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Antarafacial Hydride Transfer in a New Chiral NADH Model with C_2-Symmetry

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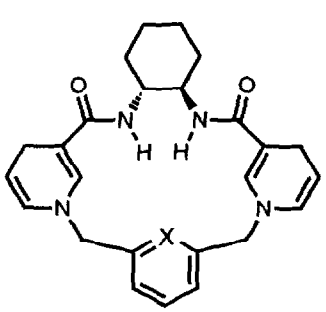
Abstract *A C_2-symmetric macrocyclic NAD$^+$/NADH-model, **1**, in which hydride transfer occurs in an antarafacial way, has been prepared. On reduction of methyl benzoylformate with **1**, methyl mandelate is formed in 95% ee.*

In the enzymatic reductions catalysed by dehydrogenases, the coenzyme NAD(P)H specifically transfers one of the two diastereotopic hydrogens at the 4-position in the dihydropyridine ring to the substrate. The reaction is usually regarded as a hydride transfer reaction but the detailed mechanism is still under debate and the function of metals as co-catalysts and other related questions are still unanswered.

A large number of model studies have been reported highlighting various aspects of the reaction. Our approach has been governed by the following considerations. The conformation and degree of puckering of the dihydropyridine ring must be considered in detail as recently has been done in calculations by Houk et al[1]. A boat-like conformation of the dihydropyridine ring with considerable pyramidalization of the ring nitrogen should facilitate coordination of metals, such as Mg^{2+} or Zn^{2+}, which are essential for the stereospecific reduction of carbonyl compounds. In almost all model systems reactivity of the pro-(R) and the pro-(S) hydrogens have been controlled[2] by using a remote sterically-demanding side chain or by incorporating a methyl substituent at the reaction centre. We would like to control the reactivity by a defined conformation of a chiral model compound.



1 X = C
2 X = N

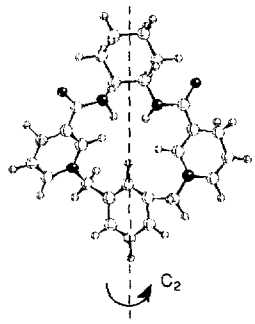


Fig.1 Assumed conformation of *1*

With the hope to contribute with solutions to some of the problems stated above, we have prepared and studied a simple NADH model consisting of two identical halves ***1***. The chirality derives from trans-1,2-diamino-cyclohexane and a phenyl-1,3-bismethylene unit is used as spacer and bridge between the two dihydropyridine nitrogens. Our model retains the simple structure of dihydronicotinamide (NAH), is chiral and, due to the C_2-symmetry element, the analysis of its reactions is simplified. The presence of two identical dihydro-nicotineamides at a close distance has further advantages. It should be possible to arrange the two dihydropyridine units in a C_2-symmetric ring system in such a way that only one of the two hydrogens in the 4-positions can become axial. Another advantage is that any interaction between the two units should affect the redox potential of the system and, thus, more reactive reagents could result as discussed below.

The model compound ***1*** was prepared[3] by treatment of nicotinic acid chloride with *trans*-1,2-diaminocyclohexane in pyridine followed by a ring forming reaction of the product with 1,3-bis(bromomethyl)benzene in DMF. This was then reduced with sodium dithionite/sodium carbonate in water to give ***1*** in a total yield of 40% after separation on Sephadex LH-20 with methanol as the eluant. The 1,3-bis(bromomethyl)benzene gave the best result. The corresponding ortho isomer gave mainly polymers and a cyclic dimer beside a small yield of the desired product. The para isomer gave mainly a cyclic dimer besides the desired isomer of ***1***. In order to facilitate the coordination of metal ions to the NADH-model we also prepared the isomer ***2*** with an extra pyridine nitrogen by using 2,6-bis(bromomethyl)pyridine in the ring forming reaction. Derivatives with three methyl groups on the bridging *meta*-substituted benzene ring was also prepared as well as a straight chain analogue of ***1*** by using 1,5-dibromopentane in the ring-forming reaction.

