

Conformational study of erythritol and threitol in the gas state by density functional theory calculations

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Received 25 June 2004; received in revised form 26 November 2004; accepted 27 November 2004

Abstract—Density functional theory calculations using the B3LYP functional and the 6-311++G(d,p) basis set were carried out on the isolated molecules of erythritol and L-threitol. For the *meso* isomer, a relatively large number of conformers have to be considered to describe the gas state structure. The lowest energy conformer is characterized by the establishment of a strong intramolecular H-bond between the two terminal hydroxyl groups, giving rise to a seven-membered ring and two additional weaker H-bonds between vicinal OH groups. In the case of L-threitol, two conformers are predominant in the gas state, and both are stabilized by the formation of a cyclic system of four intramolecular hydrogen bonds involving all OH groups. The conformational stability in both diastereomers is discussed in terms of the electronic energy and of the Gibbs energy. The weighted mean enthalpy of both diastereomers in the gas state at 298.15 K was obtained from the thermodynamic data and Boltzmann populations of the low-energy conformers.

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Keywords: Erythritol; Threitol; Conformation; DFT; Intramolecular H-bonds; Enthalpy; Gibbs energy

1. Introduction

Threitol and erythritol are diastereomers of tetritol (1,2,3,4-butanetetrol). The first is a chiral and the second is a *meso* form. The presence of four hydroxyl groups attached to different carbon atoms gives rise to a complex system of intermolecular and intramolecular hydrogen bonds, which play an important role in the molecular structure of these compounds and, therefore, in many properties of polyols, namely the sweetness,¹ hygroscopicity² and cryopreservation,^{3,4} among others.

Despite the existence of some published data concerning the solid state,^{5–12} we are not aware of any theoretical or experimental data on the structure of erythritol and threitol in the gas state. The molecular flexibility and the presence of four OH groups result in a high number of possible conformations accounting for the

energy of the isolated molecules. This makes it difficult to calculate the energy and the structure. Extensive work of this kind has only been performed for alditols with fewer than four carbon atoms.^{13–16}

Apart from the specific interest in the study of the conformational space of the isolated molecules of polyols, these calculations are the first step to understand the possible conformations in the condensed states of matter. Moreover, the energy values calculated for the gas state can be used to estimate the corresponding values in solid or liquid states, provided the experimental values for sublimation or vaporization enthalpies are known. This is a valuable method for getting information on the solid or liquid structures, especially because the energy calculations for these states are more difficult to perform.

Thermodynamic properties corresponding to the molecular transference from solid or liquid states to gas state or vice versa are commonly used to investigate the structure of the former states. The differences in the values found for the systems under consideration are

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often ascribed to structural differences between the condensed states of matter. However, such interpretation is valid only for systems with the same gas state energy level. Flexible polyfunctional molecules in the gas state can give rise to conformations stabilized by internal bonds with significant energy differences. Thus, structures as similar as those of isomers can present different energy levels in the gas state, and these have to be determined to interpret the transference properties involving this state. This question has already been addressed in our previous studies on the vaporization enthalpies and conformational properties of butanediol isomers,¹⁷ in which we concluded that the energy differences among these isomers in the gas state are greater than in the liquid state. Thus, the molecular interpretation of the thermodynamic properties of transference requires a careful evaluation of energies in the gaseous reference state.

The aim of this work is to investigate the low-energy conformers of erythritol and L-threitol in the gas state by density functional theory (DFT) calculations and to indicate their main structural features, particularly the intramolecular hydrogen bonding. This should provide the values needed to enable the population weighted mean energy of these diastereomers in the gas state to be calculated.

2. Calculations

The backbone structure of the two tetritol isomers can be defined by the carbon chain dihedral and by the two terminal O–C–C–O dihedrals. Assuming three standard configurations for each of the three dihedrals, namely 60°, –60° and 180°, one can obtain 27 possible backbone conformations for each stereoisomer. However, as some conformations are degenerate, this number is reduced to 15 unique backbone arrangements for erythritol and to 18 for L-threitol. Then, considering the four C–OH torsions with the same three standard configurations, there are 81 conformational possibilities for each of these backbone conformations. These assumptions lead to a total of 1215 possible conformations for erythritol and 1458 for threitol. These numbers can be reduced by OH torsions degeneracy.

