JOURNAL OF THE CHEMICAL SOCIETY

Chemical Communications

Number 15
1985

Regio- and Stereo-selective Hydride Uptake in Model Systems related to 3-Carbamoyl Pyridinium Compounds

Peter M. T. de Kok* and Henk M. Buck

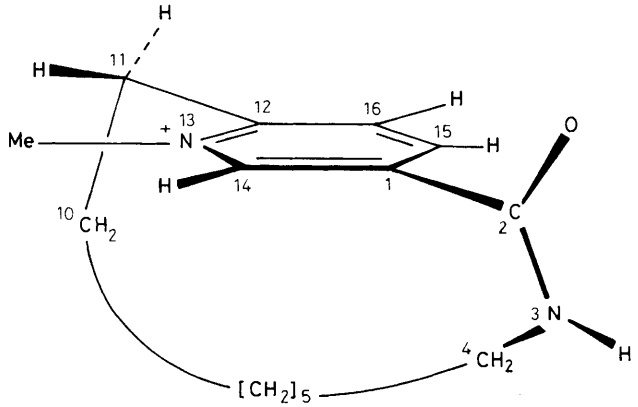
Department of Organic Chemistry, Eindhoven University of Technology, Eindhoven, The Netherlands

The hydride reduction of 13-methyl-3-aza-13-azonia-bicyclo[10.2.2]hexadeca-1(14),12,15-trien-2-one iodide with sodium dithionite in an aqueous solution of sodium hydrogen carbonate resulted in its boat-shaped 13,15-dihydro analogue in which the incorporated hydrogen occupies almost exclusively (>95%) an axial position.

In order to investigate stereo- and regio-selective hydride transfer by chiral 3-carbamoyl pyridinium compounds, whose chirality originates from an out-of-plane orientation of the amide group,[1,2] 13-methyl-3-aza-13-azonia-bicyclo[10.2.2]-hexadeca-1(14),12,15-trien-2-one iodide (**1**)[3,4] was synthesized which mimics the stereoselective transfer of hydrogen by NAD^+-dependent dehydrogenases in two essential ways (*vide infra*).[5]

The possible relationship between an enantiomerically pure 3-carbamoyl pyridinium cation and its stereo- and regio-selective hydride reduction, leading to the 1,4-dihydro compound was suggested by quantum chemical calculations.[2] The results show that when the amide group is fixed, which is most likely to be in an out-of-plane orientation, the two hydrogens at C-4 in the reduced form of the pyridine moiety may migrate to the substrate (hydride acceptor) with very different rates. It was found that a low-enthalpy transition state corresponds to the carbonyl dipole of the amide group pointing towards the hydride acceptor and a high-enthalpy transition state to the carbonyl dipole pointing away from the acceptor. It is the electrostatic interaction between the acceptor and the $CONH_2$ group which prevails in the interaction enthalpy.

This communication reports that (**1**) shows a high degree of stereo- and regio-selective preference for hydride addition at C-15.† The 300 MHz ^1H n.m.r. spectrum‡ shows that one of the protons of the methylene bridge has a negative chemical shift value (δ −0.97 to −1.17), resulting from the pyridinium ring current. This anisotropic shielding corresponds to an out-of-plane orientation of the bridge with respect to the pyridinium system. The introduced rigidity reduces the conformational motion of the pyridinium ring to such an extent that interconversion between the conformational enantiomers is virtually impossible[3] and orients the amide moiety



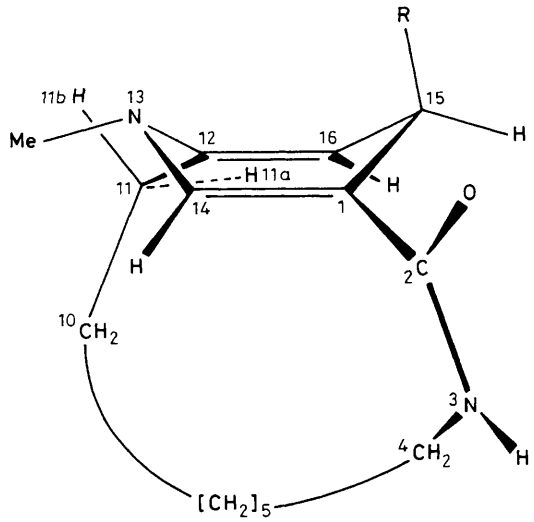
(**1**)

out of the pyridinium plane. The stereoselectivity of the hydride uptake in the reduction of (**1**) is elucidated by comparing the 300 MHz ^1H n.m.r. spectral data of the resulting 13-methyl-3,13-diaza-bicyclo[10.2.2]hexadeca-1(14),12(16)-dien-2-one (**2a**) with the data obtained from the corresponding deuterium analogue (**2b**).‡ These results lead to the conclusion that (**2**) adopts a boat conformation in which the incorporated hydrogen (deuterium) occupies almost exclusively (>95%) an axial position at C-15. The non-planarity is deduced from the coupling constants of 16-H. This hydrogen appears in the ^1H n.m.r. spectrum of (**2a**) as an eight-line pattern, owing to a vicinal coupling with 15-$H_{ax.}$ and 15-$H_{eq.}$, and an allylic coupling with 11a-H.§ This clearly indicates that the 15-H methylene protons are non-equivalent. Additional proof is obtained from the NCH_3 doublet, resulting from the coupling with 15-$H_{ax.}$.§ Absence of puckering of the dihydropyridine ring, however, would implicate a long-range coupling between the NCH_3 group and

† All reductions were carried out with sodium dithionite in a 1 M aqueous solution of sodium hydrogen carbonate.

‡ ^1H N.m.r. data were obtained on a Bruker CXP 300 spectrometer with Me_4Si (δ 0.0) as an internal standard. The n.m.r. spectrum of (**1**) was recorded in CD_3OD, the spectra of (**2a**) and (**2b**) in $CDCl_3$.

§ Coupling constants (in Hz) for (**2a**): J(16-H–15-$H_{ax.}$) 1.7, J(16-H–15-$H_{eq.}$) 6.8, J(16-H–11a-H) 1.1, J(15-$H_{ax.}$–15-$H_{eq.}$) 17.5, J(NCH_3–15-$H_{ax.}$) 0.8.



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

both 15-H methylene protons.[6] Reduction of (**1**) in D_2O,† leads to (**2b**). The lack of coupling between 15-$H_{ax.}$ and NCH_3, 14-H, and 16-H, clearly indicates the axial position of the deuteride. In addition, Dreiding models unambiguously show that the carbonyl group is rotated out of the plane through C-1, C-12, C-14, and C-16 which results in the fact that the incorporated hydride is *syn*-positioned with respect to the carbonyl group. The observed stereoselectivity in the hydride uptake will originate from the two major features of this system, *i.e.* the out-of-plane orientation of the amide group with the carbonyl group *syn*-positioned with respect to the incoming hydrogen donor[1,2] and the shielding effect of the methylene bridge which prevents equatorial attack for steric reasons.[7] In these two aspects, this model system is in good agreement with recent crystallographic 3D-data obtained for the ternary complex of NAD^+ bonded horse liver alcohol dehydrogenase (A specificity) obtained by Eklund *et al.*[5] The results show that the amide group (hydrogen bonded to specific sites on the dehydrogenase) is 30° out of the plane, with the carbonyl group directed towards the A-side and shielding the B-side perfectly.

This work was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

Received, 3rd January 1985; Com. 028

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