Conformation of 4-thio-L-lyxono-1,4-lactone in solution and in the crystalline state

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Abstract

The conformation in ^2H_2O of 4-thio-L-lyxono-1,4-lactone (**1**) was studied by nuclear magnetic resonance spectroscopy, by means of homonuclear ($J_{1_H,1_H}$) and heteronuclear ($J_{1_H,13_C}$) coupling constants. The couplings were directly measured by a two-dimensional heteronucleus-coupled ω_1 hetero-half-filtered proton–proton correlation (HETLOC) experiment, which does not require ^{13}C isotopic enrichment. In solution, the thiolactone ring of **1** adopts preferentially the E_3 conformation, and its hydroxymethyl group populates mainly the *gt* rotamer. The X-ray diffraction data of a single crystal of **1** indicates that also in the solid state the thiolactone ring adopts an E_3 conformation, with a puckering somewhat larger than that observed for aldono-1,4-lactones and furanose rings. The molecules are linked by hydrogen bonds, which form chains. Particularly, O-5 is fully engaged as donor and acceptor in hydrogen bonding and the rotameric conformation of the hydroxymethyl group of **1** is fixed in the *tg* form.

Keywords: Aldopentono-1,4-thiolactone conformation; Heteronuclear ^{13}C–^1H coupling constants; 2D NMR heteronucleus-coupled H–H correlation (HETLOC)

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1. Introduction

The pseudorotation typical of furanoid rings [1] is considerably altered when a ring sp^3 carbon is replaced by an sp^2 carbon. For example, in 1,4-lactones the planarity (or near planarity) of the OC(O)R fragment restricts the ring conformation to two relatively small segments of the pseudorotational itinerary [2]. Therefore, the 1,4-lactone ring can assume, besides the planar conformation (P), only four envelope forms (^3E, E_3, ^4E, and E_4). Pseudorotation [2,3] can occur for the interconversion between ^3E and E_4 (or E_3–^4E) forms, and P is not required as intermediate. However, other possible interconversions, such as ^3E–E_3, ^4E–E_4, etc., may occur by ring inversion, through the planar conformer (P). Horton and Walaszek [4] reported a conformational analysis for D-pentono-1,4-lactones in solution, using ^{1}H-NMR data supported by ^{13}C-NMR studies. Lately, Serianni and coworkers [3] employed ^{1}H–^{1}H, ^{13}C–^{1}H and ^{13}C–^{13}C coupling constants to evaluate the aldono-1,4-lactone ring conformations. For these purposes, enriched [1-^{13}C]aldono-lactones were synthesized and the conformations deduced from NMR data were compared with the "gas-phase" structures, predicted by ab initio molecular orbital calculations. On the other hand, the X-ray diffraction studies of aldono-1,4-lactones [5] have demonstrated that they preferentially adopt ^3E or E_3 conformations.

Although the conformational characteristics of the aldono-1,4-lactones in the crystalline state as well as in solution, have been quite intensively studied, no reports are available on the influence of the replacement of the ring oxygen atom by sulphur on the ring conformation and dynamics. Therefore, we describe here our studies on the crystal structure and conformation in solution of 4-thio-L-lyxono-1,4-lactone. This is the first crystallographic study of a 1,4-thiolactone derivative.

2. Results and discussion

4-Thio-L-lyxono-1,4-lactone (1) was prepared as previously described [6]. Its 500-MHz ^{1}H-NMR spectrum, recorded in ^{2}H$_2$O, showed nicely separated signals, admitting a first-order analysis (Table 1). Although ^{1}H–^{1}H coupling constants ($^3J_{H,H}$) are a useful tool for the determination of conformations in solution, in the case of compound 1 the

Table 1
Experimental homonuclear ($^3J_{H,H}$) and heteronuclear ($^1J_{C,H}$, $^2J_{C,H}$, and $^3J_{C,H}$) coupling constants for compound 1

