DIRECT O-GLYCOSYL TRICHLOROACETIMIDATE FORMATION.

NUCLEOPHILICITY OF THE ANOMERIC OXYGEN ATOM [1]

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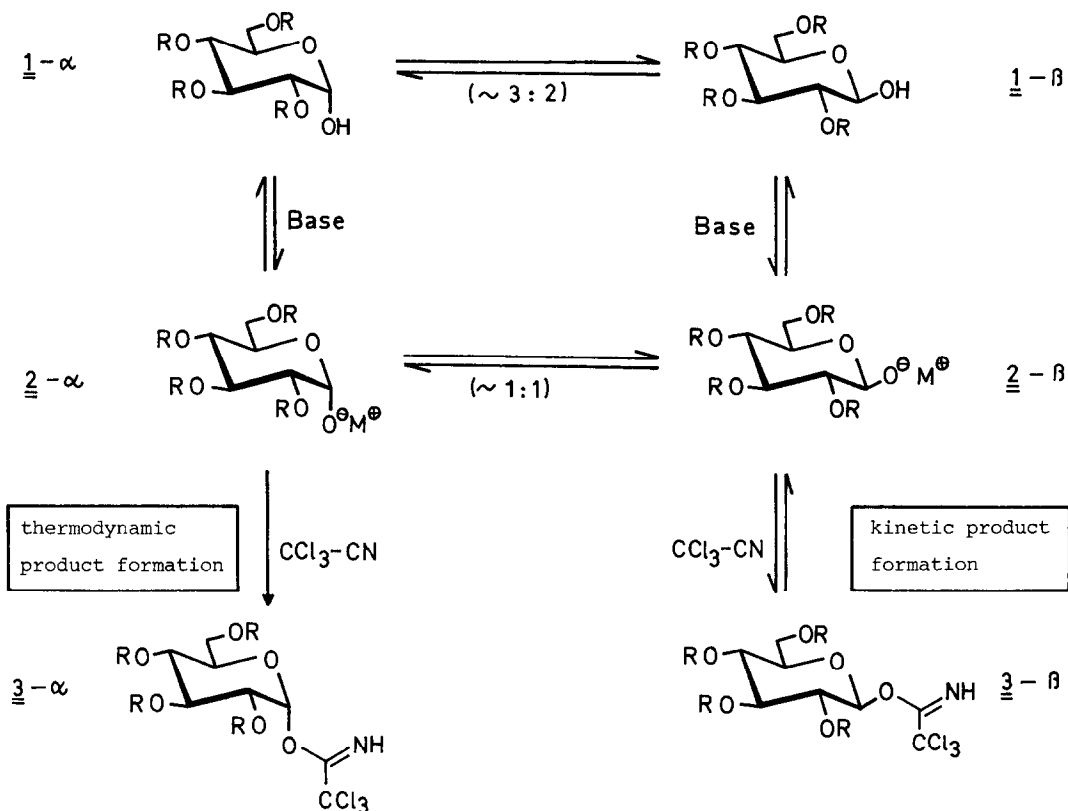Fakultät Chemie, Universität Konstanz
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Abstract: *Tetra-O-benzylglucose 1 and trichloroacetonitrile afford in a base catalyzed, fast,
and reversible reaction the ß-O-glycosyl imidate 3-ß, which is transformed slowly
into the α-isomer 3-α. Both results, the reactivity differences of 2a,ß and the
stability differences of 3-a/ß are due to lone pair repulsions implicated in the
anomeric effect.*

The excellent α- and ß-diastereoselectivities obtained in the 1-O-alkylation of 1-O-metalated
glycopyranoses and glycofuranoses were explained by intermolecular versus intramolecular com-
plexation of the metal cation, by different steric requirements, and by anomeric effect derived
differences in the nucleophilicity of the anomeric oxide oxygen atom [2]. However, these alkyla-
tion reactions are irreversible reactions therefore the question of kinetic versus thermody-
namic product formation was not clarified and the contribution of stereoelectronic effects to
reactivity differences could not be clearly separated.

In the synthesis of complex glycosides and oligosaccharides the O-glycosyl trichloroacetimidate
procedure [3,4] has proven to be an efficient alternative to the Koenigs-Knorr procedure and its
valuable modifications [5]. The base catalyzed direct O-glycosyl trichloroacetimidate formation
is now demonstrated to be a reversible reaction. With tetra-O-benzylglucose 1 the increased
nucleophilicity of the ß-1-oxide oxygen of 2-ß and the increased stability of the α-imidate
3-α are important (Scheme 1). The differences in reactivity of 2-α/ß and in stability of 3-α/ß,
respectively, enable a separation of kinetic and thermodynamic stereoelectronic effects and in
addition a highly diastereoselective synthesis of 3-α and 3-ß, thus enhancing the versatility
of the trichloroacetimidate procedure.

