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# Regioselectivity in the ring opening of 2-phenyl-1,3-dioxan-2-yl radicals derived from cyclic benzylidene acetals and comparison with deoxygenation of a carbohydrate diol via its cyclic thionocarbonate

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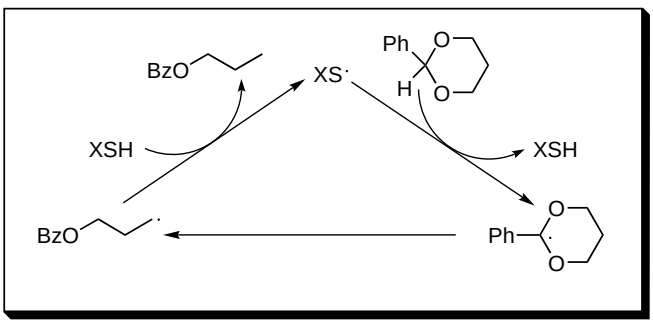
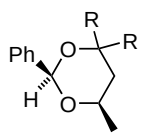
**Abstract**—Ring-opening β-scission of monocyclic 2-phenyl-1,3-dioxan-2-yl radicals gives preferentially the more stabilised alkyl radical. However, analogous bicyclic radicals derived from two 4,6-*O*-benzylidene glucopyranosides afford primary radicals in preference to secondary radicals, a result that can be rationalised with the aid of DFT calculations. The report by Barton and Subramanian, that the opposite regioselectivity results from the tin hydride mediated reductive ring-opening of a corresponding glucosidic thionocarbonate, is shown to be in error. 

We have reported recently[1] that cyclic benzylidene acetals derived from 1,2- and 1,3-diols undergo an efficient radical-chain redox rearrangement to give benzoate esters, in the presence of a thiol that acts as a protic polarity-reversal catalyst.[2] For example, in the presence of 2,2-di-*tert*-butylperoxybutane (DBPB) as initiator and *tert*-dodecanethiol or tri-*tert*-butoxysilanethiol (TBST) as catalyst in refluxing octane (internal temperature ca. 130°C), the 1,3-dioxane **1** is converted almost quantitatively into the benzoate esters **2** and **3** in the ratio 87:13.[1,3] The propagation stage of the chain mechanism is illustrated in Scheme 1 for the unsubstituted 2-phenyl-1,3-dioxane and the selective formation of the benzoate **2** results from the preference of the intermediate 2-phenyl-4-methyl-1,3-dioxan-2-yl radical to undergo β-scission to yield the more stabilised secondary alkyl radical. Similarly, redox rearrangement of **4** gives **6** almost exclusively (**6**:**5** = 99:1), because the intermediate dioxanyl radical cleaves to give a tertiary, rather than a secondary, alkyl radical. Thus, the regioselectivity of the ring-opening β-scission of these monocyclic 2-phenyl-1,3-dioxanyl radicals reflects the stability of the alkyl radical formed.

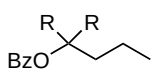



**Scheme 1.**

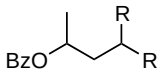
However, under similar conditions in refluxing octane–chlorobenzene the bicyclic 4,6-*O*-benzylidene glucoside **7** yielded mainly the 6-deoxybenzoate **8**, resulting from β-scission to give *the less stabilised* primary C6-centred radical, along with only a small amount of the 4-deoxybenzoate **9** (**8**:**9** = 97:3).[1] We have now obtained comparable results with the 2,3-di-*O*-methylated analogue **10**, which gives the benzoates **11** and **12** in the ratio 93:7, again reflecting contra-thermodynamic β-scission of the intermediate bicyclic 2-phenyl-1,3-dioxanyl radi-




**1** R = H
**4** R = Me




**2** R = H
**5** R = Me




**3** R = H
**6** R = Me

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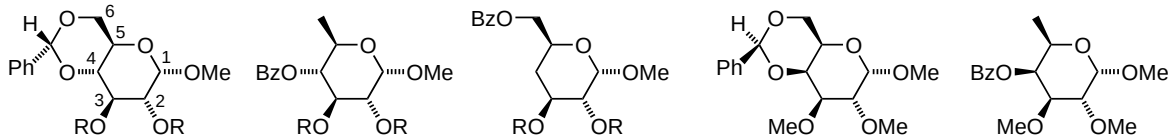
cal. Reactions were carried out under the conditions described previously[1] in the presence of DBPB, TBST and collidine.[3] In contrast, the galactoside analogue **13** gave more **12** than **14**, indicating preferential cleavage of the intermediate dioxanyl radical to give the secondary C4-centred radical, although the selectivity (**12**:**14** = 62:38) is much less than that shown by the monocyclic dioxanyl radical derived from **1**.

