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Chemistry of the S=O Bond

11*—Carbon-13 and Oxygen-17 Nuclear Magnetic Resonance Studies of Stereoisomerism in 1,3,2-Dioxathiepanes

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The stereoisomerism of some methyl-substituted 1,3,2-dioxathiepanes has been investigated by ^{13}C and ^{17}O NMR spectroscopy. The effects of substituents on the conformational equilibria of the seven-membered rings are discussed and compared with those for six-membered ring sulphites.

KEY WORDS ^{13}C NMR ^{17}O NMR Stereoisomerism 1,3,2-Dioxathiepanes

INTRODUCTION

Since the 1950s the conformational analysis of simple five- and six-membered ring sulphites has been studied using a variety of techniques.[2,3] For ethylene sulphites in solution, NMR work based on a detailed analysis of vicinal coupling constants was interpreted in terms of twist–envelope forms which interconvert rapidly on the NMR time scale.[4] A recent x-ray study confirmed this type of conformation in the solid state,[5] For trimethylene sulphites, both solid-state[6] and solution studies[7,8] have given evidence for three basic forms: a rigid chair with S=O axial, a rigid chair with S=O equatorial or twist forms with the S=O pseudoaxial or pseudoequatorial (isoclinal).

Although there have been only a few reports on the conformational analysis of seven-membered ring sulphites,[9–11] an understanding of possible ring conformations has been obtained by detailed studies of other saturated seven-membered ring heterocyclic compounds. For example, Bocian and co-workers have made detailed theoretical studies of cycloheptane[12] and 1,3-dioxepane.[13] For these compounds they identified four basic conformations, the chair, the boat, the twist–chair and the twist–boat. Computer modelling involving pseudorotation around various bonds permitted the construction of relative conformational energy surfaces, and from these the lowest energy conformation was found, namely the twist–chair. The calculated energy differences between the twist–chair (TC), twist–boat (TB), boat (B) and chair (C) forms for 1,3-dioxepane[13] were estimated to be $\Delta E = 0$, 2.32, 2.92 and 3.04 kJ mol^{-1} (0, 9.7, 12.2 and 12.7 kcal mol^{-1}), respectively. Unfortunately, no calculations have yet been carried out on seven-membered ring sulphites; the relative energy differences between TC, TB, B and C forms therefore have to be extrapolated from results for similar ring systems but presumably follow the same order and lie in the range 0–3.59 kJ mol^{-1} (0–15 kcal mol^{-1}).

The conformational analysis of seven-membered ring sulphites is extremely complicated since they consist of two main groups of mobile forms, chairs and boats, derived from two independent pseudorotational pathways. Since the orientation of the S=O bond can be axial, equatorial or isoclinal, there are a total of 28 possible orientations for each group.[11] These are shown in Figs 1 and 2. Note that by considering mirror planes enantiomeric pairs may be identified e.g. TCO3B(a), and TCO1A(a), as well as conformers related through inversion (A and B forms), e.g. TCSA and TCSB.

Despite the very flexible nature of this ring system, a large number of isomeric sulphites are possible through methyl substitution, the substituent being *cis* or *trans* to the S=O bond, which may be axial, equatorial or isoclinal. Although a maximum of 56 forms are possible for each sulphite, examination of models of the various forms shows that many of the boat and chair forms are energetically unfavourable through steric hindrance, particulary with an increasing number of methyl substituents. Nevertheless, the conformational state in solution of most of these sulphites is expected to be a conformational equilibrium of a number of conformers. On the NMR time scale this will be reflected in averaged ^{13}C and ^{17}O chemical shifts.

RESULTS

The sulphites were prepared by standard methods[7] and purified by high-performance liquid chromatography (HPLC). Detailed ^{1}H NMR spectral analysis was not carried out, but isomers were easily characterized by assignments based on well established trends of alkyl substitution on ^{13}C chemical shifts and vicinal couplings obtained from ^{1}H NMR spectra.