Reaction of 1 (1-α : 1-ß ≈ 3:2 [6]) with trichloroacetonitrile and excess sodium hydride (for
experimental details see ref. 4a) led via 2-α in a fast and quantitative reaction (96 % iso-
lated yield) to 3-α [4a]. Careful investigation of this reaction displayed, however, that ini-
tially 3-ß is formed in appreciable amount. However, 3-ß anomerizes rapidly under the reaction
conditions to 3-α (Table 1). The expected difference in reactivity between 2-α and 2-ß could be

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Scheme 1: R = Benzyl, M = Na, K

1-α RO—/OR O /OH ⇌ (∼3:2) ⇌ RO—/OR O—OH 1-β

‖ Base   ‖ Base

2-α RO—/OR O /O⊖M⊕ ⇌ (∼1:1) ⇌ RO—/OR O—O⊖M⊕ 2-β

| thermodynamic product formation | ↓ CCl₃-CN   CCl₃-CN ↑ | kinetic product formation |

3-α RO—/OR O /O—C(=NH)CCl₃   RO—/OR O—O—C(=NH)CCl₃ 3-β

Table 1. Base Catalyzed Reaction of 1 with Trichloroacetonitrile [a].

Base	Reaction Time	Retained 1 [%]	Total Yield of 3 [b] [%]	Anomer Ratio of 3 [b] 3-α : 3-β
NaH [c]	0	100	0	-
	1 min	15	85	35 : 65
	3 min	5	95	45 : 55
	5 min	2	98	50 : 50
	2.5 h	2	96	α
K₂CO₃ [d]	0	100	0	-
	5 h	5	95	1 : 4
	22 h	3	97	1 : 2
	30 h	3	97	2 : 3
	100 h [e]	10	80	1 : 1

[a] 1 g (1.85 mmol) 1 and 1 ml CCl₃-CN are dissolved in 10 ml CH₂Cl₂ at room temperature.
[b] Isolated yields; the anomer ratios were determined by ^{1}H-NMR.
[c] 30 mg NaH; [d] 1 g dry K₂CO₃; [e] partial decomposition was observed, which led to 10 % by-product formation.

demonstrated by using dry potassium carbonate as base catalyst, which catalyzed a fast 3-β
formation, however, only a slow 3-β to 3-α anomerisation (Table 1). Therefore after 5 hours
a 79 % yield of 3-β could be easily isolated as pure material [^{1}H-NMR (CDCl$_3$, internal TMS):
δ = 8.76 (s, 1H, NH); 5.88 (d, 1H, 1-H); [α]$_{578}^{20}$ = +22^0 (c = 1, CHCl$_3$)]. The base catalyzed 3-β
to 3-α anomerisation was demonstrated starting from pure 3-β (Table 2). With sodium hydride as
base 3-β is cleaved to 2-β, 2-β anomerizes to 2-α, and 2-α reacts with trichloroacetonitrile –
due to the thermodynamic anomeric effect – to the thermodynamically favored 3-α with the
electron withdrawing 1-O-substituent in the axial α-position. The large amount of 1 present
after 15 minutes (Table 2) is qualitative proof of the slow 3-α formation, which is less evi-
dent, when excess trichloroacetonitrile is used in preparative scale reactions.

Table 2. Anomerisation of 3-β to 3-α [a]

Reaction time [min]	Retained 3-β [%]	Obtained		Anomer Ratio 3-α : 3-β
		1 [%]	3-α [%]	
0	100	0	0	β
15	45	50	5	1 : 9
60	5	10	85	17 : 1

[a] 0.13 g (1.9 mmol) 3-β was dissolved in 10 ml CH$_2$Cl$_2$ and 10 mg NaH were added at room
temperature.

Because deprotonation of 1-α/β leads to a 1:1 mixture of 2-α/β [6], the kinetically preferred
3-β formation must be due to enhanced nucleophilicity of the anomeric oxide oxygen in 2-β:
This assumption is supported by unfavorable dipole/dipole-interaction in the β-anomer (2-B),
which leads to free orbital repulsion, this way increasing the accessibility of the free
electrons to electrophiles [2,7,8]. A similar increase in reactivity is not expected for the
α-anomer (2-A). Thus the anomeric stereoelectronic effect is not only a thermodynamic but
also a kinetic effect [2,7].

1) Glycosylimidates, Part 11. This work was supported by the DEUTSCHE FORSCHUNGSGEMEINSCHAFT
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7) A nucleophilicity increase for the anomeric ether oxygen due to lone pair repulsions implicated in the anomeric effect was recently suggested by V.G.S. Box, Heterocycles 19, 1939 (1982).

8) Similarly, lone pair orbital interaction between the p-type orbital of the ring oxygen and the lone pair orbitals of oxide oxygen leads to enhanced nucleophilicity in 2-β. For "p-type orbital" see: S. David in "Anomeric Effect, Origin and Consequences", Vol. 87; W.A. Szarek and D. Horton, Eds., American Chemical Society, Symposium Series, 1979, p. 12 and ref.