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Transacetalation: a convenient, nonaqueous method for effecting the deprotection of isopropylidene and benzylidene derivatives of sugars

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ABSTRACT

Sugar isopropylidene and benzylidene derivatives can be readily deprotected under nonaqueous conditions by treatment of a dichloromethane solution of the protected sugar with an excess of a sacrificial glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid. The reaction is conveniently monitored by GLC, and the fully or partially deprotected product precipitates from solution.

INTRODUCTION

The removal of carbohydrate isopropylidene and benzylidene protecting groups is normally carried out using aqueous hydrolysis techniques or, in the case of benzylidene derivatives, catalytic hydrogenolysis[1–5]. While transacetalation has been used to prepare acetal derivatives[2,4], there do not appear to be any systematic studies of deprotection via this reaction. In the course of extending our studies of the metal-catalyzed hydrogenation of carbohydrates[6], we found that the partially protected alditol 1,2:5,6-di-*O*-isopropylidene-D-mannitol underwent isopropylidene scrambling and disproportionation when treated with (cyclopentadienyl)tungsten (tricarbonyl)(triflate), a Lewis acid catalyst (see also Debost et al.[7]). We have now developed this observation into a convenient transacetalation technique for deblocking sugar acetals. In its simplest form, the method consists of treating a dichloromethane solution of a protected sugar with an excess of sacrificial glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) (eq *1*). The blocking group is thereby transferred to the glycol, and the resulting deprotected sugar typically precipitates in near-quantitative yield, in good purity, within hours

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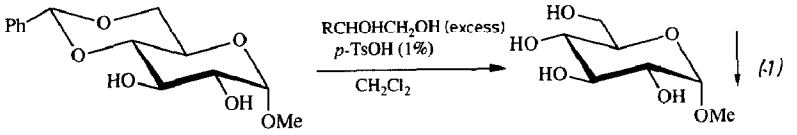
at room temperature (Table I). While not completely general, this nonaqueous method offers several advantages over conventional hydrolysis, including mild reaction conditions, facile reaction monitoring, and rapid product isolation.



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RESULTS AND DISCUSSION

Effect of solvent.—Test experiments show that the kinetics of glycol transacetalation are rapid only in solvents whose conjugate acid has a pK_a lower than about −6 (comparable to the −7 of *p*-TsOH itself). This is presumably the consequence of a mechanistic requirement for initial protonation of the sugar acetal oxygen atoms[8] (estimated pK_a −4 to −5 based on the pK_a of ether conjugate acids). Similarly, trifluoroacetic acid (pK_a 0.25) is too weakly acidic to effectively catalyze glycol exchange. Thermodynamically, transacetalation is an equilibrium phenomenon. Therefore, practical application of the method depends on using a large excess of sacrificial glycol or, preferably, exploiting solubility differences between the protected and deprotected sugar in order to drive the deprotection to completion. In addition, the solubility characteristics of reaction intermediates are a major factor in determining whether partially deprotected products can be readily isolated in good yield and purity (vide infra).

An unexpected "solvent" effect concerns the physical characteristics of the precipitated product. Thus for certain combinations of solvent and sugar, the product precipitates in a form that causes the entire reaction mixture to set up into a gel. A final solvent constraint is imposed by the low solubility of *p*-TsOH and some glycols in most appropriate solvents. Most of our studies have utilized dichloromethane.

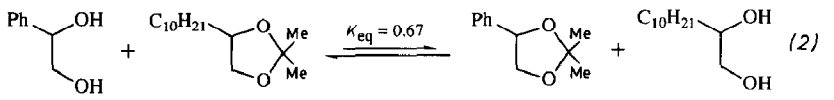
Effect of glycol.—A second major reaction variable is the choice of glycol. Using 1,2:3,5-di-*O*-isopropylidene-α-D-xylose as a model substrate, various glycols were tested for their ability to effect deprotection. All glycols examined (ethylene and propylene glycols, 2,3-butanediol, pinacol, 1,2-dodecanediol, and (±)-1-phenyl-1,2-ethanediol) gave satisfactory results. For large-scale reactions, propylene glycol is probably the most desirable due to its low cost and higher solubility in organic solvents than ethylene glycol. For purposes of monitoring reactions, however, a higher boiling glycol is advantageous because it permits better GLC analysis under the silylation conditions required for derivatization of the sugars[9]. We specifically examined 1,2-dodecanediol (DDD) and (±)-1-phenyl-1,2-ethanediol (PED) in this

