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BIOMIMETIC REDUCTION OF SULFURIC ACID

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Inorganic sulfate was reduced by treatment with either arenesulfenyltriphenylphosphonium arenethiolate or iodotriphenylphosphonium iodide to triphenylphosphine sulfide via formation of hydrogen sulfide. The reaction of sulfate to sulfide is considered to proceed via the course which resembles the biological reaction path involved in the assimilatory metabolism of inorganic sulfate in microorganisms.

Inorganic sulfate which has the highest oxidative state of sulfur atom is one of the most inert species toward any reducing agent among the naturally occurring sulfur compounds, and hence the reduction of inorganic sulfate by any chemical method under mild conditions has been considered to be rather difficult. Meanwhile, many plants, fungi and microorganisms are known to reduce inorganic sulfate in their assimilatory metabolisms which eventually convert sulfate to some sulfur-containing amino-acids as shown below[1).

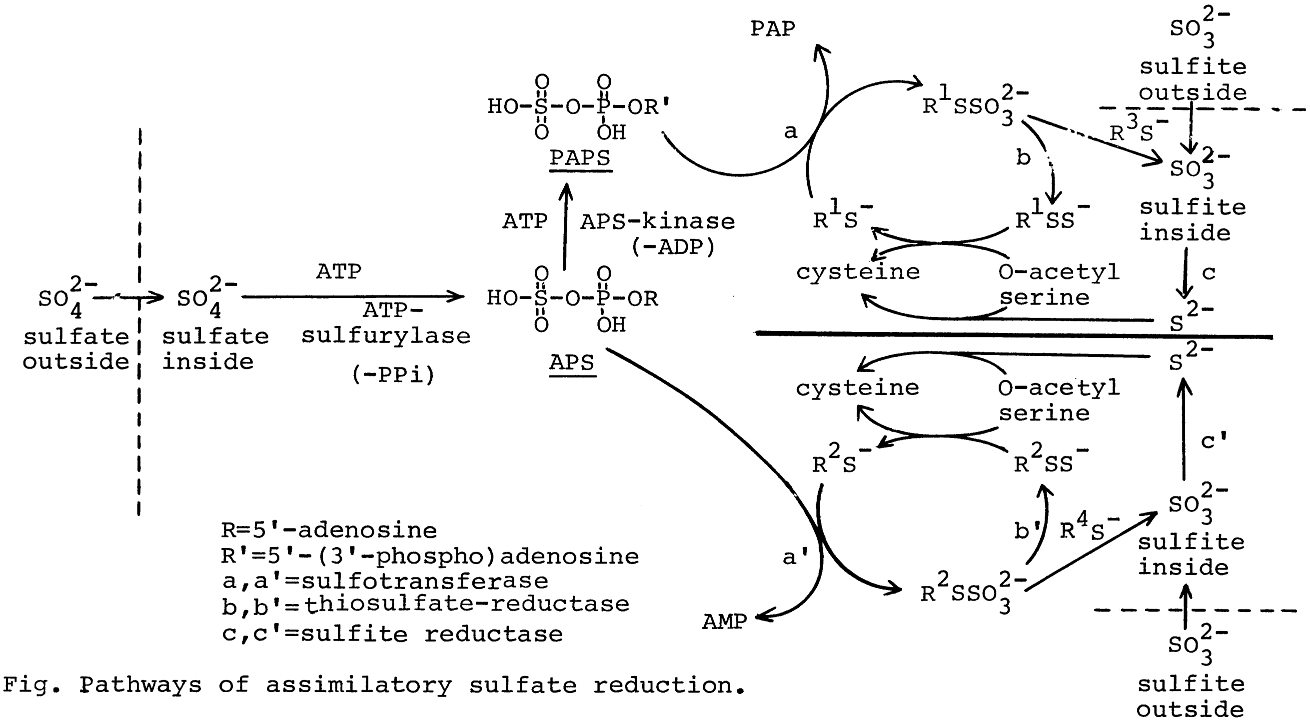


Fig. Pathways of assimilatory sulfate reduction.

