Torsional effects on reactivity in glycosyl transfer

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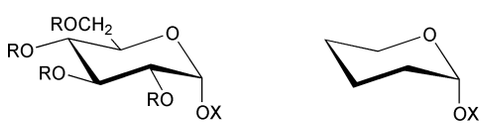
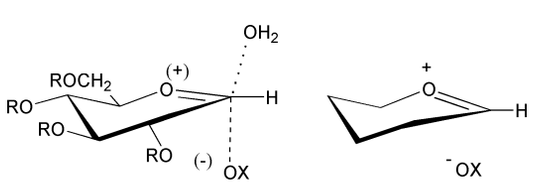
The net effect of the four substituents on a hexapyranoside is to reduce reactivity at the anomeric centre by a factor of $>10^7$ compared with the parent tetrahydropyranyl acetal. The magnitude of the steric contribution to this factor is assessed by measuring the effect of four equatorial methyl groups on the rate of hydrolysis of 4-nitrophenyl tetrahydropyranyl acetal. Though the electronic effects of methyl substituents will be to increase the rate of hydrolysis, the net effect of the four equatorial methyl groups is a 4-fold decrease, evidence for an opposing steric effect estimated at two orders of magnitude. Torsional effects in a glycopyranoside thus contribute a factor of up to 50 towards the total of 10^7.

Intrinsic reactivity in glycosyl transfer reactions depends on the pattern of substitution on the sugar ring. Substituent effects are large: the acid-catalysed hydrolysis of methyl α-D-glucoside (**1**, R = H, X = Me) is over 10^7 times slower than that of the corresponding tetrahydropyranyl acetal **2** (X = Me),[1] and the ratio remains of the order of 10^6 for the spontaneous hydrolysis of the corresponding 2,4-dinitrophenyl acetals (**1** and **2**, R = H, X = 2,4-DNP).[2,3]



1 **2**

There is general agreement that these effects reflect destabilisation by the four electronegative OH groups of the sugar of the transition state **3** for glycosyl transfer. Glycosyl transfer involving a typical hexose is "borderline-concerted,"[4] because the oxocarbenium ion intermediate barely lives long enough in water to be a fully-equilibrated intermediate of the sort **4** involved in the hydrolysis of a tetrahydropyranyl acetal. For a given leaving group XO^- the transition state will be later for the much slower reaction of a glycoside, and the build-up of positive charge on the glycone correspondingly greater than for the tetrahydropyranyl system **2**. The transition state for glycosyl transfer thus involves almost complete rehybridisation of the anomeric carbon to sp^2, with a substantial build up of positive charge, primarily on the ring oxygen. Whatever the detailed transition structure in a particular case, the oxocarbenium ion is a convenient model, with electronegative substituents expected to be electronically destabilising. ‡



3 **4**

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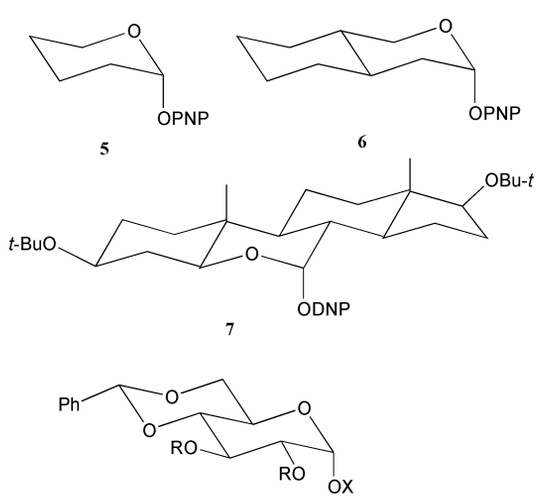
‡ Withers and his coworkers[3] suggest that this electronic destabilisation is primarily a field effect, since it is generally greater for substituents in the 4- compared with the 3-position.

The effects of substituents are certainly primarily electronic, as indicated by the decreasing reactivity of systems **1** with OX = (solvated) OH > O–alkyl > O–acyl > F. But there are good reasons to suppose, as suggested frequently in the literature, that other factors—steric and conformational—are also significant.[3,5] This work is concerned specifically with estimating the magnitude of torsional effects on glycopyranosyl transfer.