Proton	δ (ppm)	Coupled carbon [$J_{13_C,1_H}$ (Hz)]				Coupled proton	$^3J_{H,H}$ (Hz)
		C-2	C-3	C-4	C-5		
H-2	4.648	143.2	−0.5	0.3		H-3	4.0
H-3	4.592	−1.1	155.9	1.8	1.3	H-4	3.0
H-4	4.181	0.5	1.2	133.3	−5.2	H-5	6.3
H-5	4.105		2.3	−1.1	145.6	H-5′	−11.4
H-5′	3.916		2.9	−2.9	148.3	H-4	8.0

measured $^3J_{H,H}$ values cannot be used alone to assess conformational preferences, as ^1H–^1H ring couplings are expected to be similar for all the possible conformers. Therefore, $^3J_{1_H,13_C}$ couplings were employed as an alternative approach for conformational discrimination. Vicinal ^{13}C–^1H couplings through C–C bonds, show an orientational dependence analogous to that for protons: i.e., dihedral angles of 60–100° are associated with smaller couplings (0–3 Hz) than angles of 140–180° (4.5–5.5 Hz) [7]. Molecular orbital calculations [8] performed on propane, predict the dihedral angle (θ) dependence of $^3J_{1_H,13_C}$ described by (1).

$$^3J_{1_H,13_C} = 4.26 - 1.00\cos\theta + 3.56\cos2\theta \tag{1}$$

The intensive use of ^{13}C–^1H long range couplings has been limited as isotopically enriched compounds are required for their measurement. However, pulse sequences have been recently described [9,10] for determining the couplings to proton-bearing heteroatoms, without the necessity of enrichment of the heteronucleus. Thus, for compound 1 the 2D NMR spectrum was determined by means of the two-dimensional heteronucleus-coupled ω_1 hetero-half-filtered proton–proton correlation (HETLOC) experiment [9,10]. In the $F1$ dimension, the cross peaks give the direct coupling to the heteronucleus ($^1J_{C,H}$) and in $F2$, they give the heteronuclear long-range coupling to the same heteronucleus through the shift of the multiplet. For example, Fig. 1 shows expanded contour plot obtained from the HETLOC spectrum of 1, with the cross peaks between: (a) H-2 (ω_2) and H-3 (ω_1), and (b) H-5 (ω_2) and H-3 (H-3 is bonded to C-3). The shift of the signals with respect to one another gives the heteronuclear coupling constants, which are shown in Table 1.

In order to evaluate $^3J_{C,H}$ from the expected E_3 or ^3E conformation of 1, energy minimization was performed on both structures. From the local minimun, dihedral angles (ϕ) between vicinal H,H and H,^{13}C ring-atoms were measured, and their values employed for calculating the corresponding couplings (Table 2). For $^1H,^1H$ couplings, the Altona relationship [11] was employed, and $^1H,^{13}C$ couplings were calculated by means of Eq. (1). The small experimental values for $^3J_{H,C}$ couplings are in good agreement with those predicted for the E_3 (L) conformation, indicating a strong preference of this conformer for the thiolactone 1, in aqueous solution. Similarly, D-lyxono-1,4-lactone, both in aqueous [3] and nonaqueous solvents [4] prefers the ^3E conformation (E_3 in the L series). The general statement that the conformational equilibrium of aldono-1,4-lactones is strongly shifted towards the envelope which has the HO-2 group quasiequatorially oriented [3,4], seems to be also valid for 4-thioaldono-1,4-lactones.

