

Direct measurement of the anomeric effect in sulfoxides: conformational analysis and X-ray crystal structures of 2-bromo- and 2-chloro-1,3-dithiane *trans*-1,3-dioxides

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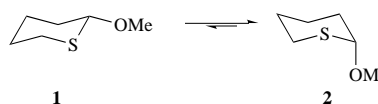
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X-Ray analysis of the title compounds has shown that crystalline 2-chloro-1,3-dithiane 1,3-dioxide adopts the conformation in which the chlorine substituent is axial, while the analogous 2-bromo compound crystallises in the alternative conformation, with bromine equatorial. However, variable-temperature NMR experiments have revealed that the halogen substituents of both compounds exhibit a pronounced axial preference in dichloromethane solution. This axial preference has been attributed to a combination of anomeric and dipole–dipole interactions between the sulfoxides and the C–X bonds.

Introduction

It has been shown that second row heteroatoms exhibit a substantial anomeric effect.^{1–4} For example, Zefirov³ found that 2-methoxytetrahydrothiopyran **1** in CCl₄ solution has a strong preference for the conformation in which the methoxy group is axial. He obtained an estimated value for the anomeric effect of 1.8 kcal mol⁻¹, defined as the difference between the free energy of the conformational equilibrium in the given system and that of the conformational equilibrium in the analogously substituted cyclohexane. There is a well recognised problem with the use of cyclohexane substituent values in this way,⁵ because the 1,3-diaxial steric interactions in saturated heterocycles are not directly comparable with those in cyclohexane due to the different C–X bond lengths and C–X–C angles.⁶ The anomeric effects in sulfur heterocycles therefore tend to be overestimated, and those in oxygen ones underestimated. However, this simplified analysis has been widely used^{2,7} and provides useful information for comparison of anomeric effects in similar systems.



Sulfoxides would be expected to show a reduced anomeric effect compared to sulfides, as the sulfur lone pair is lower in energy and therefore less available to donate electrons. Indeed, evidence for a significant but reduced anomeric effect has been found in 2-substituted tetrahydrothiopyran *S*-oxides, *e.g.* **2**.⁷ In this case, both the equatorial preference of the bromide (in bromocyclohexane) and the slight axial preference of the sulfoxide oxygen⁸ (in thiane oxide) were taken into account when calculating the anomeric effect, as ring inversion results in both conversion of the equatorial bromide into the axial position and conversion of the axial sulfoxide oxygen into the equatorial position (Fig. 1). Again, the accuracy of the calculated value depends on the validity of the assumption that these conformational effects are additive in the bis-functionalised system.

Ideally, ring inversion should only result in a change in the position of the halogen atom. A study of 2-bromo- and 2-chloro-1,3-dithiane *trans*-1,3-dioxides⁹ **3** and **4** allows this; ring

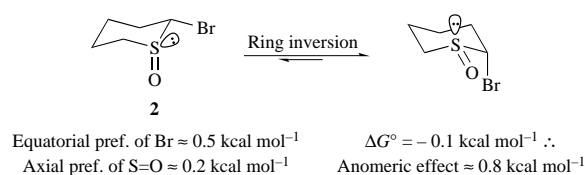


Fig. 1

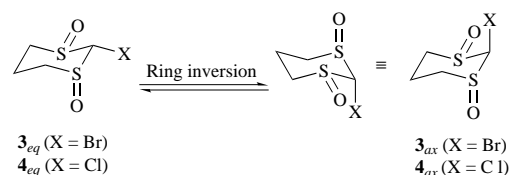


Fig. 2

inversion results in net movement of the halogen substituent from an equatorial to an axial position, the relative positions of the sulfoxides remaining the same (Fig. 2). We have therefore studied the solution and solid state structures of these molecules.

Results and discussion

NMR studies of **3** and **4**

The room-temperature 400 MHz ¹H NMR spectra of **3** and **4** in CD₂Cl₂ both show the proton in the 2-position as a narrow triplet (**3**, *J* = 1.5 Hz; **4**, *J* = 1.1 Hz).¹⁰ The coupling constants between the protons attached to C-4, C-5 and C-6 are characteristic of axial and equatorial protons in a conformationally locked cyclohexane system (Fig. 3). The multiplets for the equatorial protons attached to C-4 and C-6 can be simplified by irradiation at the frequency of the C-2 proton. This suggests that in CD₂Cl₂ solution the halogen substituent is predominantly axial, allowing its geminal proton to *W*-couple across the ring. In order to determine whether chair–chair isomerism is taking place, the solutions were cooled and 400 MHz ¹H NMR spectra recorded at 183, 213, 223, 248 and 271 K. The changes in the spectra with temperature are shown in Figs. 4 and 6. The signal at $\delta = 5.32$ in each spectrum is due to the solvent (CD₂Cl₂).

