Reduction of a Thiol Ester by Dihydropyridine Derivatives. A Model Reaction of Glyceraldehyde-3-phosphate Dehydrogenase

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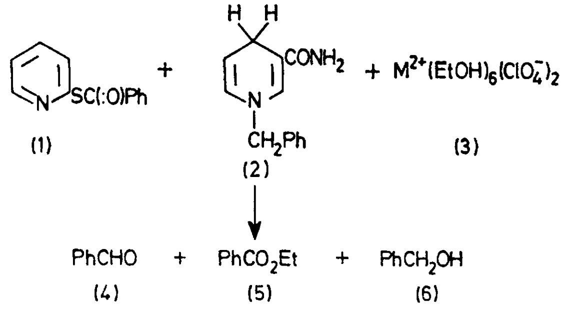
Summary 1,4-Dihydropyridine derivatives reduce *S*-(2-pyridyl) thiobenzoate in the presence of metal ethanolate complexes.

A NUMBER of dehydrogenases which catalyse the reduction of thiol esters utilize pyridine nucleotides for their catalytic, hydrogen-transfer, step. Recent *X*-ray crystallographic studies of glyceraldehyde-3-phosphate dehydrogenase[1] suggest that the imidazole group of the histidine (176) residue polarizes the carbonyl bond of the thiol ester and thereby facilitates the hydride transfer from the reduced pyridine coenzyme. Evidence has also been presented for the role of the zinc cation, as a Lewis acid, in the mechanism of horse-liver alcohol dehydrogenase.[2] This communication presents the first case of a metal-catalysed reduction of a thiol ester by a 1,4-dihydropyridine derivative (NADH-model).



A suitable thiol ester which would be expected to coordinate with metal salts is *S*-(2-pyridyl) thiobenzoate (**1**).[3] For the maintenance of anhydrous conditions and a rigorously defined stoicheiometry, metal salts such as $Mg(ClO_4)_2$ and $Zn(ClO_4)_2$ can be most effectively employed as their crystalline alcoholates. Reaction of the ester (**1**) with 1-benzyl-1,4-dihydronicotinamide (BNAH) (**2**), in the presence of the complexes $M^{2+}(EtOH)_6(ClO_4^-)_2$[4] was examined under diverse conditions. The results of typical experiments are summarized in the Table. The products of the reaction were separated by gas chromatography and identified by comparison (retention time; i.r. spectra) with authentic samples. The yields of (**4**), (**5**), and (**6**) were determined by quantitative comparison of chromatograms of the products with those of the corresponding synthetic mixtures. In one experiment (iii) the yield of benzaldehyde was further confirmed by conversion into its 2,4-dinitrophenylhydrazone. In experiments (i) and (iii), unchanged starting ester (20 and 10%, respectively) accounted for the material balance. Similar results were obtained when 3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine was employed as the reductant. No reduction products could be detected in the absence of the metal salts.

Table. Reduction of *S*-(2-pyridyl) thiobenzoate with 1-benzyl-1,4-dihydronicotinamide (BNAH)[a,b]

Expt.	M^{2+} in (**3**)	Solvent	Temp./ °C	Yield (%) (**4**)	(**5**)	(**6**)
(i)	Zn	MeCN	82	21	59	—
(ii)	Zn	MeCN	82	37	44·5	18·5
(iii)	Mg	Tetrahydrofuran	20	15	65	10

[a] Reactions were followed until BNAH had been consumed (t.l.c.). [b] A 10-fold excess of BNAH was used in experiment (ii).

The formation of benzaldehyde (**4**) is unequivocal evidence that the thiol ester is reduced by the dihydropyridine. Furthermore, it is also established that the metal cations serve as catalysts for the reduction. While the precise nature of the binary-complexes between the thiol ester and the metal alcoholates remains to be elucidated, it is suggested that the cation catalyses the hydrogen (presumably a hydride) transfer step, by simultaneous co-ordination with both the pyridine-nitrogen and the carbonyl-oxygen of (**1**). Whether the dihydropyridine reagent is also associated, with the aforementioned complex, to give a 'ternary'-system[5] which decomposes to the reduction products, is at the moment an open question. The formation of ethyl benzoate (**5**) can be readily explained on the basis of ligand-exchange between the metal alcoholates and the solvent and/or the dihydropyridine species, followed by a metal-catalysed transesterification. This is supported by comparison of experiments (i) and (ii). Utilization of a ten-fold excess of BNAH directs the reaction in favour of the reduction product (**4**), indicating that the dihydropyridine (BNAH) competes with ethanol in a nucleophilic attack upon the polarized ester carbonyl group. Particularly noteworthy is the observation that a significant quantity of benzyl alcohol (**6**) is formed under the conditions of the reaction in experiment (ii). Monitoring of the latter reaction showed that the chromatographic band for (**6**) increased with time as the amount of benzaldehyde decreased.

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