Tetrahedron Letters,Vol.23,No.31, pp 3189-3192,1982 0040-4039/82/313189-04$03.00/0
Printed in Great Britain

REDUCTION OF DIARYL DISULFIDES WITH 1-BENZYL-1,4-DIHYDRONICOTINAMIDE

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Summary : Reduction of diaryl disulfides with 1-benzyl-1,4-dihydronicotinamide (BNAH) proceeded through a radical chain reaction, while dialkyl disulfides were found to be inert to BNAH.

Thiols, such as glutathione, and redox enzymes whose active site possesses two cysteine residues in proximity, reduce phisiologically important substances in living organisms.[1] In this process the thiol group in these coenzymes and enzymes is converted to the corresponding oxidized disulfide which is then reduced back to the original thiol with NADPH by the aid of the corresponding disulfide reductases, such as glutathione reductase, thioredoxin reductase, *etc.*[2]

Earlier, Wang *et al.* reported, based on only the spectral change of the reaction mixture after one month at room temperature under nitrogen in the dark, that both diphenyl disulfide and lipoamide were successfully reduced to the corresponding thiols with BNAH, a model of NADPH, though they did not isolate the reduction products.[3] When we followed their experiment under the same conditions as Wang *et al.* applied, no reaction between diphenyl disulfide and BNAH was found to take place. However, the reduction of diaryl disulfides with BNAH was found to proceed nicely in a radical chain process, when the reaction was initiated by a certain radical initiator or irradiation with visible light. This letter deals with this reaction of diaryl disulfides with BNAH.

When a solution of *p,p'*-dichlorodiphenyl disulfide ($\underline{1}_a$, 0.20 mmole) and BNAH (1.00 mmole) was heated at 80°C in 2 ml of solvent in a degassed sealed tube, *p*-chlorobenzenethiol was found to be formed upon HPLC analysis at the initial stage of the reaction. After all the disulfide was consumed, 1-benzyl-6-(*p*-chlorophenylthio)-1,4,5,6-tetrahydronicotinamide ($\underline{2}_a$)[4] benzyl *p*-chlorophenyl sulfide and nicotinamide were isolated as the major products, however the thiol was not detected in the final product mixture. The initial step of the reaction between $\underline{1}_a$ and BNAH would involve an electron transfer and may be expressed by eq.1, forming the intermediate (BNA^+), which

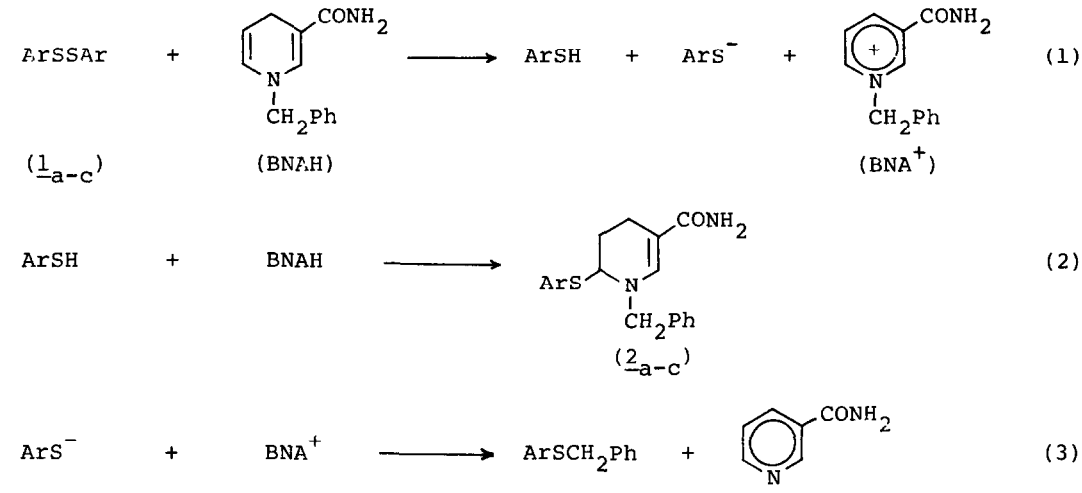
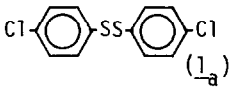


Table Reduction of disulfides with BNAH at 80°C in the dark

Disulfide (1)	Solvent	Time(hr)	Products(mole/mole%) (2)[a]	Sulfide[b]	Nicotinamide[a]
 (1a)	EtOH	12	130	61	56
(1a)	CH_3CN	12	85	72	85
(1a)	C_6H_6	12	37	d)	d)
(1a)	CH_2Cl_2	12	28	d)	d)
(1a)	CH_3CN	0.5[c]	90	d)	d)
(1a)	EtOH	12[e]	97	0	0
PhSSPh (1b)	EtOH	20	140	55	58
p-TolSSTol-*p* (1c)	EtOH	24	83	75	73
$PhCH_2SSCH_2Ph$ (1d)	EtOH	24	trace[f]	-	-

