¹H NMR Spectra and Conformational Analysis of Some 1,4-Dithiepan-6-ones

Michael J. Cook,* Ghoabad Ghaem-Maghami and Festus Kaberia

School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, UK

Knut Bergesen

Department of Chemistry, University of Bergen, N-5014 Bergen, Norway

¹H NMR Parameters are reported for five 1,4-dithiepan-6-ones. 1,4-Dithiepan-6-one 1-oxide exists in solution as an equilibrium involving two different twist-chair conformations, which contrasts with its conformational behaviour in the solid state. Twist-chair conformers are also adopted by other members of the series, the favoured form varying with ring substitution. The S=O bond in 1,4-dithiepan-6-one 1-oxide and in its 5,5-dimethyl analogue exhibit a preference for the pseudoaxial site.

INTRODUCTION

Cycloheptanone exists in twist-chair (TC) conformations and results of calculations predict that the TC₁ and TC₂ forms (Fig. 1) are the most stable.¹⁻³ Twistchairs are also adopted by the substituted ring,⁴⁻⁹ and recent results indicate that the favoured form may well



Figure 1. TC1 and TC2 conformations of cycloheptanone.

depend upon the substitution pattern.^{10–12} Replacement of one or more of the CH_2 units of the ring with heteroatoms introduces further perturbations to the conformational energy profile,¹³ and various studies bear testament to the assortment of conformer types which become energetically feasible. Thus, while highly substituted 1,3-dioxepan-5-ones adopt TC forms,¹⁴ oxepan-2-ones exist as deformed chair conformers¹⁵ and 3-methyl-1,4-dioxepan-2-one favours a twist-boat geometry.¹⁶ Recently, we examined¹⁷ the crystal structure of 1,4-dithiepan-6-one 1-oxide (**1**), a ring in which bond lengths and angles are particularly different from those in cycloheptanone itself, and found that the compound adopts a highly puckered chair conformation (torsion angle within S-1--C-2--



* Author to whom correspondence should be addressed.

C-3--S-4 = 76.3°) with C-5 and C-6 in the flat region. In this paper we investigate whether **1** retains this conformation in solution, and we also appraise data for a number of other 1,4-dithiepan-6-one derivatives, **2–5**.

RESULTS

Chemical shifts, coupling constants and assignments are given in Table 1, the two sets of *cis* sites being designated 2, 3, 5, 7, and 2', 3', 5', 7', respectively. Assignments are based on standard considerations of group anisotropies, signal multiplicity, etc. Values for untabulated coupling constants are taken as 0.0 ± 0.3 Hz.

The 400 MHz spectra of 1 and 2 are readily analysed by first-order theory. Simulated spectra, calculated with the LAOCOON program¹⁸ using the parameters listed in Table 1, are in excellent agreement with those obtained experimentally. Coupling constants are considered reliable to within ± 0.2 Hz. A feature of the spectrum of **1** is a 32-line pattern for H-2 arising from a geminal coupling, two vicinal couplings, a four-bond coupling to H-7 and a five-bond coupling to H-5'. Four-bond couplings between other pairs of protons are also evident in the spectra of both 1 and 2. The spectrum of 1 was also obtained at temperatures down to -57 °C (at 220 MHz), below which crystallization occurred. Coupling constants showed little variation and changes in chemical shifts were small.

The 100 MHz spectrum of **3** showed two singlets which did not broaden over the temperature range 22 to -112 °C; below -112 °C the material precipitated. Limited coupling constant data are available from the analysis of the ¹³C--H satellite spectrum¹⁹ for the protons bonded to C-2 and C-3. Because J(CH) is large compared with J(HH), the five-line pattern of each satellite is conveniently analysed by A_2X_2 theory. Six recordings of the upfield satellite gave mean values of L = 5.84 Hz and N = 10.14 Hz (usual notation),