The existence of a large number of possible conformations makes a systematic investigation of all of them quite difficult. Therefore, a preliminary conformational search method employing random generation and subsequent molecular mechanics energy minimization was used to obtain a reasonable sampling of the low-energy conformations (10,000 structures were generated). These calculations were carried out with the Cerius2 (version 3.5) molecular modelling package¹⁸ running on an SGI O²/RS5000 workstation. All molecular mechanics minimizations were performed using the CFF91 force

field.^{19,20} The lower energy conformations thus generated, that is, those with energies up to 20 kJ mol^{–1}, corresponding to 35 unique structures for erythritol, and 18 for L-threitol, were fully optimized by a DFT method^{21,22} using the B3LYP functional,^{23–25} and the 6-311++G(d,p) basis set. The B3LYP functional has been proven to predict with great accuracy the relative energies and structure for the most significant conformers of gas phase molecules with intramolecular hydrogen bonds, like glycerol^{14–16} and amino acids.²⁶ The combination of the B3LYP functional with the 6-311++G(d,p) basis set has also been successfully applied recently to the study of five monosaccharides.²⁷ The DFT calculations were performed with the GAUSSIAN 98 program package,²⁸ running in a PC. The vibrational frequencies were calculated and the absence of imaginary frequencies confirmed that the resulting equilibrium geometries were true energy minima in the potential energy surfaces. The electronic energy (E_{elec}) was corrected with the zero-point vibrational energy (E_{ZPE}) and thermal corrections ($E_{\text{trans}} + E_{\text{rot}} + E_{\text{vib}}$). The enthalpy (H) of each conformer at 298.15 K was determined from the electronic energy by the following expression:²⁹

$$H = E_{\text{elec}} + E_{\text{ZPE}} + E_{\text{trans}} + E_{\text{rot}} + E_{\text{vib}} + RT \quad (1)$$

The values determined for the enthalpy and for the entropy (S), calculated according to the standard statistical thermodynamic methods based on the ideal gas-rigid rotor-harmonic oscillator model,³⁰ also described in a ‘Gaussian white paper’,³¹ were used to obtain the values of the Gibbs energy (G), using the well known equation:

$$G = H - TS \quad (2)$$

The values taken for the enthalpy and Gibbs energy of the diastereomers in the gas state are the weighted mean values found for the thermodynamic functions, calculated as follows:

$$Z_{\text{gas}} = \sum_i Z(i)P(i) \quad (3)$$

Z stands for the enthalpy or the Gibbs energy and $P(i)$ for the equilibrium population of each conformer.

3. Results and discussion

As mentioned above, both tetritols can assume a great number of conformational possibilities. Hence, a clear nomenclature should be established for their steadfast identification. The conformers are labelled with three capital letters, defining the orientation of the dihedrals O–1–C–1–C–2–O–2, C–1–C–2–C–3–C–4 and O–3–C–3–C–4–O–4, respectively (see Figs. 1 and 3 for atom numbering scheme). The letters used are G (*gauche clockwise*), G' (*gauche anticlockwise*) and T (*trans*) representing