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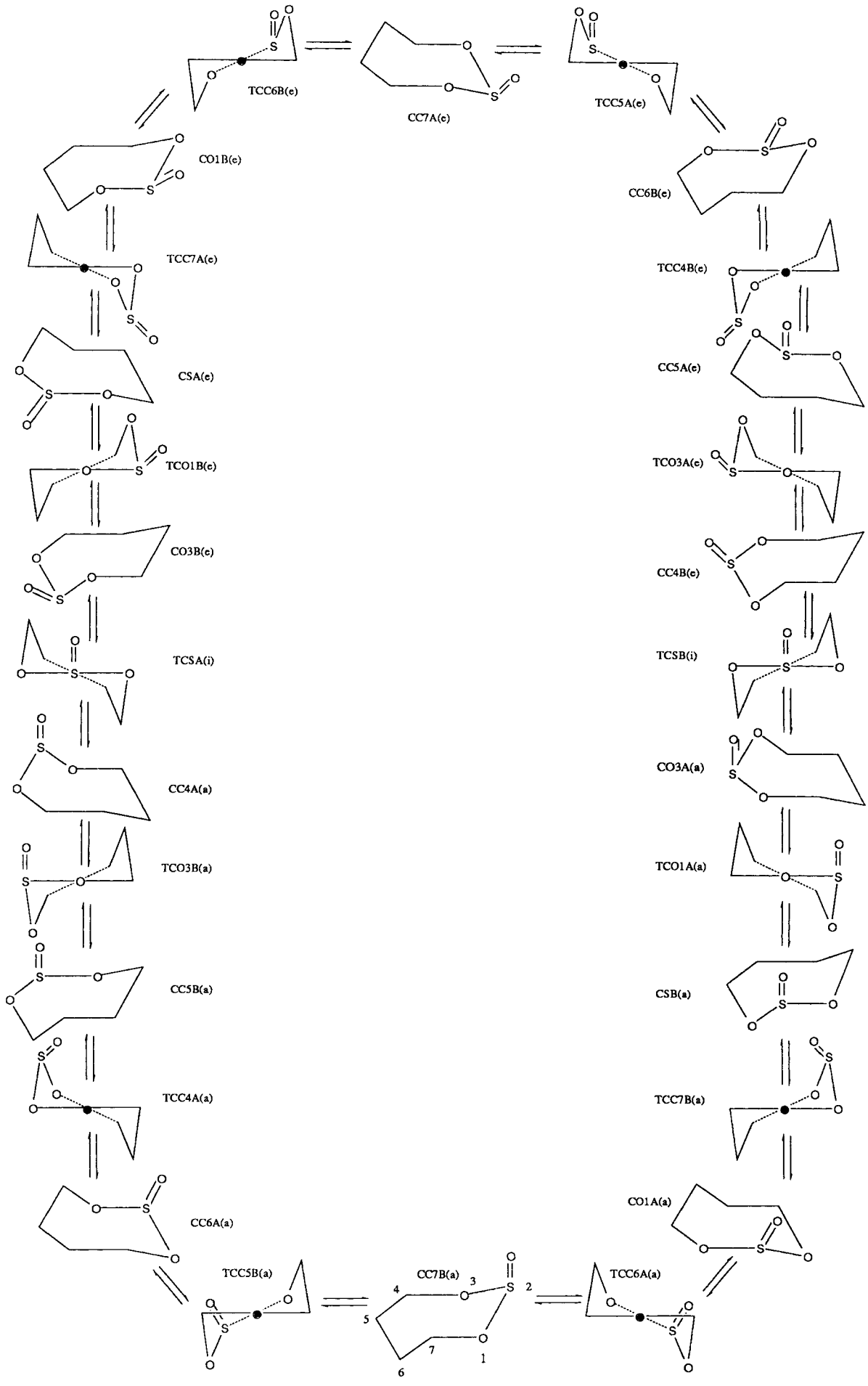

Figure 1. Pseudorotation pathway for the chair family. C = Chair; T = twist; TC = twist–chair; TB = twist–boat; O = oxygen; C = carbon; S = sulphur; a = axial; e = equatorial; i = isoclinal; A = inverted in relation to B; B = inverted in relation to A.

