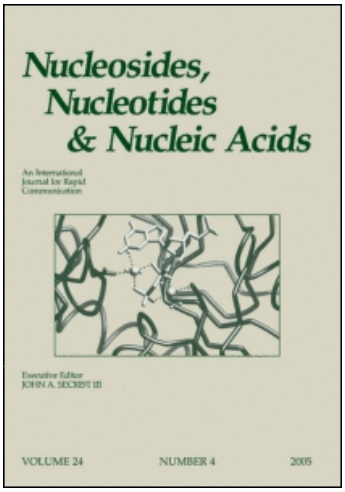

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Conformationally Restricted 2-Substituted Wyosine Derivatives. ^{1}H, ^{13}C, and ^{15}N NMR Study

Daniel Baranowski[a]; Bozenna Golankiewicz[a]; Janez Plavec[b]
[a] Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznan, Poland [b] NMR Centre, National Institute of Chemistry, Ljubljana, Slovenia

Online publication date: 09 August 2003

To cite this Article Baranowski, Daniel , Golankiewicz, Bozenna and Plavec, Janez(2003) 'Conformationally Restricted 2-Substituted Wyosine Derivatives. ^{1}H, ^{13}C, and ^{15}N NMR Study', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 1669 — 1672
To link to this Article: DOI: 10.1081/NCN-120023109
URL: http://dx.doi.org/10.1081/NCN-120023109

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 1669–1672, 2003

Conformationally Restricted 2-Substituted Wyosine Derivatives. ^{1}H, ^{13}C, and ^{15}N NMR Study

Daniel Baranowski,[1,*] Bozenna Golankiewicz,[1] and Janez Plavec[2]

[1]Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznan, Poland
[2]NMR Centre, National Institute of Chemistry, Ljubljana, Slovenia

ABSTRACT

It was found by ^{1}H, ^{13}C and ^{15}N NMR study that substitution of 4,9-dihydro-4, 6-dimethyl-9-oxo-3-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl) imidazo [1,2-*a*]purine (wyosine triacetate, **1**) at C2 position with electronegative groups CH_3O and $C_6H_5CH_2O$ results in a noticeable electron distribution disturbance in the "left-hand" imidazole ring and a significant increase in the North conformer population of the sugar moiety.

Key Words: Wyosine derivatives; Restricted conformation ^{1}H, ^{13}C, ^{15}N NMR study; North conformation preference.

From numerous X-ray and NMR studies of the nucleoside/nucleotide structure it is well established that the sugar moieties can adopt two distinctly different conformations: *North* (C3′-*endo*-C2′-*exo*) and *South* (C2′-*endo*-C3′-*exo*) being dynamically interconverting in solution.[1–8] Sugar or base modifications of nucleoside/nucleotide structure may influence both conformational preferences and thermodynamic equilibria in solution. The most important, interdependent conformational

*Correspondence: Daniel Baranowski, Polish Academy of Sciences, Institute of Bioorganic Chemistry, ul. Noskowskiego 12/14, Poznan PL-61-704, Poland; Fax: +48 61 852 0532.

DOI: 10.1081/NCN-120023109
1525-7770 (Print); 1532-2335 (Online)

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

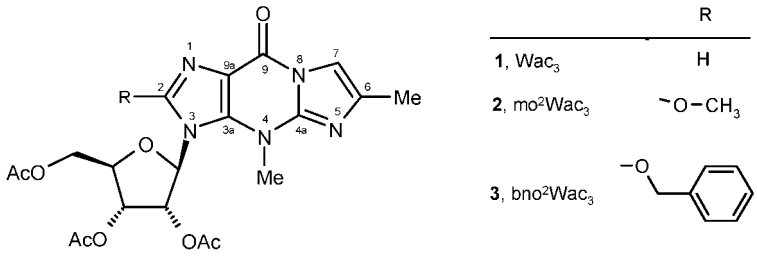

Figure 1.

parameters are sugar pucker and the torsional angles around the glycosylic and C4′-C5′ bonds.[3–5]

Here we report the results of a detailed ^{1}H, ^{13}C and ^{15}N NMR study of 4,9-dihydro-4,6-dimethyl-9-oxo-3-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)imidazo[1,2-a]purine (wyosine triacetate, **1**) and its new congeners bearing methoxy (**2**) or benzyloxy (**3**) substituent at C2 position of tricyclic base moiety. (Fig. 1)

Our previous studies on the parent compound wyosine indicated very high preference for *anti* conformer around glycosylic bond and near 1 : 1 ratio of N ⇔ S equilibrium.[9,10] It seemed of interest to investigate the conformational arrangements resulting from introduction of bulky electronegative substituent into C2 position, analogous to C8 in guanosine. Substitution at the latter enforces *syn* conformation.