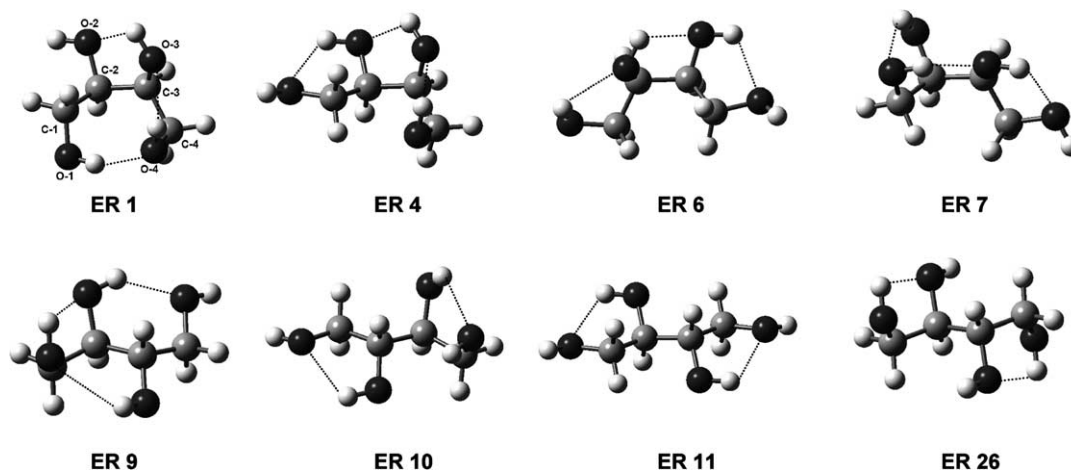


Figure 1. B3LYP/6-311++G(d,p) optimized geometries of some of the most important conformers of erythritol with atom numbering scheme in ER1. Intramolecular hydrogen bonds are represented by dashed lines. The chiral atoms C-2 and C-4 have configurations *R* and *S*, respectively.

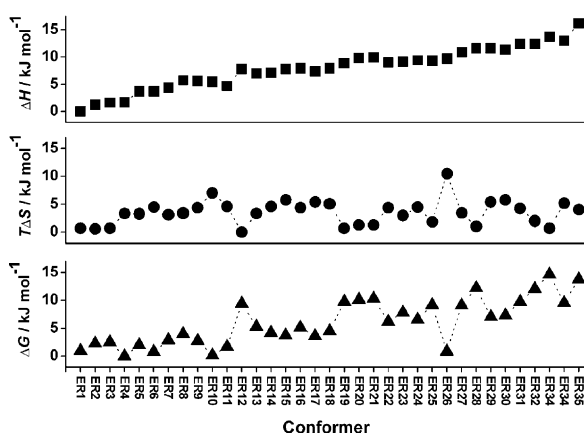


Figure 2. Relative values of H , TS and G of erythritol conformers at 298.15 K. The reference conformers are ER1, ER12 and ER4, respectively.

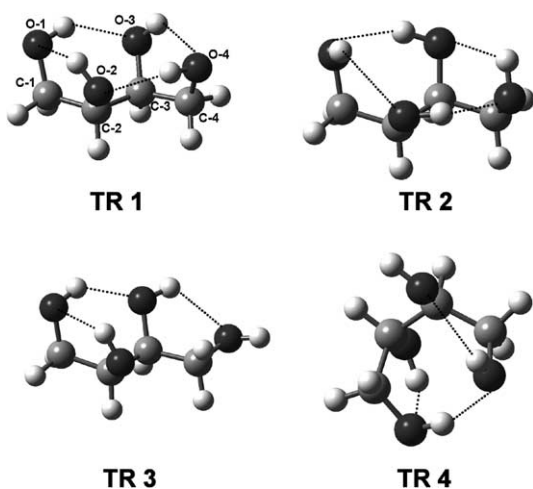


Figure 3. B3LYP/6-311++G(d,p) optimized geometries of the lowest energy conformers of L-threitol with atom numbering scheme in TR1. Intramolecular hydrogen bonds are represented by dashed lines.

dihedrals of 60° , -60° and 180° , respectively, within a tolerance of $\pm 30^\circ$. The backbone designation is followed by a number that discriminates conformers with the same backbone conformation but different orientations of the OH groups. These numbers are in ascending energy order. Hydroxyl groups are labelled throughout this work as 1, 2, 3 and 4, according to the number of the carbon atom to which they are attached.

The conformers generated from the molecular mechanics conformational search method and further optimized by DFT were found to lie within a range of about 17 and 26 kJ mol^{-1} above those of the lowest energy conformers of erythritol and threitol, respectively. The conformers are named according to increasing order of the electronic energy throughout this work. The values of dihedral angles (φ) for the optimized conformers of each diastereomer are given in Tables 1 and 4. Cartesian coordinates for every conformer considered for both molecules are given as Supplementary data. The electronic energy, enthalpy, Gibbs energy and equilibrium population at 298.15 K are presented in Tables 2 and 5. The equilibrium population values were calculated according to the Boltzmann distribution, based on the Gibbs energy at 298.15 K and taking into account the degeneracy degree (g) of each conformer (including an $-RT\ln(g)$ term in the Gibbs energy). We are aware that considering a reduced number of conformers could introduce some error in the Boltzmann distribution calculation. However, as only high-energy conformers are neglected (see energy cutoff values above), this error should not be significant.

