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CONTROL PARAMETERS ON THE STEREOSELECTIVITY OF THE MICHAEL-TYPE ADDITION TO SUGAR NITROOLEFINS

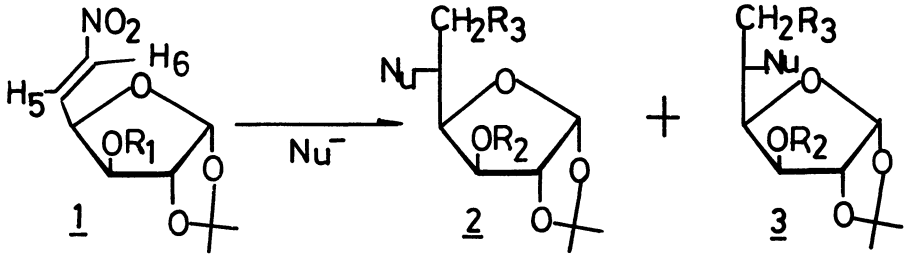
Masuo FUNABASHI*, Yuzuru OKAMURA, Kazutoshi MIKAMI, and Juji YOSHIMURA
Laboratory of Chemistry for Natural Products, Faculty of Science,
Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152

The stereoselectivity on the addition reaction of nucleophiles (CH_3O^- and $PhCH_2S^-$) to three model compounds, 6-deoxy-1,2-O-isopropylidene-6-nitro-3-O-substituted-α-D-*xylo*-hex-5-enofuranoses (1a, 1b and 1c) was examined in terms of six control parameters.

The Michael-type additions to sugar nitroolefins have been reported so far not only in the case of linear nitroolefins[1] , but also in the case of cyclic nitroolefins[2] , and interestingly, most of them are rather stereoselective despite of lack of proper informations about " What kind of factors determines the direction of such stereoselectivity, and which is more predominant in such reaction , kinetic or thermodynamic control ?".

We, therefore, wish to describe here about several control parameters which might affect the addition reaction of nucleophiles (CH_3O^- and $PhCH_2S^-$) to three simple model compounds, namely, 6-deoxy-1,2-O-isopropylidene-6-nitro-3-O-substituted-α-D-*xylo*-hex-5-enofuranoses (1a, 1b and 1c).

The following six parameters were selected and examined individually; (A) bulkiness of the substituents at C-3, (B) reaction solvent, (C) reaction temperature, (D) reaction time, (E) bulkiness of the nucleophiles, (F) ground state conformation of the starting materials. If the reaction depends on kinetic control, factor A, C, D, E and F might play especially important roles.



1

a : $R_1 = COCH_3$
b : $R_1 = CH_3$
c : $R_1 = CH_2Ph$

2

a : $R_2 = H$, $R_3 = NO_2$
b : $R_2 = CH_3$, $R_3 = NO_2$
c : $R_2 = CH_2Ph$, $R_3 = NO_2$

3 (Nu = OCH_3)

d : $R_2 = CH_3$, $R_3 = OH$
e : $R_2 = CH_2Ph$, $R_3 = OH$

The reaction was effected mostly in methanol by changing one of the conditions corresponding to the above factors and by taking the aliquots at proper intervals for analysis. The product ratio (G/I) of D-*gluco* (2) to L-*ido* isomer (3) was esti-

mated mainly by NMR (comparison of the proton intensities of H_1, OCH_3 or OCH_2Ph). In case that the compound 2 is unknown, the mixture of 2 and 3 was transformed by successive reduction and deamination into 5-O-methyl-D-*gluco* and -L-*ido* derivatives (2d-2e, 3d-3e) and analyzed[3] by GLC in addition to NMR. The authentic specimen (2d, 2e) for D-*gluco* isomer was prepared in the usual manner by successive 6-O-tritylation, 5-O-methylation and detritylation of 1,2-O-isopropylidene-3-O-substituted-α-D-glucofuranoses.

The following results were obtained by keeping five of six parameters in the same condition.

1) Parameter A: No remarkable differences are found in this case as is shown in Table 1 and the discrepancy between NMR and GLC analysis must be due to some isomerization during the reduction of the mixture by lithium aluminum hydride.