The conformation of the exocyclic hydroxymethyl group on C-4 of 1 was established on the basis of homonuclear and heteronuclear couplings. Inspection of the structure of the three possible staggered rotamers along the C-4–C-5 bond (gg, gt, and tg), indicates the presence of a destabilizing 1,3-parallel interaction between HO-5 and the axially oriented HO-3, in the gg conformation. Probably for this reason this form would be poorly populated in the conformational equilibrium, as experimentally indicated by the large $^3J_{H-4,H-5}$ and $^3J_{H-4,H-5'}$ values, and also by the geminal $^2J_{C-5,H-4}$ coupling. It has been established that the magnitude of geminal heteronuclear $^2J_{1_H,13_C}$ couplings is strongly influenced by the orientation of an oxygen atom in a ^1H–C–^{13}C–O system
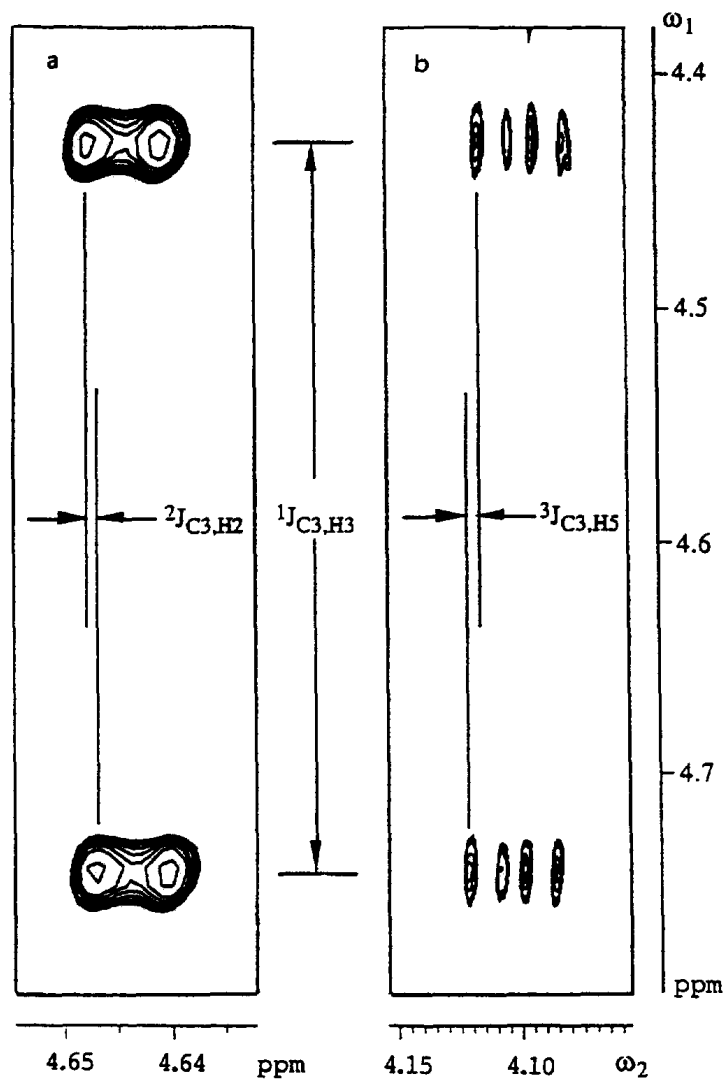
Fig. 1. Expanded contour plot for two regions of the HETLOC spectrum of **1**: (a) cross peak between H-2 (ω_2) and H-3 (ω_1), and (b) cross peak between H-5 (ω_2) and H-3.

Table 2
Estimated dihedral angles and coupling constants for the E_3 and ^3E conformation of **1**

Coupled nucleus	E_3		^3E		
	Φ (°)	J(calc.) (Hz)	Φ (°)	J(calc.) (Hz)	J(exp.) (Hz)
H-2, H-3	− 44.0	4.2	38.0	4.8	4.0
H-3, H-4	42.6	4.0	− 40.0	6.5	3.0
H-2, C-4	75.6	0.9	153.6	7.3	0.3
H-4, C-2	− 77.2	0.8	− 156.0	7.5	0.5
H-3, C-5	− 76.3	0.9	− 162.2	8.1	1.3

[12]. In fact, the observed $^2J_{1_H,13_C}$ coupling is smaller when an oxygen atom is in the plane of the coupling pathway than when out of the plane. These situations are respectively met, for example, when a HO group is antiperiplanar or *gauche* to the vicinal, coupled ^1H nucleus. Thus, the relatively large $^2J_{C-5,H-4}$ value (−5.2 Hz) in 1 clearly indicates a preference of the HO-5 group *gauche* to H-4. Furthermore, the small $^2J_{C-4,H-5}$ coupling (−1.1 Hz), and the somewhat larger $^2J_{C-4,H-5'}$ coupling (−2.9 Hz), suggest a preferential antiplanar disposition for H-5 (*gauche* for H-5′) and the ring sulfur atom, and hence that the *gt* rotamer would be the favored form in the equilibrium. Furthermore, the atomic disposition along the C-4–C-5 bond of 1, deduced from the NMR data, indicates that the more shielded C-5 proton (H-5′) is pro-*R*, as observed for pentofuranosides [13]. This result validates Serianni's study [3] on the conformation of the exocyclic chain of aldopentono-1,4-lactones, in which the H-5, responsible for the upfield resonance, was assumed to be pro-*R*. For the hydroxymethyl group of D-lyxono-1,4-lactone a preference for the *gt* conformer, and not for the *tg* as previously predicted [4], was also established [3].