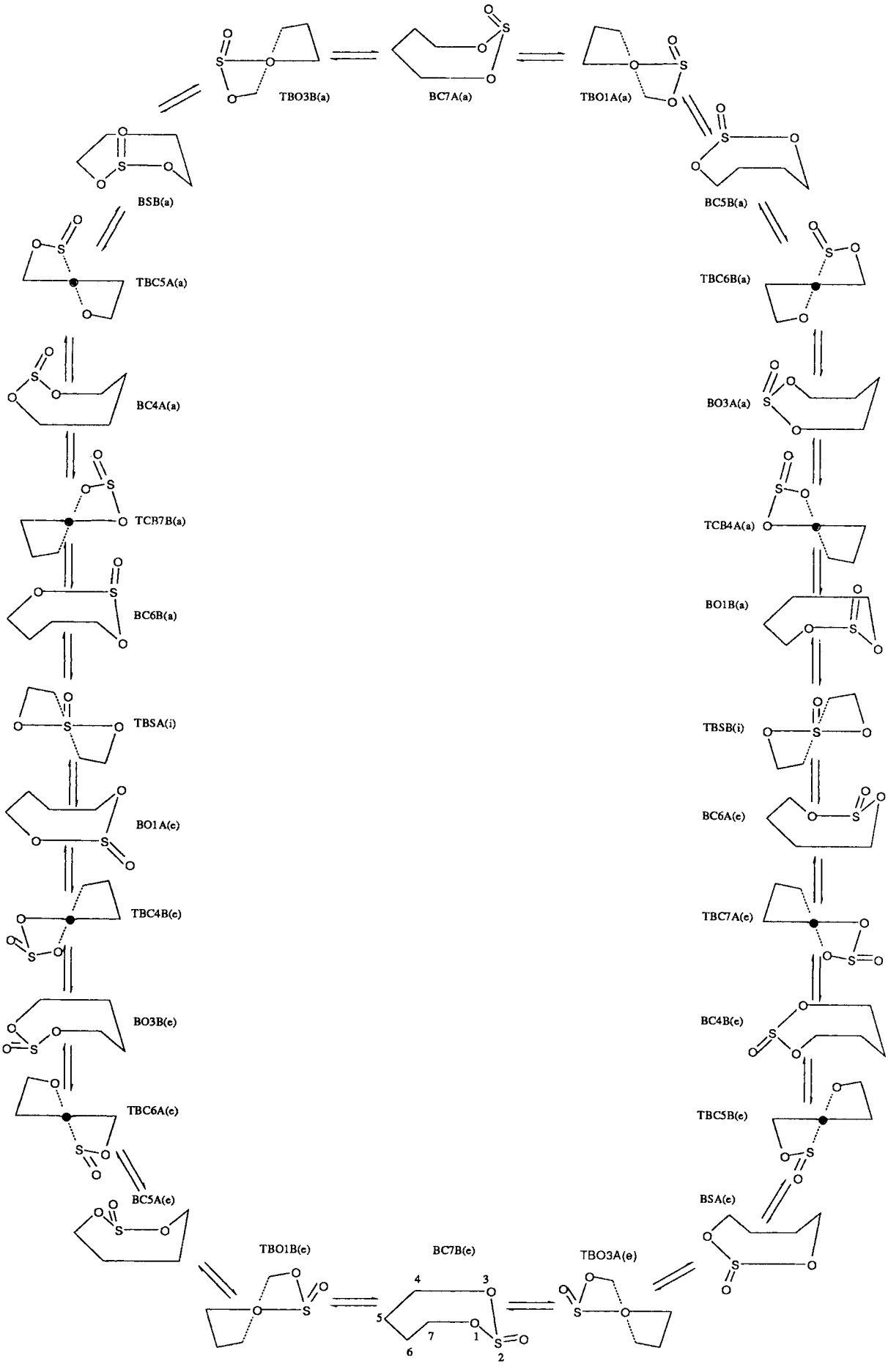

Figure 2. Pseudorotation pathway for the boat family. Abbreviations as in Fig. 1.

