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The Chemical Synthesis and X-Ray Structure of the Sulfone of 4'-Thiothymidine

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Abstract: Oxidation of 4'-thiothymidine with MCPBA results in its smooth conversion in high yield to the corresponding sulfone. The X-ray structure of this novel analogue showed that the sugar ring has a very similar conformation (C2'-endo, C3'-exo, S) to that found in thymidine and 4'-thiothymidine. However, because of steric interactions between the sulfone oxygen atoms and the pyrimidine ring, the glycosidic torsion angle S4'-C1'-N1-C6 is 85.5° compared with usual values which are in the range of 33-59°.

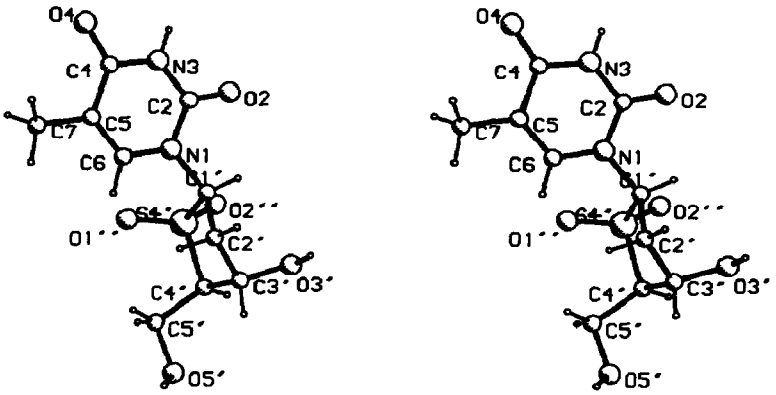
There is currently much interest in nucleoside analogues, mainly as potential antiviral agents but increasingly as potential building-blocks in antisense strategy. Recently we reported[1,2] the efficient synthesis of a novel class of deoxyribonucleosides, 4'-thio-2'-deoxyribonucleosides, in which the oxygen atom in the sugar ring has been replaced by sulfur. Among the analogues reported was 4'-thiothymidine (1). The conformation of this nucleoside has been determined by X-ray and NMR spectroscopy[3] and the compound has been incorporated into oligodeoxyribonucleotides.[4] The conformation of 4'-thiothymidine in the crystal is South (C2'-endo, C3'-exo) with an anti- base orientation, whereas in solution at equilibrium, 27% of the North (C3'-endo, C2'-exo) conformation is present.[3] Oligonucleotides containing 4'-thiothymidine only suffer subtle perturbations to their structures and the stability of self-complementary duplexes.[4] 4'-Thiothymidine has antiviral (antiherpesvirus) properties but is also quite toxic.[2]

We here describe the synthesis of a further analogue, the sulfone of 4'-thiothymidine (2). This compound has neither antiviral properties nor is it toxic. We have determined the structure by X-ray crystallography and the glycosidic torsion angle of 85.5° is so unusual that it is most unlikely that the analogue could be a kinase substrate and hence this would explain its lack of biological activity.

The structure of the sulfone of 4'-thiothymidine was established by X-ray crystallography.[5] Cell dimensions and intensity data, up to $\theta=26°$ were measured with MoKα radiation on an Enraf-Nonius CAD4 diffractometer. A total of 1884 reflections [$F>5\sigma(F)$] (Friedel pairs not merged) were used in the analysis. The structure was solved by direct methods with SHELXS 86[6] and refined by least

squares with SHELX 76,[7] using anisotropic thermal parameters for all atoms except hydrogens, which were refined isotropically. The final R and Rw values are 0.0335 and 0.0384, $w=1/[\sigma^2(F)+0.0005F^2]$. The inverse structure gave R, Rw 0.0342, 0.0395, in agreement with the known absolute configuration of the thiosugar as depicted in Figure 1.[8] Atomic coordinates, thermal parameters, bond lengths and angles have been deposited with the Cambridge Crystallographic Data Centre.