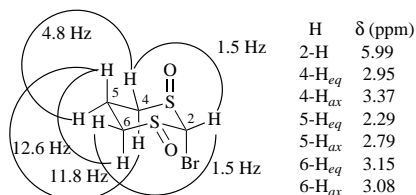


Fig. 3 Chemical shifts and selected coupling constants in the 400 MHz ^1H NMR spectrum of 2-bromo-1,3-dithiane dioxide **3** in CD_2Cl_2 at 293 K

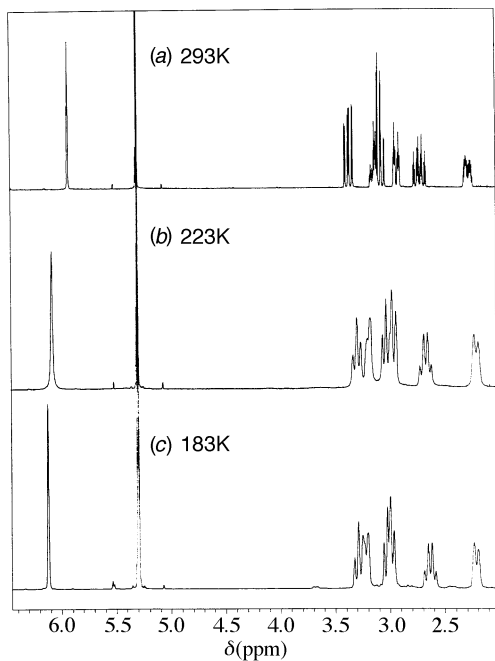


Fig. 4 The 400 MHz ^1H NMR spectra of 2-bromo-1,3-dithiane dioxide **3** in CD_2Cl_2 at (a) 293 K, (b) 223 K and (c) 183 K

(i) 2-Bromo-1,3-dithiane 1,3-dioxide **3**

In the ^1H NMR spectrum of **3** at 223 K [(b), Fig. 4], the peaks can be seen to have broadened and the C-2 proton signal (around 6 ppm) to have shifted relative to the room-temperature spectrum. At 183 K [(c), Fig. 4] two sets of sharper signals are observed, corresponding to the axial (major) and equatorial (minor) conformers. The $\mathbf{3}_{ax}:\mathbf{3}_{eq}$ ratio at 183 K was measured as 95:5 by comparison of the peak integrals.

The signals corresponding to the C-2 protons are at 6.14 ppm ($\mathbf{3}_{ax}$) and 5.56 ppm ($\mathbf{3}_{eq}$). The chemical shift of this proton in the room-temperature (293 K) spectrum is at 5.99 ppm, whereas the expected position for a weighted average peak at room temperature, assuming that ΔG° is not temperature dependent (*i.e.* $\ln K \propto 1/T$) would be at 6.06 ppm, representing a 6.3:1 ratio of isomers. The actual position, if taken as a weighted average, represents only a 2.9:1 ratio. The chemical shifts of other peaks can also be seen to have changed in an unpredictable manner with temperature. These observations could result from temperature dependence of the chemical shifts of the axial and equatorial conformers, or temperature dependence of the energy difference ΔG° .

Binsch¹¹ has shown that coupling constants in bromo- and chloro-substituted cyclohexane systems are independent of temperature over a range of temperatures below coalescence, while chemical shifts can vary significantly with temperature. Unfortunately, due to the broad nature of the signals in our spectra at 183 K it was not possible to measure the low temperature coupling constants accurately. Further reductions in temperature led to crystallisation of the compounds. Spin simulation experiments have confirmed, however, that the coupling constants associated with the major conformer at 183 K are very similar to those in the room temperature spectrum. A

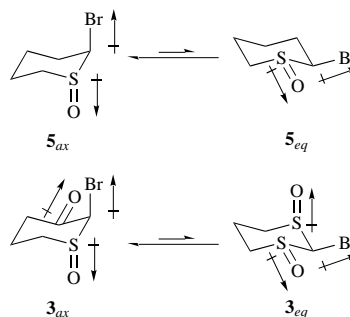


Fig. 5 Dipole contributions additionally stabilise the conformers with sulfoxide and halogen *trans* diaxial