TABLE I

Sugar deprotection by transacetalation

Protected Sugar (concd, mM)	Glycol [a] (equiv)	*p*-TsOH $\cdot H_2O$ (%)	Time (h)	Products (yield [b])
2,3:5,6,-Di-*O*-isopropylidene-α-D-mannofuranose (95)	PED (2.5)	1	24	α- and β-D-Mannose (70:30) [c] (92%, 95% pure)
Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (93)	PED (1.6)	1	1.5	Methyl α-D-glucopyranoside (94%, 100% pure)
1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (73)	PG (4.0)	5	1	1,2-*O*-Isopropylidene-α-D-glucofuranose (99%, 92% pure)
1,2:5,6-Di-*O*-isopropylidene-D-mannitol (43)	PG [d] (8.8)	33	1	D-Mannitol [c] (99%, 98% pure)
1,3:4,6-Di-*O*-benzylidene-D-mannitol (55)	PG (7.2)	20	1	D-Mannitol (99%, 95% pure)
1,2:4,6-Di-*O*-isopropylidene-α-L-sorbofuranose (111)	PED (2.8)	1	23	L-Sorbose [c] (96%, 86% pure)
1,2:3,5-Di-*O*-isopropylidene-α-D-xylofuranose (100)	PED (2.6)	1	19	[GLC] Starting material (18%), 1,2-*O*-Isopropylidene-α-D-xylofuranose (50%), D-Xylose (32%)
3-*O*-Acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (51)	PED (3.0)	2.5	0.5	[GLC] Starting material (33%), 3-*O*-Acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (55%)
3-*O*-Acetyl-1,2:5,6-di-*O* isopropylidene-α-D-glucofuranose (51)	PED (3.0)	2.5	4.5	[GLC] Starting material (5%), 3-*O*-Acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (17%), 1,2-*O*-Isopropylidene-α-D-glucofuranose (30%), 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (7%)
1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose (98)	PED (2.7)	1	48	< 10% conversion by GLC

[a] PED = (±)-1-Phenyl-1,2-ethanediol, PG = 1,2-propylene glycol. [b] Isolated products unless otherwise noted; purity by comparison of GLC response factor with an authentic sample. [c] Intermediates detected by GLC. [d] When a 0.1 M solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol was treated with 2.53 equiv of PED and 1% *p*-TsOH, a mixture of mannitol and a partially deprotected product were formed after 24 h.



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regard. Transacetalation of their respective isopropylidene acetals (eq 2) shows that DDD is the stronger thermodynamic ketone acceptor, but only by a small margin. In contrast, independent side-by-side reactions show that PED kinetically deprotects 1,2:3,5-di-*O*-isopropylidene-α-D-xylose about seven times faster than DDD. [(±)-1-Phenyl-1,2-ethanediol is also a better kinetic acceptor than propylene glycol by a factor of 3:1.] In an internal competition experiment, however, the kinetic selectivity is reversed, favoring transfer of the protecting group to DDD over PED by a factor of 2:1. Finally, the initial rate of deprotection shows a slight inverse dependence upon the amount of glycol employed, decreasing by about 25% on going from one to four equivalents of PED. It is possible to rationalize these unusual results in terms of the various competing equilibria present (e.g., protonation of glycol(s) vs. acetal) and how these combine with the different kinetic nucleophilicities of the glycols. In view of the complex situation found for the analogous hydrolysis of acetals[8], however, detailed mechanistic speculation based on the data in hand seems unwarranted.

Effect of sugar.—The third primary reaction variable is one that is common to both aqueous hydrolysis and transacetalation, namely, the nature of the sugar acetal with respect to ring size, stereochemistry, and protecting group. This general area has been the subject of extensive investigations[1,4] and was deemed to be beyond the scope of the present work. Our qualitative observations, however, are consistent with the trends typically observed. For example, non-anomeric acetals are much more readily cleaved than anomeric acetals. It is worth noting in this regard that the nonaqueous method reported here is far easier to optimize for partial deprotection than are aqueous hydrolysis schemes. First, partially protected products often have low solubilities in dichloromethane and hence precipitate, dramatically slowing their complete deprotection. Second, the monitoring of graded aqueous hydrolyses is normally tedious since most of the water must be evaporated prior to derivatization for GLC analysis. This is not necessary for nonaqueous samples[9] and, therefore, analysis throughput can be much higher, permitting more careful and timely monitoring of the reaction profile. In addition, the nature of the product(s) formed can be altered by changing the solvent or glycol and by varying the amount of catalyst or glycol, together with the length of reaction.