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	Compound								
Parameter ^a	15	2	3	4	5				
δH-2	3.66 (3.72)	3.43)		3.20	1.38 (Me)				
δH-2′	2.98 (3.03)	3.04		2.93	3.28				
δН-З	3.50 (3.44)	3.15	3.06	3.14	2.88				
δΗ-3′	3.01 (3.14)	2.89		3.14	3.16				
δH-5	3.65 (3.65)	ָרֹ (Me) רָ		4.39	3.89				
δH-5′	3.36 (3.43)	1.39 (Me)		1.40 (Me)	3.39				
δH-7	4.14 (4.18)	4.14 } ^{3.6}		3.37	3.43				
δ Η-7 ′	4.63 (4.88)	4.66		3.93	3.91				
²J(22′)	14.5	-14.4	с	14.9	7.0 (H, Me)				
²J(33′)	-15.8	16.5	с	-14.6	-14.5				
²J(55′)	-16.9		с	7.0 (H, Me)	16.0				
²J(77′)	-13.4	-10.8	с	-17.0	-16.0				
³ J(23)	1.9	2.0)	2.1	2.1					
³ J(2'3')	2.6	2.4 ∫	2.14	2.6	2.4				
³ J(23′)	5.5	7.1)	70	4.8					
³ J(2′3)	11.8	10.2	7.9 ₉	11.1	8.9				
⁴ J(27)	-1.1	-0.8	с	1.0	_				
^₄ J(2′7′)	-0.3	~0.4	с	0.0	d				
⁴J(3′5′)	-1.4		с		đ				
⁴ J(5′7)	-0.8		с		d				
⁵J(25′)	0.5	_	с		-				

Table 1.	'H NMR	parameters	for	compounds	1	to	5	as	solutions	in	CDCl ₃
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^a Chemical shifts in ppm relative to tetramethylsilane as internal standard; coupling constants measured in Hz.

^b Figures in parentheses refer to chemical shifts at -57 °C.

^cNo measurement possible.

^d Peak broadening observed.

leading to J = 7.99 and J' = 2.14 Hz. These are assigned to $\sum^{3} J(trans)/2$ and $\sum^{3} J(cis)/2$, respectively.

The spectrum of **4**, measured at 220 MHz, is rendered complex by the near equivalence of H-3 and H-3'. Coupling constants and chemical shifts for H-2, H-2', H-3 and H-3' were obtained by iterative computation, analysing the signals in terms of a five-spin system to take account of coupling between H-2 and H-7. Fifty-three calculated transitions were fitted to 37 observed lines assigned to the four protons (RMS error of fit = 0.096). Calculated 'probable errors' are highest for J(23) and J(23') (0.17 Hz); the remainder are all less than 0.07 Hz.

The 220 MHz spectrum of **5** is readily interpretable by first-order theory. Parameters so obtained for the C-2 methyl group, H-2', H-3 and H-3' were refined using iterative computation (A₃BCD theory); 78 calculated transitions were fitted to 24 observed lines, RMS error = 0.066. Probable errors for the parameters are all calculated to be less than 0.02 Hz. Longrange coupling broadens the signals for one of the C-5 and one of the C-7 protons. It is not clear whether these protons are coupled to each other or to protons bonded to C-2 and C-3.

DISCUSSION

Conformational analysis of 1

The chemical shifts of six of the eight protons vary by no more than 0.07 ppm on lowering the temperature from 25 to -57 °C. The largest shift, 0.25 ppm, is

observed for H-7'. This, together with only minor changes in coupling constants at the lower temperature, is consistent with either an equilibrium involving conformers differing only in their geometry in the C-7 region or a highly biased equilibrium, the shift in δ H-7' arising from temperature-dependent association phenomena. Both interpretations imply that the S-1-C-2-C-3-S-4 unit is essentially locked in one geometry which, on the basis of the ${}^{3}J$ values, is puckered. Calculation of the endocyclic torsion angle, ψ , within this fragment, using the Lambert-Buys Rvalue method,²⁰ where $R = \sum^{3} J(trans) / \sum^{3} J(cis)$ and $\cos \psi = |3/(2+4R)|^{1/2}$, gives $\psi = 66^\circ$, a value significantly less than the 76.3° angle measured for the solid state.¹⁷ The deshielding of H-3 and H-5 and shielding of H-3', a manifestation of the syn axial effect, shows that the pseudoaxial S=O bond found in the crystal is retained in solution.