2.9:1 mixture of isomers at room temperature would be expected to produce a very different spectrum to that observed [Figs. 3 and 4(a)], with coupling constants between adjacent *trans* related protons representing a weighted average of the axial-axial and equatorial-equatorial values. It is therefore concluded that the wandering signals at low temperatures are due mainly to the temperature dependence of the chemical shifts and that the entropy component of ΔG° is small. Indeed, the conformational entropy of bromocyclohexane was calculated by Binsch¹¹ as $0.06 \pm 0.03 \text{ cal mol}^{-1} \text{ K}^{-1}$; a similar value in our system would result in a < 1% change in ΔG° over the 183 to 293 K temperature range.

A possible explanation for the temperature dependence of the chemical shifts is the increased aggregation of the molecules at low temperatures. This theory was tested by recording the low temperature (192 K) 400 MHz NMR spectra of **3** at a series of different dilutions. A systematic decrease in the chemical shift of the C-2 proton with increasing dilution was observed. Upon dilution by a factor of four, a change of 0.04 ppm was seen, from 6.132(1) to 6.091(1) ppm.

The observed 95:5 ratio of $\mathbf{3}_{ax}:\mathbf{3}_{eq}$ corresponds to an energy difference ΔG° of $-1.07 \text{ kcal mol}^{-1}$. Simply subtracting 0.5 kcal mol^{-1} for the equatorial preference of Br in bromocyclohexane would give a value for the S(O)-C-Br anomeric effect of $-1.57 \text{ kcal mol}^{-1}$, which is much higher than that found by Juaristi for the monosulfoxide ($-0.8 \text{ kcal mol}^{-1}$).⁷ The reason for this over-estimation is that dipole-dipole interactions also stabilise the axial conformer over the equatorial one. These dipole effects vary with solvent polarity. Juaristi⁷ found an energy difference between $\mathbf{5}_{ax}$ and $\mathbf{5}_{eq}$ in CD_2Cl_2 of 0.3 kcal mol^{-1} , where no alignment of the sulfur lone pair with $\sigma^* \text{C-Br}$ is possible in either conformer (Fig. 5). Taking into account the equatorial preference of Br (0.5 kcal mol^{-1}) and axial preference of S=O (0.2 kcal mol^{-1}) reveals an additional stabilisation of $\mathbf{5}_{ax}$ amounting to 0.6 kcal mol^{-1} , which can be attributed to dipole interactions between C-Br and S=O. This should be the same as the dipole contribution to the energy difference between $\mathbf{3}_{eq}$ and $\mathbf{3}_{ax}$ (Fig. 5). The value of the S(O)-C-Br anomeric effect in our system is therefore approximately 1.0 kcal mol^{-1} .

(ii) 2-Chloro-1,3-dithiane 1,3-dioxide **4**

The variation with temperature of the 400 MHz ^1H NMR (CD_2Cl_2) spectrum of **4** (Fig. 6) follows a similar pattern. The signals corresponding to the C-2 protons at 183 K are at 6.09 ppm ($\mathbf{4}_{ax}$) and 5.54 ppm ($\mathbf{4}_{eq}$). The ^1H chemical shifts change unpredictably with temperature, but a visual comparison of the coupling patterns in the room temperature and 183 K spectra again suggests that this is not due to a strongly temperature dependent ΔG° . The value obtained by Binsch¹¹ for the conformational entropy of chlorocyclohexane is $0.32 \pm 0.03 \text{ cal mol}^{-1} \text{ K}^{-1}$ which in our system would result in a < 4% change in ΔG° over the 183 to 293 K temperature range.

The $\mathbf{4}_{ax}:\mathbf{4}_{eq}$ ratio at 183 K was measured as 93:7 by comparison of integrals in the ^1H NMR (CD_2Cl_2) spectrum (Fig. 6). This corresponds to $\Delta G^\circ = -0.94 \text{ kcal mol}^{-1}$. Subtraction of the