Table 1. Substituents Dependence of G/I Value

Starting material	G/I NMR	G/I GLC
1a	1.3	——
1b	1.9	1.7
1c	1.6	1.5

reaction condition:
solvent ; methanol
base ; sodium methoxide (2 molar equivalents)
temperature; 20°C
time ; 2 hr

2) Parameter B: The table 2 shows that the factor B is quite suggestive, but complicated. Whistler and Pyler[4] reported that α-toluenethiol adds to the compound 1a in piperidine to give exclusively D-*gluco* isomer, whereas G/I value changed to 1.7 when we followed the same reaction in methanol. Furthermore, when the mixture of 2a and 2b was subjected to the former condition in piperidine, L-*ido* isomer (2b) disappeared and gave only D-*gluco* isomer (2a). This means that L-*ido* isomerizes to D-*gluco* in piperidine.

On the other hand, the G/I value decreased in the case of compound 2c from 1.6-1.9 to 0.8 by changing the solvent from methanol to triethylamine-methanol (10/1) system.

Table 2. Solvent Dependence of G/I Value

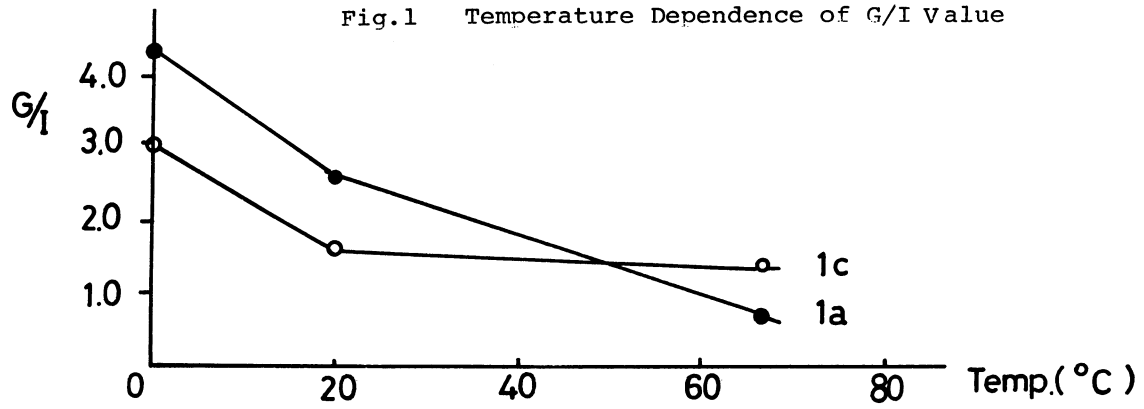
	Solvent	Nucleophile	Time(hr)	G/I
1a	methanol	$PhCH_2SNa$	24	1.7
	piperidine	$PhCH_2SH$	24	only D-*gluco*[4]
1c	methanol	MeONa	2	1.6
	methanol	NaOH	2	1.9
	triethylamine -methanol (10/1 V/V)	MeONa	2	0.8

(Temperature ; 20°C)

3) Parameter C: A remarkable change occurred in this case as shown in Fig 1. The G/I value decreased from 3-4 to 1-1.5 by changing the temperature from 0°C to

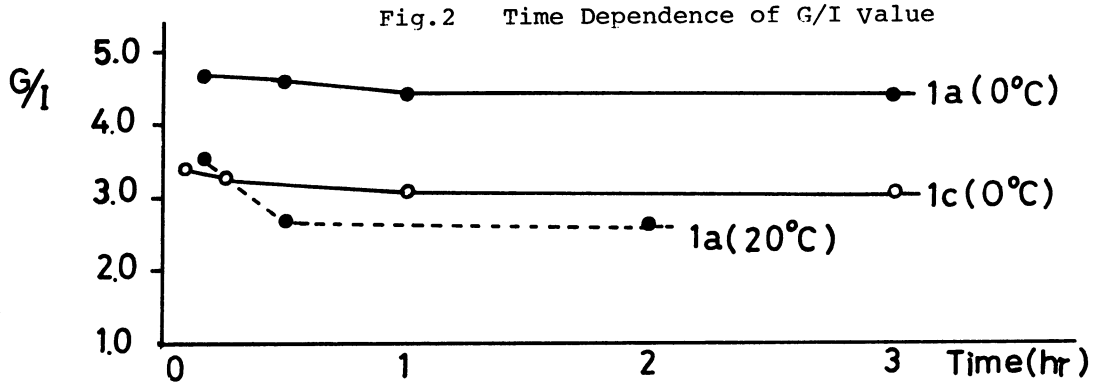
63°C. This clearly means that the D-*gluco* more rapidly isomerizes to L-*ido* in a higher temperature.