Conformational restraints have a significant effect on the reactivity of tetrahydropyranyl acetals. The oxadecalin and oxasteroid acetals **6** and **7**, with one and two *trans*-bridgeheads, respectively, are hydrolysed 2–3 and over 200 times more slowly than the parent system **5** (PNP = *p*-nitrophenyl).[6] The benzhydryl derivatives **8** of glycopyranosides show a similar effect, which has been put to good use in selective glycosylation procedures.[7]



5 **6** **7** **8**

The simple explanation of these effects is that a *trans*-bridgehead, which inhibits ring-inversion, also hampers the formation of the transition state for cleavage of the C–OX bond. This is to be expected, since the two processes involve similar half-chair conformations **9** and **10**, respectively.

A full complement of equatorial substituents (as in a β-glucoside) also increases the barrier to ring-inversion,[8–10] so may also be expected to reduce the rate of glycosyl transfer reactions. To get some idea of the order of magnitude of the

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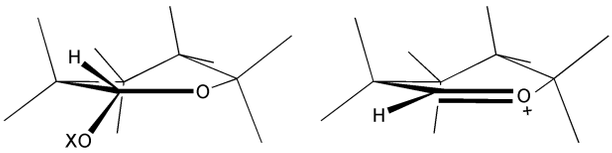
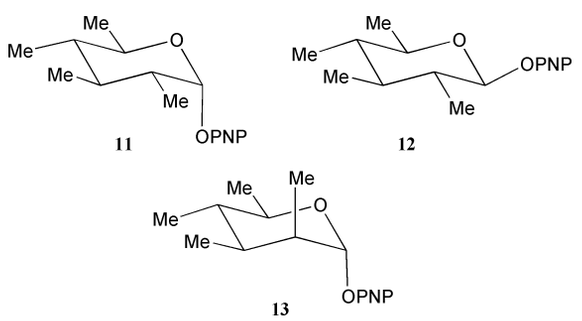


9 10

effect—how much it might contribute to the 10^7-fold difference in reactivity between a glucoside and the corresponding tetrahydropyranyl acetal—we have prepared and studied the all-equatorial tetramethyltetrahydropyranyl acetals **11** and **12**.

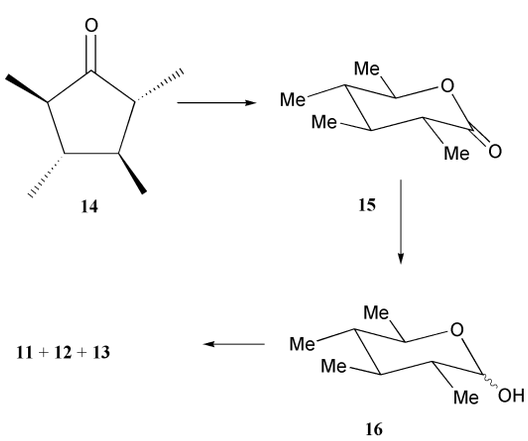
Methyl groups are conformationally bigger than OH groups, so any significant effect should be readily identified and quantified.

The synthesis also produced small amounts of diastereoisomer **13**. We report a study[11] of the hydrolysis of **11**–**13**, and comparisons with the reactivity of the parent 4-nitrophenyl tetrahydropyranyl acetal **5** under the same conditions.



Results and discussion

Synthesis was relatively straightforward. The known tetramethylcyclopentanone **14**[12] was converted by Baeyer–Villiger oxidation to the lactone **15**. This was reduced to the mixture of lactols **16**, which were converted to the 4-nitrophenyl acetals *via* the *O*-acetyl derivatives. Separation and characterisation of the three diastereoisomers showed that the third product was the isomer **13** with one axial methyl group. Some epimerisation at C(2) had occurred during the final, acetal formation step, presumably by an elimination–addition mechanism.



Reactivity

Rates of spontaneous hydrolysis of 4-nitrophenyl acetals were measured under standard, pseudo-first order conditions, in dilute KOH solutions at 39 °C. Consistent with the very polar transition state the reaction of the equatorial compound **12** shows high sensitivity to the amount of organic solvent present (as also shown by earlier work[13]), though it is curiously insensitive to the ionic strength (Fig. 1). The results for the full set of acetals summarised in Table 1 are for aqueous solvent containing 20% v/v dioxane (for solubility reasons), with ionic strength maintained at 1.0 mol dm^{-3}, to facilitate direct comparison with previous work.

