Radical-chain racemisation of tetrahydrofurfuryl acetate under conditions of polarity-reversal catalysis: possible implications for the radical-induced strand cleavage of DNA

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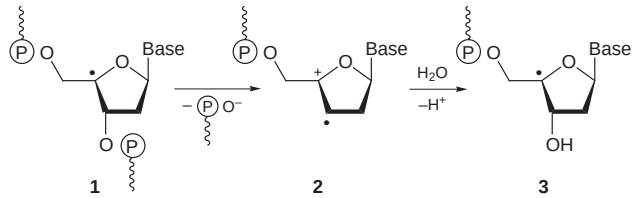
Alkanethiols with electron-withdrawing *S*-alkyl groups and silanethiols act as polarity-reversal catalysts to promote the radical-chain racemisation of (*R*)-tetrahydrofurfuryl acetate at 60 °C, while simple alkanethiols are ineffective.

There is now good evidence that, at least under anaerobic conditions, strand cleavage of DNA which involves the 4′-radical **1** proceeds as shown in Scheme 1, *via* an intermediate radical cation **2** which can subsequently trap a nucleophile to give an α- alkoxyalkyl radical of the type **3**.[1] In principle, if the radical **3** (or a similar oligonucleotide-derived α-oxyalkyl radical) were to abstract hydrogen from an undamaged strand to regenerate the 4′-radical **1**, a homolytic *chain* process for the cleavage of DNA could be established. If such a radical-chain mechanism for the destruction of DNA could be promoted when desirable in a therapeutic context (*e.g.* to amplify the effects of radiation damage to a tumour or to increase the effectiveness of the various antineoplastic agents that operate *via* radical pathways[2]), the biological implications would be of considerable importance.

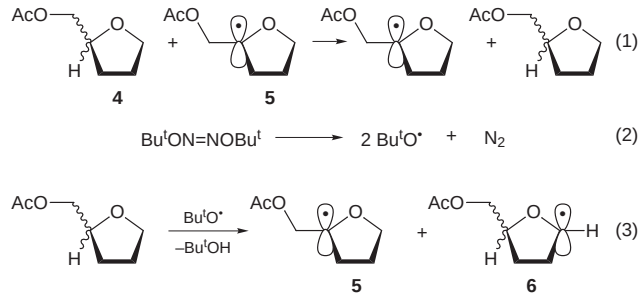


1 **2** **3**

Scheme 1

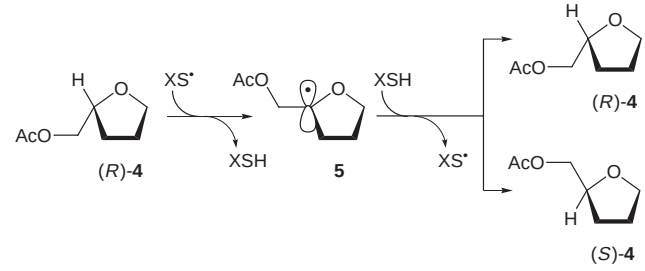
However, hydrogen-atom abstraction by **3** from the 4′-position in DNA is an (essentially) thermoneutral process that involves two radicals of almost identical electronegativity, and such reactions would be expected to be very slow at moderate temperatures.[3] The radicals **1** and **3** should be nucleophilic species, with relatively low ionisation energies, and it occurred to us that the overall transfer of hydrogen from DNA to **3** (or to another α-oxyalkyl radical) might be promoted by a suitable polarity-reversal catalyst[4,5] of the type El–H, where El• is an electrophilic radical. Here we report the results of experiments designed to investigate this general possibility, by examining the effects of polarity-reversal catalysts on the identity reaction [eqn. (1)] of tetrahydrofurfuryl acetate **4**.