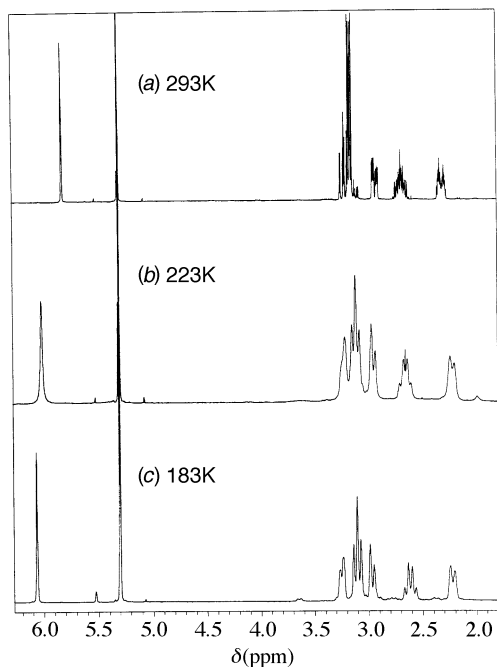


Fig. 6 The 400 MHz ^1H NMR spectra of 2-chloro-1,3-dithiane dioxide **4** in CD_2Cl_2 at (a) 293 K, (b) 223 K and (c) 183 K

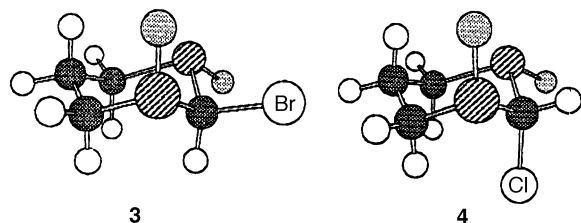


Fig. 7

equatorial preference of chlorocyclohexane ($0.5 \text{ kcal mol}^{-1}$) and the dipole stabilisation of the axial conformer⁷ ($-0.65 \text{ kcal mol}^{-1}$) gives a value for the $\text{S}(\text{O})\text{-C-Cl}$ anomeric effect of around $0.8 \text{ kcal mol}^{-1}$.

The values determined for the anomeric effect are slightly higher than those obtained by Juaristi, which were $0.8 \text{ kcal mol}^{-1}$ for $\text{S}(\text{O})\text{-C-Br}$ and $0.7 \text{ kcal mol}^{-1}$ for $\text{S}(\text{O})\text{-C-Cl}$.⁷ The discrepancy is probably due to the assumption that the equatorial preference of the halogen in these systems is the same as that in halogenocyclohexane. In fact, the combined effect of the longer $\text{C-S}(\text{O})$ bonds (1.82 \AA) compared to the C-C bonds in cyclohexane (1.54 \AA) and the smaller $\text{C-S}(\text{O})\text{-C}$ bond angles ($94.7 \pm 0.4^\circ$ in **3** and **4**) may reduce the unfavourable steric interactions in the axial conformer, so the equatorial preference of the halogen is smaller in 2-halogenotetrahydrothiopyran *S*-oxide than in halogenocyclohexane and smaller still in 2-halogeno-1,3-dithiane 1,3-dioxide, causing slight overestimation of the anomeric effect.

X-Ray crystal structures of **3** and **4**

X-Ray analysis shows that the preferred conformation of crystalline **3** is with bromine in the equatorial position, while that of **4** is with chlorine in the axial position (Fig. 7). Crystalline **3** therefore adopts the opposite conformer to that which predominates in solution, as shown by the NMR data. This can be attributed to crystal packing forces, which are different in each case due to the different sizes of the halogen atoms and different C-X bond lengths. There are examples of tetrahydropyranyl acetals in which the alkoxy group occupies the axial position in solution but the equatorial position in the solid state and this has similarly been attributed to crystal packing forces.¹²

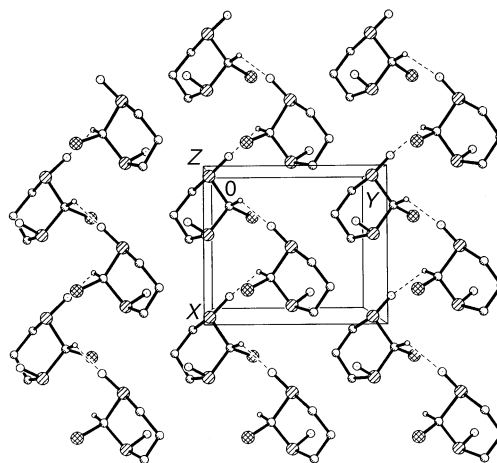


Fig. 8 Hydrogen bonding interactions in crystalline 2-chloro-1,3-dithiane dioxide **4**

Examination of the crystal structures of both compounds reveals hydrogen bonding interactions between the C-2 protons and sulfoxide oxygens in neighbouring molecules (Fig. 8); this provides a possible explanation for the aggregation of the molecules at lower temperatures, leading to the observed temperature dependence of the chemical shifts.

