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Note

Base-catalyzed formation of 1,6-anhydro-β-D-glucopyranose from phenyl α-D-glucopyranoside

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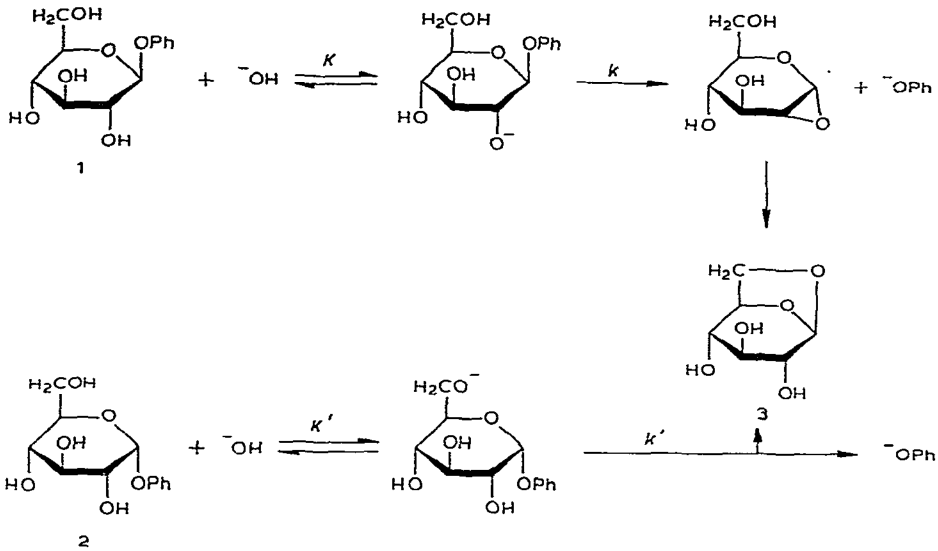
It is well established[1–3] that base-catalyzed cleavage of phenyl β-D-glucopyranoside (**1**) proceeds through the intermediate formation of a 1,2-anhydride, providing a facile method[4] for the preparation of 1,6-anhydro-β-D-glucopyranose (levoglucosan, **3**) (see Scheme 1), but the mechanism for the corresponding α-D anomer (**2**) has not been clarified.

A nucleophilic, aromatic substitution[5] has often been considered, on the basis that the aryl α-D-glucopyranosides do not produce levoglucosan under mildly alkaline conditions (1.3M KOH at 100°). It should be noted that phenyl α-D-glucopyranoside is essentially stable under these conditions; its behavior at elevated temperatures has not been investigated. On the other hand, a novel mechanism involving the initial migration of the nitrophenyl group (O-1 → O-2 → O-3) and the formation of Meisenheimer complexes as the reactive intermediates, has been reported for *p*-nitrophenyl α-D-glucopyranoside[6,7].

However, alkaline cleavage of closely related glycosides, phenyl α-D-galactopyranoside[8] and a variety of unsubstituted and substituted phenyl 2-deoxy-α-D-glucopyranosides[9], gives the corresponding 1,6-anhydride as the major product, indicating the direct involvement of the ionized 6-hydroxyl group. Such an intramolecular-displacement mechanism was further supported by the results of kinetic studies[10,11] on methyl α-D-glucopyranoside, and is now confirmed with phenyl α-D-glucopyranoside (**2**; see Scheme 1) by the identification of the anticipated product, levoglucosan, as now discussed.

Samples of the D-glucoside **2** (0.04M), with D-glucitol (0.06M) as an internal standard, in 4.3M sodium hydroxide were sealed in 10-mL ampoules under a nitrogen atmosphere, and heated isothermally at 170° in an oil-bath for various periods of time. The solution was cooled, neutralized with Amberlite IR-120 (H^+) resin, and concentrated under vacuum. Thin-layer chromatography of an aliquot of the mixture on silica gel IB-F (Baker-Flex) with 1:9 acetone–water revealed the presence of unreacted **2** and a component having a mobility identical with that of an authentic sample of **3**.



Scheme 1 Possible mechanisms for the alkaline cleavage of phenyl β- and α-D-glucopyranoside

For quantitative determination of the 1,6-anhydride and unreacted glycoside, the reaction mixtures were per(trimethylsilyl)ated, and the products analyzed by gas–liquid chromatography using a stainless-steel column packed with 3% of SE-52 on Gas Chrom Q. The resulting data, given in Table I, indicate that, for the sample

TABLE I

PRODUCTS OF BASE-CATALYZED CLEAVAGE OF PHENYL α-D-GLUCOPYRANOSIDE IN 4.3M SODIUM HYDROXIDE AT 170°

Starting material	*Reaction time (min)*	*D-Glucoside remaining (%)*	*1,6-Anhydro-β-D-glucose*		
			Analyzed (%)[a]		*Calc. (%)*[b]
			Pyranose form	*Furanose form*	
Phenyl α-D-glucopyranoside	20	78.0	8.6	1.0	13.9
	40	60.3	10.7	1.7	25.0
	60	35.7	16.1	1.6	40.5
1,6-Anhydro-β-D-glucopyranose	20		91.8	—	
	40		65.3	5.0	
	60		54.5	4.0	

[a]Based on the original D-glucoside. [b]Theoretical yield based on the fraction of D-glucoside reacted.

heated for 20 min, the total yield of levoglucosan and its furanose isomer is ~70% based on the degraded glycoside. The yield is decreased by increasing the reaction time, because these anhydrides are subject to further degradation under the prevalent reaction-conditions. Traces of D-glucose were also detected among the product mixtures; the free sugar is partially formed through the alkaline degradation of levoglucosan, as shown by parallel experiments on model compounds.

These data confirm that base-catalyzed cleavage of phenyl α-D-glucopyranoside, like that of phenyl α-D-galactopyranoside and phenyl 2-deoxy-α-D-glucopyranoside, is facilitated by the anchimeric assistance of the hydroxyl group on C-6; but it takes place at a rather high temperature. As the intramolecular-displacement process requires a coplanar arrangement of the atomic centers involved, the marked difference in the reactivity of these α-D-glycosides must be due to the relative stabilities of their $^1C_4$(D) conformers.

However, the maximum yield of **3** and its furanose isomer, calculated on the assumption that, when formed, these anhydrides are stable, is no more than 75%, indicating the involvement of other mechanisms, such as a bimolecular, nucleophilic, aromatic substitution.

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