Tetrahedron Letters,Vol.23,No.52,pp 5545-5548,1982 0040-4039/82/525545-04$03.00/0
Printed in Great Britain

STEREOSELECTIVE NUCLEOPHILIC ADDITION REACTIONS TO NITRO SUGARS

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Summary: Nucleophile(s) almost exclusively added from the equatorial side of 2-nitro-β-D-2-enopyranoside and the axial side of 2-nitro-D-*ribo*-1-enitol. On the other hand, methoxide and *tert*-butyl peroxide ions approached from the equatorial side of 2-nitro-α-D-2-enopyranoside, whereas methanol and hydrogen peroxide ion from the axial side.

Stereochemistry of the Michael type reaction to six-membered ring systems including sugar derivatives is extensively studied and the results are generally accounted for on the basis of two factors:[1-3] i) axial attack generally preponderates over equatorial attack, because the former leads a thermodynamically more stable chair-like transition state, whereas the latter a less stable boat-like transition state for stereoelectronic reason,[4] and ii) steric hindrance between an approaching nucleophile and the γ-substituent. In general, however, the role of the β'-substituent for determining the approaching direction of a nucleophile is hardly evaluated.

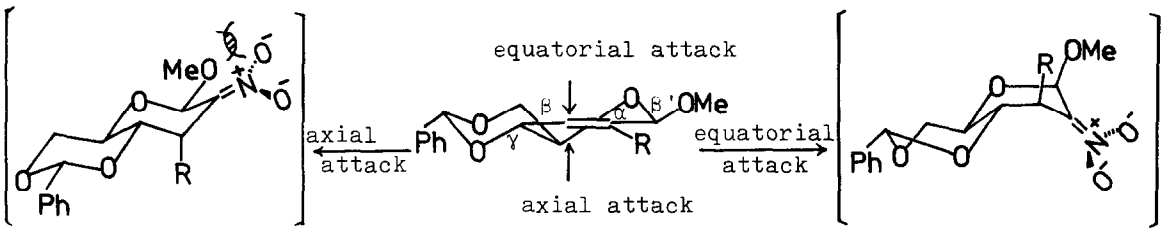
In this communication we wish to report the stereoselective Michael type reaction to nitro sugars, in which the β'-substituent seems to play an important role.

Firstly, treatment of 2-nitro-β-D-2-enopyranoside 1 with hydrogen cyanide in 1,4-dioxane in the presence of a catalytic amount of potassium cyanide afforded a mixture (76% yield) of the glucopyranoside 2 (mp 139.5-140.5°) and allopyranoside 3 (mp 143.5-144.5°) in the ratio of 4.5 : 1 as calculated from ^{1}H-NMR spectroscopy. Under the same conditions, the allopyranoside 3 was almost recovered, together with traces of the cyano olefin 4 (mp 164-165°), revealing that the addition of a cyanide ion proceeded, at least mostly, under kinetic control. This result conflicts with the fact[5] that observed in the reaction of 2-cyano-β-D-2-enopyranoside 5 with hydrogen cyanide; in which a cyanide ion approached from the axial side of the molecule under the kinetically controlled conditions. Most plausible explanation for such a difference is as follows. Contrary to the linear cyano group, a chair-like transition state, derived by axial attack to the nitro olefin 1 is destabilized by steric ($A^{1,3}$ strain[6]) and electrostatic repulsion between the nitronate group and the β'-substituent (the anomeric methoxyl group)[factor iii)], which is absent in a boat-like transition state, derived by

equatorial attack. In other words, cis addition to the β'-substituent is blessed by the factor iii.

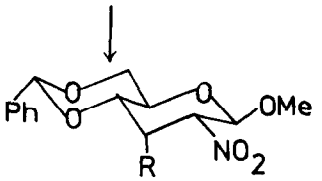
Thus equatorial attack almost exclusively occurred in the reaction of 1 with refluxing methanol to provide the glucopyranoside 6 (mp 135-136°) in 71% isolated yield. The alternative isomer, the allopyranoside 7,[7] was recovered quantitatively under the same conditions.

An acetylacetonate ion also approached from the equatorial side of 1 to give the glucopyranoside 8 (mp 111-112°) in 87% yield.[8]

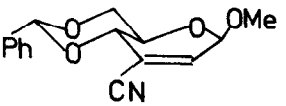


1; R=NO$_2$
5; R=CN

chair-like t. s.

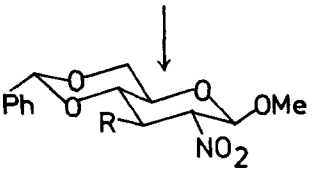


3; R=CN
7; R=OMe



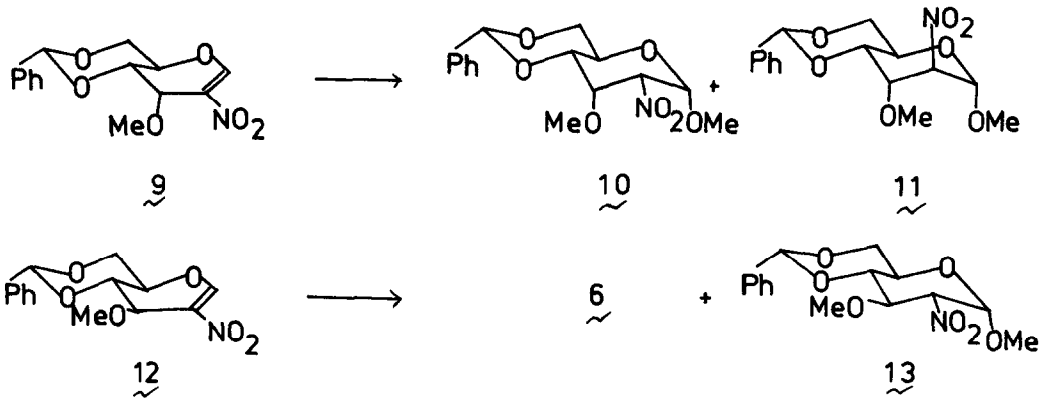
4

boat-like t. s.



