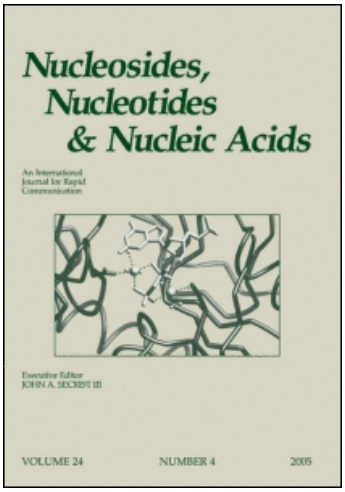

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THE ROLE OF THE CARBOXAMIDE GROUP IN NICOTINAMIDE ADENINE DINUCLEOTIDE IN RELATION TO HYDRIDE TRANSFER: THE REDUCED FORM OF THE DINUCLEOTIDE AS REMEDY IN THE MODULATION OF NEUROTRANSMISSION

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▫ *The stereochemical significance of the carboxamide group in combination with the ring nitrogen in NADH-NAD$^+$ conversions has been demonstrated. This has been shown in model systems as well as under enzymatic conditions. The role of the carboxamide group in selective regiospecific interactions has been discused for neurodegenerative diseases.*

INTRODUCTION

From our theoretical and experimental studies on model systems related to the redox coenzyme NAD$^+$-NADH it is well known that the stereo- and regiospecificity is related to an out-of-plane orientation of the carboxamide group. It was found that a low enthalpy transition state (TS) corresponds to the carbonyl dipole of the carboxamide group pointing to the hydride acceptor. If the carbonyl dipole points away from the acceptor a high enthalpy TS is obtained.[1,2]

A strong support for this description of the hydride transfer has been established by Miwa et al. with an accurate crystal structure of nicotinamide from X-ray and neutron diffraction measurements.[3] They found that the asymmetric electrostatic potential field observed above and below the pyridine-ring plane is related to the rotation of the carboxamide group with respect to the pyridine plane. The asymmetry of the potential at C_4 is consistent with the stereospecificity of the hydride transfer.

Although the various theoretical and experimental studies demonstrate the high stereo-and regiospecificity, it must be emphasized that under biological conditions an effective role of the hydrogen-bridging network is present. Apparently this well-organized arrangement gives sufficient room for the aforementioned dynamic description of the carboxamide group within a variety of acidic sites of the different

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enzymes. So it was recently suggested by us that hydride transfer to NAD^+, which results in parking of the hydride at C_4 *and* the storage of two π electrons at the ring nitrogen may be effectuated by changing the planar geometry of the pyridinium ring into a boat conformation *assisted by hydrogen-bond bridging with the ring nitrogen*.[2] Through "protonation" of NADH at the ring nitrogen a planar geometry cannot be maintained as a result of angle strain. This description is supported by our quantum-chemical calculations based on variation of the one-center core integral of the ring nitrogen thereby simulating the hydrogen bridging.[4] Experimental evidence was given by Beis et al.[5] with an X-ray structure of NADH under enzymatic conditions. Examination of the active site of the enzyme (dTDP-D-glucose 4,6-dehydratase) revealed that the phenolic oxygen atom of tyrosine (Tyr 161) is located directly above the nitrogen of the dihydropyridine ring. Therefore, they suggested that the tyrosine residue could be hydrogen bonded to nitrogen resulting in a boat conformation.

The boat conformation realized in this way will be supported by the principle of conservation of orbital symmetry. Using the LUMO (lowest unoccupied molecular orbital) of pyridinium as entrance for the reaction course, it is evident that the MO corresponding with one of the E_{2u} MOs of benzene determines the stereo-and regio specificity of the addition of the activated hydrogen molecule.