The structure of ***1*** follows from its mass and NMR-spectra[4]. The ^{1}H NMR-spectrum of ***1*** shows the average C_2-symmetry of the compound. No temperature dependence of the ^{1}H NMR spectrum was observed (-90- +90°C).

The interaction[5] (the electrostatic repulsion in the ox-ox form should be the most important one) between the two closely located pyridinium-dihydropyridine rings in our model compound should change the redox potential and equilibria.

$$red\text{-}red \;+\; ox\text{-}ox \rightleftharpoons 2\; red\text{-}ox$$

On standing in DMSO-d_6, a mixture of the red-red and ox-ox form of ***1*** slowly reacts to form an equilibrium mixture from which the equilibrium constant K was determined by integrating the appropiate ^{1}H NMR signals.

$$K = [red\text{-}ox]^2 / [red\text{-}red] \times [ox\text{-}ox] = 17$$

Reduction of ***1*** in the ox-ox form with sodium dithionite in D_2O at room temp led to a stereoselective deuterium incorporation of 72:28 (eq:ax) at the 4-position. The labeled product was then used for reduction of hexachloroacetone in CH_2Cl_2 with $Mg(ClO_4)_2$ to give yield the *ox-ox* form, now with 72% deuterium in the 4-positions. At lower temperature the reduction was less selective and di-deuterium incorporation was observed as a result of intra- or intermolecular hydride transfer. Apparently, the incoming hydride ends up preferably at the equatorial position and leaves exclusively from the axial position.

The selective transfer of only one of the two diastereotopic C-4 hydrogens is a prerequisite for asymmetric reduction of carbonyl compounds. Reduction of methyl benzoylformate with the R,R-form of *1*[6] in CH_2Cl_2 with $Mg(ClO_4)_2$ at -25 - +25°C gave the R-(-) methyl mandelate in an enantiomeric excess of 95% in 78% yield. The enantiomeric excess was determined both by specific rotation and via ^{1}H-NMR of Mosher Ester of the methyl mandelate as described by A.I. Meyers et al[7]. Reduction of the corresponding ethyl ester by *1* or its pyridine analog *2* also gave R-(-) ethyl mandelate but with slightly lower ee.

In order to understand the reduction reaction in detail, the reactive conformation must be known. Of particular interest is the orientation of the amide group relative to the dihydropyridine ring and the conformation of the dihydropyridine ring. The function and coordination site of the common cocatalysts, Mg^{2+} and Zn^{2+} has to be defined. Finally, different hypothetical geometries of the transition state complex could then be tested. The present experimental data is not sufficient for a conclusive discussion but a few reasonable assumptions will enable us to test the most common hypothesis on transition state geometry[2].

The reactive conformation of *1* (assumed to be the preferred conformer in solution) in the reduction of methyl benzoylformate to methyl mandelate can be deduced from ^{1}H NMR data. The shift and coupling constants of the protons on the carbon next to the amino group is best explained by the orientation of the amide group as shown in Fig.1. The orientation of the carbonyl group close to the reactive hydrogens is the normal one and should give a long wavelength UV absorption maximum close to the observed one (346 nm). The resulting conformation is not as compact as some alternative ones and the two dihydropyridine rings have one side only partially blocked. The CD-spectrum of the R,R-form of *1* show a distinct pair of bands centered at 350 nm (+ -). The exciton model applied to this pair and the conformation in Fig. 1 gives the correct order of signs for the two bands (+ -). However, the conformation in Fig. 1 is not the only one consistent with the observed CD-spectrum.