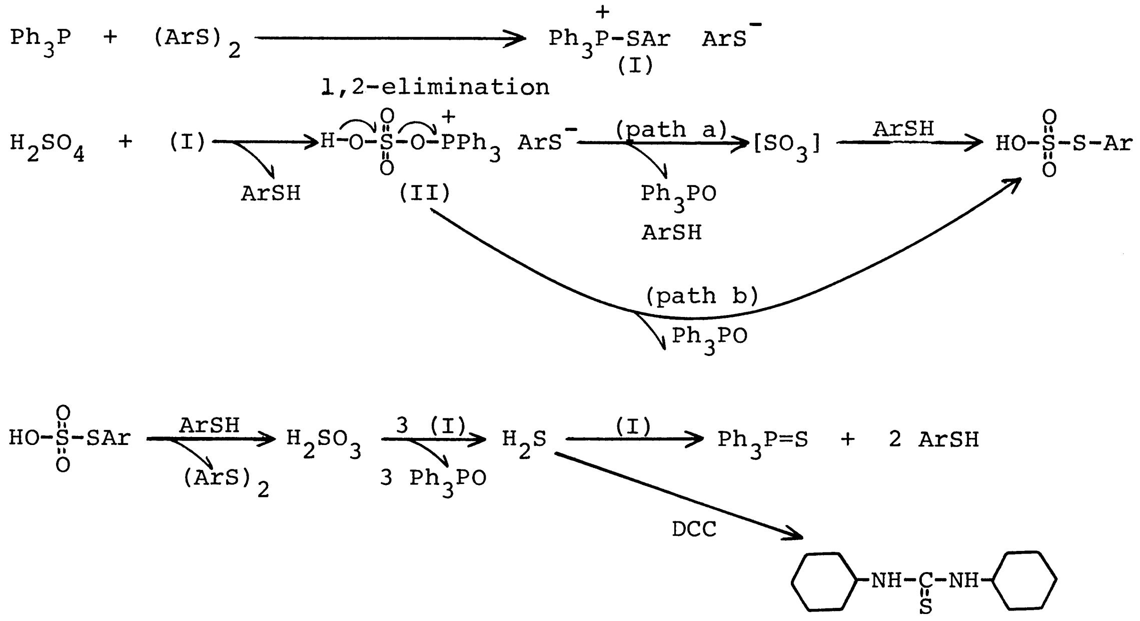
The biological reduction of sulfate to sulfide is consisted of the following two key steps, i.e. conversion of sulfate to the mixed anhydride, APS or PAPS, to activate sulfate to be ready for the subsequent second reaction, and the subsequent nucleophilic attack of protein-thiol on the sulfur atom of APS or PAPS to generate protein bound thiosulfate of which the sulfenyl sulfur can be easily displaced by other thiol group in the enzyme to give sulfite which is ultimately reduced to hydrogen sulfide, or of which the sulfo group is reduced by thiosulfate reductase to form R^1SS^- or R^2SS^- 1). This paper deals with a chemical model reaction for the assimilatory biological reduction of inorganic sulfate.

As arenesulfenyl group in arenesulfenyltriphenylphosphonium ion (I)[2] is known to be replaced easily by oxygen nucleophile[3], inorganic sulfate may react with (I), presumably forming an intermediate (II). Since the intermediate (II) has a P-O-S bonding as APS or PAPS does and bears a positive charge on the phosphorus atom, it should be a better source than APS or PAPS[4] to afford sulfur trioxide, which has been postulated as an active intermediate to react with thiols in the subsequent reducing step. Thus the intermediate (II), if formed, is expected to be reduced by the thiols in the same manner as APS or PAPS which is reduced by the thiol groups in APS- or PAPS-sulfotransferase. Indeed, inorganic sulfate is successfully reduced by this system to afford triphenylphosphine sulfide as the final product. As the control experiment revealed that hydrogen sulfide reacted with (I) to form triphenylphosphine sulfide and arenethiol, hydrogen sulfide once formed from inorganic sulfate is

$$H_2SO_4 + 5\ Ph_3P + X_2 \longrightarrow Ph_3P{=}S + 4\ Ph_3P{=}O + 2\ HX \quad \text{- - - - - 1)}$$

considered to be converted to triphenylphosphine sulfide upon encountering with (I) in our reducing system. In fact hydrogen sulfide can be isolated as dicyclohexylthiourea in the trapping experiment with dicyclohexylcarbodiimide (DCC) ;namely when nitrogen gas was bubbled into the reaction mixture and the exhausted gas was introduced into a benzene solution of DCC(0.99M), dicyclohexylthiourea was obtained, though in a low yield. Undoubtedly most of hydrogen sulfide is readily consumed in the facile reaction with compound (I).