Table 1 Observed rate constants for the spontaneous hydrolysis of 4-nitrophenyl acetals **5**, **11**–**13** and **17**–**18** followed at λ = 405 nm at 39 °C, in aqueous buffers containing 20% dioxane, I = 1 mol dm^{-3}

Substrate	k_{obs}/s^{-1}	k_{rel}
5	$9.19 \pm 0.07 \times 10^{-5}$	3.91
12	$8.39 \pm 0.19 \times 10^{-5}$	3.57
11	$2.35 \pm 0.06 \times 10^{-5}$	**1.00**
13	$1.96 \pm 0.06 \times 10^{-5}$	0.83
17	$9.83 \pm 0.09 \times 10^{-5}$	4.18
18	$1.10 \pm 0.01 \times 10^{-3}$	46.8

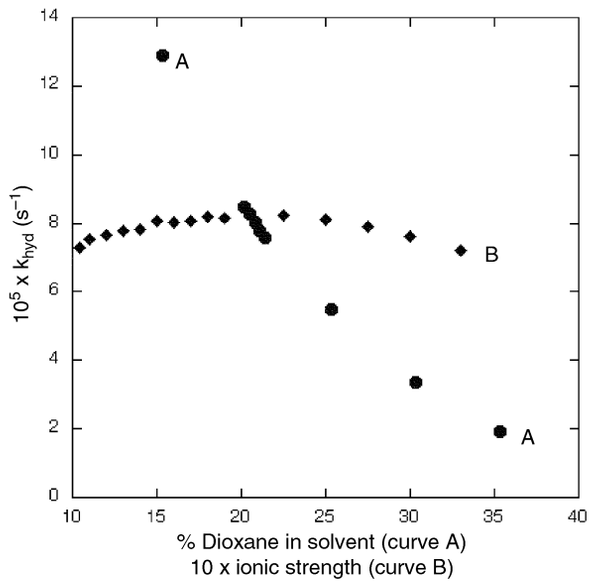
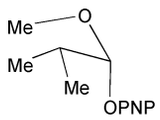


Fig. 1 Dependence of the rate of hydrolysis of equatorial compound **12** on the polarity of the medium (curve **A**, filled circles, scale represents % dioxane (v/v) in mixed dioxane–water solvent) and ionic strength (curve **B**, diamonds, scale represents ionic strength × 10 (0–4 M KCl).

Significantly, the axial all-equatorial-tetramethyl acetal **11** is the least reactive of this set of compounds. (Its equatorial anomer **12** is hydrolysed 3.6 times faster, as expected for these systems, where reactivity is controlled by ground state stability and the axial anomer is stabilised by the anomeric effect.[6]) The net effect of the four equatorial methyl groups is a four-fold decrease in reactivity (the tetrahydropyranyl acetal **5** is hydrolysed 3.9 times faster than **11**). This effect is not large, but is *prima facie* evidence for a larger torsional/conformational effect because additional methyl groups are known to activate conformationally flexible acetals towards hydrolysis.[14]

Of various ways of estimating the magnitude of the electronic activation expected from the four methyl substituents based on linear free energy relationships for related acetals,[11] the most appropriate uses the ρ_I-values of Withers and his co-workers, measured separately for individual positions on the glycosidic ring (−8.3, −2.9 and −5.1 for the glucose 2-, 3- and 4-positions, respectively).[3] We use a σ_I-value of 0.046[15] for the methyl group and assume that effects are additive. The missing value is for the carbon adjacent to the ring oxygen: for this position we use the relative rates estimated by Kankaanperä[16] for the loss of methanol from the conjugate acids of methoxymethyl acetals $ROCH_2OMe$. For the series RO = MeO, EtO and *i*-PrO these were 1 : 4.6 : 24, corresponding to an increase of 4.9 ± 0.3 per methyl group. The cumulative effect of the four methyl groups of **11**, thus predicted, is a 28-fold rate acceleration. That this is not unreasonable (and, in particular, not exaggerated) is shown by our data (Table 1) for the two acetals

17 and **18**, derived from 2-methylpropanal. Thus **18**, with the two (ring-CHMe) groups of **12** replaced by (MeCHMe) groups, is hydrolysed 47 times faster. The combined torsional effects of the four methyl groups thus account for a rate factor of 110.