2; R=CN
6; R=OMe
8; R=CHAc$_2$

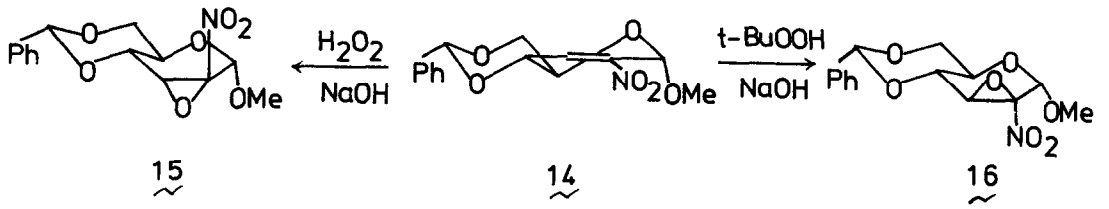
An important role of the factor iii is also illustrated by the following example. Axial attack almost exclusively occurred in the reaction of 2-nitro-D-ribo-1-enitol 9 with refluxing methanol to provide a mixture of α-D-allopyranoside 10 (mp 123.5-124.5°) and α-D-altropyranoside 11 (mp 155-156°) in high yield. On the other hand, similar reaction of the 3-epimer 12 afforded almost equal amount of the β-D-glucopyranoside 6 and α-D-glucopyranoside 13 (mp 158-159°) in 89% yield. Anomerization of these products was not observed under the employed conditions. These results are apparently not explainable by the factors i and ii only. In these reactions, the factor ii may be ignored due to the lack of the γ-substituent. In compound 9, axial attack is favorable by both the factors i and iii, and indeed the α-anomers were almost exclusively obtained, whereas in compound 12, the favorable direction due to the factor i and iii differs each other, affording almost equal amounts of α- and β-anomers.



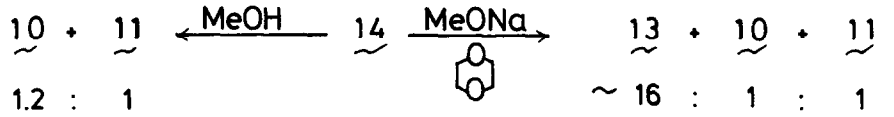
Secondly, the β'-substituent is likely to participate in determination of the approaching direction of a nucleophile, in different sense from the factor iii, as shown in the following example.

2-Nitro-α-D-2-enopyranoside 14 has not only the oxygen atom at the γ-position (C-4), but also the quasi-axial methoxyl group at the β'-position, therefore, axial attack should be remarkably suppressed, especially in the case of a sterically bulky and/or negatively charged nucleophile, by steric and electrostatic repulsion due to these substituents. This expectation was realized and we have succeeded in highly stereoselective synthesis of the nitro epoxides and 3-O-methyl derivatives.

Treatment of 14 with 35% aqueous hydrogen peroxide in 1,4-dioxane in the presence of sodium hydroxide immediately yielded a precipitate, of which recrystallization afforded the nitro epoxide 15 (mp 243-345°) in 89% yield. The same product was obtained in 81% yield by treatment of 14 with hydrogen peroxide in benzene-1M aqueous sodium hydroxide in the presence of tributylhexadecylphosphonium bromide as a phase-transfer catalyst. The configuration of 15, however, was not assigned, because it is insufficiently soluble in common solvents used for ^{1}H-NMR spectroscopy and it partially decomposed in warm DMSO-d_6. On the other hand, epoxidation of 14 with tert-butyl peroxide in the heterogeneous system (benzene-0.5M sodium hydroxide) in the presence of the phase-transfer catalyst provided the nitro epoxide 16 (mp 195-197°), together with a small amount of 15. Assignment of the manno configuration to 16 was based on the coupling constant,[9] $J_{3,4} \sim 0$Hz; therefore, the alternative isomer 15 may be assumed to have the allo configuration.



When compound 14 was treated with sodium methoxide in methanol-1,4-dioxane, a mixture mainly consisted of the gluco 13, allo 10, and altro isomer 11 in the ratio of ca. 16 : 1 : 1, as estimated by ^{1}H-NMR spectroscopy, was obtained, from which the gluco isomer 13 was isolated in 64% yield. On the other hand, treatment of 14 with refluxing methanol (bath temperature, ca. 70°, for 20 min) gave a mixture mainly consisted of the allo 10 and altro 11 in the ratio of 1.2 : 1. Epimerization at C-2 but not at C-3 was observed by treatment of 10 or 11 under the conditions employed for the preparation of 13, suggesting that a nucleophilic attack in these reactions was controlled kinetically.



These results strongly suggest that the β'-substituent should also be taken into consideration for predicting the approaching direction of a nucleophile.

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8. This reaction also seems to be controlled kinetically, because the elimination of the anomeric methoxyl group should predominate over the Retro-Michael reaction as indicated in the reaction of 14 with dimethyl malonate; T. Sakakibara, Y. Tachimori, T. Minami, and R. Sudoh, Carbohydr. Res., 91 (1981) 67.
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(Received in Japan 27 August 1982)