Two paths (a and b) are conceivable for the reaction of (II) with thiols. While path b may be unfavorable due to the stereo-electronic repulsion between the nucleophile, i.e.arenethiolate anion and negative oxygen poles of bulky sulfate group of (II) at the transition state of the S_N2 reaction on the sulfur atom of (II),



path a would be quite likely since hydrogen bound to the oxygen atom of (II) is extremely acidic while the formation of triphenylphosphine oxide must be a big driving force. Thus the 1,2-elimination reaction of (II) to form arenethiol,sulfur trioxide and triphenylphosphine oxide (path a) should take place quite readily$^{4)}$. Sulfur trioxide thus formed may react with arenethiol to afford thiosulfate which is subsequently reduced with the thiol giving sulfite$^{5,6)}$. Sulfite ion is reduced further with this system to hydrogen sulfide. Meanwhile, Tagaki and Eiki$^{8)}$, and Benkovic and Hevey$^{7)}$ showed independently that nucleophilic substitution of phenylphosphosulfate(PPS), an APS or PAPS model compound, by OH^- proceeded sluggishly, however, hydrolysis of PPS easily took place in an acidic medium or in the presence of some metal ions in aprotic solvents$^{8)}$. These results also suggest an elimination-addition mechanism involving formation of sulfur trioxide in the facile acid- or metal-catalyzed reaction. In the light of all these observations, path a is more favorable than path b. In keeping with this conceivable mechanism, an introduction of electronegative substituent on aryl group in (I) increases the reactivity of (I), and electron-donating p-methyl substituent reduces its reactivity, while iodotriphenylphosphonium iodide which is prepared from triphenylphosphine and iodine appears to be a much stronger reducing agent of sulfate than (I). Thus the nucleophilic attack of inorganic sulfate on the phosphonium reagent (I) to generate (II) is considered to be involved in the rate-determining step of the reduction of sulfate in our system.

Table Reduction of Sulfuric Acid with $Ph_3\overset{+}{P}X\ X^-$ in Benzene a)

X_2	$(H_2SO_4)/Ph_3P/X_2$ (mmol)	Temp. °C	Time hr	product Yields b) (%) $Ph_3P=S$	H_2S c)	HX
$(p\text{-}ClC_6H_4S)_2$ d)	0/14.3/7	140	5	0	-	g)
" d)	2/14.3/7	"	4	77	-	90
" d)	2/14.3/7	"	10	99	-	92
" h),d)	3/11/9	reflux e)	7	7	trace	g)
$(C_6H_5S)_2$ d)	2/14.3/7	140	10	60	-	g)
$(p\text{-}CH_3C_6H_4S)_2$ d)	2/14.3/7	"	10	45	-	85
$(C_6H_5Se)_2$	2/14.3/7.8	135-137	13	79	-	90 f)
I_2	2/14.3/6.1	reflux	3	91	-	g)
" h)	3/15.8/8	r.t.	3	18	4	g)
" h)	"/"/"	40-45	3	89.4	2.5	g)
"	2 i)/14.3/6.1	reflux	4	61	-	g)

a) Sulfuric acid was dissolved in 6 ml of benzene. b) Yields were calculated based on sulfuric acid according to stoichiometry, as shown in the eq.1).
c) Hydrogen sulfide was isolated as dicyclohexylthiourea by treatment with dicyclohexylcarbodiimide. d) After this reaction, a mixture of 500mg of H_2O and 3 ml of dioxane were added and the miture was refluxed for 0.5h. e) p-Xylene was used as solvent. f) Isolated as diphenyl diselenide. g) Not determined.
h) 20 ml of benzene was used. i) $[(n\text{-}Bu)_3NH]_2^+\ SO_4^-$ as sulfate was used.

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