CHEMISTRY LETTERS, pp. 67-70, 1982.

A NOVEL STEREOCHEMICAL ASPECT OF NITRO SUGAR DERIVATIVES: " AXIAL " NITRO GROUP PREDOMINATED OVER EQUATORIAL ONE IN EQUILIBRIUM

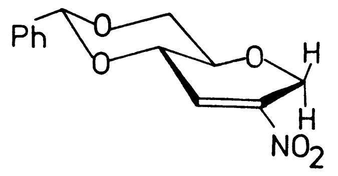
Tohru SAKAKIBARA, Toshiaki MINAMI, Yoshiharu ISHIDO, and Rokuro SUDOH
Department of Chemistry, Faculty of Science, Tokyo Institute of
Technology, O-okayama, Meguro-ku, Tokyo 152

2-Nitro sugar derivatives bearing an axial nitro group were proved to be thermodynamically more stable than the corresponding 2-epimers, bearing an equatorial nitro group.

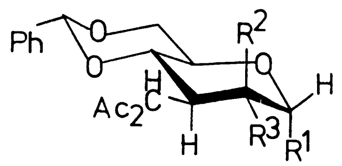
Extensive studies on the Michael and Michael type reaction of 3-nitro-2-enopyranosides$^{1)}$ as well as protonation and halogenation of sugar 3-nitronates$^{2)}$ have revealed the remarkable tendency of the nitro group to occupy an equatorial orientation. In fact, no product bearing an axial nitro group has been isolated under thermodynamically controlled conditions.$^{3)}$ Such pronounced preference of an equatorial nitro group compared with the unsubstituted nitrocyclohexane$^{4)}$ has been attributed to the severe syn-diaxial and increased gauche interaction.$^{2)}$

In this communication, we report a novel stereochemical aspect found in the case of some 2-nitro sugar derivatives which is inconsistent with the above generalization in the 3-nitro sugar chemistry.

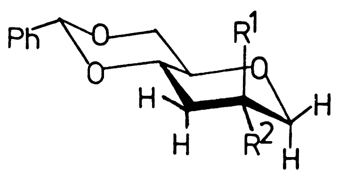
Treatment of 1,5-anhydro-4,6-O-benzylidene-2,3-dideoxy-2-nitro-D-*erythro*-hex-2-enitol (**1**)$^{5)}$ with 2,4-pentanedione in benzene - 0.1 M (=1 mol dm^{-3}) aqueous sodium hydroxide solution in the presence of hexadecyltributylphosphonium bromide as a phase transfer catalyst afforded the *gluco* isomer **2** (15% yield), mp 128-129°C, $[\alpha]_D^{22}$ -19.4° (*c* 1, acetone), and the *manno* isomer **3** (67% yield), mp 134-136°C, $[\alpha]_D^{22}$ -20.8° (*c* 1, acetone). The *gluco* and *manno* configurations with $^4C_1$ configuration for 2 and 3, respectively, were assigned on the basis of the coupling constants; $J_{1a,1e}$=13.5, $J_{1a,2}$=10, $J_{1e,2}$=4.9, $J_{2,3}$=10, and $J_{3,4}$=10 Hz for **2**, $J_{1a,1e}$ =13.5, $J_{1a,2}$=2.4, $J_{1e,2}$=1.2, $J_{2,3}$=4.3, and $J_{3,4}$=10.5 Hz for **3**. Each of the epimers gave a 1 : 2.2 mixture of **2** and **3** upon equilibration under the conditions used; this indicates that **3** is thermodynamically more stable than **2** by 0.5 kcal/mol.



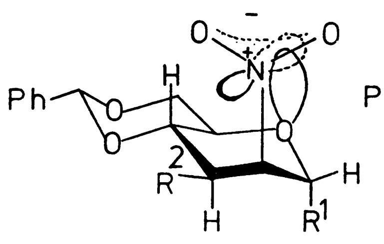
1



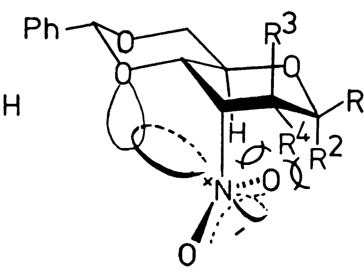
2; $R^1=R^2=H, R^3=NO_2$
3; $R^1=R^3=H, R^2=NO_2$
4; $R^1=OMe, R^2=H, R^3=NO_2$
5; $R^1=OMe, R^2=NO_2, R^3=H$



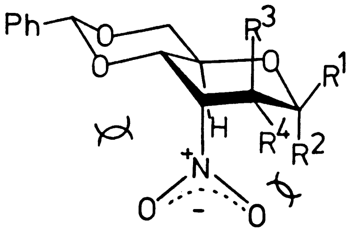
6; $R^1=NO_2, R^2=H$
7; $R^1=H, R^2=NO_2$



a



b



c

Similar equilibration between the epimers of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-(diacetyl)methyl-2-nitro-α-D-glucopyranoside (4) and -α-D-mannopyranoside (5)[7] also gave a mixture in which 5 predominates over 4 by 0.2 kcal/mol.

