

2(S),5(S)-BIS(HYDROXYMETHYL)-3(R),4(R)-DIHYDROXYPYRROLIDINE.

OBTENTION, SYMMETRY AND LIQUID STATE CONFORMATION

Marie-Thérèse Martin and Christophe Morin*

Laboratoire de Chimie Appliquée aux Corps Organisés

Muséum National d'Histoire Naturelle

63, rue de Buffon, 75231 Paris Cedex 05, France

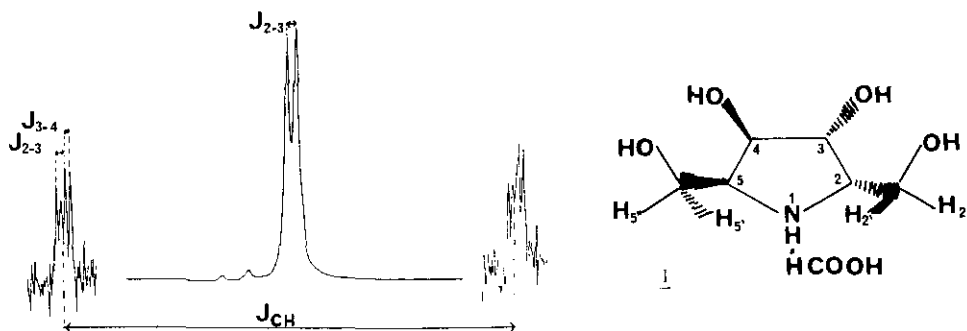
Abstract - A chiral polyhydroxylated pyrrolidine bearing a C_2 -axis of symmetry has been obtained. Full 1H nmr assignments could be made allowing determination of 4_3T as the liquid state conformation.

Optically active hydroxylated pyrrolidines are of current interest as chiral inducers^{1,2} or glycosidase inhibitors³⁻⁹. The recent announcement by two teams^{10,11} of the synthesis of an isomer of the title compound prompts us to disclose hereby our results in that area.

It had been shown earlier that a tricyclic pyrrolidine could be obtained in four steps¹² from a bis-acetal of D-glucitol¹³. It was then realized that removal (formic acid-90°C-150 min) of both acetals would lead to a symmetry-bearing chiral polyhydroxylated pyrrolidine, namely **1**, which was isolated in 97% yield as its formate salt: m.p. 114°C (softens), 145°C (fully melts); $[\alpha]_D = -10.1^\circ$ ($c = 0.64$, H_2O).

Although the synthetic design from D-glucosamine^{12,13} secures a built-in symmetry, a detailed nmr work was undertaken to shed light in particular on the conformational features of **1**. A C_2 -axis of symmetry (on the time-averaged nmr scale) was quickly revealed by the off-resonance 20 MHz ^{13}C spectrum which showed only three types of carbon [D_2O , δ ppm: 74.9 (C_3, C_4), 65.0 (C_2, C_5), 57.5 (CH_2OD)]. The symmetry was confirmed by observation of a single resonance for H_3 and H_4 , and a single coupling (with neighbouring H_2 and H_5) in the 1H nmr spectrum. So as to get the lacking J_{3-4} , an analysis of ^{13}C satellites was carried out: the $H_3-^{12}C-^{13}C-H_4$ array leads to non-equivalence of H_3 and H_4 which allows direct observation (Fig.1) of J_{3-4} . Thus a complete set of values (δ , J) for all protons of **1** was obtained (see Table 1), using PANIC (Program for Iterative Simulation, Bruker Software) to solve the ABCX system.

 Table 1 δ ppm H_2 & H_5 : 3.94 ; H_3 & H_4 : 4.32 ; H_2' & H_5' : 3.87 ; H_2'' & H_5'' : 3.97

 J Hz $J_{2-2'} = J_{5-5'} = 8.8$; $J_{2-2''} = J_{5-5''} = 5.0$; $J_{2-3} = J_{4-5} = 2.9$; $J_{2'-2''} = J_{5'-5''} = -12.4$; $J_{3-4} = 1.7$

 Figure 1 - ^{13}C satellite bands observed for H_3 and H_4

There is a key point of interest: when compared with literature values^{3,4}, J_{3-4} is unexpectedly low. This discrepancy has to be explained as this might reflect a conformational effect. In fact, theoretical calculations in proline series clearly demonstrated that substituent effects on the coupling constants were mainly due to their action on conformation¹⁵. This was exemplified in 4-hydroxyproline and furthermore with cyclo-(Pro)₃ in which differing geometries for each pyrrolidine ring were reduced thus yielding two ranges (1-3 and 8-11 Hz) for J_{3-4} coupling constants¹⁶⁻¹⁸; these ranges were thus reflective of individual ring geometries.