Table 1. ^{13}C chemical shifts (ppm) of ring carbons (rounded to nearest 0.1 ppm)

Compound	Name	C-4	ΔC-4	C-5	ΔC-5	C-6	ΔC-6	C-7	ΔC-7
1	1,3,2-Dioxathiepane 2-oxide (DJP)	64.1		28.5		28.5		64.1	
5	5-methyl-DTP, isomer 1	67.4	3.3	37.1	8.6	32.7	4.2	63.5	−0.6
6	5-methyl-DTP, isomer 2	69.5	5.4	35.9	7.4	34.1	5.6	61.3	−2.8
7	5,5-dimethyl-DTP (predicted)	72.9	8.8	44.5	16.0	38.3	9.8	60.7	−3.4
7	5,5-dimethyl-DTP (observed)	71.4	7.3	42.1	13.6	34.2	5.7	60.7	−3.4

Sulphite **1** is the parent compound for the series of methyl sulphites **2–18**. Although the ^{1}H spectrum is extremely complex, the ^{13}C and ^{17}O spectra contain only two peaks, confirming the symmetry of the molecule. The IR spectra show a strong peak at 1200 cm^{-1}, indicating an axial S=O bond, and considering the steric interactions of the hydrogens it is probable that the conformational equilibrium is dominated by twist–chair/twist–boat forms with an axial S=O bond.[8]

The values of the ^{13}C chemical shifts show the effects of substitution at C-4, C-5, C-6 and C-7. A number of observations can be made from comparison of the α, β and γ deshielding effects. The α effect arises from mono- or di-substitution on C-4–C-7 and causes deshielding of these carbons relative to **1**. For example, a deshielding of 9.7 or 6.8 ppm is found for C-4 on substitution of a methyl group in the C-4 axial (**2**) or C-4 equatorial (**3**) position, respectively. Similar substitution on C-5 gives values for **5** and **6** of 8.6 and 7.4 ppm, respectively. A geminal dimethyl group on C-4, as in **4**, **14**, **15** and **17** shifts the resonance substantially downfield (*ca.* 23 ppm). In contrast, a geminal dimethyl on C-5, as in **7** and **16**, gives a lower effect of *ca.* 14 ppm.

The β effect occurs when a C-4 or C-7 methyl group deshields C-5 or C-6 or a C-5 or C-6 methyl group deshields C-4 or C-7, respectively. Of particular note is the *trans*-methyl group on C-4 of **3**, deshielding C-5 by *ca.* 15 ppm compared with the *cis* methyl value for **2** or *ca.* 8 ppm. Further, disubstitution on C-4 gives a larger deshielding (*ca.* 12 ppm) than does disubstitution on C-5 (*ca.* 7 ppm).

In addition to α and β effects, γ and δ effects are evident in sulphites **2–13**. The δ effect for sulphites **2**, **4**, **5** and **6**, is in fact shielding. The same has been found for trimethylene sulphites,[13] although for seven-membered ring sulphites the effect is larger.

The magnitude of the α and β effects can be calculated using additivity relationships similar to those successfully used for trimethylene sulphites.[14] Comparison of the observed and calculated values shows that for most of the compounds, e.g. **2**, **3**, **4**, **8**, **9**, **10** and **17**, no simple correlations are found. This supports the prediction that the seven-membered ring sulphites are a complicated mixture of several forms, each sulphite being unique. Only for sulphites **5**, **6** and **7** do the observed and calculated chemical shifts agree reasonably well, as shown in Table 1. The calculated effect of the dimethyl group on C-5 and other carbons (α, C-5; β, C-4 and C-6; γ, C-7) may suggest that the addition of a second methyl group to C-5 does not change drastically the equilibrium mixture of conformations. For all three sulphites, twist forms with isoclinal S=O are predicted to be dominant (see Table 2).

