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Selective Radical-Chain Epimerisation at C-H Centres α to Oxygen Under Conditions of Polarity-Reversal Catalysis

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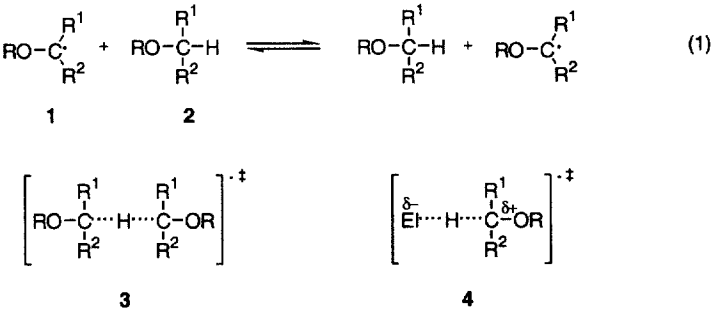
Abstract: *Polarity-reversal catalysis by tri-*tert*-butoxysilanethiol has been applied to promote radical-chain epimerisation selectively at carbon centres of the type $R^1R^2C^*(H)OR$.*

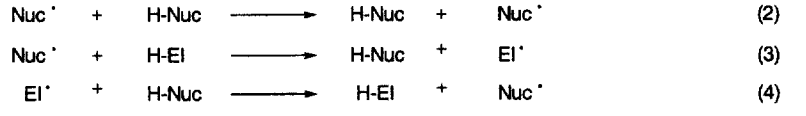
(Keywords: epimerisation; radicals and radical reactions; catalysis; thiols)

Thermoneutral hydrogen-atom transfer reactions of the type generalised in eqn. (1) have relatively large activation energies and are thus slow at moderate temperatures. A long-established explanation for the sluggishness of such identity processes emphasises the importance of 'polar effects' in reactions of electrically-neutral free radicals.[1] In terms of this concept, the symmetrical transition state **3** lacks any stabilising charge-transfer interaction between the incoming and outgoing α-alkoxyalkyl-radical fragments and, as a consequence, is of higher energy than that (structure **4**) for a similarly-exothermic reaction in which an electrophilic radical El• abstracts hydrogen from **2**.[2,3] In the latter case, the dipolar transition state **4** is stabilised by charge transfer as



(1)

shown, because the α-alkoxyalkyl radical **1** has a relatively low ionisation energy and is nucleophilic (Nuc•). This analysis implies that reaction (1) should be subject to *polarity-reversal catalysis*[4] (PRC) by a *protic* catalyst H-El, in the presence of which an unfavourable direct hydrogen-atom transfer of the general type shown in eqn. (2) is replaced by the pair of consecutive reactions (3) and (4), both of which benefit from favourable charge-transfer stabilisation of their respective transition states.[5]



(2)

(3)

(4)

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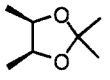
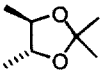
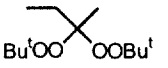
If the substrate **2** is chiral and non-racemic, then the occurrence of reaction (1) will be accompanied by racemisation of the starting material[6] and, if more than one chiral centre is present in the substrate, PRC could be applied to bring about selective radical-chain epimerisation at a chosen centre in the molecule. Of course, any change in diastereoisomeric composition brought about in this way will necessarily be in the direction towards thermodynamic equilibrium. Using a protic catalyst, epimerisation can be directed to a carbon centre bearing an electron donating group, while PRC using an *hydridic* catalyst[5] of the general type H-Nuc might be applied in the same way to direct epimerisation to a carbon centre bearing an electron-withdrawing group. Fine control of the site of epimerisation could be exerted by tailoring the steric demands and electronically-influenced properties of the catalyst and of the radical derived from it by hydrogen-atom abstraction.



