An Intramolecular NADH Model Containing an Activating Acidic Group

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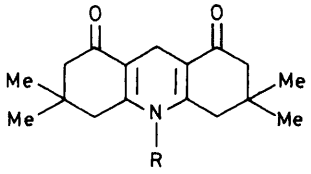
The acridan derivative (**1**) as a model for NADH reduces alcohols and imines without any external activation by acids whereas similar models such as (**2**) with equimolar amounts of acetic acid in neutral solvents did not effect any reduction; an analogy with similar reductions by oxidoreductases is demonstrated.

The catalytic sites in pyridine nucleotide-dependent oxidoreductases mostly possess[1] either a metal cation or an acidic group for substrate activation in addition to the coenzyme. Studies with NADH models have been carried out successfully[2] where the substrate is intramolecularly bound or complexed to the activating group, but attempts to bring together the 1,4-dihydropyridine moiety and the activating acidic groups have generally been unsuccesful.[3] Shinkai[4] reported the synthesis of an NADH model (**3**) stable to acidic media and also possessing a carboxylic group. Attempts to reduce electron-deficient carbonyl substrates such as hexachloroacetone or trifluoroacetophenone *via* intramolecular activation failed in aprotic solvents such as acetonitrile although in the presence of external acids such as acetic acid and triethylammonium chloride reduction was possible. Apparently, the carboxylic group as an intramolecular catalyst was not suitably placed in relation to the negative charge developing on the carbonyl oxygen in the transition state during hydrogen transfer. Also the carboxylic group at position 3 deactivates the dihydropyridine by acting as an electron-withdrawing group. We earlier reported[5] that the dihydropyridine moiety can be acid-stabilised by incorporating it into a tricyclic system where it still retained reducing properties, even in strongly acidic medium. We now report the synthesis and use of the NADH model (**1**)† bearing a carboxylic side chain which appears not only to be suitably positioned to donate a proton to the negative charge developing on carbonyl oxygen but also is separated from the dihydropyridine by two methylene groups. Unlike Shinkai's model (**3**) our model reduces substrates in acetonitrile in the absence of any external acid as efficiently as the corresponding model (**2**) would in the presence of a 10^3 molar excess of acetic acid.

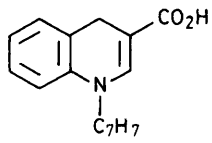
Compound (**1**) was easily prepared from bis-(4,4-dimethyl-2,6-dioxocyclohexyl)methane and β-alanine and had $\lambda_{max.}$ 376

† Satisfactory spectroscopic data and microanalyses were obtained for the compounds mentioned.



(1) R = $CH_2CH_2CO_2H$

(2) R = Me



(3)

nm characteristic of 1,4-dihydropyridine. Compound (**1**), when heated in refluxing dry acetonitrile with triphenylmethanol, gave a fairly good yield (80%) of triphenylmethane whereas the *N*-methyl analogue (**2**) of (**1**) when similarly treated in the presence of an equimolar amount of acetic acid gave only a trace. A kinetic investigation of this process revealed that whereas compound (**1**) alone showed an appreciable rate of reduction ($t_{\frac{1}{2}}$ 45 h) of triphenylmethanol in acetonitrile at 50 °C under pseudounimolecular conditions, compound (**2**) required a *ca.* 1.5×10^3 molar amount of acetic acid in addition in order to approach a similar rate with a pseudounimolecular concentration of substrate. With an equimolar concentration of acetic acid in acetonitrile at 50 °C, compound (**2**) did not show any change in its u.v. absorbance in the presence of excess of triphenylmethanol even after one week. Almost identical results were obtained for the reduction of 1,1-diphenylethene and *N*-benzylideneaniline. Thus, the carboxylic side chain appears to provide a highly effective acid concentration close to the reducing centre such that the alcohol gives rise to a cation-like intermediate close to the 1,4-dihydropyridine to be immediately reduced. A similar phenomenon of activation by acid and reduction of the imine bond is well established[6] in glutamate dehydrogenase, whereas in steroid biosynthesis, alkenes and alcohols are believed to be reduced by NADH in the same fashion. Investigations are in progress on the synthesis of similar models with functionalised side chains and their kinetic evaluation with different substrates.

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