RESULTS

Analysis of chemical shifts in **1**–**3** shows that the introduction of electronegative substituent at C2 of imidazo[1,2-a]purine nucleobase significantly decreases aromatic character of the ''left-hand'' imidazole ring. The largest downfield ^{13}C chemical shift change of 16.6 ppm in **2** and **3** (150.1 ppm each) relative to **1** (133.5 ppm) is observed at C2 of the nucleobase. The decrease of electron density at C2 is compensated with upfield shift of C9a by Δδ of 17.5 and 6.5 ppm in **2** and **3**, respectively (from 117.1 to 99.6 or 110.6 ppm). Smaller shielding effects are observed at C3a and C9. The decrease of the aromatic character in the ''left-hand'' imidazole ring is also manifested by upfield chemical shifts of N1 by the value of $\Delta\delta = 147.3$ ppm in **2** and N3 in **2** and **3** (Δδ: 25.6 ppm and 22.1 ppm respectively) with respect to **1**. The significant upfield ^{15}N chemical shift changes suggest the reduction of the double bond character between C2 and N1 and a change in the nitrogen N1 character from a pyridine-like to amine-like nitrogen.

North ⇔ *South* thermodynamic equlibrium in solution ($CDCl_3$) of **2** and **3** is significantly biased towards *North* sugar pucker type compared with parent compound **1**, where S-type conformer is preferred. Pairwise comparison of the %N population in **1** and C2 substituted derivatives **2** and **3** shows that modified **1** congeners exhibit a considerably higher contribution of N-type conformer in N⇔S equilibrium by 51 and 46% respectively. The high preference for N-type conformers of **2** and **3** is stabilized by positive free energy (ΔG°) value of 4.7 and

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

3.7 kJ·mol^{-1}, whereas for **1**, ΔG° value is -1.4 kJ·mol^{-1} which denotes stabilization of S-type sugar.

Pseudorotational analyses of **1**–**3** based on $^{3}J_{HH}$ measured in a wide range of temperatures from 223 to 318 K ($CDCl_3$) have revealed that sugar moiety in **2** and **3** adopts conformations in a narrow range between C3′-endo-C4′-exo and C4′-endo but in **1** sugar moiety pucker is grouped within the C2′-endo-C3′-exo range. An increase of medium polarity by change of solvent from $CDCl_3$ to DMSO-d_6 causes increase of %N conformer population by 24% for **1**, 10 and 16% for **2** and **3**.

Conformation around glycosylic bond (C1′-N3) in **1**–**3** is constrained to *anti* which has been proved by two independent methods: 1 D difference NOE experiments and three bonds couplings $^{3}J_{H1'C2}$ and $^{3}J_{H1'C3a}$ measurements. In all compounds the NOE enhancements at H1′ upon saturation of $N4CH_3$ were very high suggesting near distance of H1′-$N4CH_3$ and *anti* or high *anti* orientation with regard to the sugar ring. Additionally, **1** exhibits higher NOE enhancements at H2′ and H3′ compared to H1′ upon saturation of H2 which confirms *anti* or high *anti* orientation about glycosyl bond and is in agreement with the previously published results. Combined use of three bonds couplings $^{3}J_{H1'C2}$ and $^{3}J_{H1'C3a}$ is another way of determination of conformational preferences around glycosylic bond based on the Karplus-derived equation. If $^{3}J_{H1'C2} > {}^{3}J_{H1'C3a}$ then conformation is *anti*.