In order to calculate the rotamer distribution for the C-4 hydroxymethyl group of 1, a combination of $^3J_{H,H}$ and $^3J_{C,H}$ couplings was used. This approach has been previously employed for the conformational analysis of amino acids [14]. The observed $^3J_{H,H}$ coupling constants can be related to the true general J_g (*gauche* coupling) and J_t (*trans* coupling) as follows:

$$^3J_{H-4,H-5'} - {}^3J_{H-4,H-5} = (x_{gt} - x_{tg})(J_t - J_g) \tag{2}$$

The values employed in (2) for J_g (1.5 Hz) and J_t (11.5 Hz) were the same as for aldonolactones [4].

An equation similar to (2) can be deduced for $^3J_{C,H}$ long-range couplings

$$^3J_{C-3,H-5'} - {}^3J_{C-3,H-5} = (x_{tg} - x_{gg})(J_T - J_G) \tag{3}$$

J_T and J_G being the *trans* and *gauche* couplings. Their values were estimated as J_T 6.0 Hz and J_G 1.5 Hz, according to experimental $^3J_{C,H}$ values measured for methyl β-cellobioside [15] and other carbohydrate derivatives [7]. The resolution of Eqs. (2) and (3), together with $\Sigma x_i = 1$, led unambiguosly to the rotamer distribution for the hydroxymethyl group of 1, being *gt* 49%, *tg* 32%, and *gg* 19%.

The conformation of 1 in the solid state was established by X-ray diffraction analysis (Fig. 2) of a single crystal, obtained by crystallization of 1 from acetone. Data collection information, and details on the structure and refinement are described in Table 3. The atomic positions for the correct enantiomer are reported in Table 4, while the details of the molecular geometry are quoted in Table 5.

The X-ray structure of 1 (Fig. 2) shows an E_3 (L) conformation for the thiolactone ring, similar to that established for 1 in solution. The small C-4–S-4–C-1–C-2 torsion angle (−3.5°) indicates a slight deviation from planarity. The E_3 conformation is also evidenced by the puckering parameter described by Cremer and Pople [16]. Thus, compound 1 shows a puckering amplitude $q = 0.452$ Å and a phase angle $\varphi_m = 107.28°$, which agrees with the theoretical value of φ_m (108°) predicted for the E_3 conformer. The C–S–C=O bond lengths show the characteristic shortening of the S–C-1 (1.756 Å)
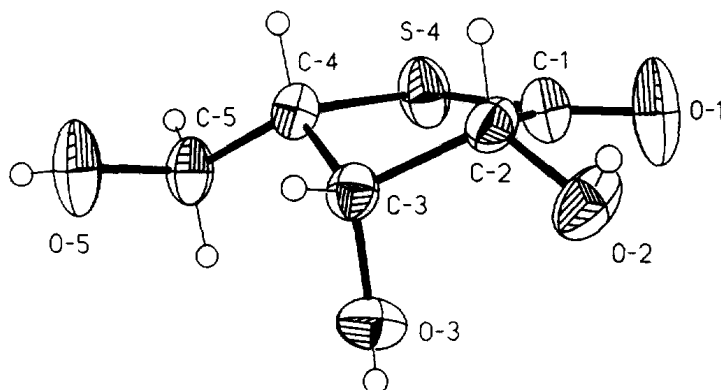
Fig. 2. Schematic drawing (XP in SHELXTL-PC package [21]) of 4-thio-L-lyxono-1,4-lactone (1) with the numbering scheme used. Thermal displacement ellipsoids are shown at a 50% level.

and the lengthening of the C-4–S (1.840 Å) bonds, because of contributions from the valence-bond resonance form C^+–S=C–O^-, as observed for the carboxylic function of aldono-1,4-lactones [5]. The C–OH bond lengths are normal, ranging from 1.405 to 1.419 Å, as are the C–C bonds (Table 5).

Table 3
Crystal data and structural determination and refinement data for 1

Crystal data

Molecular formula: $C_5H_8O_4$ S; mol wt: 164.17; orthorhombic, $P2_12_12_1$ (no. 19), $Z = 4$.

Cell dimensions (Å, at 293 K): $a = 8.344(2)$, $b = 4.675(1)$, $c = 17.729(4)$.