Finally, the ^{13}C chemical shifts are invariably similar

Table 2. ^{13}C chemical shifts for the ring carbons of 1,3,2-dioxathiepane-2-oxides

Compound	Name	Chemical shift (ppm) C-4	C-5	C-6	C-7	Predicted biasing of conformers in solution[a]	$\nu_{S=O}$ (cm^{-1})
1	DTP	64.1	28.5	28.5	64.1	TC(a) and TB(a)	1200
2	*cis*-4-Methyl-DTP, isomer 1	73.79	36.62	27.15	61.95	TC(i) and some TC(a)	1215, 1190
3	*trans*-4-Methyl-DTP, isomer 2	70.93	43.56	28.97	65.59	TC(i) and some TC(a)	1215, 1190
4	4,4-Dimethyl-DTP	87.51	40.36	30.44	62.93	TC(a) and some TC(i)	1190
5	*cis*-5-Methyl-DTP, isomer 1	67.41	37.11	32.73	63.53	TC(i)	1215
6	*trans*-5-Methyl-DTP, isomer 2	69.54	35.89	34.07	61.34	TC(i) and some TC(a)	1215, 1195
7	5,5-Dimethyl-DTP	71.40	42.10	34.21	60.70	TC(i)	1220
8	*trans, trans*-4,7-Dimethyl-DTP, isomer 1	71.90	33.40	33.40	71.90	TC(a)	1200
9	*cis, trans*-4,7-Dimethyl-DTP, isomer 2	73.20	36.10	34.00	70.00	TC(i)	1220
10	*cis, cis*-4,7-Dimethyl-DTP, isomer 3	75.00	33.00	33.00	75.00	TC(e)	1230
11	*trans, trans*-5,6-Dimethyl-DTP, isomer 1	66.75	37.10	37.10	66.75	TC(i)	1212
12	*cis, trans*-5,6-Dimethyl-DTP, isomer 2	67.82	38.78	40.03	65.37	TC(i)	1212
13	*cis, cis*-5,6-Dimethyl-DTP, isomer 3	66.68	36.85	36.85	66.68	TC(i)	1212
14	*cis*-4,4,7-Trimethyl-DTP, isomer 1	86.88	39.95	33.24	70.84	TC(a)	1180
15	*trans*-4,4,7-Trimethyl-DTP, isomer 2	87.01	38.99	33.12	73.50	TC(a)	1209br
16	5,5,6,6-Tetramethyl-DTP	69.32	38.71	38.71	69.32	TC(i)	1212
17	4,4,7,7-Tetramethyl-DTP	84.23	36.71	36.71	84.23	TC(i)	1212
18	*cis*-4,5,5,6,6,7-Hexamethyl-DTP	81.50	43.49	43.49	81.50	TC(a)	1200

[a] Neat solution. TC(a), twist–chair, axial forms; TC(e), twist–chair, equatorial form; TC(i), twist–chair, isoclinal forms; TB(a), twist–boat, axial forms.