One might expect differences in the C-S and C-Cl bond lengths for **4** due to the anomeric stabilisation: a shortening of the equatorial $\text{S}(\text{O})\text{-C2}$ bond relative to the axial $\text{S}(\text{O})\text{-C2}$ bond and a lengthening of the C-Cl bond. The two C-S bond lengths are the same, however, (1.82 \AA) and the C-Cl bond length is similar [$1.769(3)$] to the standard estimate¹³ [$1.803(11)$]. Evidently the relatively small anomeric stabilisation is not sufficient to cause a change in bond lengths.

Experimental

Variable-temperature ^1H NMR spectra were recorded on an AMX2-400 (400 MHz) spectrometer. For analytical purposes, ^1H and ^{13}C NMR spectra were recorded on the same instrument at 400.13 and 100.6 MHz, respectively. All coupling constants are given in Hz and chemical shifts on the δ scale in ppm. In the 1,3-dithiane 1,3-dioxide ring, position 1 is arbitrarily assigned to the sulfur with oxygen equatorial.

trans-1,3-Dithiane 1,3-dioxide

This compound was prepared according to a previously reported procedure.¹⁴

2-Bromo-1,3-dithiane 1,3-dioxide **3**

trans-1,3-Dithiane 1,3-dioxide (500 mg, 3.3 mmol) was dissolved in dichloromethane (20 ml) under N_2 and *N*-bromosuccinimide (880 mg, 4.9 mmol) was added to the solution. The reaction mixture was stirred in the dark at room temperature for 45 h after which it was evaporated *in vacuo*. Purification of the residue by flash column chromatography, eluting with 10% EtOH-EtOAc, yielded **3** (664 mg, 85%), an analytical sample of which was recrystallised from CHCl_3 -light petroleum; R_f (10% EtOH-EtOAc) 0.16; mp $157\text{--}158^\circ\text{C}$ (Found: C, 20.65; H, 3.15; S, 27.75; Br, 34.7. $\text{C}_4\text{H}_7\text{BrS}_2\text{O}_2$ requires C, 20.8; H, 3.0; S, 27.7; Br, 34.6%); ν_{max} (KBr)/ cm^{-1} 2980, 2950, 2930 (CH), 1030 and 1040 (SO); δ_{H} (CD_2Cl_2) 2.29 (1 H, dddd, J 16.6, 6.4, 4.8, 2.9, 2.7, 5- H_{eq}), 2.71 (1 H, dddd, J 16.6, 12.6, 11.8, 2.9, 2.7, 5- H_{ax}), 2.95 (1 H, dddd, J 14.7, 4.8, 2.7, 1.5, 0.8, 4- H_{eq}), 3.08 (1 H, ddd, J 13.1, 11.8, 2.7, 6- H_{ax}), 3.15 (1 H, dddd, J 13.1, 6.4, 2.9, 1.5, 0.8, 6- H_{eq}), 3.37 (1 H, ddd, J 14.7, 12.6, 2.9, 4- H_{ax}) and 5.99 (1 H, t, J 1.5, 2-H); δ_{C} (CD_2Cl_2) 15.1 (C-5), 41.9 (C-4), 47.0 (C-6) and 69.2 (C-2); m/z 232, 230 (M^+ ; 20, 19%), 136 (99), 103 (34), 90 (83), 87 (42) and 73 (100).

Crystallography. Crystal data for $C_4H_7BrO_2S_2$; $M = 231.13$. Crystallises from dichloromethane as clear oblongs; crystal dimensions $0.65 \times 0.35 \times 0.20$ mm. Monoclinic, $a = 7.917(9)$, $b = 10.688(7)$, $c = 9.427(5)$ Å, $\beta = 106.04(5)^\circ$, $U = 766.6(11)$ Å³, $Z = 4$, $D_c = 2.003$ Mg m⁻³, space group $P2_1/n$ (a non-standard setting of $P2_1/C_{2h}$, No. 14), Mo-K α radiation ($\lambda = 0.71073$ Å), $\mu(\text{Mo-K}\alpha) = 5.833$ mm⁻¹, $F(000) = 456$.