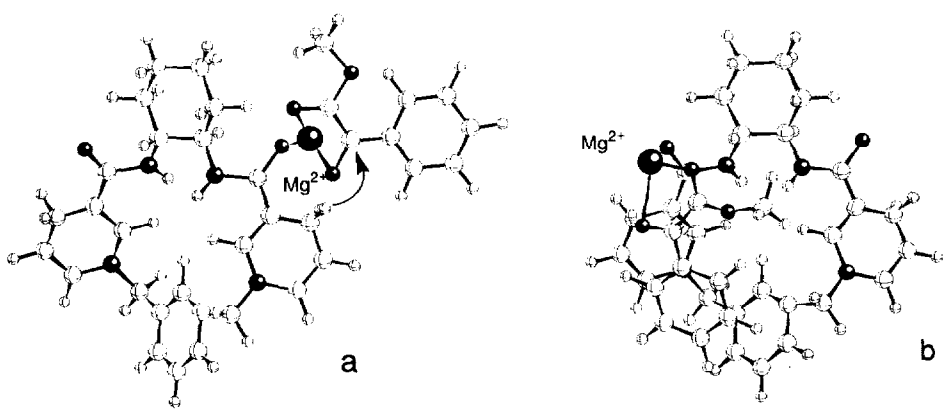


Fig 2. Possible T.S for the NAH *1* reduction of methyl benzoylformate.

We know that the reactive hydrogen specifically leaves from the opposite side to which it enters in the reaction with hexachloroacetone. From the chemical shifts and coupling constants of the protons in the dihydropyridine ring we can conclude that the dihydropyridine ring is slightly boat-shaped. The steric interactions between the phenyl group in the substrate and the cyclohexane ring in the reagent should favour the approach of the reacting species as shown in Fig. 2., where the metal ion coordinate to the all three carbonyl groups[2], as well as two other geometries of the transition state which can be omitted since they lead to the wrong enantiomer of the product. A final assumption that the reaction occur on the least hindered side of *1* would select the transition state Fig. 2a to be the more probable one. However, these results are based on a number of assumptions. Further work with this model should, however, allow for a clear distinction between the most reasonable T.S for the enantioselective NAH-reduction of carbonyl compounds.

Acknowledgements

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References and notes

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4. abs. mass 430.2366, calc. for $C_{26}H_{30}N_4O_2$ 430.2371; m/e 430 (58%), 325 (48%), 270 (31%), 241 (52%), 211 (76%), 202 (68%), 183 (73%), 175 (63%), 123 (37%), 106 (100%), 96 (73%).
UV (MeOH); 346 nm, $\varepsilon=9.10^3$
^{1}H-NMR (DMSO-d_6) *1*; 1.30 (m,2H), 1.56 (m,2H), 1.77 (m,4H), 2.94 (d of d, *J*=4 and 18Hz,2H), 3.17 (d of m, *J*=1, 3 and 18Hz,2H), 3.78 (m,2H), 4.32 (d,*J*=16Hz,2H), 4.56 (d, *J*=16Hz,2H), 4.69 (d of d of d, *J*=3,4 and 8Hz,2H), 5.91 (d of d, *J*=1 and 8Hz,2H), 6.37 (d, *J*=9Hz,2H), 7.02 (d, *J*=1Hz,2H), 7.22 (d of d, *J*=2 and 8Hz,2H), 7.34 s (1H), 7.38 (tr, *J*=8Hz,1H),
^{13}C-NMR ($CDCl_3$) *1*; 22.5, 25.4, 32.5, 54.0, 57.1, 100.4, 104.0, 123.8,126.4,128.9, 139.1, 139.5, 168.6,
^{1}H-NMR (DMSO-d_6) ox-ox form of *1*; 1.42 (m,2H), 1.77 (m,2H), 1.89 (d,2H), 2.03 (d,2H), 4.02 (m,2H), 6.04 (q,4H), 7.01 (s,1H), 7.66 (tr, *J*=8Hz,1H), 7.80 (d, *J*=8Hz,2H), 8.53 (d of d, *J*=6 and 8Hz,2H), 9.07 (d, *J*=8Hz,2H), 9.16 (d, *J*=8Hz,2H), 9.25 (s,2H), 9.60 (d, *J*=6Hz,2H).
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6. ee for (R,R)-**1** >98%. Enantiomeric purity determined by NMR spectroscopy using Eu(TFC)$_3$.
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