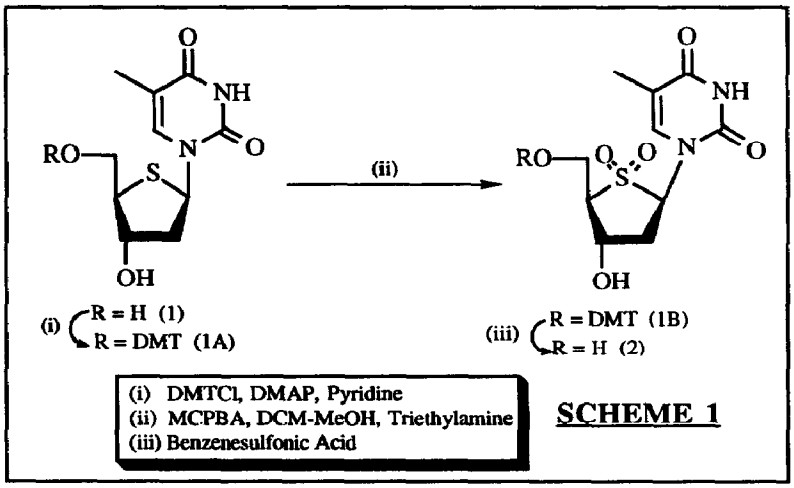
FIGURE 1 Stereodiagram of the X-ray structure of the sulfone of 4'-thiothymidine



The thiosugar has the C2'-endo, C3'-exo conformation, these two atoms being displaced by respectively, 0.40 and 0.33Å on opposite sides of the S4'-C1'-C4' plane. This conformation is similar to that found in the crystal structures of 5-fluoro-4'-thio-2'-deoxyuridine,[9] 4'-thiothymidine,[3] and (E)-5-(2-bromovinyl)-4'-thio-2'-deoxyuridine,[3] but differs from the C3'-endo, C2'-exo pucker of the thioribose in the crystal structure of 4'-thiouridine.[10] The O5'-C5'-C4'-C3' torsion angle is -65.8° (g^- conformation). The major conformational difference between the sulfone of 4'-thiothymidine and the other thionucleosides for which X-ray structural data is available is in the glycosidic torsion angle S4'-C1'-N1-C6. This is in the range 33-59° in the thiosugars cited above; however in the title compound it has the larger value of 85.5°, presumably the effect of steric interactions between the sulfone oxygen atoms and the pyrimidine ring. The angle between the accurately planar pyrimidine ring and the mean plane of the thiosugar ring is 77.9°. In the crystal, the molecules form intermolecular hydrogen bonds, O3'-H....O4, N3-H....O3' and O5'-H....O2'' (sulfone oxygen).

The sulfone of 4'-thiothymidine was prepared using a straightforward 3-step synthetic route (Scheme 1). The 5'-O-dimethoxytritylation of 4'-thiothymidine (1) proceeded smoothly in a yield of 82%. Subsequent oxidation of the ring sulfur atom

was achieved using MCPBA according to the method described by Robins *et al.*[11] Commercial MCPBA contains m-chlorobenzoic acid impurity and this acid is also a by-product of the oxidation. It has been reported[12] that even at temperatures below 0°C, approximately 2% (w/v) of this acid remains dissolved in dichloromethane. By omitting triethylamine from the reaction mixture the oxidation yield was reduced by 50% and this is presumably due to the cleavage of the acid-labile DMT protecting group. The addition of 2% (v/v) triethylamine to the oxidation mixture ensured excellent yields (90%) of the 5'-O-DMT-sulfone (1B). Removal of the DMT protecting group was achieved using 4% benzenesulfonic acid in chloroform[13], affording the product as a white solid which could be recrystallised from methanol.[14]



