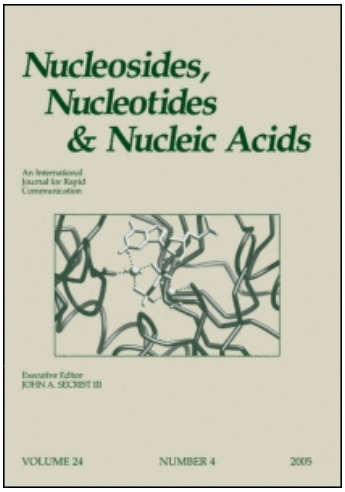

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Nicotinamide Adenine Dinucleotide a Unique Compound for Theoretical and Synthetic Model Studies: Chirality as Source for High Stereospecificity

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ABSTRACT

A dynamic model is given for the hydride transfer of the redox couple NAD^+-NADH with model systems and quantum chemical calculations.

Key Words: NADH-NAD^+ models; Hydride transfer; Site specificity; MO calculations.

It is well-known that nicotinamide adenine dinucleotide (NAD)-dependent dehydrogenases give reversible and stereo- and regioselective transfer of one of the C_4 hydrogens of the dihydronicotinamide moiety (NADH) to a hydride-accepting substrate under formation of NAD^+, the oxidized form of NADH. X-ray data obtained for stable complexes revealed that the amide carbonyl dipole is *syn*-orientated with respect to the transferring hydride. With NAD^+-DMSO-LADH resulting in C_4-H_R transfer (A-specificity) there is an out-of-plane orientation of the $CONH_2$ group of 30°, and in the case of NAD^+-GAPDH the C_4-H_S is transferred (B-specificity) with an out-of-plane orientation of 22°. Quantum chemical calculations and synthetic model systems show that the stereospecificity of hydride

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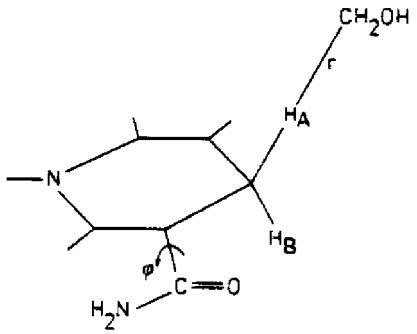
transfer (indeed) may be related to an out-of-plane orientation of the $CONH_2$ group in the transition state (TS). In a model suitable for calculations and strongly related to NADH-H_2COH^+ (protonated formaldehyde) with the $CONH_2$ group in a fixed out-of-plane conformation the H_R (H_A) and H_S (H_B) migrate to H_2COH^+ with very different rates. A low enthalpy TS corresponds to the carbonyl dipole of the $CONH_2$ group pointing to the hydride acceptor (*syn* orientation). If the carbonyl dipole points away from the acceptor (*anti* orientation) a high enthalpy TS is obtained.[1,2] Enantioselective C=O and C=N reductions in the presence of Mg^{2+} show that C_4-H_R and C_4-H_S hydride transfer is connected with *P*- and *M*-axial chirality (with respect to the orientation of the $CONH_2$ group) of the oxidized *R*- and *S*-3-(dimethylcarbamoyl)-1,2,4-trimethyl-1,4-dihydropyridine under formation of the *R*- and *S*-configuration of the reduced substrate. The axial chirality is accompanied with an optical yield of $\geq$95%.[3,4] Recently it has been found that the NADH model system 1,4,6,7-tetrahydro-1,6,11-trimethyl-5-oxo-5*H*-benzo[*c*]pyrido[2,3-*e*]-azepine which has been oxidized with a series of *p*-benzoquinone and derivatives in the presence of Mg^{2+} indeed shows a preference for *syn* hydride transfer. The model compound has an axial chirality with respect to the orientation of the carbonyl dipole. In the *absence* of Mg^{2+} the *anti* hydride transfer is favored.[5] Calculations have shown that the electrostatic interaction between the acceptor (H_2COH^+) and the $CONH_2$ group dominates in the interaction enthalpy. In the absence of H^+ (experimentally in the absence of Mg^{2+}) this favored interaction is absent and thus resulting in an electrostatic repulsion between the C=O dipoles of the $CONH_2$ group and H_2CO which leads to an *anti* hydride transfer. This process (*deprotonation* of H_2COH^+) may be of importance for the reverse reaction. Both processes for H_R^-(H_A^-) and H_S^-(H_B^-) transfer are illustrated for 3-carbamoyl-1,4-dihydro-pyridine to H_2COH^+ in dependence of the reaction coordinate indicated as the out-of-plane rotation of the $CONH_2$ group:



In the initial state ($\varphi = 0°$) the oxygen of the $CONH_2$ group is *syn*-orientated with respect to C_4. A rotation of 90° toward the hydride acceptor facilitates the H_A^- transfer and disfavors the H_B^- transfer. In the same process with H_2CO as acceptor thus in absence of H^+ activation of the acceptor rotation of 270° results in H_A^- transfer and thus disfavoring the H_B^- transfer. The calculations further show that the hydride transfer is effectuated by a C_4 trigonal pyramidal (TP) geometry. The axial C-H bond is 1.28 – 1.32Å which means an increase in bond length of about

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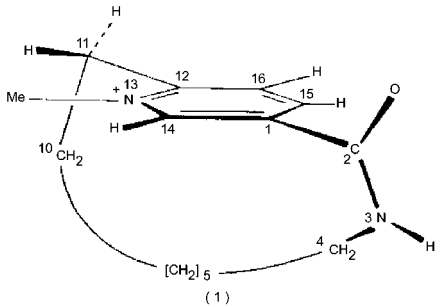
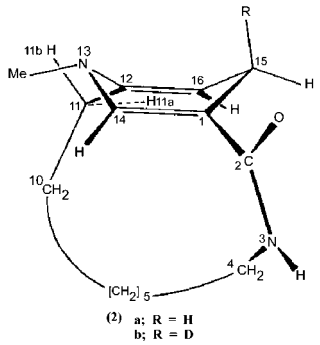
20% compared with the tetrahedral configuration which is in good correspondence with earlier ab initio calculations.[2,6,7] An essential property of a TP is the presence of intramolecular charge transfer.[6,8] The axial linkage accommodates the hydride transfer, making C_4 chiral, whereas the equatorial bonds are electron-donating. The biochemical relevance can be made now acceptable by the following course of the reaction. Energy lowering of the TP is delivered by the $CONH_2$ group in which the polar $C^{\delta+}$–$O^{\delta-}$ group with $O^{\delta-}$ shields the equatorial $H^{\delta+}$. Out-of-plane of $CONH_2$ promotes the hydride transfer by destabilizing the TP geometry. Counterclockwise rotation facilitates H_A^- transfer. Activation of the aldehyde by hydrogen bonding (or Zn^{2+} complexation) completes the process. The reverse process starts with hydrogen-bond breaking thereby stimulating hydride transfer to NAD^+. The parking of the hydride at C_4 and the storage of two electrons at the ring nitrogen may be effectuated by changing the planar geometry of pyridium into a boat conformation assisted by hydrogen-bond bridging with the ring nitrogen. In the overall enzymatic process this means a proton shift between at least two acid-base sites.



(1)



(2) a; R = H
b; R = D

The conversion of a planar geometry of pyridinium into a boat conformation has been demonstrated in the $H^-(D^-)$ reduction of 13-methyl-3-aza-13-azoniabicyclo[10.2.2]hexadeca-1(14),12,15-trien-2-one iodide(1) in the boat-shaped geometry in which the incorporated H(D) occupies almost exclusively (>95%) at C15 a *syn* position with respect to oxygen of the carbonyl group (2).[9]

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