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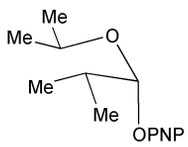

18

To translate this approximate figure into the torsional effect relevant to glucosyl transfer we must correct for the smaller size of OH compared with methyl groups. The least imperfect measure of group size in this context is the conformational preference for the equatorial position, corresponding to *A*-values in cyclohexanes. Values are different for the different positions of a tetrahydropyran: 12.0, 5.98 and 8.16 kJ mol^{-1} for methyl groups in the 2-, 3- and 4-positions, corresponding respectively to the 5-, (4- and 2-) and 3-positions of a pyranoside.[17] The data are not available for the OH group, but Franck[18] has pointed out that at least for substituents in the 2-position of a tetrahydropyran, conformational preferences are greater than for cyclohexane by a constant factor. So scaling the values for methyl quoted above according to the relative (Me *vs.* OH) *A*-values should give reasonable estimates of the values for the OH group in the various positions of a tetrahydropyran. The *A*-value for OH depends strongly on the solvent, so to set limits on the effects we do the calculation for the two extreme situations, based on *A*-values of 0.60 (2.51 kJ mol^{-1}) in apolar cyclohexane and 1.25 (5.23 kJ mol^{-1}) in water.[19] The values obtained are 4.31 and 5.86 kJ mol^{-1} for hydroxy groups in the (4- and 2-) and 3-positions of a pyranoside in water, and 2.05 and 3.81 kJ mol^{-1} for the same groups in cyclohexane.

Given the substituent size parameters a simple linear free energy relationship calculation is possible. The sum of the parameters for the four methyl groups of **11** is 32.1, (and for hydrogen zero) so $\log (k/k_0) = 2.033 = 32.1 \times c$, giving a value for the sensitivity parameter c of 0.0634. The sum of the substituent parameters for the three equatorial OH groups and CH_2OH (taken to be the same as for methyl) of glucose is 26.5 and 19.9 (kJ mol^{-1}) for water and cyclohexane, respectively (in reasonable agreement with the energy differences between the two chair forms of glucopyranosides).[20] So the torsional effects on the rate of glucosyl transfer reactions are estimated as 47 and 18 in water and cyclohexane, respectively.

Torsional effects on reactivity are thus significant, but not large, consistent with the general observation that the rates of hydrolysis of glycosides increase as the total number of axial OH groups increases.[3] The effect of a particular group will depend on its position (as well as the presence and nature of other groups on the ring). Our data do not allow a more detailed analysis, but the point is made very clearly by the rate constant for compound **13**, with one axial methyl group, which is actually hydrolysed slightly more slowly than the all-equatorial-tetramethyl diastereoisomer **11**. Substituents in the (corresponding) 2-position of glycosides often confer special properties, an axial 2-OH group, for example, enhancing the anomeric effect.[20] Perhaps as a consequence 2,4-dinitrophenyl mannoside is hydrolysed some five times more slowly than the corresponding glucoside,[3]§ but it is hard to see how this explanation could apply to the comparison between **11** and **13**. We know that reactivity is very sensitive to the electronic effects of substituents at this position: the evidence indicates that it is also very insensitive to steric, including torsional effects.

§ Prompting the authors' comment that "the relief of steric strain is not a key factor for sugars with an axial 2-substituent".

Experimental

All solvents for reactions were dried and distilled by standard procedures prior to use. All potentially moisture sensitive reactions were carried out under an inert atmosphere of either argon or nitrogen. All glassware was dried under reduced pressure using a hot air blower, or assembled directly from the oven and allowed to cool under an inert atmosphere. Commercial grade reagents were used without further purification. Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). NMR spectra were recorded at ambient probe temperature on Bruker DPX250, DPX400, DRX400 and DRX500 Fourier transform spectrometers using the indicated solvent as internal deuterium lock. Chemical shifts are given in units of δ ppm downfield from TMS, where δ(TMS) = 0 ppm. Couplings, *J*, are given in Hz. Broadband proton decoupling was used for ^{13}C NMR experiments. Infra-red spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Mass spectra were recorded on Kratos MS890 (EI), Kratos FAB MS890 (FAB) and MSI Concept IH (LSIMS) mass spectrometers. Melting points were measured on a Stuart Scientific SMP1 melting point apparatus and are uncorrected.