Coupling via four bonds is favoured through a planar W pathway and J(3'5') = -1.4 and J(35) = 0 Hz indicate that atoms H-3'-C-3-S-4--C-5-H-5' approach coplanarity. It follows that the C-3 and C-5 methylene groups are at similar orientations with respect to S-4 and, thus, the difference between J(33')and J(55') does not arise from the angle dependence of ²J in the $-S-CH_2$ unit²² but from the angle dependence of ²J in the --CH₂--C=O moiety.²³ A similar argument holds for the difference between J(22') and J(77'). These differences are a valuable conformational probe²⁴ and the fact that J(55') is more negative than J(33'), whereas J(77') is less negative than J(22'), shows that, in the average geometry, puckering between the planes containing the S-1-C-7 and C==O bonds is greater than between the planes containing the C=O and S-4-C-5 bonds.



Figure 2. Conformations of 1,4-dithiepan-6-ones. A, B and C = chair, $TC_{C-6}(S=O_{ax})$ and $TC_{C-5}(S=O_{ax})$ forms of 1, respectively; $D = TC_{C-5}(S=O_{ax})$ form of 2; $E = TC_{C-7}(Me_{eq})$ form of 4; $F = TC_{C-6}(Me_{eq})$ form of 5.

There are three conformations, free of angle strain and severe non-bonded interactions, which satisfy at least a substantial proportion of the data. These are the chair, A, found in the solid state (albeit less puckered within the S-1-C-2-C-3-S-4 region), and the twistchairs, B and C (Fig. 2). The last two are denoted TC_{C-6} and TC_{C-5}, respectively, and correspond to the TC1 and TC2 forms of cycloheptanone; A is intermediate between B and C on the pseudo-rotation pathway. (The subscript refers to the atom through which the axis of symmetry would pass if the ring were viewed as twist-chair cycloheptane, cf. Ref. 14.) However, none of the three forms is consistent with all facets of the NMR data. Thus, the coplanar arrangement of S-4-C-5-C-6=O which is present in A should cause J(55') to be ca 6 Hz more negative than J(33')²⁴ while similar puckering of S-4—C-5—C-6=O and S-1-C-7-C-6=O (as in B) was ruled out earlier. Form C should give rise to the least possible negative value for J(77') but the observed value (-13.4 Hz), though less negative than J(22') by 1.1 Hz, is significantly more negative than J(77') =-10.8 Hz found in 2 (see below). We conclude that 1 adopts no single conformational type, but pseudorotates rapidly between two or more forms. An equilibrium involving B and C is fully consistent with the data, but a modest contribution from the chair form cannot be ruled out.

Conformational analysis of 2

The R-value method gives a torsion angle of 66° for the S-1—C-2—C-3—S-4 fragment, the same (to within experimental error) as that in **1**. With regard to the rest of the molecule, however, the coupling constant J(77') = -10.8 Hz provides convincing evidence that the conformational behaviour of **2** differs from that of **1**. Two conformations could give rise to a small negative value for J(77'). In the first, the chair corresponding to form A of **1**, one of the C-5 methyl groups is in close proximity to H-3. This interaction, however, is minimized in the second conformation, the TC_{C-5} form (D in Fig. 2), and we deduce that this is the favoured geometry. Interestingly, the alicyclic analogue of **2**, i.e. 2,2-dimethylcycloheptanone, adopts the corresponding TC₂ form.¹⁰

As in 1, H-3 is deshielded relative to H-3' by virtue of its proximity to the S=O bond. However, the *trans* couplings J(2'3) and J(23') are smaller and larger, respectively, than the corresponding values in 1, showing that the inverted TC_{C-5} conformer (having the S=O bond pseudoequatorial) is occupied to some extent.