Scope of reaction.—The reaction has been successfully applied to a variety of carbohydrate derivatives (Table I). Mixed functional groups have been only briefly investigated. In the case of 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, acetate transesterification was partially competitive with transacetalation. The ability to vary the glycol, however, offers potential opportunities to alter the deprotection selectivity in ways that are not available in aqueous hydrolysis schemes. For example, the use of a tertiary glycol such as pinacol might permit the removal of isopropylidene groups in the presence of a trityl group.

EXPERIMENTAL

General.—Dichloromethane was dried over molecular sieves. (Wet solvents can lead to hydrolysis in competition with transacetalization. In the absence of hydrolysis, the reaction progress can be monitored by GLC using both disappearance of starting sugar and appearance of glycol acetal, permitting an accurate assessment of the extent of reaction, even when partially and/or fully deprotected products precipitate from the reaction mixture. The glycol acetals are much more accurately quantitated than is acetone resulting from hydrolysis.) Most reactions employed a stock solution of *p*-TsOH · H_2O in CH_2Cl_2 at near the solubility limit of about 0.5 mg/mL (the kinetics of dissolution are quite slow). GLC analyses were performed as described elsewhere[9]. Authentic isopropylidene and benzylidene acetals of the sacrificial glycols required for GLC response factor calibration were prepared *in situ* from the glycol and an excess of 2,2-dimethoxypropane and α,α-dimethoxytoluene, respectively.

Control reaction of (±)-1-phenyl-1,2-ethanediol (PED) with p-*TsOH.*—A solution of PED (57.4 mg, 415 μmol), bibenzyl (31.9 mg), and *p*-TsOH (1.7 mg, 8.9 μmol, 0.02 equiv) in CH_2Cl_2 (2.0 mL) was allowed to stand at room temperature. GLC monitoring over a period of 3 days showed that the amount of PED present remained constant within experimental error (436 μmol at 5 min, 426 μmol at 1.5 h, 448 μmol at 6.5 h, 418 μmol at 28 h, and 421 μmol at 3 days).

*Deprotection of 2,3:5,6-di-*O*-isopropylidenemannose with (±)-1-phenyl-1,2-ethanediol (PED).*—An aliquot of a *p*-toluenesulfonic acid stock solution (4.0 mL, 10.5 μmol, 0.01 equiv) was added to a solution of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (270 mg, 1.04 mmol), bibenzyl (51.4 mg, internal standard), and PED (362 mg, 2.62 mmol, 2.53 equiv) in CH_2Cl_2 (7 mL). Within 10 min, the reaction mixture turned cloudy. After 35 min, GLC analysis showed 67% conversion of starting material to a mixture of mannose (not accurately quantitated due to precipitation), ~500, 70, and 50 μmol of three unidentified intermediates (presumably monoisopropylidene mannose derivatives), together with the formation of 803 μmol PED isopropylidene acetal (77% of 1 equiv). At 3.5 h 1540 μmol of PED acetal (1.48 equiv) has formed. After 24 h, formation of PED acetal reached 1950 μmol (94% of 2 equiv) and less than 5% of the starting sugar could be accounted for by soluble sugar species. The reaction was then worked up by centrifugation, repeated washing, and re-centrifugation (3 × 10 mL CH_2Cl_2), and the resulting solid was dried under vacuum to give 172 mg of hygroscopic white material identified by GLC as a 70:30 mixture of α- and β-D-mannopyranose (172 mg, 92%, 95% pure by GLC based on comparison of response factor with an authentic sample).

*Deprotection of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with (±)-1-phenyl-1,2-ethanediol (PED).*—The reaction was carried out identically to that described above for 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose except using methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (262 mg, 0.928 mmol), bibenzyl (53.1 mg), and

PED (201.0 mg, 1.455 mmol, 1.57 equiv) in CH_2Cl_2 (6 mL). A precipitate started to form within 5 min. After 35 min, GLC analysis showed the formation of 808 μmol PED benzylidene acetal isomers (87%) and that less than 10% of the starting material remained. The reaction was essentially complete at 1.5 h at which time it was worked up as for the previous reaction to give methyl α-D-glucopyranoside (169 mg, 94%, 100% pure by GLC based on comparison of response factor with an authentic sample). A similar reaction employing propylene glycol (4.35 equiv) gave essentially identical results, except that the product formed as beautiful white needles.