V (Å³) = 691.6(3); $M = 164.18$; Dx (g cm^{-3}) = 1.58; $F000 = 344$.

Structure determination and refinement data

Crystal dimensions (mm): 0.28×0.25×0.20, colorless prisms.

Number of reflections measured: 1128 (29 rejected) (SIEMENS P4 diffractometer, $\omega/2\theta$ scan).

Number of unique reflections: 901; R_{int}: 0.016, for 198 pairs; Number with $F^2/\sigma(F^2) > 4$: 885(98%);

Average $(F^2/\sigma (F^2))$: 46.0; Radiation: $Mo_{k\alpha}$ ($\lambda = 0.71073$ Å, graphite monochromator); θ range(ᶜ): 2.30–22.55; index range: $0 \leq h \leq 9, 0 \leq k \leq 5, -19 \leq l \leq 19$.

Max./min. semi-empirical absorption corrections (Psi-scan): 0.916/0.814; μ(mm^{-1}) = 0.42.

Flack's parameter for absolute configuration determination [a]: $-0.03(10)$.

Structure solution. Direct methods plus difference Fourier (SHELX-86). [b] Hydrogens found in difference Fourier synthesis and refined with constrained distances to the host atoms.

Structure refinement. (SHELXL-93). [c] Weighted [d] full-matrix least-squares on F^2, for the whole unique data set. Anisotropic displacement factors for non-H atoms, overall isotropic for H atoms. Observation to parameter ratio: 9.9.

Final agreement factors

Goodness-of-fit on F^2: $[F^2 > 2\sigma(F^2)]$: 1.095 [all data]: 1.104

$R1(F)$ [e], $wR2(F^2)$ [f] $[F^2 > 2\sigma(F^2)]$: 0.022, 0.057 [all data]: 0.022, 0.058

Maximum peak, hole in final difference Fourier map: 0.12, -0.11 e Å^{-3}

[a] See [18].
[b] See [19].
[c] See [20].
[d] $w = 1/[\sigma^2(Fo^2)+(0.049P)^2 +0.218P]$, $P = (Fo^2 +2Fc^2)/3$.
[e] $R1 = \Sigma//Fo/-/Fc///\Sigma/Fo/$.
[f] $wR2 = [\Sigma[w(Fo^2 - Fc^2)^2]/\Sigma[w(Fo^2)^2]]^{0.5}$.

Table 4

Atomic coordinates and equivalent isotropic displacement parameters ($\mathring{A}^2$) for **1**. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor

Atom	x	y	z	U_{eq}
S-4	− 0.7148(1)	0.0072(1)	− 0.9625(1)	0.0450(2)
O-1	− 1.0173(2)	0.0252(5)	− 0.9215(1)	0.0735(6)
O-2	− 0.9454(2)	− 0.1411(3)	− 0.7750(1)	0.0458(4)
O-3	− 0.6620(2)	0.1814(3)	− 0.7962(1)	0.0397(4)
O-5	− 0.3078(2)	− 0.1520(4)	− 0.8510(1)	0.0556(5)
C-1	− 0.8832(2)	− 0.0495(5)	− 0.9050(1)	0.0399(5)
C-2	− 0.8362(2)	− 0.2028(4)	− 0.8331(1)	0.0321(5)
C-3	− 0.6648(2)	− 0.1103(4)	− 0.8169(1)	0.0297(5)
C-4	− 0.5775(2)	− 0.1450(4)	− 0.8919(1)	0.0316(5)
C-5	− 0.4159(2)	0.0006(6)	− 0.8979(1)	0.0383(5)

The hydrogen-bonding scheme is shown in Fig. 3 and Table 6. The three available O–H groups of **1** are involved in strong H-bond interactions: O-2 and O-5 are fully engaged both as donors, as well as acceptors; O-3 and the carbonyl O-1 instead, display a single interaction, as donor and acceptor, respectively. The above-mentioned interactions define strongly connected two-dimensional layers. This fact can be visualized if thought as built up by infinite chains running along the a direction, with the O-5–H-5...O-1 bond acting as a joining link between translationally related molecules. These chains, in turn, are tightly held together by the strong interactions O-3–H-3...O-5 and O-2–H-2...O-2′, thus defining an infinite two-dimensional molecular network normal to the crystallographic c axis, in the vicinity of z 0.25 and z 0.75. The interaction between layers is of the van der Waals' type.