The extent to which the overall reaction [eqn. (1)] takes place was judged by starting with (*R*)-tetrahydrofurfuryl acetate[6] and monitoring the enantiomeric excess (ee) of the remaining ester as a function of time, using chiral-stationary-phase GLC (Supelco β-DEX 120, 30 m × 0.25 mm bore capillary column; 0.25 μm coating containing permethylated β-cyclodextrin). When a benzene solution containing (*R*)-**4** (99.4% ee, 0.50 mol dm^{-3}), *tert*-butylbenzene or methyl benzoate (0.30 mol dm^{-3}, as an internal concentration standard for GLC analysis) and di-*tert*-butyl hyponitrite[7] (TBHN, 0.025 mol dm^{-3}) was heated at 60 °C under argon for 3 h, *ca.* 10% of **4** was consumed and the ee of the remaining (*R*)-ester was undiminished. The TBHN acts



4 **5** **6**

as a thermal source of *tert*-butoxyl radicals [eqn. (2)]‡ which, in the absence of other reagents, will abstract hydrogen from **4** to give mainly the α-alkoxyalkyl radicals **5** and **6** [eqn. (3)].§ We conclude that neither **5** nor **6** abstracts hydrogen directly from **4** to give **5** at a significant rate under the reaction conditions. The experiment was then repeated in the presence of small amounts (usually 5 mol% based on **4**) of various thiols as potential polarity-reversal catalysts, and the results are presented graphically in Fig. 1. Under these conditions, only a trace of tetrahydrofurfuryl acetate was consumed during the first 90 min, although a small amount (⩽5%) of the ester was consumed subsequently when the thiol concentration had become very low. It can be seen that while 5 mol% of a simple alkanethiol such as *tert*-dodecanethiol (mixture of isomers) or dodecane-1-thiol causes only a very small amount of racemisation of (*R*)-**4**, thiols with electron-withdrawing groups attached to sulfur bring about a significant increase in the rate of racemisation and evidently act as polarity-reversal catalysts for the overall reaction [eqn. (1)], according to the chain propagation cycle shown in Scheme 2. Thus, 1-thio-β-D-glucopyranose tetraacetate, 2,2,2-trifluoroethanethiol¶ and, in particular, triphenylsilanethiol are efficient catalysts. The more sterically-demanding triisopropylsilanethiol and the less acidic methyl thioglycolate (MeO_2CCH_2SH) were less effective while, as expected, L-cysteine ethyl ester (a model for glutathione) was totally ineffective. Of course, hydrogen-atom abstraction by XS• to form **6** followed by 'repair' to regenerate **4** is an unobservable process in the present system.‖ Abstraction of hydrogen from **4** by XS• is evidently more efficient when the substituent X is an electron-withdrawing group, probably



Scheme 2

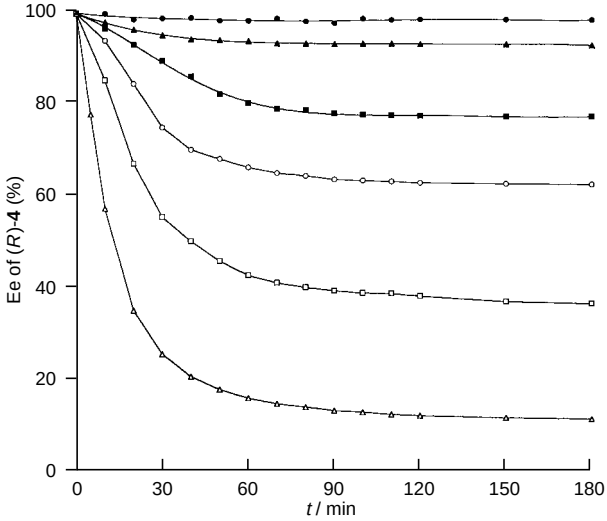


Fig. 1 The racemisation of (*R*)-tetrahydrofurfuryl acetate in benzene at 60 °C in the presence of various thiols (5 mol% based on the acetate): (●) *tert*-dodecanethiol, (▲) dodecane-1-thiol, (■) methyl thioglycolate, (○) 2,2,2-trifluoroethanethiol, (□) 1-thio-β-D-glucopyranose tetraacetate and (△) triphenylsilanethiol (in order of increasing efficiency as catalysts)

because the S–H bond is stronger and the thiyl radical is more electrophilic when the sulfur atom is relatively electron deficient.[3b,5c] The silyl group acts as a π-electron-pair acceptor.

