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FLAVIN CATALYZED REDUCTION OF DIARYL DISULFIDE WITH 1-BENZYL-1,4-DIHYDRONICOTINAMIDE

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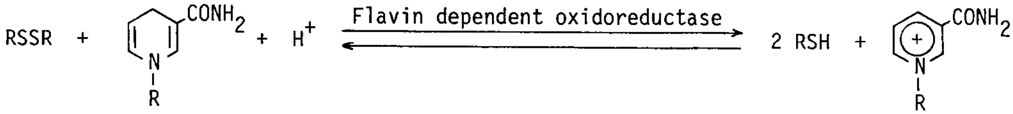
Summary : Diaryl disulfides were found to be reduced smoothly to the arenethiols by BNAH in the presence of a catalytic amount of 3-methyllumiflavin under mild conditions.

The redox reaction between thiol and disulfide is very important in living bodies.2)(eq.1) This reaction is promoted by emzymes, such as lipoamide dehydrogenase, glutathione reductase, thioredoxin reductase, which possess commonly FAD and cystine residue at their active sites.3)



(eq.1)

In the previous paper,4) we reported that diaryl disulfides can be reduced directly by 1-benzyl-1,4-dihydronicotinamide(BNAH), a model of NAD(P)H, at 80° in the dark or under irradiation with visible light through radical chain mechanism to give the corresponding arenethiols which react further with BNAH eventually affording the adducts(A). The mechanism of the reduction of flavins with thiols, *i.e.*, a part of the backward reaction of eq.1 has been extensively studied with biomimetic systems,5) however, the forward reaction has not yet been investigated. This communication will describe that a catalytic amount of 3-methyllumiflavin promotes smoothly the reduction of diaryl disulfide by BNAH under mild conditions.

When a diaryl disulfide was treated with four equivalents of BNAH in the presence of 0.5 mole% of 3-methyllumiflavin in a carefully degassed sealed tube at 40° in the dark, reduction of the disulfide was found to take place smoothly and the corresponding thiol was identified by HPLC analysis. The arenethiol formed as the primary product reacted further with BNAH eventually to give the adduct(A). The results are summarized in Table. Under the same conditions no reduction took place in the absence of flavin as catalyst. Electron defficient disulfides reacted faster in this system than electron rich ones, while dibenzyl disulfide, an aliphatic one, was not reduced at all.

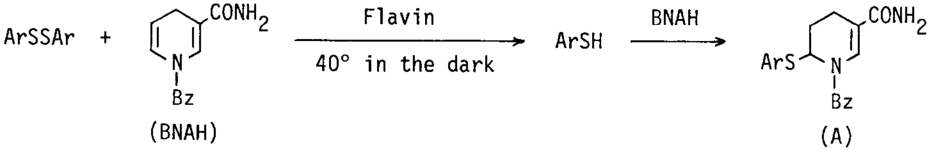
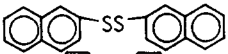
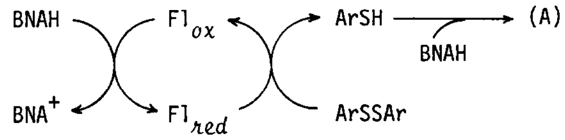


Table Reduction of disulfides with 3-methyllumiflavin/BNAH system at 40°

disulfide	solvent	time(hr)	adduct(mol/mol%)	recover(%)	
	EtOH	25	trace	98	without flavin
"	"	9	89	0	
"	$CHCl_3$	9	24	54	
	EtOH	18	82	5	
	"	24	41	48	
	"	24	51	38	
	"	24	28	43	
$PhCH_2SSCH_2Ph$	"	50	0.4a)	∿100	

a) α-Toluenethiol : This thiol does not react with BNAH giving the adduct under the condition.

Scheme



When the reduced form of 3-methyllumiflavin which was generated by photoreduction was allowed to react with bis(*p*-chlorophenyl)disulfide in argon atmosphere, the reduction of the disulfide took place affording *p*-chlorobenzenethiol and the flavin of oxidized form. Since flavin derivatives of oxidized form are well known6) to be reduced easily by 1,4-dihydropyridines to the corresponding flavin derivatives of reduced form, the flavin catalyzed reduction of diaryl disulfides with BNAH may proceed as shown in the Scheme. The results in Table show 3-methyllumiflavin turns the cycle of the reduction of bis(p-chlorophenyl)disulfide 180 times in the Scheme.

Thus flavin alone can catalyze the reduction of diaryl disulfides with dihydropyridine, however, is not an effective catalyst enough to reduce dialkyl disulfide, unlike the actual enzymes. Further investigation on the chemical models for pyridine nucleotide-disulfide oxidoreductases is now underway in this laboratory.

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