Syntheses

***rel*-(3*R*,4*S*,5*S*,6*R*)-3,4,5,6-Tetramethyltetrahydropyran-2(2*H*)-one 15.** 3-Chloroperbenzoic acid (345 mg, 2.00 mmol) was added to a stirred solution of the ketone **14**[12] (172 mg, 1.23 mmol) in CH_2Cl_2 (10 cm^3). Toluene-4-sulfonic acid (100 mg, 0.53 mmol) was added and the mixture was heated at reflux for 5 h. The mixture was cooled to room temperature, diluted with diethyl ether (100 cm^3), washed successively with 2% aqueous sodium thiosulfate (50 cm^3), saturated aqueous sodium bicarbonate (20 cm^3), brine (20 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was chromatographed (SiO_2, CH_2Cl_2) to yield the lactone **15** (169.2 mg, 88%) as a colourless oil with a strong fruity smell; $R_f(CH_2Cl_2)$ 0.15; $\nu_{max}(CDCl_3)/cm^{-1}$ 1720 (C=O); δ_H(250 MHz, $CDCl_3$) 4.00 (1 H, dq, *J* 9.7 and 6.3, 6-CH), 2.01 (1 H, dq, *J* 9.8 and 7.1, 3-CH), 1.33 (3 H, d, *J* 6.3, 6-CH_3), 1.30 (3 H, d, *J* 7.1, 3-CH_3), 1.19 (1 H, m, 4-CH or 5-CH), 1.07 (1 H, m, 4-CH or 5-CH), 0.98 (3 H, d, *J* 6.0, 4-CH_3 or 5-CH_3) and 0.90 (3 H, d, *J* 6.2, 5-CH_3 or 4-CH_3); δ_C(62 MHz, $CDCl_3$) 174.2, 81.24, 42.9, 41.0, 39.8, 20.3, 17.5, 15.9 and 14.6; *m*/*z* (+EI) 156 (M^+, 6%), 112 (45, $M^+ - CO_2$), 110 (9), 83 (17), 69 (35), 57 (33), 56 (100), 55 (34) and 41 (60) (Found: M^+, 156.1149. $C_9H_{16}O_2$ requires, *M* 156.1150).

(3*R*,4*S*,5*S*,6*R*)-3,4,5,6-Tetramethyltetrahydropyran-2(2*H*)-ol 16 (racemic mixture of anomers). Diisobutylaluminium hydride (3.47 cm^3 of a 1 mol dm^{-3} solution in CH_2Cl_2, 3.47 mmol) was added to a stirred solution of the lactone **15** (217 mg, 1.39 mmol) in dry toluene (10 cm^3) at −78 °C (dry ice–acetone bath) under an argon atmosphere. The reaction mixture was stirred for 4 h at −78 °C, then MeOH (2 cm^3) was added carefully. After warming to room temperature, the reaction mixture was diluted with diethyl ether (50 cm^3), washed with cold 10% HCl (5 cm^3) and water (2 × 20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. Column chromatography (SiO_2, CH_2Cl_2–MeOH, 9 : 1) afforded the *lactols* **16** as a colourless oil with a strong smell (214 mg, 97%); $R_f(CH_2Cl_2$–MeOH, 9 : 1) 0.47. ^1H and ^{13}C NMR spectra showed that the product **16** is a mixture of anomers at C-2 (~2 : 1). δ_H(400 MHz, $CDCl_3$): 4.94 (0.6 H, t, *J* 5.0, 2-CH of axial isomer), 4.56 (0.4 H, d, *J* 6.7, 2-CH of equatorial isomer), 4.27 (0.6 H, t, *J* 6.7, 6-CH of axial isomer), 4.06 (0.4 H, d, *J* 2.0, 6-CH of equatorial anomer), 3.72 (dq, *J* 10.0 and 6.2), 3.20 (dq, *J* 9.3 and 6.2), 1.21–1.50 (m), 1.21 (d, *J* 6.2), 1.13 (d, *J* 6.2) and 0.70–1.00 (m); δ_C(100.6 MHz, $CDCl_3$) 99.9, 94.7, 77.3, 77.0, 76.7, 76.4, 69.4, 43.7, 43.5, 43.1, 41.9, 40.7, 35.6, 19.7, 19.6, 16.3, 16.0, 14.9, 14.6, 14.6 and 14.1.