As HO-5 is involved in two hydrogen bonding in the crystalline state, the rotameric conformation of the hydroxymethyl group of **1** is fixed in the *tg* form. Fig. 2 shows that

Table 5

Selected interatomic bond lengths ($\mathring{A}$), angles (°) and torsion angles (°) for **1**

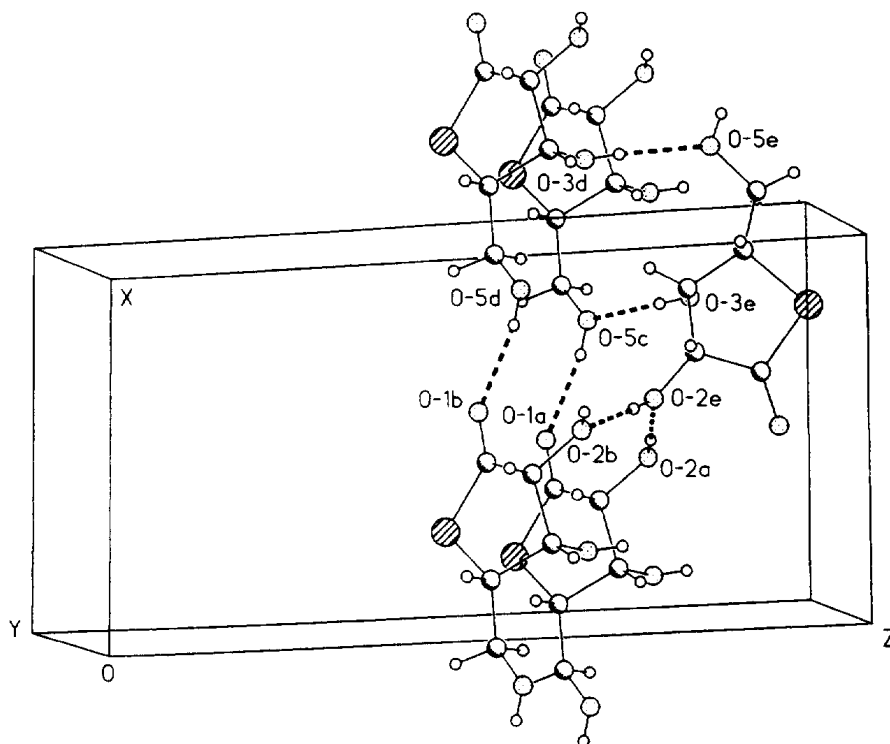| S-4–C-1	1.756(2)	S-4–C-4	1.840(2)
O-1–C-1	1.208(3)	C-1–C-2	1.514(3)
C-2–C-3	1.522(3)	C-3–C-4	1.525(3)
C-4–C-5	1.514(3)		
C-1–S-4–C-4	92.6(1)	C-1–C-2–C-3	105.5(2)
C-2–C-1–S-4	110.7(2)	C-5–C-4–C-3	116.0(2)
C-2–C-3–C-4	104.7(2)	C-3–C-4–S-4	104.8(1)
C-5–C-4–S-4	109.5(2)		
C-4–S-4–C-1–O-1	176.5(2)	C-4–S-4–C-1–C-2	− 3.5(2)
O-1–C-1–C-2–O-2	− 25.7(3)	S-4–C-1–C-2–C-3	30.1(2)
O-2–C-2–C-3–O-3	− 52.8(2)	C-1–C-2–C-3–C-4	− 47.6(2)
O-3–C-3–C-4–C-5	47.8(2)	C-2–C-3–C-4–C-5	165.2(2)
C-2–C-3–C-4–S-4	44.4(2)	C-1–S-4–C-4–C-3	− 23.8(2)
S-4–C-4–C-5–O-5	− 171.2(2)		

Fig. 3. Crystal packing of **1** (XP in SHELXTL-PC package [21]), showing a detail of the hydrogen-bonding scheme.