Table 3. ^{17}O chemical shifts for substituted 1,3,2-dioxathiepane 2-oxides

Compound	Name	Chemical shift (ppm) O-3	O-1	S=O
1	DTP	145.2	145.2	181.8
2	*cis*-4-Methyl-DTP, isomer 1	168.8	146.9	180.0
3	*trans*-4-Methyl-DTP, isomer 2	167.7	146.4	179.4
4	4,4-Dimethyl-DTP	175.5	152.8	184.3
5	*cis*-5-Methyl-DTP, isomer 1	139.9	145.0	181.2
6	*trans*-5-Methyl-DTP, isomer 2	143.7	150.0	181.7
7	5,5-dimethyl-DTP	137.5	144.7	182.5
8	*trans, trans*-4,7-Dimethyl-DTP, isomer 1	169.9	169.9	176.2
9	*cis, trans*-4,7-Dimethyl-DTP, isomer 2	169.7	169.7	180.2
10	*cis, cis*-4,7-Dimethyl-DTP, isomer 3	170.1	170.1	179.8
11	*trans, trans*-5,6-Dimethyl-DTP, isomer 1	138.1	138.1	179.2
12	*cis, trans*-5,6-Dimethyl-DTP, isomer 2	137,5	137.5	181.0
13	*cis, cis*-5,6-Dimethyl-DTP, isomer 3	142.0	142.0	183.9
14	*cis*-4,4,7-Trimethyl-DTP, isomer 1	183.5 broad		
15	*trans*-4,4,7-Trimethyl-DTP, isomer 2	173.4 broad		
16	5,5,6,6-Tetramethyl-DTP	136.0	136.0	180.4
17	4,4,7,7-Tetramethyl-DTP	169.2	169.2	195.1
18	*cis*-4,5,5,6,6,7-Hexamethyl-DTP, isomer 1	162.0	162.0	194.0

between isomeric pairs, as in **5** and **6**, **14** and **15** and between three stereoisomers, as in **8**, **9** and **10** and particularly **11**, **12** and **13**. The small differences may be attributed to unequal α and β effects and/or changes in the equilibria (see Table 2).

The S=^{17}O chemical shifts show that most compounds resonate at or near 180 ppm, comparable to the average value for six-membered ring sulphites. Increased methylation leads to a greater deshielding of the S=O group, as shown for **17** and **18**. The values for ^{17}O-1 and ^{17}O-3 given in Table 3 show the usual effect of methyl substitution. For the mono- and dimethylated series, the shielding of the ring oxygens by an axial methyl on C-6 and/or C-5 is now a recognized effect.[2,15] This is apparent for **5**, **7**, **11**, **12** and **16**. For some sulphites, such as **9** and **12**, only one peak is observed, for the ring oxygens, despite the asymmetry of the molecules. In the extremes of conformational equilibrium, the chemical shift difference between the ring oxygens must still be less than the natural line widths.

Some isomeric sulphites show very similar ^{17}O chemical shifts e.g. the isomeric pair **2** and **3** and the three isomers **11**, **12** and **13**. Sulphites **8**, **9** and **10** also have virtually identical ^{17}O-1 and ^{17}O-3 chemical shifts. These results show that, as for trimethylene sulphites,[2] ^{17}O NMR spectroscopy is not very sensitive to the study of the equilibria of twist conformations which derive from changes in the ring carbon stereochemistry.

Although there is a correlation between the ^{17}O chemical shift of the ring oxygens and the chemical shift of the adjacent carbon, given by the relationship, e.g.

$$\delta(^{17}O\text{-}3) = \delta(^{13}C\text{-}4) \times 2.2$$

the error limit on the multiplication factor is ± 0.2, rendering this expression of only limited value.

Finally, IR studies in the region 1100–1250 cm^{-1} were used to identify the predominant forms. Based on extensive studies of cyclic sulphites,[8,10] it is now recognized that the position of the band is dependent on the orientation of the S=O bond and solvent, with $\nu_{S=O}$ (axial) $\approx$ 1190 cm^{-1}, $\nu_{S=O}$ (equatorial) $\approx$ 1230 cm^{-1} and $\nu_{S=O}$ (isoclinal) $\approx$ 1215 cm^{-1}. The IR results are summarized in Table 2 together with the predicted biasing of conformation.

