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# REDUCTION BY A MODEL OF NAD(P)H. XXIV. APPLICATION OF A PHASE-TRANSFER SYSTEM

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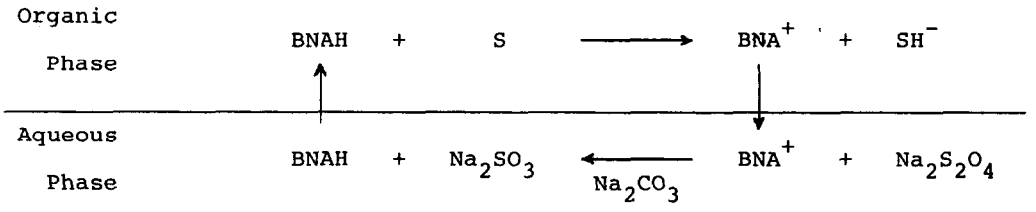
Bio-mimetic reductions with NAD(P)H-model compounds have been investigated extensively.[1] Some reports have devoted to bio-mimetic oxidations with $NAD(P)^+$-model compounds.[2] However, none has been concerned with the catalytic use of NAD(P)H-$NAD(P)^+$-model compounds. This is reasonable, because mimetic reductions and oxidations require completely different reaction condition.

The annoyance may be improved when a phase-transfer system is introduced to the redox reaction: 1-benzyl-1,4-dihydronicotinamide (BNAH) is soluble to various organic solvents but insoluble to water, while its oxidized form ($BNA^+$) is insoluble to organic solvent but soluble to water. Therefore, BNAH-$BNA^+$ species may transfer themselves through organic-inorganic surface.




It is interesting to point out that the oxidation and reduction of NAD(P)H-$NAD(P)^+$ in enzymic systems proceed at different sites of enzymes.[3]

We now wish to report the results from attempts for catalytic reduction of thiopivalophenone and one-step preparation of 4,4-dideuterio-1-benzyl-1,4-dihydronicotinamide (BNAH-4,4-$d_2$). A solution of thiopivalophenone (18 mg, 0.1 mmol) in 2 ml methylene chloride was mixed with a 5 ml aqueous solution containing

$BNA^+Cl^-$ (16.7 mg, 0.067 mmol), $Na_2S_2O_4$ (135 mg, 0.75 mmol), $Na_2CO_3$ (80 mg, 0.75 mmol), and trimethyl benzylammonium chloride (50 mg, 0.27 mmol) under an argon atmosphare in the dark, and allowed to react at a room temperature. After 2 days the color of thiopivalophenone disappeared completely. The organic portion was separated, washed with water, dried over sodium sulfate, and the solvent was evaporated *in vacuo* remaining 31 mg of oily product. The nmr spectrum of the product showed no signal except for those from BNAH and 1-phenyl-2,2-dimethyl-propanethiol. The molar ratio of these two compounds was calculated to be 1 : 1.7, which means that both BNAH and the thiol were produced quantitatively. A controlled experiment revealed that the thioketone was recovered quantitatively from the reaction mixtrue when the reaction was run without $BNA^+Cl^-$.

In another experiment with 0.2 mmol of thiopivalophenone, 0.04 mmol of $BNA^+Cl^-$, 0.78 mmol of $Na_2S_2O_4$, 0.75 mmol of $Na_2CO_3$, and 0.27 mmol of trimethyl benzylammonium chloride in a methylene chloride (3 ml)- water (5 ml) mixture, all the thioketone was reduced after 3 days remaining 63% (based on the added $BNA^+Cl^-$) of BNAH in the organic phase. Thus, $BNA^+Cl^-$ turned over more than 5 cycles in this system. Although higher (>10) cycles are possible, $SO_3^{--}$ anion is formed and accumulated in the mixture as the reaction proceeds, and this anion interferes the conversion of $BNA^+Cl^-$ to BNAH. Consequently, the reaction is decelerated extensively. Trimethyl benzylammonium chloride can be replaced by other substituted or unsubstituted ammonium halides. However, trimethyl benzylammonium chloride appeared to be the best among those we tried. The role of the ammonium salt is not known.[4]

The above result prompted us to apply the method for the preparation of BNAH-4,4-$d_2$. $BNA^+Cl^-$ (0.5 mmol) was allowed to react with $Na_2S_2O_4$ (1.2 mmol), $Na_2CO_3$ (1.5 mmol), trimethyl benzylammonium chloride (0.27 mmol), and thiopivalophenone (2 mmol) in a methylene chloride (7 ml)-$D_2O$ (99.8% D, 10 ml). After 2 days the aqueous layer was separated from the organic portion and the former was washed with methylene chloride (5 ml x 2). Into this aqeous solution $Na_2S_2O_4$ (1 mmol), $Na_2CO_3$ (1.2 mmol), and methylene chloride (10 ml) were added and the whole mixture was stirred for 1 hr. Then, the organic portion was separated from the aqueous layer, and the latter was washed with methylene chloride (10 ml).

The combined organic solution was washed with water (5 ml x 2) and the solvent was evaporated *in vacuo* remaining yellow solid. The solid was recrystallized from aqueous ethanol yielding BNAH-4,4-$d_2$ in a 90% yield.[5] The nmr spectrum of the product revealed that the deuterium-content on the 4-position was 92.5 ± 0.1%. With increased amounts of $Na_2S_2O_4$ (5 equivalent mol to $BNA^+Cl^-$), $Na_2CO_3$ (4.6 eq. mol), and thiopivalophenone (6 eq. mol), the deuterium-content in BNAH-4,4-$d_2$ was found to be 98.0 ± 0.05%, but the chemical yield decreased to 56%.

Several methods have been reported to prepare BNAH-4,4-$d_2$ or its analog.[6] All of these involves repeated reductions and oxidation of $BNA^+$ in $D_2O$ in order to obtain BNAH-4,4-$d_2$ with a deuterium content of more than 90%. The present method has great advantage over the other in saving both effort and time.

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