Now if calculations, using the cyclo-(Pro)₃-tailored Karplus equation¹⁶, are made for 1 a $85 \pm 7.5^\circ$ value is found for the $H_3C_3-C_4H_4$ dihedral angle. Among all existing 5-membered ring conformations obtained with the pseudorotation concept¹⁸, only four of them incorporate the desired symmetry: ^NE and ⁴T (and their mirror images). The former is excluded as this would yield a much higher coupling constant^{3,4}.

Therefore, ⁴T (or ³T, its mirror image) is retained as the solution conformer for 1.

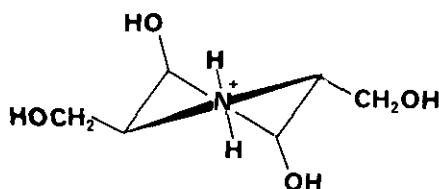
Full assay of the biological activity should allow to know whether this is of significance^{8,14}.

ACKNOWLEDGMENTS

Drs C.Convert and D.Davoust (Université P.et M. Curie) are thanked for 500 MHz experiments.

REFERENCES AND NOTES

1. J.K.Whitecell and S.W.Felman, *J.Org.Chem.*, 1977, 42, 1663.
2. Y.Ito, T.Katsuki, and M.Yamaguchi, *Tetrahedron Lett.*, 1985, 26, 4643.
3. A.Welter, J.Jadot, G.Dardenne, M.Marlier, and J.Casimir, *Phytochemistry*, 1976, 15, 747.
4. R.Nash, E.A.Bell, G.W.J.Fleet, R.H.Jones, and J.M.Williams, *J.Chem.Soc., Chem.Comm.*, 1985, 738.
5. D.W.Jones, R.J.Nash, E.A.Bell, and J.M.Williams, *Tetrahedron Lett.*, 1985, 26, 3125.
6. P.DeShong, D.R.Sidler, D.A.Kell, and N.N.Aronson Jr., *Tetrahedron Lett.*, 1985, 26, 3747.
7. G.W.J.Fleet, S.J.Nicholas, P.W.Smith, S.V.Evans, L.E.Fellows, and R.J.Nash, *Tetrahedron Lett.*, 1985, 26, 3127.
8. G.W.J.Fleet, *Tetrahedron Lett.*, 1985, 26, 5073.
9. C.J.Rule, B.A.Wurzburg, and G.Ganem, *Tetrahedron Lett.*, 1985, 26, 5379.
10. P.J.Card and D.W.Hitz, *J.Org.Chem.*, 1985, 50, 891.
11. G.W.J.Fleet and P.W.Smith, *Tetrahedron Lett.*, 1985, 26, 1469.
12. C.Morin, *Tetrahedron Lett.*, 1984, 25, 3205.
13. C.Morin, *Carbohydr.Res.*, 1984, 128, 345.
14. Preliminary results (M.Baran-Marszak and R.Labia) indicated that 1 was inhibitor of Jack bean α -mannosidase (50% inhibition at $6.7 \cdot 10^{-6} M$).
15. F.A.A.M. de Leeuw, A.A.Van Beuzekom, and C.Altona, *J.Comput.Chem.*, 1983, 4, 433.
16. H.Kessler, A.Friedrich, and W.E.Hull, *J.Org.Chem.*, 1981, 46, 3892.
17. H.Kessler, W.Bermel, A.Friedrich, G.Krack, and W.E.Hull, *J.Am.Chem.Soc.*, 1982, 104, 6297.
18. C.Altona and M.Sundaralingam, *J.Am.Chem.Soc.*, 1972, 94, 8205.



⁴T conformation of 1

Received, 2nd December, 1985