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Facile Desulfurization of Thiocarbonyl Groups to Carbonyls by Superoxide. A Model of Metabolic Reactions

Several types of thioamides and thioureas including thiouracils were readily desulfurized to the carbonyl compounds by superoxide, generated by KO_2 and 18-crown-6 or electrolysis of oxygen in aprotic solvent at room temperature. Such desulfurization may provide a model of metabolic reactions catalyzed by oxygenases.

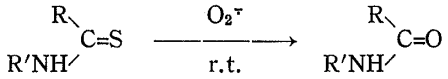
Keywords——desulfurization; potassium superoxide; superoxide; thiouracil; thiouridine; thiocarbonyl

Oxidative desulfurization of thio-xenobiotics is one of the important *in vivo* metabolic processes catalyzed by oxygenases.[1] Medicinal drugs,[2] thiobarbital (5,5-diethyl-2-thiobarbituric acid) and ethionamide(2-ethylthioisonicotinamide) as well as thiouracils are known to be metabolized *in vivo* to their carbonyl derivatives with no evidence to show any intervention by activated species of oxygen such as superoxide which is distributed widely in living cells.

In connection with bio–organic studies on the activation mechanism of molecular oxygen,[3] the present study was undertaken to explore the desulfurization of thio-carbonyl compounds by superoxide as a model of metabolic reactions.

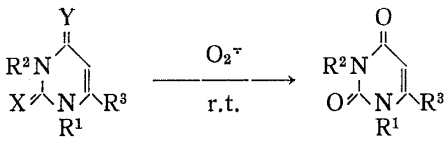
The superoxide was generated by potassium superoxide (KO_2) with the catalyst crown ether or by electrolysis of oxygen.[4]

On treatment with the KO_2-crown ether reagent in aprotic solvent at room temperature, cyclic and acyclic thioureas, thio-barbital and N,N'-diphenylthiourea were readily desulfurized within 1 h to form carbonyl compounds almost exclusively (71% or 88% based on consumed



material and 61% yields, respectively).

This superoxide was also effective for the desulfurization of thioamide groups of thioisonicotinamide and the 2-ethyl derivative and thionicotinamide to give the amides in 69%, 61% and 71% yields, respectively, though the reaction proceeded much more sluggishly. This type of desulfurization was also performed with thiobarbital and thioisonicotinamide in acetonitrile by the highly purified superoxide generated by electrolysis of oxygen.



1a—h **2a—f**

This reaction was successfully applied also to thiouracils and thiouridine. Thus, 2- and/or 4-thiouracils (**1a—f**), some of which are recognized as minor bases in t-RNA or metabolic inhibitors,[5] were converted to the desulfurized uracils in good yields, while 1,3-disubstituted thio compounds (**1g, h**) with no enolizable hydrogens failed to give normal products and resulted in an exclusive cleavage of carbon-nitrogen bonds (Table I).

2,4-Dithiouracil apparently was desulfurized stepwise *via* 2-thiouracil in view of large difference in the rate between thiourea and thioamide groups. 4-Thiouridine was similarly converted to uridine under identical conditions. The following procedure provides a typical example. To a solution of 2,4-dithiouracil (**1c**) (5 mmol) in DMF (30 ml) were added KO_2 (15 mmol) and 18-crown-6 (1.5 mmol) with cooling and the mixture was stirred at room temperature for 3 days. The cooled mixture was treated with 10% hydrochloric acid and extracted with ethyl acetate. A usual work-up of the aqueous solution gave uracil (80%) in addition to small amounts of 4-thiouracil (6%) and some unchanged material (7%) was recovered from the organic layer.

The mechanism of this reaction is not clear at present, but a key step may be oxidation to sulfones or sulfonates which are quite labile and removable under acidic and basic conditions.[6] For such conversion of the thiocarbonyl groups, some oxidizing agents such as hydrogen peroxide or potassium permanganate are also reported to be effective,[7] but only under much more drastic conditions.

Table I. Conversion of Thiouracils (**1**) to Uracils (**2**) by Superoxide[a]

Compound	X	Y	R^1	R^2	R^3	Yield(%)[b]	(%)
a	S	O	H	H	H	60	(1)
b	O	S	H	H	H	61	(4)
c	S	S	H	H	H	80	(7)
d	S	O	H	H	CH_3	79	(5)
e	S	O	H	H	Ph	86	(2)
f	S	O	H	H	NH_2	51	(17)
g	O	S	CH_2Ph	CH_2Ph	H	Trace	(10)[c]
h	O	S	CH_3	CH_3	H	Trace	(13)

a) Thiouracils were treated with KO_2 (3 eq) and 18-crown-6 (0.3 eq) in dimethyl formamide (DMF) at room temperature for 3 days.
b) Isolated yields. Recovery of the starting material is given in parentheses.
c) Benzoic acid (9%), N,N'-dibenzylurea (4%) and benzaldehyde (1%) were isolated.

This desulfurization which proceeds readily under mild conditions may suggest a critical role of superoxide in metabolic desulfurization *in vivo*.

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