(2*R*,3*R*,4*S*,5*S*,6*R*)-, (2*S*,3*R*,4*S*,5*S*,6*R*)-, and (2*R*,3*S*,4*S*,5*S*,6*R*)-3,4,5,6-Tetramethyl-2-(4-nitrophenoxy)tetrahydro-2*H*-pyrans 11, 12 and 13 (racemic mixtures). Acetic anhydride (0.149 cm^3, 1.58 mmol) was added to a stirred solution of the lactols **16** (100 mg, 0.63 mmol) in anhydrous pyridine (5 cm^3) at room temperature. After 3 h, the volatile products were evaporated under reduced pressure (bath temperature should not exceed 70 °C). The residue (used without further purification) was dissolved in CH_2Cl_2 (5 cm^3), and 4-nitrophenol (88 mg, 0.63 mmol) and $BF_3{\cdot}Et_2O$ (20 mg) were added. The reaction mixture was stirred at room temperature under argon for 2.5 h. The mixture was diluted with diethyl ether (100 cm^3), washed with 10% NaOH (10 cm^3) and water (2 × 20 cm^3), dried (Na_2SO_4) and evaporated. The residue was chromatographed (SiO_2, CH_2Cl_2) to give a mixture of stereoisomers as an oil (80 mg, 45%, based on the lactol); $R_f(CH_2Cl_2)$ 0.65. This mixture contains three isomers, which were separated by HPLC (ZORBA® SIL column, eluent EtOAc–hexane, 1 : 20). Analysis of the spectroscopic data using COSY, HMBC and HMQC spectra allowed us to assign all the three compounds, which eluted in the order **13**, **11**, and finally **12**.

Data for ***11****.* δ_H(400 MHz, $CDCl_3$) 8.19 (2 H, d, *J* 7.2, 3′-H and 5′-H), 7.16 (2 H, d, *J* 7.2, 2′-H and 6′-H), 5.35 (1 H, d, *J* 3.2, 2-H), 3.50 (1 H, dq, *J* 10.5 and 6.2, 6-H), 1.64 (1 H, dqd, *J* 10.5, 6.7 and 3.2, 3-H), 1.48 (1 H, tq, *J* 10.5 and 6.5, 4-H), 1.12 (3 H, d, *J* 6.2, 6-CH_3), 1.08 (1 H, tq, *J* 10.5 and 6.6, 5-H), 0.99 (3 H, d, *J* 6.7, 3-CH_3), 0.96 (3 H, d, *J* 6.5, 4-CH_3) and 0.87 (3 H, d, *J* 6.6, 5-CH_3); δ_C(100.6 MHz, $CDCl_3$) 162.8, 141.8, 125.7, 116.3, 99.9, 71.2, 43.2, 40.7, 38.4, 19.8, 16.2, 14.9 and 14.8; *m*/*z* (+FAB) 279 (M^+, 20%), 278 (40), 206 (100) and 141 (100). (Found: $M^+ - H$, 278.1397. $C_{15}H_{20}NO_4$ requires, 278.1392).

Data for ***12****.* δ_H(500 MHz, $CDCl_3$) 8.19 (2 H, d, *J* 9.2, 3′-H and 5′-H), 7.17 (2 H, d, *J* 9.2, 2′-H and 5′-H), 4.76 (1 H, d, *J* 8.67, 2-H), 3.39 (1 H, dq, *J* 9.44 and 6.14, 6-H), 1.35 (1 H, tq, *J* 8.67 and 6.46, 3-H), 1.29 (3 H, d, *J* 6.14, 6-CH_3), 1.10 (1 H, m, 5-H), 1.08–1.00 (7 H, m, 3-CH_3, 4-CH_3 and 4-H) and 0.92 (3 H, d, *J* 6.39, 5-CH_3); δ_C(125.7 MHz, $CDCl_3$) 162.7, 142.1, 125.7, 116.1, 103.3, 77.0, 43.0, 42.1, 41.8, 19.8, 16.4, 14.7 and 13.8.

Data for ***13****.* δ_H(400 MHz, $CDCl_3$) 8.19 (2 H, d, *J* 7.2, 3′-H and 5′-H), 7.16 (2 H, d, *J* 7.2, 2′-H and 6′-H), 5.37 (1 H, d, *J* 1.2, 2-H), 3.41 (1 H, dq, *J* 10.1 and 6.2, 6-H), 1.99 (1 H, dqd, *J* 10.1, 6.9 and 4.5, 4-H), 1.91 (1 H, qdd, *J* 7.3, 4.5 and 1.2, 3-H), 1.31 (1 H, tq, *J* 10.1 and 6.5, 5-H), 1.12 (3 H, d, *J* 6.2, 6-CH_3), 1.02 (3 H, d, *J* 7.3, 3-CH_3), 0.96 (3 H, d, *J* 6.9, 4-CH_3) and 0.83 (3 H, d, *J* 6.5, 5-CH_3); δ_C(100.6 MHz, $CDCl_3$) 162.4, 141.3, 125.7, 116.1, 101.1, 72.0, 37.8, 37.5, 32.6, 19.6, 16.5, 14.5 and 11.1.