Conformational analysis of 3 and 4

The mean torsional angle within the S-1-C-2-C-3-S-4 fragment for 3 and 4, calculated from the Rvalues, are 65° and 64°, respectively. Unfortunately, no further conclusions can be drawn about the geometry of 3 because of insufficient data. However for 4, the individual ${}^{3}J(trans)$ values [J(2'3) = 11.1 and J(23') = 4.8 Hz show that the S-1--C-2--C-3--S-4 region is essentially locked. The value J(27) = -1.0 Hz points to near coplanarity of the atoms H-2-C-2-S-1---C-7---H-7, and the difference between J(77') =-17.0 Hz and J(22') = -14.9 Hz is therefore taken to arise from the spatial arrangement of the atoms within the CH₂—C=O unit, cf. $\overline{\mathbf{1}}$ above. Inspection of the curve²⁴ relating geometry to the variation of ${}^{2}J$ shows that a TC_{C-7} conformer, in which the methyl group is assumed to be at the 5' pseudoequatorial position (E in Fig. 2), is particularly compatible with the data.

Conformational analysis of 5

The vicinal *cis* coupling constant J(2'3') is similar to values found in other members of the series, which argues in favour of a further recurrence of the puckered geometry in the S-1-C-2-C-3-S-4 region. As before, values of the geminal couplings are particularly useful for elucidating the shape of the remainder of the ring. J(55') and J(77') are the same, which suggests the ring either adopts the TC_{C-6} geometry or exists as an equilibrium of approximately equal amounts of the TC_{C-5} and TC_{C-7} forms. However, the TC_{C-6} geometry is more compatible with the further observation that J(55') and J(77') are 1.5 Hz more negative than J(33').²⁴ Finally, the value for J(2'3) =8.9 Hz, although substantial, is less than that in 4. We conclude, therefore, that 5 exists predominantly as conformer F but that the inverted TC_{C-6} form, having the 2-methyl group pseudoaxial, is populated to some extent. CD studies^{9,11} of chiral 4-methylcyclo-heptanone showed that a TC_1 conformer, the carbocyclic analogue of F, is favoured marginally over TC_2 and TC_7 forms, while an NMR study revealed that TC₁ is the principal form adopted by 4-tert-butylcycloheptanone.12

CONCLUSIONS

The chair conformation adopted by **1** in the crystal is not the favoured form in the solution phase, where twist-chair conformers are prevalent. Other members of the series also adopt twist-chair conformations in solution, but the predominant form varies. Where comparisons are possible, the conformational properties of individual compounds resemble closely those of the corresponding cycloheptanone, a finding which has important implications for the development of the conformational analysis of seven membered ring heterocycles.

Values for the torsional angle in the S-1—C-2—C-3—S-4 region of **1–4**, calculated using the *R*-value method, all fall in the range 64–66°. The method is an established technique for determining six-membered ring geometry²⁰ and is also considered to be reliable for seven-membered rings.^{25,26} The large difference between the torsional angle for **1** in the crystal and in solution is, thus, taken to be real rather than an artefact of the method, and is a demonstration that the S-1—C-2—C-3—S-4 geometry changes substantially as the molecule pseudo-rotates from the chair of the crystal to the twist-chair forms in solution.

The S=O bond in **1** is pseudoaxial in the crystal, and a strong preference for this site is sustained in solution. The same preference is exhibited by the S=O bond in **2** but to a lesser extent. The spatial arrangement of the S=O and C=O bonds in conformer B, and to a lesser extent in conformer C, is closely similar to that found in the predominant conformer of thian-3-one 1-oxide.²⁷ We surmise that this arrangement sustains a stabilising interaction between the two functionalities.