5-*cis*



5-*trans*



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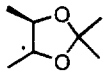

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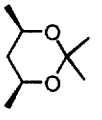
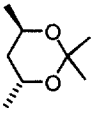


8-*cis*



8-*trans*

We report here the use of thiols as protic polarity-reversal catalysts for selective epimerisation at carbon centres bearing electron-donating α-oxygen substituents.[7] Initial experiments designed to explore the viability of the approach were carried out with the cyclic ketal **5**. When a nonane solution containing **5-*cis*** (*ca.* 1 M) and 5 mol% of 2,2-di(*tert*-butylperoxy)butane[9] **6** (DBPB, present as an initiator) was heated under argon at 125 °C for 3 h, no conversion to the *trans*-isomer was observed by GLC analysis,[10] showing that the radical **7** does not abstract hydrogen from the parent dioxolane under these conditions.[11] However, when the experiment was repeated in the presence of 5 mol% *tert*-dodecanethiol (TDT),[12] slow epimerisation of **5-*cis*** to the more stable **5-*trans*** was observed and a final *cis*:*trans* ratio of 63:37 was achieved after 1 h. In the additional presence of 2,4,6-trimethylpyridine (collidine, 10 mol%), the function of which is probably to remove traces of acid formed from thiols under the reaction conditions,[13] the *cis*:*trans* ratio was 46:54 after 1 h and reached a final value of 43:57 after 2 h. We have found previously[6,14] that silanethiols are often more effective protic polarity-reversal catalysts than alkanethiols and when the TDT was replaced by triphenylsilanethiol (TPST), isomerisation of **5-*cis*** proceeded further and more rapidly (*cis*:*trans* = 24:76 after 1 h). However, when collidine was also present very little isomerisation took place, probably because TPST is susceptible to nucleophilic attack at silicon which results in removal of the catalyst. Tri-*tert*-butoxysilanethiol [(Bu^{t}O)$_3$SiSH; TBST] is much less sensitive to nucleophilic substitution and is reported not to react with water during 100 h at 37 °C.[15] This silanethiol also proved to be a very efficient catalyst for the epimerisation of **5-*cis***, especially in the presence of 10 mol% of collidine. The progress of the isomerisation of **5-*cis*** catalysed by TBST is shown in Figure 1, along with results for the epimerisation of **5-*trans*** under the same conditions, and it is evident that the *cis*:*trans* ratio of 16:84 corresponds to thermodynamic equilibrium at 125 °C. Molecular mechanics calculations[16] indicated that the *trans*-isomer is 6.3 kJ mol^{-1} more stable than the *cis* and, assuming that this value corresponds approximately to the free-energy difference between the two isomers at 125 °C, the predicted *cis*:*trans* equilibrium ratio is 13:87.

Epimerisation of the 1,3-dioxanes **8**, obtained from pentane-2,4-diol, was carried out under similar conditions in octane solvent at 125 °C (bath temperature) in the presence of collidine and TBST as polarity-reversal catalyst. The pure *trans*-isomer was prepared from the (*R*,*R*)-diol and a 53:47 *cis*:*trans* mixture was prepared from a commercially-available mixture of *meso*- and *dl*-diols. Whatever the isomeric composition of the

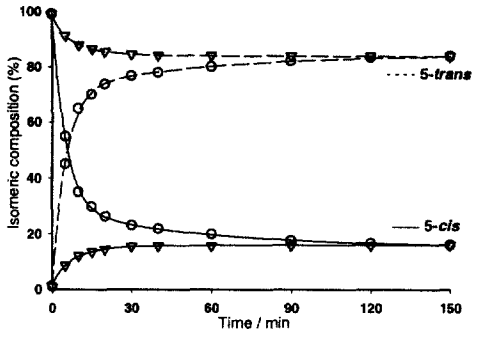
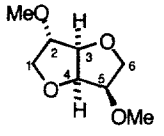


Figure 1: Epimerisation of 2,2,4,5-tetramethyl-1,3-dioxolane at 125 °C, in the presence of tri-*tert*-butoxysilanethiol; circles = starting from **5-*cis***, triangles = starting from **5-*trans***

starting dioxane, an equilibrium mixture consisting of 93% **8-*cis*** and 7% **8-*trans*** was obtained within 1 h. Molecular mechanics calculations predict the *cis*-isomer to be the more stable by 15.6 kJ mol^{-1}, which corresponds to an equilibrium ratio of 99:1 in favour of **8-*cis*** at 125 °C.