3.1. Erythritol

As can be seen in Table 2, the 35 conformers were found within an electronic energy range of about 17 kJ mol^{-1} above the global minimum. The energy difference

Table 1. Dihedral angles for the B3LYP/6-311++G(d,p) optimized structures of the low-energy conformers of erythritol

Conformer	Label	Dihedral angles/deg ^a						
		φ_1	φ_2	φ_3	φ_4	φ_5	φ_6	φ_7
ER1	TGG1	167.5	58.9	53.0	74.2	-51.5	-174.0	-53.2
ER2	TGG2	170.3	59.8	46.8	-161.4	85.8	-29.8	76.3
ER3	TGG3	170.7	59.7	47.0	-78.3	84.6	-30.1	76.8
ER4	GGG1	53.6	56.4	53.1	-171.4	-41.2	-171.7	-52.8
ER5	GGG2	49.9	58.9	54.8	83.5	-36.1	-173.1	-54.4
ER6	GG'G'1	62.6	-57.9	-53.5	-51.7	179.8	42.4	167.1
ER7	GG'G1	55.1	-80.3	49.6	-168.6	-48.0	-35.3	62.6
ER8	GG'G2	63.7	-62.0	50.1	-54.6	-158.4	-22.7	59.2
ER9	G'TT1	-71.6	161.5	178.3	60.2	173.6	163.2	-174.9
ER10	GTG1	57.3	-169.1	59.1	-172.6	-43.3	-42.1	84.1
ER11	GTG'1	56.2	180.0	-56.2	-172.4	-44.3	44.3	172.4
ER12	G'GG1	-66.9	25.2	41.5	59.4	116.7	-25.0	60.7
ER13	GG'G3	59.3	-53.3	74.1	-46.6	73.4	-89.0	-166.2
ER14	GG'G'2	62.3	-56.1	-54.5	-169.2	-54.9	-84.3	46.2
ER15	G'TT2	-69.4	167.2	179.7	60.1	174.0	161.6	89.8
ER16	G'TG1	-52.9	180.0	52.9	-88.9	37.8	-37.8	89.0
ER17	TTG'1	165.8	174.2	-55.9	54.8	-61.3	46.0	172.4
ER18	TTG'2	166.0	172.1	-53.1	55.1	-62.9	39.8	-82.7
ER19	TTT1	175.3	-180.0	-175.3	-79.1	162.8	-162.8	79.1
ER20	TGG4	163.4	58.3	48.6	74.2	71.8	93.6	-49.7
ER21	TGG5	164.9	60.6	52.8	73.9	82.1	-42.9	-159.6
ER22	G'TT3	-53.2	-177.3	-170.1	170.9	38.2	65.9	-54.7
ER23	TTT2	174.4	-178.4	-174.5	177.6	162.2	-158.9	77.5
ER24	G'TT4	-51.0	-179.8	-168.9	-86.6	-35.9	53.6	-52.9
ER25	TTT3	173.1	-180.0	-173.1	177.0	157.6	-157.6	-177.0
ER26	G'TG2	-63.6	179.6	63.3	60.1	-154.9	155.2	-59.9
ER27	GGG3	54.4	56.8	51.0	-45.8	85.6	-40.4	-165.1
ER28	G'GG2	-85.0	57.9	64.5	-88.8	87.1	-78.6	-85.0
ER29	GTG2	62.5	-155.9	73.2	-51.6	-164.4	179.9	-63.5
ER30	GGT1	52.3	55.7	179.3	-169.8	-42.0	-172.6	72.6
ER31	G'GT1	-49.9	59.8	176.1	-58.0	22.1	162.9	173.4
ER32	TTT4	164.3	180.0	-164.3	51.9	-64.9	64.9	-51.9
ER33	G'GG3	-76.8	35.9	40.6	152.8	97.2	-29.7	56.3
ER34	TTG'2	-176.2	-168.6	-54.6	174.9	-157.3	-175.4	46.9
ER35	TTT5	162.1	166.6	-179.8	57.0	171.0	76.7	-172.3