SCHEME 1

Acknowledgement

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References and Notes

1. Dyson, M. R.; Coe, P. L.; Walker, R. T. *Carb. Res.* **1991**, *216*, 237
2. Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Med. Chem.* **1991**, *34*, 2782
3. Koole, L. H.; Plavec, J.; Liu, H.; Vincent, B. R.; Dyson, M. R.; Coe, P. L.; Walker, R. T.; Hardy, G. W.; Rahim, S. G.; Chattopadhyaya, J. *J. Am. Chem. Soc.* **1992**, *114*, 9936.
4. Hancox, E. L.; Connolly, B. A.; Walker, R. T. *Nucl. Acids Res.* **1993**, *21*, 3485.
5. Crystal data for sulfone of 4'-thiothymidine: $C_{10}H_{14}N_2O_6S$, Mr=290.3 orthorhombic, space group $P2_12_12_1$, a=6.506(3), b=13.406(4), c=14.075(4)Å, U=1227.6Å^3, Z=4, D_C=1.571gcm^{-3}, μ(MoKα)=0.275mm^{-1}.
6. Sheldrick, G. M. *SHELXS 86, Program for the Solution of Crystal Structures*, University of Gottingen 1987.
7. Sheldrick, G. M. *SHELX 76, Program for Crystal Structure Determination*, University of

Cambridge 1976.

8. Motherwell, W. D. S.; Clegg, W. PLUTO 88, *Program for Plotting Crystal and Molecular Structures, Cambridge Structural Database System*, Users Manual, 1988.
9. Bobek, M.; Block, A.; Parthasarathy, R.; Whistler, R. L. *J. Med. Chem.* **1975**, *18*, 784.
10. Vitali, J.; Parthasarathy, R.; Fu, Y. L.; Bobek, M. *Am.Cryst.Assoc.,Summer Meeting, Abstracts* 1977; pp.69.
11. Robins, M. J.; Wnuk, S. F.; Mullah, K. B.; Dalley, N. K. *J. Org. Chem.* **1991**, *56*, 6878.
12. Patai, *Chemistry of the Functional Groups, Suppl. E, Part 1*; John Wiley and Sons, Inc.: New York, 1980; pp..539-608,
13. Stawinski, J.; Hozumi, T.; Narang, S. A.; Bahl, C. P.; Wu, R. *Nucl. Acids Res.* **1977**, *4*, 353.
14. *To a solution of (1A) (0.36mmol) in dichloromethane/methanol (15ml, 9:1) at -10°C was added MCPBA (1.78mmol) dissolved in dichloromethane, dropwise with stirring. Triethylamine (2% v/v) was added and the solution was left at 5°C overnight. The crude product was washed successively with a saturated aqueous solution of sodium bicarbonate, saturated brine solution and water, dried ($MgSO_4$)and evaporated in vacuo The compound was purified by column chromatography to reveal the product (1B) as a white foam (90%). To a solution of (1B) (0.5mmol) stirring in chloroform at 0°C, was added benzenesulfonic acid (21ml, 4% w/v in chloroform) dropwise with stirring. The solution was stirred at 0°C for 90min after which the solvent was evaporated in vacuo. The crude product was purified by column chromatography to give the product (2) as a white solid which was subsequently recrystallised from methanol.*
300MHz ^1H nmr (d_6-DMSO): δ 11.64(1H,s,NH); 5.99(1H,dd,H-1'); 5.88(1H,d,D_2O-exchangeable,OH-3'); 5.24(1H,t,D_2O-exchangeable,OH-5'); 4.37-4.31(1H,m,H-4'); 3.82-3.74(2H,m,H-5'); 3.23-3.18 (1H,m,H-3'); 2.68-2.36(2H,m,H-2'); 1.79(3H,s,CH_3)
FAB Mass Spectrum: m/z = 308$(M+NH_3)^+$; 291$(M+H)^+$ (100%)
Elemental Analysis: $C_{10}H_{14}N_2O_6S$ requires C 41.38%, H 4.86%, N 9.65%; found C 41.56%, H 4.94%, N 9.83%

All other new compounds gave satisfactory analytical and spectroscopic characteristics.

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