Fig.1 Temperature Dependence of G/I Value



4) Parameter D: Fig. 2 shows that the time course of the isomerization of D-*gluco* to L-*ido* is very slow, though the final equilibrium could not be exactly determined at present (1 or 2 days seem to be required for the equilibrium).

Fig.2 Time Dependence of G/I Value

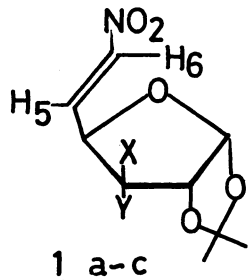


5) Parameter E: No significant differences are recognized between two nucleophiles.

6) Parameter F: The most important thing to consider this parameter is the fact that the coupling constant ($J_{4,5}$) between H_4 and H_5 of any of 1a-1c in addition to the related compounds (1d, 1e) is 2.5 Hz in contrast to 7.5 Hz ($J_{4,5}$) and 4.5 Hz ($J_{2,3}$) for the 6-C-methyl derivative[5] of 1b (5) and 1-nitro-D-*gluco*-3,4,5,6,7-pentaacetoxy-1-heptene [5] (6) respectively, and furthermore, $J_{4,5}$ did not change even at a higher temperature (50°C), for instance, in the case of the compound 1a. Thus, the conformation of these compounds (1a-1e) seems to be rather rigid and the dihedral angle[6] between H_4 and H_5 can be estimated to be approximately 90° as shown in the following Newman projection (from C_5 to C_4).

If this is the case, the nucleophiles should attack from the less-hindered site opposite to the substituent at C-3 of the compound 1 to give D-*gluco* isomer initially under a kinetic control. This is, indeed, in good agreement with the fact that D-*gluco* isomer is preferentially produced in the initial reaction step. L-*Ido* isomer, therefore, must be a product under a thermodynamic control except in the case of the reaction of 1a with α-toluenethiol in piperidine, in which D-*gluco* isomer must be a product incidentally both under a kinetic and thermodynamic

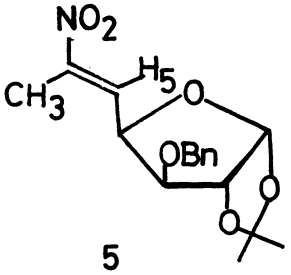
control. Though some literatures [1a,7] explained the stereoselectivity of addition of alcohols or ammonia to linear nitroolefins such as the compound 6 by applying the Cram's rule easily, we do not think that it would be proper to speculate the stereochemistry of such reaction only in terms of that rule, as it was clearly demonstrated from the several parameters (B, C, D and F) described above.



1 a-c

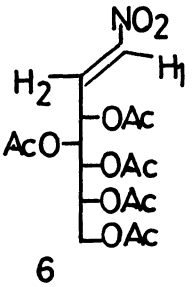
$J_{45} = 2.5$ Hz

(d: X=H, Y=OCH3
e: X=-O CH2 OCH2=Y)



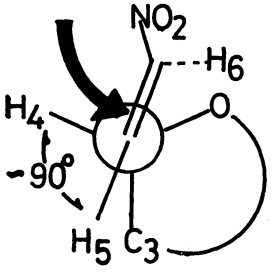
5

$J_{45} = 7.5$ Hz



6

$J_{23} = 4.5$ Hz



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3) Relative errors of g.l.c. and n.m.r. analysis are estimated to be below 10 %.

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