Three-dimensional, room temperature X-ray data were collected in the range $3.5 < 2\theta < 45^\circ$ on a Siemens P4 diffractometer by the omega scan method. Of the 1321 reflections measured, all of which were corrected for Lorentz and polarisation effects (but not for absorption), 759 independent reflections exceeded the significance level $|F|/\sigma(F) > 4.0$. The structure was solved by direct methods and refined by full matrix least-squares methods on F^2 . Hydrogen atoms were included in calculated positions and refined in riding mode. Refinement converged at a final $R = 0.0606$ ($wR2 = 0.1774$ for all 932 data, 82 parameters, mean and maximum δ/σ 0.000, 0.000), with allowance for the thermal anisotropy of all non-hydrogen atoms. Minimum and maximum final electron density -0.713 and 0.903 e Å⁻³. A weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.1202 * P)^2 + 0.00 * P]$ where $P = (F_o^2 + 2 * F_c^2)/3$ was used in the latter stages of refinement. Complex scattering factors were taken from the program package SHELXL93¹⁵ as implemented on the Viglen 486DX computer.

2-Chloro-1,3-dithiane 1,3-dioxide 4

trans-1,3-Dithiane 1,3-dioxide (250 mg, 1.6 mmol) was dissolved in dichloromethane (10 ml) under N₂ and *N*-chlorosuccinimide (242 mg, 1.8 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 23 h after which it was evaporated *in vacuo*. Purification of the residue by flash column chromatography, eluting with 10% EtOH-EtOAc, yielded **4** (275 mg, 90%); R_f (10% EtOH-EtOAc) 0.16; mp 141–142 °C (Found: C, 25.8; H, 3.8; S, 34.1; Cl, 18.75. $C_4H_7ClS_2O_2$ requires C, 25.7; H, 3.8; S, 34.35; Cl, 19.0%); ν_{\max} (KBr)/cm⁻¹ 2950 (CH), 1035, 1045 and 1055 (SO); δ_H (CD₂Cl₂) 2.31 (1 H, dm, J_d 16.3, 5-H_{eq}), 2.68 (1 H, dm, J_d 16.3, 5-H_{ax}), 2.93 (1 H, dm, J_d 14.7, 4-H_{eq}), 3.13–3.17 (2 H, m, 6-H_{ax} and 6-H_{eq}), 3.21 (1 H, ddd, J 14.7, 12.2, 2.9, 4-H_{ax}) and 5.84 (1 H, t, J 1.1, 2-H); δ_C (CD₂Cl₂) 14.8 (C-5), 42.3 (C-4), 46.0 (C-6) and 76.2 (C-2); m/z 188, 186 (M⁺; 46, 75%), 103 (66), 90 (73) and 73 (100).

Crystallography. Crystal data for $C_4H_7ClO_2S_2$; $M = 186.67$. Crystallises from dichloromethane as colourless blocks; crystal dimensions $0.54 \times 0.25 \times 0.25$ mm. Orthorhombic, $a = 6.937(2)$, $b = 7.996(2)$, $c = 12.910(6)$ Å, $U = 716.1(4)$ Å³, $Z = 4$, $D_c = 1.731$ Mg m⁻³, space group $P2_12_12_1$ (D_2^4 , No. 19), Mo-K α radiation ($\lambda = 0.71073$ Å), $\mu(\text{Mo-K}\alpha) = 1.037$ mm⁻¹, $F(000) = 384$.

Three-dimensional, room-temperature X-ray data were collected in the range $3.5 < 2\theta < 45^\circ$ on a Siemens P4 diffractometer by the omega scan method. Of the 840 reflections measured, all of which were corrected for Lorentz and polarisation effects (but not for absorption), 721 independent reflections exceeded the significance level $|F|/\sigma(F) > 4.0$. The structure was

solved by direct methods and refined by full matrix least-squares on F^2 . Hydrogen atoms were included in calculated positions and refined in riding mode. Refinement converged at a final $R = 0.0261$ ($wR2 = 0.0703$, for all 736 data, 82 parameters, mean and maximum δ/σ 0.000, 0.000), with allowance for the thermal anisotropy of all non-hydrogen atoms. Minimum and maximum final electron density -0.291 and 0.230 e Å⁻³. A weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0439 * P)^2 + 0.230 * P]$ where $P = (F_o^2 + 2 * F_c^2)/3$ was used in the latter stages of refinement. Complex scattering factors were taken from the program package SHELXL93¹⁵ as implemented on the Viglen 486DX computer.

Atomic coordinates, bond lengths and angles, and thermal parameters for compounds **3** and **4** have been deposited with the Cambridge Crystallographic Data Centre. Requests for these data should be accompanied by a full bibliographic reference together with the reference No. CCDC 207/59.†

Acknowledgements

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† For details see Instructions for Authors (1997), *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1.

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