There are also other conditions in order to obtain a boat conformations. Such a condition has been previously published by us for 3-carbamoyl pyridinium compounds with a lipophilic intramolecular bridge.[6] The 3-carbamoyl pyridinium ion has a planar geometry. After hydride uptake at C_4 a boat conformation is obtained. In the reduced form the added hydrogen occupies exclusively an axial position. This finding is in excellent agreement with recent work of Luo and Bruice.[7] They found with molecular dynamic simulation of the hydride transfer from NADH to benzyl aldehyde by horse liver alcohol dehydrogenase that steric protection of the space of the *unreactive* side of NADH and the resultant anisotropic bending of NADH towards the substrate is responsible for the stereospecificity of the dehydrogenase. So there are different possibilities to generate a boat conformation with the exclusive axial hydride transfer. This specific behavior has been theoretically discussed by us in a study on hydride abstraction from cycloheptatriene and carbamoylcycloheptatriene.[8] The enthalpy of activation for endo-hydride transfer from cycloheptatriene was found to be 26 kJ mol^{-1} lower than for exo-hydride transfer. With the out-of-plane orientation of the carboxamide group the difference in activation enthalpy is 51 kJ mol^{-1} in favor of the endo-hydride transfer. Thus the out-of-plane orientation of the carboxamide group lowers the TS and thereby directs the stereospecificity of the hydride transfer.

The role of the hydrogen-bridging network is without any doubt the key factor in realizing the right conformation of NAD^+ and NADH for the regio- and stereospecificity of the hydride transfer. The effect of such a network includes also the pre-activated state of the carboxamide group resulting in C_4-H_R transfer (A-specificity) or in C_4-H_S transfer (B-specificity).[9]

In the absence of biochemical conditions the asymmetric induction introduced by the out-of-plane orientation of the carboxamide group can be chemically introduced in model systems as 3-(*N, N*-dialkylcarbamoyl)-1,2,4-trimethyl-pyridinium cations[10] that exhibit axial chiral stability for a disubstituted amide nitrogen (NR^1R^2) with R^1 trans to the carbonyl group: $R^1 = R^2 = Me$; $R^1 = Me$, $R^2 = CH(Me)Ph$; $R^1 = CH(Me)Ph$, $R^2 = Me$; and $R^1 = CH_2Ph$, $R^2 = Me$. However, for $R^1 = H$, $R^2 = i\text{-}Pr$; $R^1 = H$, $R^2 = CH(Me)Ph$; and $R^1 = H$, $R^2 = CMe_2Ph$ the axial stability is absent caused by the hydrogen ($R^1 = H$), which preferentially occupies the amide position trans relative to the carbonyl group, thus reducing the sterical interaction with the methyl substituents of the pyridinium ring.[11] The latter compounds with $R^1 = H$ are with respect to their carboxamide group closely related to the amino acid configuration in proteins.

Interestingly after hydride addition at C_4 of the model system with $R^1 = H$ and $R^2 = CH(Me)Ph$ an X-ray crystal structure shows a unique axial chirality combined with a high stereospecificity at C_4 in which the hydrogen is syn-orientated with respect to the carbonyl group.[12] This is an important characteristic of the consequence of the out-of-plane orientation of the CONH-group which is 65°, vide supra. The X-ray crystal structure also shows that the intermolecular distances are greater than 3.10 Å, except the distance between oxygen and nitrogen in adjacent molecules which is 2.96 Å. Parallel to the twofold screw axis there is a C–NH–O = C spine that links the molecules together. This distance corresponds with comparable interactions in bio-logical systems.

In the crystal structure the methyl at C_4 is anti-orientated with respect to the carbonyl group in consequence of *sterical* hindrance. The hydrogen at C_4 is then situated in a syn position toward the carbonyl group.

The significance of a carboxamide group has been also shown by the two essential amino acids asparagine and glutamine. Interestingly certain prion domains contain several repeats of a particular amino acid sequence along with either an asparagine-rich stretch or a tract that is rich in both asparagine and glutamine.[13,14] Misfolding of proteins results in neurodegenerative diseases. On a molecular basis the filaments are hydrogen bonded to each other. In our opinion these prion proteins show transmission via the carboxamide groups based on selective regio-specific interactions. This kind of interaction has been demonstrated by us in the X-ray crystal structure of the model system for NADH, vide supra. Therefore it is tempting to suggest that the lipophilic NADH may interfere with the network of hydrogen bridges of the misfolding protein via its carboxamide group. The use of NADH as therapeutic approach for improving neurodegenerative diseases has been demonstrated in various studies of Birkmayer et al.[15]

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