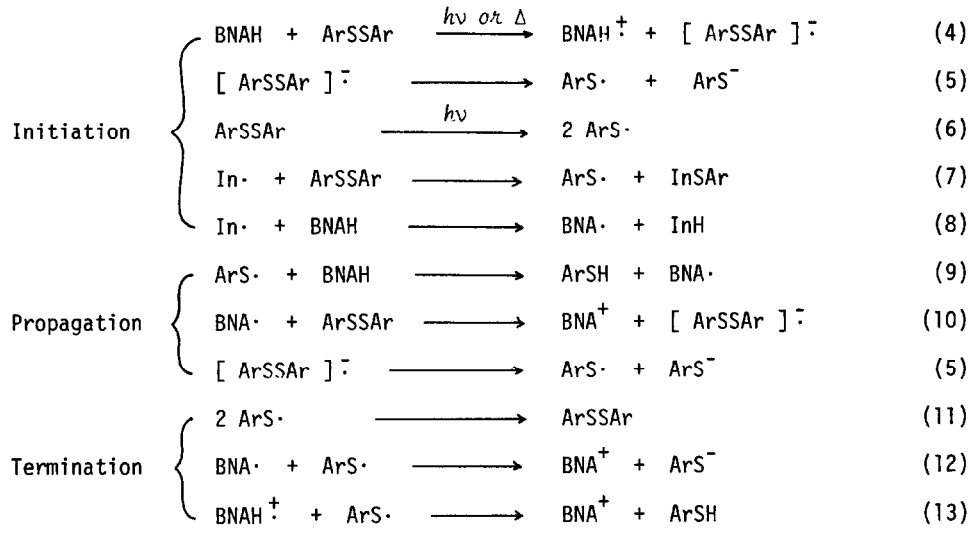
a) HPLC yield b) isolated yield c) AIBN (10 mole% of 1a) was added. d) not determined e) photochemical reaction at 18°C under irradiation with 150W W-lamp f) Starting material was recovered quantitatively.

then would be converted to the final products by the subsequent reactions as shown in eqs.2 and 3. Actually in separate control experiments, the reaction between the thiol and BNAH was found to proceed smoothly at room temperature in $CHCl_3$ affording the adduct, $\underline{2}_a$, quantitatively (eq.2), while the reaction of BNA^+ and *p*-chlorobenzenethiolate anion gave benzyl *p*-chlorophenyl sulfide and nicotinamide (eq.3) along with several unidentified minor products.

The reaction was found to be accelerated remarkably either by the addition of AIBN, a radical initiator, or by irradiation with visible light. The photochemical reduction of $\underline{1}_a$ with BNAH proceeded even at room temperature under irradiation with 150W W-lamp affording the adduct $\underline{2}_a$ and unidentified white crystals, and was found to be inhibited completely by addition of 10 mole% of galvinoxyl, a radical scavenger, in the reaction mixture of the disulfide. As soon as the color of galvinoxyl completely faded after 1 hr of irradiation, the reduction of $\underline{1}_a$ took place in the normal rate. The experimental results indicate that the reduction of $\underline{1}$ with BNAH proceeds through a radical chain process, as suggested for the reduction of alkyl nitro compounds,[5] and alkylmercury(II) acetates[6] with BNAH.

Meanwhile, both thermal and photochemical reduction of $\underline{1}_a$ with BNAH was found to increase with the increase of the polarity of the solvent: $CH_2Cl_2 < C_6H_6 < CH_3CN <$ EtOH, suggesting that the rate-limiting step of the reduction involves a polar transition state. Electron withdrawing substituents on diphenyl disulfide accelerated the reduction, while dialkyl disulfide such as $\underline{1}_d$ were found to be quite inert in this reduction. The lack of reactivity of aliphatic disulfide toward BNAH is undoubtedly due to its large bond dissociation energy. For example, the bond dissociation energy of $CH_3S\text{-}SCH_3$ is 74 kcal/mole, while that of PhS-SPh is known to be 55 kcal/mole.[7] These experimental results are nicely explained by the following scheme which involves a seris of free radical chain reactions. Photochemical reduction of $\underline{1}$ may be initiated by two processes, *i.e.*, 1) photochemical excitation of BNAH by visible light and subsequent electron transfer from the photoexcited BNAH to $\underline{1}$, followed by cleavage of the S-S bond of the disulfide anion radical[8] and 2) photochemical cleavage of the S-S linkage of $\underline{1}$.[9] Thermal reduction of the disulfide may involve an electron transfer from the ground state BNAH to the disulfide as Ohno *et al.* suggested in the reduction of ketones by NAD(P)H model compounds.[10] The radical initiator may start the reaction by either reaction 7 or 8. Since BNA· must be an excellent electron donor, the propagation step would involve the reactions shown by eqs.9, 10 and 5. The effect of the substituent will be reflected on the reaction shown by eq.10.

Scheme



In: radical initiator

Acknowledgement: This research was supported by Toray Science and Technology Prize and Grants, and Grant-in-Aid for Scientific Research B of Ministry of Education, Science and Culture which are gratefully acknowledged. We wish to thank Prof. A. Ohno for useful discussion.

References and Notes

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2) C. H. Williams., Jr, " The Enzymes ", Vol.13, ed by P. D. Boyer, Academic Press, New York, (1976).
3) C-H. Wang, S. M. Linnel, R. Rosenblum and N. Wang, Experientia, 27, 243(1971).
4) m.p. 90.5-91°C, decomp. 140°C, NMR ($CDCl_3$) : δ= 7.17-7.55 (10H, m. aromatic and =CH-CH), 5.32 (2H, s. NH_2), 4.44-4.60 (1H, br. CH), 4.34 (2H, ABq. J=14.4Hz, benzyl), 2.00-2.65 (4H, m. CH_2CH_2). IR (KBr) 3375, 3175, 3050, 2840, 1655, 1475, 1370, 1095 and 1010 cm^{-1} Anal. Found: C, 63.14; H, 5.33; N, 7.54%, Calcd for $C_{19}H_{19}N_2SOCl$: C, 63.58; H, 5.33; N, 7.80%.
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7) S. M. Benson, Chem. Rev., 78, 23(1978).
8) Disulfide anion radical is known to be formed as a meta-stable intermediate, e.g., glutathione disulfide anion radical has been observed spectrophotometrically in the pulse radiolysis of aqueous solution of the disulfide. M. Z. Hoffman and E. Hayon, J. Am. Chem. Soc., 94, 7950 (1972) and references cited therein.
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(Received in Japan 27 April 1982)