2-Methylpropanal methyl (17) and isopropyl (18) 4-nitrophenyl acetals. A solution of 4-nitrophenol (2.78 g, 20 mmol) in methanol (10 cm^3) was added dropwise to a stirred solution of sodium methoxide (1.12 g, 20.7 mmol) in methanol (10 cm^3). The mixture was stirred overnight and evaporated under reduced pressure to yield sodium 4-nitrophenolate as an orange solid which was used without further purification. 1-Chloro-2-methylpropyl isopropyl ether[21] (1.00 g, 6.6 mmol) in Et_2O (5 cm^3) was added dropwise to a stirred suspension of sodium 4-nitrophenolate (1.07 g, 6.6 mmol) in Et_2O (5 cm^3). The mixture was stirred at room temperature for 2 h and the solvent removed under reduced pressure. ^1H NMR spectroscopy of the residue indicated the presence of two products in addition to starting material and decomposition products. The residue was chromatographed (SiO_2, hexane–CH_2Cl_2, 1 : 1) to give the *acetal* **17** (22 mg, 2%) as a colourless oil which was stored at −18 °C because it decomposed at room temperature. R_f(hexane–CH_2Cl_2, 1 : 1) 0.32; $\nu_{max}(CDCl_3)/cm^{-1}$ 1608 (Ar), 1593 (Ar), 1515 (NO_2), 1495 (Ar), 1343 (NO_2), 1252 (C–O) and 1113 (C–O); δ_H(400 MHz; $CDCl_3$) 8.18 (2 H, d, *J* 9.3, 3′-H and 5′-H), 7.09 (2 H, d, *J* 9.3, 2′-H and 6′-H), 4.93 (1 H, d, *J* 6.8, OCHO), 3.35 (3 H, s, OCH_3), 2.20 (1 H, oct, *J* 6.8, CC*H*$(CH_3)_2$), 1.00 (3 H, d, *J* 6.8, CCH*Me*$_A$Me$_B$) and 0.99 (3 H, d, *J* 6.7, CCHMe$_A$*Me*$_B$); δ_C(100.6 MHz; $CDCl_3$) 162.8, 142.0, 125.9, 116.5, 107.3, 52.9, 30.7, 17.6 and 17.1; *m*/*z* (+LSIMS) 226.1 (MH^+)(Found: MH^+, 226.1081. $C_{11}H_{16}NO_4$ requires, 226.1074).

The second product was the *acetal* **18** (38 mg, 2%), obtained as a colourless oil which also had to be stored at −18 °C because it decomposed at room temperature. R_f(hexane–CH_2Cl_2, 1 : 1) 0.35; $\nu_{max}(CDCl_3)/cm^{-1}$ 1606 (Ar), 1592 (Ar), 1514 (NO_2), 1494 (Ar), 1343 (NO_2), 1256 (C–O) and 1112 (C–O); δ_H(400 MHz; $CDCl_3$) 8.15 (2 H, d, *J* 9.3, 3′-H and 5′-H), 7.07 (2 H, d, *J* 9.3, 2′-H and 6′-H), 5.06 (1 H, d, *J* 6.3, OCHO), 3.86 (1 H, sept, *J* 6.2, OC*H*$(CH_3)_2$), 2.14 (1 H, oct, *J* 6.7, CC*H*$(CH_3)_2$), 1.16 (3 H, d, *J* 6.2, OCH*Me*$_A$Me$_B$), 1.12 (3 H, d, *J* 6.1, OCHMe$_A$*Me*$_B$), 0.99 (3 H, d, *J* 6.7, CCH-*Me*$_A$Me$_B$) and 0.94 (3 H, d, *J* 6.8, CCHMe$_A$*Me*$_B$); δ_C(100.6 MHz; $CDCl_3$) 162.8, 141.7, 125.8, 116.9, 106.3, 70.3, 31.7, 23.2, 22.0, 17.6 and 17.2; *m*/*z* (+LSIMS) 254.1 (MH^+)(Found: MH^+, 254.1389. $C_{13}H_{20}NO_4$ requires, 254.1387).