Deprotection of mannitol derivatives with propylene glycol.—Dichloromethane (4.5 mL) was added to 1,3:4,6-di-*O*-benzylidene-D-mannitol (89.1 mg, 249 μmol), crystalline *p*-TsOH (9.5 mg, 49.9 μmol), bibenzyl (61.6 mg), and propylene glycol (135.7 mg, 1783 μmol) resulting in the formation of a gelatinous precipitate within 5 min. GLC analysis after 1 h showed that no starting sugar remained. The reaction mixture was transferred to a centrifuge tube with the aid of additional CH_2Cl_2, an equal volume of diethyl ether was added, and the mixture was centrifuged. The precipitate was washed and re-centrifuged with 50:50 CH_2Cl_2–ether (2 × 8 mL) and the solid was dried under vacuum to give mannitol (45 mg, 99%, 95% pure by GLC based on comparison of response factor with an authentic sample). GLC–MS analysis of the supernatant of a similar reaction confirmed the formation of the benzylidene acetal of propylene glycol.

A similar reaction employing 1,2:5,6-di-*O*-isopropylidene-D-mannitol gave similar results (Table I), but when the deprotection of 1,2:5,6-di-*O*-isopropylidene-D-mannitol was carried out analogously to that described above for 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose [*i.e.*, using less catalyst and a smaller quantity of a different glycol (PED)], the resulting precipitate was found after 24 h to consist of a mixture of mannitol (~ 80%) and an unknown, presumably 1,2-*O*-isopropylidene-D-mannitol[7].

Other deprotections.—The other deprotections listed in Table I were carried out similarly, using the reaction conditions described in the Table.

Transacetalation equilibrium between (±)-1-phenyl-1,2-ethanediol (PED) and 1,2-dodecanediol (DDD).—2,2-Dimethoxypropane (22 μL, 179 μmol) was added to a solution of PED (29.5 mg, 214 μmol), bibenzyl (29.7 mg), and *p*-TsOH (2.7 mg, 14 μmol) in CH_2Cl_2 (2.0 mL) in a screw-capped Erlenmeyer flask under Ar. GLC analysis at 20 and 60 min both indicated that the solution now contained 58 μmol of PED and 162 μmol of PED isopropylidene acetal. (Note that this reaction, involving exchange of a free glycol with a monohydridic alcohol acetal, is also rapid in *N*-methyl-2-pyrolidinone despite the pK_a of the latter, ~ 0.) DDD (41.9 mg, 207 μmol) was then added. After 30 min GLC analysis of the solution showed that it contained PED (141 μmol), PED isopropylidene acetal (78 μmol), DDD (132 μmol), and DDD isoproppylidene acetal (87 μmol) ($K_{obs} = 0.85$ for eq *2*). Analysis at 2.8 and 6 h gave identical results (±1 μmol): PED (145 μmol), PED acetal (71 μmol), DDD (125 μmol), and DDD acetal (91 μmol), correspond-

ing to a $K_{eq} = 0.67$ for eq 2. A similar reaction was conducted reversing the order of addition of the glycols. In this case, GLC analysis at 30 min gave a $K_{obs} = 0.36$ for eq 2. Analysis at 2.8, 6, and 24 h gave identical results (± 3 μmol), corresponding to a $K_{eq} = 0.65$, 0.66, and 0.67 for eq 2 at the three different times, respectively.

Comparison of rates of deprotection.—A standard experiment consisted of treating a solution of 1,2:3,5-di-*O*-isopropylidene-α-D-xylose (24.4 mg, 106 μmol), (±)-1-phenyl-1,2-ethanediol (PED) (27.7 mg, 200 μmol), bibenzyl (30.6 mg) in CH_2Cl_2 (1.0 mL) with an aliquot of a *p*-TsOH stock solution (1.0 mL, 2.5 μmol) in a screw-capped Erlenmeyer flask. Aliquots were removed at various times and analyzed by GLC for all starting materials and products. For independent, side-by-side comparisons, 1,2-dodecanediol (DDD) or propylene glycol (PG) were substituted for the PED. For internal competition experiments, 100 μmol of each glycol was employed. The effect of glycol concentration was determined using 101, 200, and 420 μmol of PED. Representative data for the experiments are as follows (equiv of glycol employed, μmol of 1,2-*O*-isopropylidene-α-D-xylose formed). (A) 5 min: 1.0 PED, 20.1; 2.0 PED, 17.7; 4.2 PED, 15.3; 2.0 DDD, 2.8; 2.0 PG, 4.9; 1.0 PED + 1.0 DDD, 4.9 (PED acetal, 1.4; DDD acetal, 2.5). (B) 15 min: 1.0 PED, 43.6; 2.0 PED, 44.5; 4.2 PED, 44.4; 2.0 DDD, 5.4; 2.0 PG, 15.7. (C) 25 min: 1.0 PED + 1.0 DDD, 16.0 (PED acetal, 4.7; DDD acetal, 8.6). (D) 45 min: 2.0 PED, 75.6; 2.0 DDD, 10.4; 2.0 PG, 45.

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