EXPERIMENTAL

All the compounds investigated were characterized by correct elemental analysis data and IR data, in addition to their NMR spectra. Compounds **1**, **4** and **7–10** have been synthesized previously.[9–11] Further, for **2** (n_D^{20} = 1.4539); **3** (n_D^{20} = 1.4552); **5** (n_D^{20} = 1.4660); **6** (n_D^{20} = 1.4735); **11** (n_D^{20} = 1.4685); **12** (n_D^{20} = 1.4631); **13** (n_D^{20} = 1.4650); **14** (n_D^{20} = 1.4405); **15** (n_D^{20} = 1.4420); **16** (m.p. 80 °C); **17** (n_D^{20} = 1.4722); **18** (unstable, 80% pure).

General procedure

To a stirred solution of butane-1,4-diol (Aldrich) (0.13 mol) and pyridine (0.33 mol) dissolved in benzene (200 cm^3) was added dropwise (1 h) a benzene solution (100 cm^3) of thionyl chloride (0.14 mol). The solution was further stirred at room temperature for 3 h. The pyridine hydrochloride was filtered off and the clear solution was washed with aqueous $NaHCO_3$ and dried for several hours over anhydrous $MgSO_4$. Removal of solvent at reduced pressure yielded crude 1,3,2-dioxathiepane 2-oxide (**1**) (0.09 mol, 70%). The crude product was purified by HPLC; n_D^{20} = 1.4661.

The purification of sulphites and the separation of diastereoisomers were effected by HPLC on a Nucleosil 50 5 μm column with a mixture of ethyl acetate and light petroleum (b.p. 60–80 °C) as eluent. Generally, these sulphites are not as stable as trimethylene sulphites and tend to decompose on standing after about 2 days, particularly **14–18**.

Spectra

Stereochemical assignments for isomers were based on ^{1}H NMR and ^{13}C spectral data analysis. The protons on C-4 and/or C-7 *cis* to the S=O bond resonate at lowest field and, from a knowledge of their ^{3}J couplings with the C-5 and/or C-6 protons, it is possible to assign the orientation of the substituent methyl groups. Thus **3**, **5**, **11**–**13**, **14** and **18** all gave ^{3}J axial–axial couplings between 10 and 12 Hz and ^{3}J axial–equatorial couplings of *ca.* 2.5 Hz. The assignments were also confirmed by ^{13}C chemical shift values of the relevant ring carbons, whose deshielded values can be interpolated and partly predicted by examining models of the different isomers.[10]

The ^{17}O spectra were recorded on a Bruker Spectrospin WM400 spectrometer equipped with a 10 mm probe operating at 54.25 MHz in the FT mode at a probe temperature of 30 °C. Samples (natural ^{17}O abundance) were typically 1 M solutions in $CDCl_3$. Spectral settings were as follows: 25–30 kHz spectral width, 4096 data points, 90° pulse angle corresponding to 25 μs pulse width, 80 μs acquisition time with no acquisition delay and 5000–25 000 scans. Under these conditions, the observed signals had half band-widths of *ca.* 300 Hz or less. Chemical shifts were measured without proton decoupling relative to external tap water reference and were considered to be accurate to ±0.5 ppm.

The ^{13}C FT NMR spectra were recorded on a Bruker AM 250 spectrometer operating at 62.895 MHz. The spectra were obtained from samples of sulphites, diluted to *ca.* 20% v/v in $CDCl_3$ using 10 mm o.d. sample tubes with internal ^{2}H lock to $CDCl_3$. Tetramethylsilane was used as an external reference; a single pulse sequence with a pulse width of 3 μs was used, corresponding to a 40° mutation; 16K data points were used over 15 000 Hz for accumulation of spectra. The proton decoupled ^{13}C spectra were recorded after performing 1000–2000 spectral accumulations.

The IR spectra were recorded as neat solutions on NaCl windows on a Perkin-Elmer Model 577 grating infrared spectrophotometer. Frequency absorption could be quoted to ±1 cm^{-1} except where peak broadening occurred.

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