Triisopropylsilanethiol is a less effective catalyst than triphenylsilanethiol, which may be a consequence of relatively slow transfer of a hydrogen atom from and to a tertiary site when the XS group is bulky. With 5 mol% TBHN and 5 mol% thiol catalyst, racemisation does not go to completion (see Fig. 1). Apart from depletion of the initiator, this is presumably a result of removal of thiyl radicals by self-coupling to give disulfide and, especially in the later stages of the reaction when the thiol concentration is reduced, by combination of XS$^{\bullet}$ with the radicals **5** or **6**. When the initial amount of Ph_3SiSH was increased to 10 mol%, under otherwise identical conditions, the rate of racemisation of (*R*)-**4** *decreased*, while with 2.5 mol% Ph_3SiSH the initial rate of racemisation was slightly greater than that achieved with 5 mol% catalyst, although the final ee after 3 h (33%) was appreciably larger. We interpret these results as indicating that at high thiol concentrations rotational exchange between the enantiomeric conformations of **5** becomes competitive with trapping of this radical by thiol to regenerate **4**, so that **5** begins to retain a memory of the absolute configuration of the molecule of **4** from which it was derived. It follows that the rate of racemisation provides a lower limit for the rate of the overall reaction [eqn. (1)] under conditions of polarity-reversal catalysis.

We conclude that the thermoneutral reaction shown in eqn. (1) is subject to polarity-reversal catalysis by appropriately substituted thiols. Provided that the possible protective effect of glutathione can be overcome (perhaps by reversible binding of the polarity-reversal catalyst to DNA), it may be possible to apply this principle to amplify radical-induced damage to DNA *in vivo*, especially in the oxygen-deficient environment present in many types of tumour cell.[9] Encouragingly, racemisation of (*R*)-**4** still takes place in the presence of *both* Ph_3SiSH (5 mol%) and *tert*-dodecanethiol (5 mol%), albeit at an initial rate about six times slower than that observed in the presence of the silanethiol alone.

These results will also have implications for the design of enantioselective radical-chain reactions based on the use of homochiral thiols as polarity-reversal catalysts,[5e] when it is obviously important to *suppress* racemisation of the product.

We are very grateful to Drs D. J. Madge and A. B. Tabor for useful discussions and to Dr P. Anastasis (Kiralchem Ltd.) for all his help in supplying the enantiopure tetrahydrofurfuryl alcohol from which (*R*)-**4** was prepared.

Notes and References

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‡ The half-life of TBHN at 60 °C is *ca*. 55 min [ref. 7(*a*)].

§ When a cyclopropane solution containing **4** and di-*tert*-butyl peroxide was irradiated with UV light while the sample was in the microwave cavity of an EPR spectrometer (ref. 8), overlapping EPR spectra of **5** and **6** were observed between 180 and 280 K; at 270 K the value of [**5**]/[**6**] was *ca*. 0.7. At 270 K, the radical **5** showed $a(2\ H_{\beta}^{exocyclic})$ 8.60, $a(2\ H_{\beta})$ 26.14, $a(2\ H_{\gamma})$ 0.75 and $a(2\ H_{\delta})$ 2.08 G, and g 2.0030; the radical **6** showed $a(1\ H_{\alpha})$ 13.50, $a(1\ H_{\beta})$ 30.89, $a(1\ H_{\beta}')$ 25.26, $a(2\ H_{\gamma})$ 0.75 and $a(1\ H_{\delta})$ 2.25 G, and g 2.0032. The hyperfine splitting constants confirm that the radical **5** preferentially adopts the conformation shown, in which the exocyclic C_{β}-O bond eclipses the formal C_{α}–$2p_{\pi}$ SOMO, although two-fold rotation about the C_{α}–C_{β} bond is evidently sufficiently fast at 270 K to render the two faces of the ring magnetically-equivalent. However, below *ca.* 260 K, selective line-broadening was observed in the spectrum of **5**, indicating that rotational exchange between the two enantiomeric conformations is no longer fast on the EPR timescale.

¶ This thiol is volatile (bp 36 °C) and some could have been lost by evaporation during the reaction.

‖ While the *tert*-butoxyl radical abstracts hydrogen at comparable rates from the two carbon atoms adjacent to the ring-oxygen in **4**, it is likely that thiyl radicals (especially the less bulky ones) will be more selective and give mainly **5** by attack at the tertiary CH group.

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Received in Liverpool, UK, 11th February 1998; 8/01381K