Tetrahedron Letters Vol. 22, pp 59 - 60 0040-4039/81/0101-0059$02.00/0

SYNTHESIS OF THE FIRST TRULY REACTIVE POLYMER-BOUND NADH MODELS

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Abstract : Improved reduction of benzaldehydes has been obtained with reactive polymer-bound NADH models

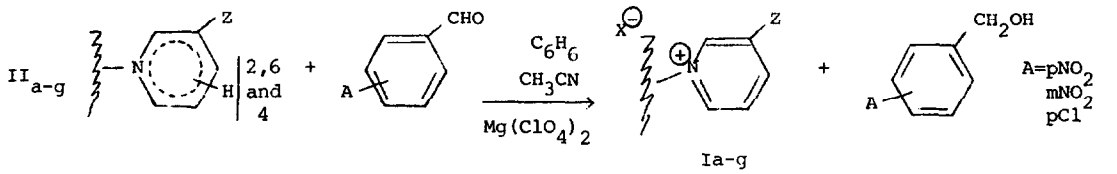
More than a hundred publications dealing with NADH model reactions are found in the litterature of the five last years. NADH model reactions have been studied up to now essentially in order to throw light on the biochemical mechanism. At the same time a growing number of organic functions have been proved to be reducible by dihydropyridines. Nevertheless, little effort has been made to obtain reactive pyridinium salts/dihydropyridines easy to use in organic synthesis. The major difficulties come from the separation of the reduction products which requires usually chromatographic techniques. We felt that this problem would be best solved if the NADH models could be immobilized on insoluble polymers.

Indeed, partially halogenomethylated copolymers of styrene and divinylbenzene reacted in acetonitrile with 3-substituted pyridines to produce polymer-bound NAD^+ analogues Ia-g.

Nicotinamide was quaternarized with polymers containing 0.61, 1.49 and 3.07 mmole/g chloromethyl functions, to yield polymers Ia containing respectively 0.39, 1.46 and 2.59 mmole/g pyridinium rings. Polymers Ib-g contained an average of 1.1 mmole/g pyridinium salts. Thus, it appears possible to immobilize all the pyridines used up to now in NAD models on our halogenomethylated copolymers.

Due to their hydrophobic features, polymers I were not easy to reduce by the usual dithionite method[1]. On the other hand, it is known that the borohydride reduction of NAD^+ gives a mixture[2] of the 1.2, 1.4 and 1.6 isomers of NADH which has only half of the activity of true NADH[3]. However $NaBH_4$ reduction of polymer Ia yielded a yellow polymer IIa which contained less than 0,5 % chlorine on microanalysis and showed to be a promising reducing reagent. All the other bound NAD^+ models could be readily reduced in the same way. They are presently under investigation and appear to be even more reactive than polymer IIa.

By reducing for 61 h in a sealed tube 1 mmole of m-nitrobenzaldehyde with 1g (1,3 mmole) of polymer IIa and 1,13 mmole of $Mg(ClO_4)_2$[4] in a 1/1 mixture of anhydrous acetonitrile and benzene, a 75 % yield of m-nitrobenzyl alcohol was obtained. (NMR determined after filtration and removal of the solvent). Ohnishi et al.[5], who had obtained the highest yields published for the reduction of substituted benzaldehydes by NADH models, reported for the same reduction by the corresponding "free" NADH model used in a 10-fold excess a yield as low as 29 %.



Ia-f : X = Cl ; Z = $CONR_1R_2$; Ia[6] amino, Ib dimethylamino, Ic diethylamino, Id pyrrolidino, Ie piperidino, If morpholino. Ig : X = I ; Z = morpholinosulfonyl.

Moreover, pure p and m-nitrobenzyl alcohol and p-chlorobenzyl alcohol were obtained easily by increasing the reaction time or the polymer/substrat ratio.

Thus the polymer-bound NADH models are effective reducing reagents. We plan of course to explore the various features of these systems, such as selectivity and stereoselectivity. Kinetic features of our system are also currently under study.

References and footnotes.

1) Quantitative dithionite reduction could be recently achieved. The first experiments show that the dithionite reduced polymers give slightly better reduction yields than the corresponding $NaBH_4$ reduced polymers. Dithionite reduction was achieved according to F.H. Westheimer et al. (J. Amer. Chem. Soc., 77, 2261 (1955)).

2) S. Chaykin, Ann. Rev. Biochem., 36, 149 (1967).

3) M.B. Mathews and E.E. Conn, J. Amer. Chem. Soc., 75, 5428 (1955).

4) No reduction occured without $Mg(ClO_4)_2$.

5) Y. Ohnishi and M. Kitami, Tetrahedron Letters, 4033 (1978).

6) A.S. Lindsey et al. (Polymer, 7, 479 (1966)), Y. Kurusu et al. (Kogyo Kagaku Zasshi, 71, 934 (1968)), S. Shinkai et al. (Bull. Chem. Soc. Jap., 1918 (1975)) and U.K. Pandit et al. (Rec. Trav. Chim. Pays-Bas, 96, 215 (1977)) synthesised analogous polymers but only dyes and some other highly reducible molecules were reduced with these polymers (after reduction of the latter). In any case the efficiency of the polymer-bound NADH model was lower than that of N-benzyl-1,4 dihydronicotinamide.

(Received in France 18 July 1980)