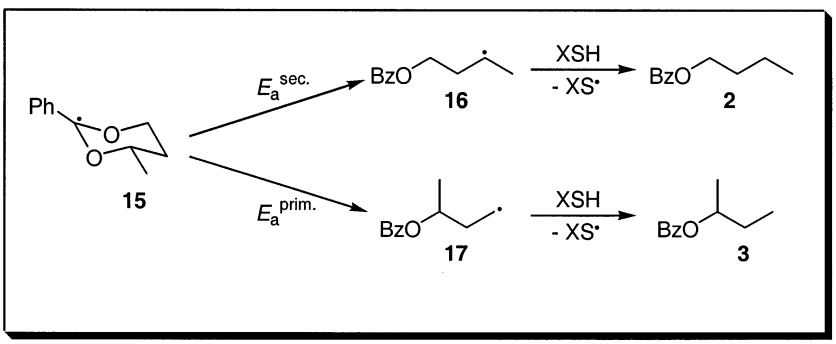


**7** R = Ac **8** R = Ac **9** R = Ac **13** **14**
**10** R = Me **11** R = Me **12** R = Me

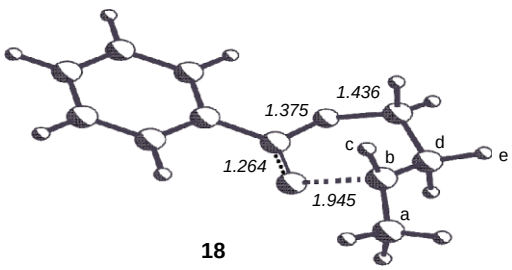
The activation energies for the two possible modes of β-scission of the 2-phenyl-4-methyl-1,3-dioxanyl radical **15**, derived from **1**, were calculated using density functional theory at the B3LYP/6-31G(d,p) level in conjunction with the Gaussian 98 suite of programs.[4] Geometries of **15** and of the two possible transition states (Scheme 2) were optimised without any constraints and the normal vibrational frequencies were computed at the same level of theory, enabling the Arrhenius activation energies $E_a^{sec.}$ and $E_a^{prim.}$ to be estimated as 71.8 and 78.9 kJ mol$^{-1}$, respectively. Assuming similar $A$-factors for the two modes of cleavage, β-scission to give the secondary radical **16** is predicted to occur ca. 8.3 times faster than cleavage to give the primary radical **17** at 130°C, as compared with the experimental yields of the benzoates **2** and **3** which are in the ratio 6.7:1.

The calculated structure of the transition state **18** leading to the secondary radical **16** occurs at a late stage along the reaction coordinate, such that the bond angles at the nascent radical centre have widened to a point where this is nearly planar; in particular, the angle a–b–d is 120.0°. If this angle is fixed at 110° and the dihedral angle a–b–d–e is fixed at −60°, values close to those imposed by the bicyclic framework present in the glucosidic radical **19** derived from **10** (Scheme 3), and the remainder of the structure is re-optimised, $E_a^{sec.}$ is increased to 84.8 kJ mol$^{-1}$. The activation energy for β-scission to give the primary radical is now *lower* by 5.9 kJ mol$^{-1}$, which would translate into a benzoate ratio **2**:**3** of ca. 1:5.8 at 130°C. Thus, it seems likely that the contra-thermodynamic cleavage of **19** to give predominantly the primary radical **20** can be attributed mainly to the prevention of bond-angle opening at the C4-bridgehead site in the transition state for its formation.

As estimated by molecular mechanics calculations,[5] the galactosidic radical **22** derived from **13** is less stable than the glucosidic analogue **19** by 12.8 kJ mol$^{-1}$. The moderate preference of **22** for cleavage to give the secondary radical **21**, rather than the primary radical **23**, can be understood in terms of the greater reduction of strain present in this *cis*-fused bicyclic structure when the axial bridgehead C4–O bond stretches en route to **21** (as compared with stretching of the C6–O bond leading to the *cis*-4,5-substituted **23**), which acts to offset the bridgehead angle strain effect that favours formation of the primary radical.[6]

