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PYRIDINE-DINUCLEOTIDE MODELS IV[1-3]; STEREOSELECTIVE HYDRIDE TRANSFER AT A BRIDGED PYRIDINIUM-ION

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Abstract: Two achiral bridged 1,4-dihydro-3,5-biscarboxamido pyridines are described. In one of these the bridging induces significant diastereotopy of the C-4 protons. This not only leads to magnetic anisochrony of these protons, but also allows for highly stereoselective (≥ 90%) substitution of one of them by deuterium via hydride exchange with a simple deuterated dihydropyridine.

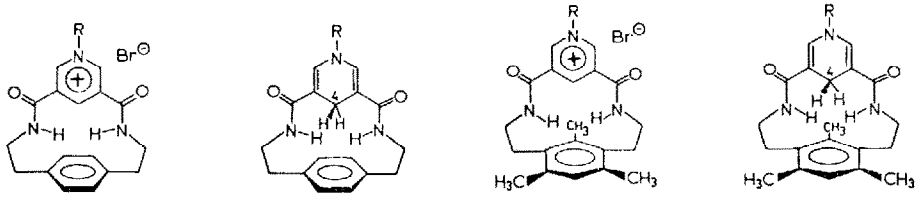
INTRODUCTION

The development of molecular systems matching enzymes in their efficiency and specificity of reaction, constitutes one of the main challenges in modern organic chemistry. The many studies[4] on hydride transfer mediated by 1,4-dihydropyridines -as related to the reactions catalyzed by pyridine nucleotide dependent dehydrogenases- epitomize such efforts and have revealed important catalytic factors[4,5] while also providing several chiral dihydropyridines[3,6,7] capable of (partly) asymmetric reduction of a limited number of prochiral substrates. However, none of the many pyridine-nucleotide models developed up till now has been shown to display the A/B-stereoselective hydride transfer at a single diastereotopic face of a pyridine ring, characteristic for the enzymatic reactions[8].

RESULTS AND DISCUSSION

Since we expected[9] bridging to provide an efficient tool to induce diastereotopy of the two faces of the pyridine ring, we synthesized the bridged dihydropyridines 1 and 2 and their precursors 1a and 2a via a modification of a method described by Dittmer et al.[10] for the preparation of related systems containing a polymethylene bridge. In 1 and 2 the bridge incorporates an aryl group which not only increases its rigidity but whose magnetic anisotropy is expected to facilitate conformational analysis by NMR spectroscopy.

The X-ray crystal structure analysis[11] of 1 (Fig. 1) suggests that the two C-4



1a 1 2a 2

R = Benzyl

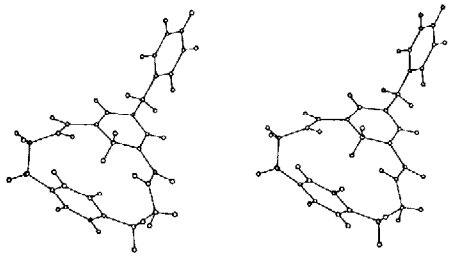


Fig. 1 Stereo drawing of 1.

protons reside in different magnetic environments, especially due to the pronounced boat shape of the dihydropyridine ring, a phenomenon that has also been observed for another bridged dihydropyridine[12].
The ^{1}H-NMR of 1 however shows complete isochrony of the C-4 protons in solution even at 360 MHz and -80°C ($CDCl_3$).
Apparently, rapid inversion of the dihydropyridine ring and a concomittant reorientation of the bridge occur in solution, leading to a time averaged conformation in which the dihydropyridine ring is oriented perpendicular to the bridging aryl group. This provides overall C_{2v} symmetry and thus removes the diastereotopy of the C-4 hydrogens. The isochrony observed for the aryl protons of the bridge as well as the four by four isochrony of the bridge methylene protons support this view.
In contrast the ^{1}H-NMR spectrum of 2 displays a well resolved AB-pattern for the C-4 protons (cf. Fig. 2) $^2J_{AB}$ = 14 Hz; $\Delta\delta_{AB}$ = 0.13 ppm ($CDCl_3$).

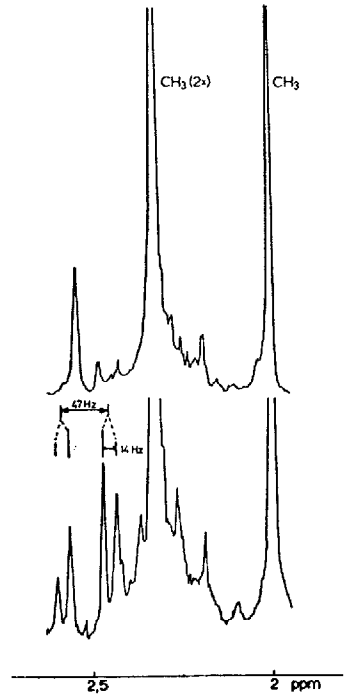
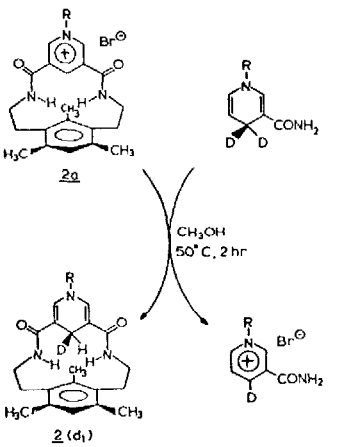


Fig. 2 Partial ^{1}H-NMR spectrum of 2 (lower trace) and of 2(d_1) (upper trace). Conditions: 360 MHz, 20°C in $CDCl_3$.

Of even more significance is the observation, that preparation of monodeuterated 2(d_1) via hydride exchange between 2a and 1-benzyl-1,4-dihydronicotinamide-(4,4-d_2)[13] leads to highly stereoselective (≥ 90%)[14] introduction of deuterium at the magnetically most shielded diastereotopic C-4 position (cf. Fig. 2) tentatively assigned to be the position closest to the center of the bridging aryl group (cf. Scheme 1)[15].



Scheme 1
Stereoselective hydride transfer from 1-benzyl-1,4-dihydronicotinamide(4,4-d_2) to 2a.

The conformational stability of 2 is testified by the finding, that storage of 2(d_1) in $CDCl_3$ solution at 60°C for periods of over 5 hrs does not lead to any detectable deuterium scrambling between the two C-4 positions.
Thus the couple 2a/2 constitutes the first example of a system capable of mimicing the A/B stereoselective hydride transfer properties displayed by the NAD/NADH couple[8] under enzymatic conditions.
Further studies on the nature of the factors governing the observed stereoselectivity and its dependence on the structure of the substrate are in progress.

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11. A.M. van Herk, A.R. Overbeek, K. Goubitz and C.H. Stam, to be published.
12. R.H. van der Veen, R.M. Kellogg and A. Vos, J. Chem. Soc., Chem. Commun. 923 (1978).
13. The deuterium content of 1-benzyl-1,4-dihydronicotinamide was determined by mass spectral analysis to be 96% (d_2).
14. As evident from Fig. 2 the high-field part of the AB-pattern disappears below the baseline upon deuteration while the low-field part collapses to give a slightly broadened singlet which shows a minor isotopic upfield shift. Integration of this singlet showed that it corresponds to 0.93 ± 0.03 protons.
15. Model studies, based on the X-ray structure of 1, indicate that this is the pseudo-axial position if the dihydropyridine ring adopts a boat shape Enhanced reactivity of the axial over the equatorial position has been postulated earlier (H.R. Levy and B. Vennesland, J. Biol. Chem. 228, 85 (1957)).

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