CONCLUSION

The electron distribution disturbance in the ''left-hand'' imidazole ring upon introduction of oxygen at C2 of nucleobase has a great influence on the *North* $\Leftrightarrow$ *South* thermodynamic equlibrium in solution ($CDCl_3$). Lack of essential differences in the conformational preferences between 2-methoxy and much more bulky 2-benzyloxy C2 substituted derivatives may let us assume that steric interaction between sugar moiety and C2 substituent does not play an important role in shaping sugar conformation. On the contrary, steric interaction between sugar moiety and N4-methyl group is strong enough to prevail over the *syn* directing tendency of C2 substituent, preserve *anti* conformation and enforce North sugar pucker. The stabilization of N-type sugar conformation can be attributed to the strengthening of the anomeric effect due to more favourable overlap between the electron pair orbital of endocyclic O4′ and the vacant antibonding σ^* orbital of the glycosylic bond (i.e., $n_{\sigma 4'} \rightarrow \sigma^*_{C1'\text{-}N9}$) and probably additional interaction of the electron pair orbital of the oxygen of C2 substituent and the ''left-hand'' imidazole ring of nucleobase.

REFERENCES

1. de Leeuw, H.P.M.; Hasnoot, C.A.G.; Altona, C. Empirical correlations between conformational parameters in β-D-furanoside fragments derived from a statistical survey of crystal structures of nucleic acid constituents. Full description of nucleoside molecular geometries in terms of four parameters. Isr. J. Chem. **1980**, *20*, 108–126.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

2. Hoffmann, R.A.; van Wijk, I.; Leeflang, B.R.; Kamerling, J.P.; Altona, C.; Vliegenthart, J.F.G. Conformational analysis of the α-L-arabinofuranosides present in wheat arabinoxylans from proton-proton coupling constants. J. Am. Chem. Soc. **1992**, *114*, 3710–3714.
3. Saenger, W. *Principles of Nucleic Acid Structure*; Springer-Verlag: Berlin, 1988.
4. Altona, C.; Sundaralingam, M. Conformational analysis of the sugar ring in nucleosides and nucleotides. A new description using the concept of pseudorotation. J. Am. Chem. Soc. **1972**, *94*, 8205–8212.
5. Altona, C.; Sundaralingam, M. Conformational analysis of the sugar ring in nucleosides and nucleotides. Improved method for the interpretation of proton magnetic resonance coupling constants. J. Am. Chem. Soc. **1973**, *95*, 2333–2344.
6. Plavec, J.; Tong, W.; Chattopadhyaya, J. How do the gauche and anomeric effect drive the pseudorotational equilibrium of the pentofuranose moiety of nucleosides? J. Am. Chem. Soc. **1993**, *115*, 9734–9746.
7. Thibaudeau, C.; Plavec, J.; Chattopadhyaya, J. Quantitation of the anomeric effect in adenosine and guanosine by comparison of the thermodynamics of the pseudorotational equilibrium of the pentofuranose moiety in *N*- and *C*-nucleosides. J. Am. Chem. Soc. **1994**, *116*, 8033–8037.
8. Thibaudeau, C.; Plavec, J.; Chattopadhyaya, J. Quantitation of the pD dependent thermodynamics of the N ⇔ S pseudorotational equilibrium of the pentofuranose moiety in nucleosides gives a direct measurement of the strength of the tunable anomeric effect and the pK_a of the nucleobase. J. Org. Chem. **1996**, *61*, 266–286.
9. Rosemeyer, H.; Toth, G.; Golankiewicz, B.; Kazimierczuk, Z.; Burgeois, W.; Kretchmer, U.; Muth, H.P.; Seela, F. Syn-Anti conformational analysis of regular and modified nucleosides by 1D ^{1}H NOE difference spectroscopy: A simple graphical method based on conformationally rigid molecules. J. Org. Chem. **1990**, *55*, 5784–5790.
10. Sierzputowska-Gracz, H.; Guenther, R.H.; Agris, P.F.; Folkman, W.; Golankiewicz, B. Structure and conformation of hypermodified purine nucleoside. Wyosine and its isomers: A comparison of coupling constants and distance geometry solutions. Magn. Reson. Chem. **1991**, *29*, 885–892.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016