^a $\varphi_1 = \text{O-1-C-1-C-2-O-2}$; $\varphi_2 = \text{C-1-C-2-C-3-C-4}$; $\varphi_3 = \text{O-3-C-3-C-4-O-4}$; $\varphi_4 = \text{H-O-1-C-1-C-2}$; $\varphi_5 = \text{H-O-2-C-2-C-1}$; $\varphi_6 = \text{H-O-3-C-3-C-4}$; $\varphi_7 = \text{H-O-4-C-4-C-3}$.

between the two consecutive conformers was generally found to be less than 1 kJ mol⁻¹, and often a few tenths of kilojoule per mole. This makes the conformational distribution of this compound in the gas state very complex, as it lacks a clear predominating conformer over the others and since there is a relatively large number of them contributing in similar percentages to the overall population.

The lowest energy conformers observed have a G or G' orientation relative to the middle C–C torsion, which brings the middle hydroxyl groups closer together. The lowest energy structure with these OH groups in a trans arrangement (ER9) has an electronic energy 6 kJ mol⁻¹ higher than the global minimum. With respect to the backbone, the electronic energy for the first 10 conformers follows the order:



In addition to the backbone conformation, other structural features account for the energy differences among conformers, particularly the intramolecular hydrogen bonds established between the OH groups, as well as the relative orientation of these groups. The presence of four OH groups is responsible for a rather complex intramolecular hydrogen bond network, as all possible pairs of these groups can be involved in hydrogen bonds. Generally, hydrogen bonds are characterized by common structural features: the distance between the hydrogen of the donor group and the oxygen of the acceptor group, $d(\text{O}\cdots\text{H})$, and the O–H \cdots O bond angle, $\alpha(\text{O-H}\cdots\text{O})$. Cutoff limits for these parameters are usually arbitrarily imposed. Although no strict cutoff values were imposed in the present work, it was verified that the values obtained for both geometrical parameters referred are within the range usually adopted for the definition of a hydrogen bond.³² Table 3 shows the values of the geometrical parameters related to the

Table 2. Relative electronic energies (E_{elec}), enthalpies (H), Gibbs energies (G) and equilibrium populations (P) for the B3LYP/6-311++G(d,p) optimized structures of the low-energy conformers of erythritol

Conformer	Label	$E_{\text{elec}}^a/\text{kJ mol}^{-1}$	H (298.15 K)/Hartree	G (298.15 K)/Hartree	P (%) ^b
ER1	TGG1	0.00	-459.3129249	-459.3567374	8.4 (2)
ER2	TGG2	0.86	-459.3124571	-459.3562336	4.9 (2)
ER3	TGG3	1.35	-459.3123170	-459.3561405	4.4 (2)
ER4	GGG1	2.43	-459.3122779	-459.3571024	12.3 (2)
ER5	GGG2	4.36	-459.3115313	-459.3563338	5.4 (2)
ER6	GG'G'1	4.55	-459.3115318	-459.3567993	8.9 (2)
ER7	GG'G1	4.97	-459.3112698	-459.3559963	3.8 (2)
ER8	GG'G2	5.97	-459.3107390	-459.3555815	2.5 (2)
ER9	G'TT1	5.99	-459.3108150	-459.3560455	4.0 (2)
ER10	GTG1	6.54	-459.3108320	-459.3570465	11.6 (2)
ER11	GTG'1	6.56	-459.3111394	-459.3564534	6.2 (1)
ER12	G'GG1	6.91	-459.3099584	-459.3535099	0.3 (2)
ER13	GG'G3	7.49	-459.3102733	-459.3550868	1.5 (2)
ER14	GG'G'2	7.98	-459.3102180	-459.3555035	2.3 (2)
ER15	G'TT2	8.48	-459.3099299	-459.3556784	2.7 (2)
ER16	G'TG1	8.86	-459.3099154	-459.3551444	1.5 (1)
ER17	TTG'1	8.91	-459.3101315	-459.3557250	2.9 (2)
ER18	TTG'2	9.38	-459.3099228	-459.3553903	2.0 (2)
ER19	TTT1	9.62	-459.3095592	-459.3533722	0.2 (1)
ER20	TGG4	9.80	-459.3091887	-459.3532422	0.2 (2)
ER21	TGG5	9.93	-459.3091254	-459.3531769	0.2 (2)
ER22	G'TT3	10.13	-459.3095080	-459.3547325	1.0 (2)
ER23	TTT2	10.18	-459.3094479	-459.3541214	0.5 (2)
ER24	G'TT4	10.54	-459.3093353	-459.3546048	0.9 (2)
ER25	TTT3	10.66	-459.3093589	-459.3536099	0.3 (1)
ER26	G'TG2	11.27	-459.3092480	-459.3567800	8.7 (1)
ER27	GGG3	11.45	-459.3087704	-459.3536369	0.3 (2)
ER28	G'GG2	11.53	-459.3085156	-459.3524411	0.1 (2)
ER29	GTG2	11.81	-459.3088156	-459.3544171	0.7 (2)
ER30	GGT1	12.49	-459.3085845	-459.3543110	0.6 (2)
ER31	G'GT1	12.92	-459.3082108	-459.3533893	0.2 (2)
ER32	TTT4	13.73	-459.3081801	-459.3524961	0.1 (1)
ER33	G'GG3	13.88	-459.3076940	-459.3515155	0.0 (2)
ER34	TTG'2	14.43	-459.3079492	-459.3534597	0.3 (2)
ER35	TTT5	17.44	-459.3067502	-459.3518517	0.0 (2)