Kinetic measurements

Inorganic buffer reagents were of AnalaR grade. Water was triply distilled through an all glass apparatus and degassed with argon. A KOH stock solution (2 mol dm^{-3}) was made by dilution of BDH Convol® concentrate. Buffer solutions were made by appropriate dilutions of the 2.0 mol dm^{-3} stock solution of KOH in grade A volumetric flasks. The correct amount of 2.0 mol dm^{-3} KCl solution was added to adjust the ionic strength, *I*, to 1.0 mol dm^{-3}, unless otherwise stated. Dioxane (freshly dried and distilled from sodium borohydride prior to use[22]) was added to bring the final dioxane content to 20% (v/v), unless otherwise stated, and the final volume was obtained by addition of water. The pH of each buffer solution was measured under the reaction conditions of the kinetic runs using a Radiometer PHM82 pH meter fitted with a Russell CTWL electrode calibrated with standard buffer solutions.

Reactions were followed at 39.0 °C in the thermostatted cell-holder of a Varian Cary 3 spectrophotometer. Stock solutions of 4-nitrophenyl acetals (approximately 0.004 mol dm^{-3}) were made up in dioxane. Runs were started by injection of 0.020 cm^3 of stock solution into 2.5 cm^3 of preheated "buffer" solution (0.005–0.040 mol dm^{-3} KOH) in a quartz cuvette of 1.0 cm path length, giving a final substrate concentration of approximately 3×10^{-5} mol dm^{-3}, a total volume of 2.52 cm^3 and a total dioxane content of 20.3%.

Repetitive absorbance *vs.* wavelength scans from 200 to 500 nm showed isosbestic points, indicating a one-step hydrolysis process. In all cases the wavelength of maximum change in absorbance on complete hydrolysis of the substrate was approximately 405 nm, and this wavelength was used for all single wavelength investigations.

References

1 E. Dyer, C. P. J. Glaudemans, M. J. Koch and R. H. Marchessault, *J. Chem. Soc.*, 1962, 3361–3370.
2 G.-A. Craze and A. J. Kirby, *J. Chem. Soc., Perkin Trans. 2*, 1978, 354–356.
3 M. N. Namchuk, J. D. McCarter, A. Becalski, T. Andrews and S. G. Withers, *J. Am. Chem. Soc.*, 2000, **122**, 1270–1277.
4 T. L. Amyes and W. P. Jencks, *J. Am. Chem. Soc.*, 1989, **111**, 7888–7900.
5 B. Capon, M. C. Smith, E. Anderson, R. H. Dahm and G. H. Sankey, *J. Chem. Soc., B*, 1969, 1038–1047.
6 S. Chandrasekhar, A. J. Kirby and R. J. Martin, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1619.
7 S. V. Ley, D. K. Baeschlin, D. J. Dixon, A. C. Foster, S. J. Ince, H. W. M. Priepke and D. J. Reynolds, *Chem. Rev.*, 2001, **101**, 53–80.
8 H. Werner, G. Mann, M. Mühlstadt and H.-J. Köhler, *Tetrahedron Lett.*, 1970, 3563–3566.
9 H. Werner, G. Mann, H. Jancke and G. Engelhardt, *Tetrahedron Lett.*, 1975, 1917–1920.

10 Y. D. Wu, K. N. Houk, J. Florez and B. M. Trost, *J. Org. Chem.*, 1991, **56**, 3656–3664.
11 K. E. S. Dean, PhD Thesis, Cambridge, 2000.
12 T. S. Sorensen and S. M. Whitworth, *J. Am. Chem. Soc.*, 1990, **112**, 6647–6651.
13 T. H. Fife and L. H. Brod, *J. Am. Chem. Soc.*, 1970, **92**, 1681–1684.
14 M. J. Huggins and D. G. Kubler, *J. Org. Chem.*, 1975, **40**, 2813–2815.
15 L. S. Levitt and H. F. Widing, *Prog. Phys. Org. Chem.*, 1976, **12**, 119–158.
16 A. Kankaanperä, *Acta Chem. Scand.*, 1969, **23**, 1728–1732.
17 E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, John Wiley & Sons, New York, 1994.
18 R. W. Franck, *Tetrahedron*, 1983, **39**, 3251–3252.
19 A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, Berlin, Heidelberg and New York, 1983.
20 P. M. Collins and R. J. Ferrier, *Monosaccharides*, Wiley, Chichester and New York, 1995.
21 E. Schaumann and F.-F. Grabley, *Liebigs Ann. Chem*, 1977, 88–100.
22 D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, 1996.