EXPERIMENTAL

NMR measurements

Spectra were obtained for *ca* 5% solutions (w/v) in CDCl₃. Spectra at 100 MHz were obtained at 22° using a Varian HA 100 spectrometer. Spectra at 220 MHz (200 Hz sweep width; calibrations at 25 Hz intervals) were recorded at 22 °C, unless stated otherwise, at the PCMU Service Laboratory, Harwell, using a Perkin–Elmer R34 spectrometer. The spectra of **1** and **2** at 400 MHz (Bruker WH 400; SERC Service, University of Warwick) were measured at 25 °C with digitalization of 0.095 Hz per point for **1** and 0.171 Hz per point for **2**. Non-iterative and iterative spectral calculations were performed using a local version of the LAOCOON program.¹⁸

1,4-Dithiepan-6-one (3). A solution prepared from sodium (6 g) and ethane-1,2-dithiol (11.3 ml) in AnalaR methanol (100 ml), and a solution of 1,3-dichloropropanone (15.2 g) in anhydrous diethyl ether (100 ml), were added dropwise and at the same rate to a vessel containing AnalaR methanol (25 ml) and diethyl ether (25 ml) under nitrogen. When the addition was complete the mixture was poured with stirring into a mixture of diethyl ether (100 ml), 3% aqueous NaOH (250 ml) and ice (100 g). The organic layer was separated and the aqueous layer extracted with diethyl ether (3×100 ml). The organic solutions were combined, dried (MgSO₄) and evaporated to dryness. The crude ketone (8 g, 59%) was distilled at 94–98 °C at 0.4 mmHg (lit.,²⁸ b.p. 85–90 °C at 0.3 mmHg).

The procedure described above was used to prepare 5-methyl-1,4-dithiepan-6-one (4) from ethane-1,2dithiol (4.7 g) and 1,3-dibromobutan-2-one (10.6 g), b.p. 80–82 °C at 0.3 mmHg (found: C, 44.8; H, 6.3; S, 41.7%. $C_6H_{10}S_2O$ requires C, 44.4; H, 6.2; S, 39.5%); 2-methyl-1,4-dithiepan-6-one (5) from propane-1,2-dithiol (6.5 g) and 1,3-dichloropropanone (7.6 g), b.p. 100 °C at 0.7 mmHg (found: C, 44.7; H, 6.5; S, 39.1%. $C_6H_{10}S_2O$ requires C, 44.4; H, 6.2; S, 39.5%); 5,5-dimethyl-1,4-dithiepan-6-one from ethane-1,2-dithiol (3.7 g) and 1,3-dibromo-3-methylbutan-2-one (9.6 g), b.p. 68 °C at 0.1 mmHg (found: C, 47.4; H, 6.4; S, 36.0%. $C_7H_{12}S_2O$ requires C, 47.7; H, 6.8; S, 36.4%).

1,4-Dithiepan-6-one 1-oxide (1). *m*-Chloroperbenzoic acid (0.68 g) in dichloromethane (10 ml) was added dropwise with stirring to a solution of 1,4-dithiepan-6-one (0.6 g) in dichloromethane (10 ml) at 0 °C. The solution was allowed to warm to room temperature over 24 h, after which the solvent was removed by evaporation. The colourless residue was washed with diethyl ether to remove *m*-chlorobenzoic acid, leaving 1,4-dithiepan-6-one 1-oxide (1) (0.4 g, 62%) as a pale yellow solid, which was purified by elution through silica gel (acetone as eluent) to afford colourless truncated pyramids, m.p. 130 °C from dichloromethane (found: C, 36.8; H, 5.0; S, 38.9%. C₅H₈S₂O₂ requires C, 36.6; H, 4.9; S, 39.0%).

5,5-Dimethyl-1,4-dithiepan-6-one 1-oxide (2). This was prepared from 5,5-dimethyl-1,4-dithiepan-6-one (0.3 g) and *m*-chloroperbenzoic acid (0.29 g) by the method described above, m.p. 158–160 °C (found: C, 43.4; H, 6.3; S, 33.2%. $C_7H_{12}S_2O_2$ requires C, 43.75; H, 6.25; S, 33.3%).

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