Di-*O*-methyl-1,4:3,6-dianhydro-D-glucitol (isosorbide dimethyl ether) **9** is readily available commercially. If the *cis* ring junction is preserved, epimerisation can take place either at C-2 to give the corresponding dianhydro-D-mannitol derivative **10** or at C-5 to give the dianhydro-L-iditol derivative **11**. While **10** is readily obtainable by methylation of commercial isomannide, the ether **11** is much less accessible. However, molecular mechanics calculations indicate that the order of stability is **11** (0) > **9** (+6.3 kJ mol^{-1}) > **10** (+17.7 kJ mol^{-1}). An octane solution containing **9** (*ca.* 1 M), TBST (5 mol%), DBPB (5 mol%) and collidine (10 mol%) was heated at 125 °C under argon for a total of 4 h; further portions of TBST and DBPB (5 mol% of each) were added after 1 h. GLC analysis of the solution showed the ratio of ethers **9**:**10**:**11** to be 38.5:1.5:60.0 and pure **11**[17] was readily isolated by flash chromatography on silica gel (light petroleum-diethyl ether eluent).



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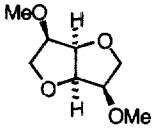

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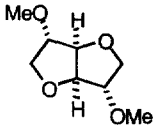
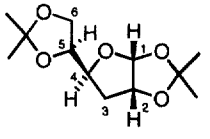


11

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-ribo-hexofuranose **12** is easily obtainable *via* Barton-McCombie deoxygenation of diacetone D-glucose.[18] Molecular mechanics calculations predict that the C-5 epimer **13** is marginally more stable than **12** (by 0.6 kJ mol^{-1}), while the C-4 epimer **14** is less stable than **12** (by 8.7 kJ mol^{-1}). The epimerisation of **12** was carried out in a similar way to that of **9**, except that further portions of TBST and DBPB (5 mol%) were added after 1, 2 and 3 h. GLC analysis showed the final ratio **12**:**13** to be 68:32 and no evidence was found for the presence of **14**. 3-Deoxy-1,2:5,6-di-*O*-isopropylidene-β-L-lxyo-hexofuranose **13**, the D-enantiomer of which has been described previously,[19] was isolated by flash chromatography (light petroleum-diethyl ether eluent) and recrystallised from hexane (isolated yield 25%).[20]



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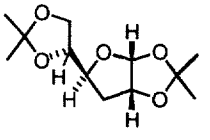

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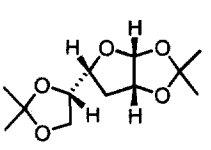

14

We conclude that selective epimerisation under conditions of PRC represents a simple and potentially useful method for the conversion of a readily-available diastereoisomer into a less common one. Although the direction of change is always towards thermodynamic equilibrium, a number of possibilities exist whereby control of the epimerisation process may be exercised. For example, to convert a diastereoisomer **A** into a less stable one **B**, the starting material could be first converted to a derivative **A-D**, chosen so that epimerisation of the latter leads to a derivative **B-D** that is *more stable* than **A-D**. Deprotection of **B-D** would then give the desired

diastereoisomer of the original compound. *Cis*-1,2-diol functionality on a 5-membered ring can be protected against isomerisation to the more stable *trans*-arrangement by conversion to a cyclic acetonide (*cf.* **12**). While *O*-alkylation of a chiral secondary alcohol centre $R^1R^2C(H)OH$ may be used to give a more convenient substrate for radical-chain epimerisation, its conversion to an ester function $R^1R^2C(H)OAc$ should *protect* that centre against epimerisation, because of the strengthening effect of acylation on the tertiary C-H bond and the less favourable polar effect for abstraction of hydrogen by the electrophilic thiyl radical, as a consequence of the reduced nucleophilicity of the radical $R^1R^2\dot{C}OAc$ compared with $R^1R^2\dot{C}OR$.