Increased preference of an epimer with an axial nitro group was interestingly found in the following cases. Sodium borohydride reduction of 1 in methanol gave 98% yield of a mixture in which the arabino isomer 6 was preponderant over the ribo isomer 7 (3.8 : 1).[8] Crystallization from ethanol gave 6 in 70% yield; mp 150-151 °C; $[\alpha]_D^{22}$ -65.5° (*c* 1, acetone); $J_{1a,1e}=13.9$, $J_{1a,2}=2.7$, $J_{1e,2}=2.3$, $J_{1e,3e}=2.3$, $J_{2,3a}=4.5$, $J_{2,3e}=2.3$, $J_{3a,3e}=13.8$, $J_{3a,4}=12$, $J_{3e,4}=4.5$, and $J_{4,5}=10$ Hz. Chromatography of a syrup obtained by evaporation of the mother liquor[9] gave 7 (3% yield); mp 160-162°C; $[\alpha]_D^{22}$ +14.3° (*c* 0.3, acetone). On the other hand, treatment of 6 with 0.1 M solution of sodium deuteroxide in deuterium oxide in acetone-d_6 gave a 7 : 1 mixture of 6 and 7 after 24h, and the ratio was unchanged even after 48 h.[8] The same treatment by use of sodium hydroxide in place of sodium deuteroxide in acetone-d_6 also gave the same result. We could expect no isomers other than 7 which should be produced by partial epimerization of **6**, although the structure of **7** was unable to confirm by ^{1}H-NMR spectroscopy. These ratios of **6** to **7** may be of a mixture in equilibrium, indicating that **6** is thermodynamically more stable than **7** by 1.1 kcal/mol. In dioxane, the equilibrium was attained within 48 h to give a 3.9 : 1 mixture of **6** and **7**8); **6** is thus thermodynamically more stable than **7** by 0.8 kcal/mol.

Obviously, these results conflict with previous interpretation2) for the equatorial preference of the nitro group on the basis of steric repulsion as well as dipole - dipole interaction which should destabilize the axially oriented nitro group. Incidentally, Eliel and his coworkers10) found that the 5-axial isomer of 2-isopropyl-5-nitro-1,3-dioxane was preponderant over the corresponding 5-equatorial isomer by 0.81 kcal/mol in dichloromethane; this fact was explained in terms of i) attractive electrostatic interaction between positively polarized nitrogen atom of the nitro group and negatively polarized ring-oxygen atoms, and ii) p-π* overlap of the ring-oxygen unshared electron pairs with the π* orbitals of the nitro group.11) Scrutinizing the structure through Stuart molecular model, 4,6-*O*-benzylidene-2-nitro sugars are likely to occupy the conformation (**a**) due to the stabilization by the factors above cited different from 4,6-*O*-benzylidene-3-nitro sugars. If the latters occupy the conformation with the axial nitro group, the nitro group should bring about 1,3-diaxial interaction with substituents at both 1 and 5 positions as seen from (**b**), which may excel the same type of stabilization as above described to force their conformation to change to (**c**). However, the conformation (**c**) is also destabilized by steric2) and electrostatic repulsion between O-4 and one of the oxygen atoms of the nitro group. On the whole, it might be reasonable to state that the isomer with equatorial nitro group is thermodynamically more stable than that with axial nitro group in the case of the 3-nitro sugar derivatives.

References

1) T. Sakakibara, A. Seta, Y. Tachimori, and R. Sudoh, Bull. Chem. Soc. Jpn, **53**, 2322 (1980) and references cited therein.

2) H. H. Baer, J. Carbohydrates· Nucleosides· Nucleotides, **6**, 51 (1979).

3) Szarek and his coworkers reported the isolation of a product with axial nitro group through sodium borohydride reduction of benzyl 2-*O*-benzyl-3,4-dideoxy-

4-nitro-α-*D*-*glycero*-pent-3-enoside; the yield was not high (48%), however, they did not mention about the formation of the corresponding 4-epimer. Thus it was not shown if the isolated product was thermodynamically more stable: W. A. Szarek, D. G. Lance, and R. L. Beach, Carbohydr. Res., **13**, 75 (1970).

4) The equatorial isomer is more stable than the axial one by approximately 1.1 kcal/mol.

5) Treatment of 1,5-anhydro-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-*D*-*erythro*-hex-2-enitol6) with sodium nitrite in a heterogeneous system of benzene-water in the presence of hexadecyltributylphosphonium bromide gave **1** (44% yield), mp 155-155.5°C, $[\alpha]_D^{22}$ +25.3° (*c* 1, acetone).

6) T. Sakakibara, Y. Nomura, and R. Sudoh, Bull. Chem. Soc. Jpn, **53**, 1642 (1980).

7) T. Sakakibara, Y. Tachimori, T. Minami, and R. Sudoh, Carbohydr. Res., **91**, 67 (1981).

8) These proportions were all calculated through ^{1}H-NMR spectroscopy.

9) Chromatography on a column of silica gel induced some decomposition of the products involved therewith.

10) M. K. Kaloustian, N. Dennis, S. Mager, S. A. Evans, F. Alcudia, and E. L. Eliel, J. Am. Chem. Soc., **98**, 956 (1976).

11) " p-π* " Overlap should be appropriate for stabilization12) although they explained it by " p-π " overlap.

12) *E. g.*, I. Fleming, " Frontier Orbitals and Organic Chemical Reactions, " John Wiley & Sons, London, 1976.

(Received October 19, 1981)