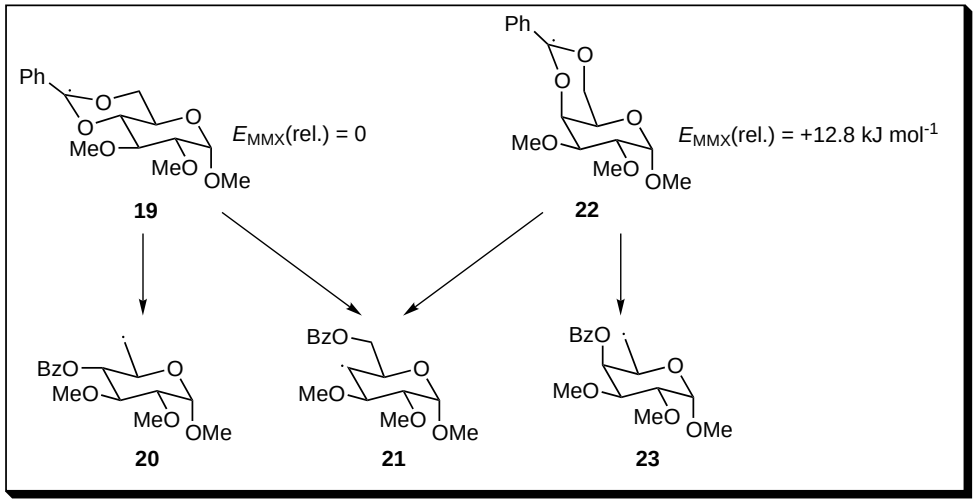



**Scheme 2.**




**18**

< a-b-c = 116.7°
< a-b-d = 120.0°
< c-b-d = 115.9°
(Bond lengths in Å)




**Scheme 3.**

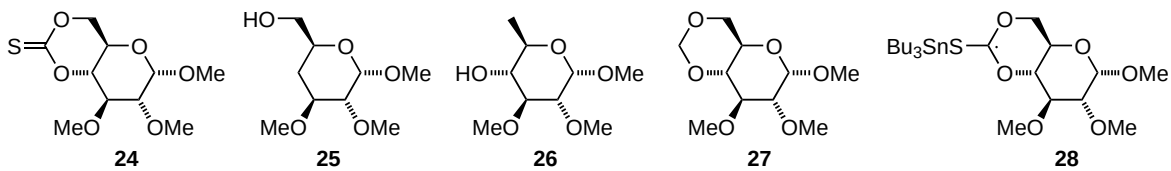
As we have pointed out previously for the redox ring-opening rearrangement of **7**,[1] the preference for formation of the 6-deoxybenzoates **8** and **11** from the benzylidene glucosides **7** and **10**, respectively, is apparently at odds with the regiochemistry of tributyltin hydride-mediated reductive ring opening of the cyclic thionocarbonate **24**, described by Barton and Subramanian (B. and S.) in the first paper on this type of reaction.[7]

Thus, reaction of the tin hydride with **24** in the presence of azobis(isobutyronitrile) (AIBN) in refluxing toluene was reported to give the 4-deoxyglucoside **25** in 61% yield, after basic hydrolysis of the first-formed *S*-stannylthiolester. However, identification of **25** relied on a comparison of the optical rotation of its 6-*O*-tosyl derivative with a value in the literature since, surprisingly, the paper by B. and S. contains no NMR data.

The conditions used by B. and S. involved slowly adding a toluene solution containing **24**, excess $Bu_3SnH$ and AIBN to refluxing toluene; more tin hydride and AIBN were added subsequently. In our hands using a standard dropping funnel, the tin hydride reduction of **24** as described by B. and S. afforded, reproducibly, the methylene acetal **27**[8] as the almost-exclusive carbohydrate product and neither of the alcohols **25** and **26** could be identified with certainty in the crude product after hydrolysis. Authentic samples of these alcohols were prepared by hydrolysis of the benzoate esters **11** and **12**.[9,10] When we repeated the reaction using a smaller excess of the stannane (1.5 equiv.), the methylene acetal **27** was still the major product, although small amounts of the alcohols were now detectable after basic hydrolysis. *However, the 6-deoxy sugar predominated to a large extent over the 4-deoxy compound* (**26**:**25** = ca. 90:10), although it was difficult to measure this ratio exactly because of the minute quantities of alcohols produced. The methylene acetal **27** is presumably formed by tin hydride-trapping of the adduct radical **28** before it undergoes β-scission, followed by tin hydride reduction of the 2-stannylthiyl-1,3-dioxane so produced.[11]

