show that the sulfinyl oxygen is more basic than the alkoxy oxygen, but the energy difference is only 22.2 kJ mol^{-1} in the gas phase.

The protonation at the alkoxy oxygen (**2b**) is less favoured, but results in the considerable elongation of the S–O_a bond to facilitate its cleavage. By contrast, the protonation at O_s (**2a**) rather strengthens the S–O_a bond.

If the reaction occurs *via* the sulfinyl protonation (**2a**), the trigonal bipyramidal (sulfurane) intermediate must be involved. When a water molecule approaches the sulfur atom of **2a** from the opposite side of the OMe or from that of the OH group, formation of an intermediate **3** or **4** results. The optimized structures of **3** and **4** are illustrated in Fig. 2. Although the S–OH_2 bond distances are very long (2.719 and 2.691 Å for **3** and **4**, respectively), both **3** and **4** are in an energy minimum. The structures are trigonal bipyramidal with the attacking water in an apical position though slightly deformed, the apical O–S–O angles of **3** and **4** being 166.8 and 167.0°, respectively. The difference in total energy is small, but the form **3** (leading to hydrolysis) is 6.3 kJ mol^{-1} less stable than **4** (leading to exchange). These results suggest that the ^{18}O exchange should have occurred extensively during hydrolysis if the reactions took place through protonation at the sulfinyl oxygen (**2a**). This is contrary to the experimental results.

Although the protonation at the alkoxy oxygen of **1** is less

favourable than the sulfinyl protonation, it facilitates greatly the departure of the OMe group and may favour the S_N2-like mechanism. In conclusion, the most likely mechanism for the hydrolysis of simple sulfinate esters is S_N2-like with protonation at the alkoxy oxygen probably in a general acidic manner as shown below.



Experimental

Materials.—Methyl benzenesulfinate (**1**) and the ^{18}O labelled substrate **1**–^{18}O were obtained as described previously.[8,11]

Water used for alkaline solutions was freed from CO_2 by boiling deionized water under argon. Aqueous NaOH solutions were prepared from a sodium methoxide solution obtained freshly by dissolving sodium metal in methanol but contained less than 1% of methanol. The concentrations were determined by titration with a standard HCl.

Isotope Exchange.—The ^{18}O contents were determined by mass spectrometry using a JMS DX303 spectrometer. In a typical run, 0.1 cm^3 of a stock solution of **1**–^{18}O (1–2 mg) was added to 5 cm^3 of an acid or alkaline solution in a flask maintained at 25 °C. After an appropriate reaction time calculated from the hydrolysis rate constant,[11] reaction was quenched by extraction with CH_2Cl_2 (3 × 5 cm^3). The combined extracts were dried ($MgSO_4$), concentrated to *ca.* 1 cm^3, and subjected to mass spectrometry. Errors in relative intensities of the peaks *m*/*z* 156 and 158 are estimated to be $< \pm 0.3\%$ and correspond to those of $< \pm 0.1\%$ in excess ^{18}O of the natural abundance calculated with the corrections for naturally occurring isotopes.

Calculations.—All the theoretical calculations were carried out using GAUSSIAN 92 program[15] on an IBM RS6000 workstation.

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