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속 보

Thiol 및 Disulfide의 ^{18}O 표식한 수산화나트륨 중에서의 자동산화 : Peroxysulfenate 중간체의 형성

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Autoxidation of Thiols and Disulfides in the ^{18}O-Labeled Sodium Hydroxide Media: Evidence for the Formation of Peroxysulfenate Intermediate

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Direct oxidations of thiols to their sulfinic or sulfonic acids have been generally known to be carried out under strong oxidation conditions such as boiling nitric acid[1], potassium permanganate[2] or Caro's acid ($KHSO_5$)[3]. While, enzymic oxidations of the cystein to the corresponding sulfinic acid have been well known to occur readily in vivo[4] and vitro[5] under mild conditions. It has been previously reported that thiols and disulfides react with activated oxygen in the alkaline media to afford the corresponding sulfinic acids and/or sulfonic acids at room temperature.

Earlier Berger demonstrated that both sulfinic and sulfonic acid products obtained from the reaction of thiols with oxygen in the presence of potassium tertiary butoxide and tertiary butanol arise *via* an oxidation of a chain carrier of sulfenate (RSO^-) and peroxysulfenate ($RSOO^-$) as shown in Scheme 1[6].

On the other hand, Wallace *et al.* later suggested that the reaction of thiols with oxygen in potassium hydroxide and dipolar solvents such as hexamethyl phosphoramide and dimethylformamide yielded only the corresponding sulfonate salts, which are produced *via* disproportionation of a sulfenate ion, (or *via* direct oxidation of a [sulfenate ion with molecular oxygen) (*Scheme* 2)[7].

$$RS^- + O_2 \longrightarrow RSOO^-$$
$$RSOO^- + RS^- \longrightarrow 2\,RSO^-$$
$$RSO^- + O_2 \longrightarrow RS(O)OO^- \longrightarrow RSO_n \quad n=2,3$$

Scheme 1.

$$RS^- + O_2 \longrightarrow RSSR \xrightarrow{^-OH} RSO^- + RS^-$$
$$3\,RSO^- \xrightarrow{\text{disproportionation}} RSO_3^- + RSSR$$
$$(\text{or } RSO^- + O_2 \longrightarrow RSO_3^-)$$

Scheme 2.

In order to differenciate between these two mechanistic path ways, $^-O^{18}H$ isotope labelling

Table 1. Yields of products and ^{18}O isotope incorporations.

Run	subst.	Reactn. temp(°C)	Reactn. time(h)	$Na^{18}OH$[a] ex ^{18}O%	$PhS^{18}O_2^-$[b] Yield (%)	ex ^{18}O%	^{18}O Incorp (%)	$PhS^{18}O_3^-$[c] Yield (%)	ex ^{18}O%	^{18}O Incorp. (%)
1	PhSSPh	60	20	1.005	70	0.280	27.8	14	0.326	32.4
2	PhSH	60	20	1.005	75	0.180	17.9	12	0.170	16.9
3	PhSSPh	25	30	1.005	75	0.250	24.9	15	0.300	29.9
4	PhSH	25	30	1.005	80	0.120	11.9	10	0.114	11.3

[a] $Na^{18}OH$/substrate=4. The ^{18}O content (1.005) of $Na^{18}OH$ was determined by measuring ^{18}O content of phenyl amide as shown below. $Ph-C\equiv N + Na^{18}OH \xrightarrow{HMPA} Ph-\overset{\overset{^{18}O}{\|}}{C}-NH_2$. [b] as $PhS^{18}O_2Me$. [c] as $(PhS^{18}O_3^-)(H_3\overset{+}{N}-\overset{\overset{NH}{\|}}{C}-S-CH_2-Ph)$.

method was employed for this autoxidations of thiol and disulfide. Reactions of thiophenol and diphenyl disulfide with oxygen molecular in the presence of $Na^{18}OH$ in hexamethylphosphoramide were carried out in a similar way to the literature procedure[7], but the yields of benzenesulfonic acid and benzenesulfinic acid (as methyl phenyl sulfone[8]) were determined by high pressure liquid chromatography[9] using calibration curves of their authentic samples. The benzenesulfonic acid was converted to its thiuronium salt[10] for measuring the ^{18}O content in it. Meanwhile, benzenesulfinic acid was methylated with methyl iodide in aqueous dioxane to the methyl phenyl sulfone. Analysis of ^{18}O content in these compounds was carried out by an adaptation of the method reported previeously[11]. The product, yields and the incorporations of ^{18}O isotope into the products are summarized in *Table* 1.

In cortrast to the results reported by Wallace *et al*[2]. main product was found to be benzenesulfinic acid (70~80 %), but not sulfonic acid. If the thiolate ion converts to the diphenyl disulfide and then a sulfenate ion formed by an attack of $^-O^{18}H$ on the sulfur atom disproportionates to the corresponding sulfonic acid, it is expected to incorporate three ^{18}O atoms into the sulfonic acid (^{18}O incorporation =100 %) as shown in Scheme 2. However, benzenesulfonic acid was found to contain ca. 11.30 % of ^{18}O incorporation in it at 25 °C and *ca.* 16.9 % of ^{18}O incorporation at even 60 °C. Therefore, possible involvement of disulfide and disproportionation of sulfenate ion can not be explained as the main path way in this autoxidation. It is noteworthy that the ^{18}O incorporation into poth sulfinic and sulfonic acid slightly increased as the reaction temperature was elevated (Run 2 and 4), which means the formation of disulfide intermediate increased also at a higher temperature. In the case of disulfide, an attack of $^-O^{18}H$ ion on the sulfur atom appears to form sulfenate ion containing ^{18}O and thiolate ion, which pick ub molecular oxygen to form peroxysulfenate ion.

When the autoxidation of diphenyl disulfide was carried out in the presence of triphenyl phosphine for trapping the activated oxygen of the peroxysulfenate intermediate[12] triphenyl phosphine oxide (*ca.* 60 %) was actually obtained along with benzenesulfinic acid (70 %) and benzenesulfonic acid (10 %). This is another evidence for the formation of peroxysulfenate intermediate in this autoxidation.

Thus, it is concluded from the above results that the main autoxidation route of a thiol is probably initiated by forming unstable peroxysulfenate ion ($R SOO^-$) at a low temberature though the exact mechanism of the sulfinic and sulfonic acid formation is not clear in this autoxidation.

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9. Column : 4 mm×50 cm, Y-Gel-5510, MeOH, Retention time (min) : Sulfonate (1.3), methyl phenyl sulfone (2.5).
10. Since sulfonic acid is hygroscopic, it was converted to thiuronium salt as a good sample for the ^{18}O isotope analysis.
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