HO-5 is *anti* to the C-4–S bond, with a S–C-4–C-5–O-5 torsion angle of $-171.2°$. In contrast, the *gt* was established as the preferred form along the C-4–C-5 bond of **1**, in solution. In this case, hydrogen bonding does not seem to be the cause of the rotamer stabilization, since the ^{1}H NMR spectrum of derivatives of **1**, which having all the HO groups blocked exclude such an interaction, show similar coupling constants and relative chemical shifts. For example, 5-*O*-acetyl-2,3-*O*-isopropylidene-4-thio-L-lyxono-1,4-lactone shows in its ^{1}H-NMR spectrum (CDCl$_3$, 200 MHz): $\delta_{H\text{-}5}$ 4.63, $\delta_{H\text{-}5'}$ 4.39, $J_{4,5}$ 6.0 Hz, and $J_{4,5'}$ 8.3 Hz [6]. These J values would indicate that, as for **1**, the *gt* rotamer would be favored in the conformational equilibrium. Similarly, the hydroxymethyl group

Table 6
Hydrogen-bonding scheme for compound **1**

Donor [a]	Acceptor	H...A [b] (Å)	D...A [c] (Å)	D-H...A [d] (°)	Symm. Oper. on A
O5-H5...	O1	2.11[1.94]	2.849	165[163]	$1 + x,\ y,\ z$
O3-H3...	O5	1.99[1.81]	2.735	171[170]	$-1 - x,\ 0.5 + y,\ -1.5 - z$
O2-H2...	O2	1.91[1.72]	2.660	177[176]	$-2 - x,\ -0.5 + y,\ -1.5 - z$

Values derived from normalized O–H values [22,23] (in brackets).
[a] d(O–H) = 0.79 Å, normalized d(O–H) = 0.94 Å.
[b,c,d] Estimated esd's 0.03 Å, 0.002 Å and 2°, respectively.

of D-lyxono-1,4-lactone preferentially adopts the *gt* conformation [3], which is expected to be more stable than the *tg* rotamer due to the "*gauche* effect" [17].

In summary, the present study confirms that, as for aldono-1,4-lactones, the conformational equilibrium of the 4-thioaldono-1,4-lactone 1 is strongly shifted towards the envelope with the HO-2 group quasiequatorially oriented. Also, the data suggest a preferential antiplanar disposition for the more deshielded C-5 proton (H-5) and the sulfur heteroatom, and hence the *gt* rotamer as the favored form in equilibrium.

3. Experimental

NMR spectra were obtained on a Bruker AMX 500 MHz at 27 °C. The samples were prepared by dissolving 10 mg of compound 1 in 0.5 mL of D_2O. The HETLOC experiment was performed by acquiring a 1024 × 4096 point matrix. The BIRD delay [24] and the relaxation delay were set to 875 and 500 ms, respectively. The ^1H pulse for the MLEV-17 mixing period was attenuated by 12 dB (90° pulse duration was 26.2 s). The duration of trim pulses was set to 2 ms and the total mixing time was 65 ms. The spectral width was 4.015 ppm, with an acquisition time of 1.02 s. Data was processed as a 1024 × 4096 matrix with Gaussian resolution enhancement.

Energy minimization was performed using the cvff forcefield of Discover, implemented within Insight II (Biosym). Calculations were performed in vacuum.

A single crystal of dimensions 0.40 × 0.25 × 0.20 mm and good diffracting power was mounted to a glass fiber, and centered into a Siemens P4 difractometer. All measurements were performed at room temperature, and the experimental details are reported in Table 3. The structure was routinely solved by direct methods using SHELXS86, with all non H atoms appearing in the first E-map. After isotropic convergence, a difference Fourier map unambiguously showed all the H atoms, which were included in the model with a refinable, overall isotopic displacement parameter, and constrained to have overall, refinable, O–H and C–H distances to their host atoms, so as to prevent drifting. At this stage, non-H atoms were allowed to refine anisotropically. Final refinement was performed with SHELXL93, minimizing $\Sigma w(F_o^2-F_c^2)^2$, and using the whole data set. The process included the refinement of Flack's parameter to discriminate the correct handedness ($F = 0.0$) from the wrong one ($F = 1.0$). Final values for $R1$, $wR2$, F of 0.0215, 0.0584, −0.03(10) and 0.0229, 0.0621, 1.03(11) unambiguously confirmed the former as the correct enantiomer. The final difference Fourier map was remarkably featureless (max. peak: 0.12 e $Å^{-3}$). The refinement data are given in Table 3, while Fig. 2 shows the numbering scheme as well as the thermal ellipsoids drawn at 50% level.

Acknowledgements

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