Acknowledgements

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7. While α-RO, α-RS and α-R_2N substituents activate the attached C-H group towards abstraction of the hydrogen atom by an electrophilic radical, a β-RO group is deactivating.[8]
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9. Obtained from Peroxid-Chemie and handled as a 50% w/w solution in involatile aliphatic hydrocarbons. The half-life of this peroxide is *ca.* 1 h at 125 °C.
10. The dioxolane **5-*cis*** was prepared from commercial *meso*-butane-2,3-diol and contained 1% of the *trans*-isomer. Epimers were assumed to give equal GLC detector (flame-ionisation) response and this was demonstrated experimentally in the case of **5-*cis*** and **5-*trans*** (prepared from the *dl*-diol).
11. Similarly, no epimerisation was observed when collidine (10 mol%) was also present.
12. This is the isomeric mixture of thiols *tert*-$C_{12}H_{25}SH$ available from the Aldrich Chemical Co.
13. It is thought likely that acid-catalysed elimination reactions lead to the formation of unsaturated compounds which act as inhibitors of the chain epimerisation process.
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16. PCMODEL, ver. 7.0 (Serena Software, Bloomington, IN 47402-3076, USA) was used for these calculations, in conjunction with the MMX force field and the GMMX stochastic conformational search routine. Enthalpy differences are reported.
17. Oil, $[\alpha]_D^{17}$ = -8.0 (*c* 4.3, $CHCl_3$). δ_H 3.39 (6 H, s, 2 Me), 3.80-3.88 (6 H, m, H^{endo}-1,6, H^{exo}-1,6, H^{endo}-2,5), 4.58 (2 H, s, H-3,4); δ_C 57.2, 71.8, 84.8 and 85.0. Found: C, 54.9; H, 8.0. $C_8H_{14}O_4$ requires C, 55.2; H, 8.1%.
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20. Colourless needles, m.p. 60-61 °C, $[\alpha]_D^{18}$ = -24.7 (*c* 1.90, $CHCl_3$). δ_H 1.32 (3 H, s, Me), 1.37 (3 H, s, Me), 1.42 (3 H, s, Me), 1.52 (3 H, s, Me), 1.72 (1 H, ddd, *J* 13.3, 10.7 and 4.9 Hz, H^{exo}-3), 2.02 (1 H, dd, *J* 13.3 and 4.6 Hz, H^{endo}-3), 3.80 (1 H, dd, *J* 8.3 and 6.6 Hz, H-6), 4.02 (1 H, dd, *J* 8.3 and 6.9 Hz, H′-6), 4.13 (1 H, ddd, *J* 7.0, 6.6 and 5.3 Hz, H-5), 4.26 (1 H, ddd, *J* 10.7, 5.3 and 4.6 Hz, H-4), 4.73 (1 H, dd, *J* 4.9 and 3.7 Hz, H-2), 5.83 (1 H, d, *J* 3.7 Hz, H-1); δ_C 25.5, 26.2, 26.3, 26.8, 34.6, 65.6, 76.8, 78.0, 80.3, 105.8, 109.8 and 111.4. Found: C, 59.0; H, 8.2. $C_{12}H_{20}O_5$ requires C, 59.0; H, 8.3%. (A trace amount of this compound was isolated previously as a by-product from the preparation of **12** by the tripropylsilane/TDT-mediated Barton-McCombie deoxygenation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose *via* the corresponding xanthate.[18b])