The reaction was repeated again, this time with very slow addition (syringe pump) of a toluene solution containing tin hydride (1.5 equiv.) and AIBN (10 mol%) to a solution of the thionocarbonate **24** in refluxing toluene.[12] Under these conditions, very much less methylene acetal and much more alcohol were obtained after hydrolysis, but still the 6-deoxy sugar predominated (**26**:**25** = 91:9); however, the reaction was not clean and other products were also formed. Using the procedure of B. and S., with tris(trimethylsilyl)silane (TTMSS, 1.5 equiv., AIBN initiator) as a less reactive hydrogen-atom donor than the tin hydride,[13] gave the deoxy sugars cleanly (**26**:**25** = 92:8) and the methylene acetal was not now detected. Similar results (**26**:**25** = 88:12) were obtained, with all reagents present initially, using the cheaper triphenylsilane (1.5 equiv.) and 1,1-di-*tert*-butylperoxycyclohexane (10 mol%) as initiator in refluxing toluene.[14] With more triphenylsilane (3 equiv.) and less solvent, the 4,6-dideoxy compound[15] was a major product, presumably arising from reduction of the $Ph_3SiSC(O)O$-group at C4 in the initial 6-deoxy product.

Contra-thermodynamic regioselectivity has been observed on a number of occasions in the tin hydride mediated deoxygenation of 1,2- and 1,3-diols via their cyclic thionocarbonate esters.[12,16] However, interpretation of the product distribution and the regioselectivity



obtained from this type of reaction is not always straightforward[17,18] because of its mechanistic complexity. In particular, several elementary steps in the chain propagation sequence are reversible and rearrangement of the starting thionocarbonate with migration of the sulfur atom into the ring can take place under the influence of both radicals and nucleophiles, to give monothiolcarbonate, subsequent reduction of which can also yield alcohol. Indeed, Redlich et al.[16] have reported that the regiochemistry observed can depend on the concentrations of the reagents used and clearly a detailed re-examination of the reductive ring opening of thionocarbonates by tin hydrides is indicated.

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5. Calculations were carried out using PCMODEL version 7.5 (Serena Software) in conjunction with the MMX forcefield.
6. The reverse of these β-scission processes, namely 6-*endo*-cyclisation of substituted 3-benzoyloxypropyl radicals, will proceed through the same (now early) transition state. A complementary approach to the interpretation of regioselectivity would be to consider the interactions that develop during the cyclisation process.
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10. NMR (500 MHz for $^{1}H$, 125 MHz for $^{13}C$, $CDCl_3$ solvent, *J* in Hz). The use of [multiplet] indicates an apparent multiplet with line spacing corresponding to an average coupling constant. Compound **25**; $\delta_H$ 1.31 (1H, [q], *J* 12.1, H-4ax), 1.99 (1H, ddd, *J* 12.8, 5.1 and 2.3, H-4eq), 2.06 (1H, dd, *J* 6.9 and 5.6, OH), 3.14 (1H, dd, *J* 9.4 and 3.6, H-2), 3.38 (3H, s, OMe), 3.40 (3H, s, OMe), 3.48 (3H, s, OMe), 3.50–3.64 (3H, m, H-3, H-6A, H-6B), 3.80 (1H, m, H-5), 4.85 (1H, d, *J* 3.6, H-1); $\delta_C$ 31.9, 55.1, 57.4, 58.7, 65.2, 68.0, 76.3, 82.2 and 98.0. IR (liq. film): 3454 $cm^{-1}$. MS (FAB): 229.1060 ($M+Na^+$); $C_9H_{18}O_5Na$ requires 229.1052. $[\alpha]_D^{25}$ +153.0 (*c* 1.10, $CHCl_3$); $[\alpha]_D^{25}$ +162.0 (*c* 1.00, MeOH); Ref. 7 reports $[\alpha]_D^{22}$ +70.0 (*c* 1.0, MeOH). Compound **26**;[9] $\delta_H$ 1.17 (3H, d, *J* 6.2, H-6), 3.00 (1H, [t]d, *J* 9.1 and 3.2, H-4), 3.05 (1H, br.d, *J* 3.2, OH), 3.12 (1H, dd, *J* 9.6 and 3.6, H-2), 3.30 (1H, [t], *J* 9.2, H-3), 3.31 (3H, s, OMe), 3.38 (3H, s, OMe), 3.52 (3H, s, OMe), 3.55 (1H, dq, *J* 9.4 and 6.2, H-5), 4.67 (1H, d, *J* 3.6, H-1); $\delta_C$ 17.5, 54.9, 58.1, 60.9, 66.7, 75.1, 82.0, 82.7 and 97.1. IR (liq. film): 3454 $cm^{-1}$. MS (FAB): 229.1045 ($M+Na^+$); $C_9H_{18}O_5Na$ requires 229.1052. $[\alpha]_D^{25}$ +136.0 (*c* 1.25, $CHCl_3$).
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