^a Electronic energies relative to the ER1 conformer ($E_{\text{elec}} = -459.4757199$ Hartree).^b Numbers in parentheses correspond to the degeneracy degree of conformers.**Table 3.** Hydrogen-bond parameters for the lowest energy conformer of each of the six lowest energy backbone structures of erythritol

Conformer	H-bonds	$d(\text{O}\cdots\text{H})/\text{\AA}$	$\alpha(\text{O}-\text{H}\cdots\text{O})/\text{deg}$
ER1	O-1-H \cdots O-4	1.89	149
	O-3-H \cdots O-2	2.24	110
	O-4-H \cdots O-3	2.31	107
ER4	O-2-H \cdots O-1	2.15	113
	O-3-H \cdots O-2	2.23	111
	O-4-H \cdots O-3	2.32	107
ER6	O-1-H \cdots O-2	2.37	107
	O-2-H \cdots O-3	2.32	107
	O-3-H \cdots O-4	2.18	113
ER7	O-2-H \cdots O-1	2.23	110
	O-3-H \cdots O-4	2.21	116
	O-4-H \cdots O-2	2.00	132
ER9	O-1-H \cdots O-2	2.59	101
	O-2-H \cdots O-4	2.02	136
	O-3-H \cdots O-1	2.50	120
ER10	O-2-H \cdots O-1	2.24	112
	O-3-H \cdots O-4	2.37	111

hydrogen bond formation for the lowest energy conformer for each backbone conformation referred above. All conformers mapped for erythritol show the presence of two or three hydrogen bonds. The structures of some of the most important conformers of erythritol are displayed in Figure 1.

The first three conformers (ER1 to ER3) are characterized by a TGG backbone. This type of structure is stabilized by three intramolecular hydrogen bonds; two of them between vicinal OH groups and the third one between the terminal OH groups. This last hydrogen bond is stronger than the other two, since it has a bigger O-H \cdots O angle and smaller O \cdots H distance. The main characteristic of these conformers is the presence of a hydrogen bond network of two condensed five-membered rings, connecting OH groups 2, 3 and 4, and a single seven-membered ring, connecting OH groups 1 and 4 (see Fig. 1 for details).

The structure shown by the ER4 and ER5 conformers is of GGG type, which is stabilized by three hydrogen

Table 4. Dihedral angles for the B3LYP/6-311++G(d,p) optimized structures of the low-energy conformers of L-threitol

Conformer	Label	Dihedral angles/deg ^a						
		φ_1	φ_2	φ_3	φ_4	φ_5	φ_6	φ_7
TR1	GTG1	49.3	174.0	49.4	60.5	-26.7	-26.7	60.5
TR2	GTG2	59.0	179.2	59.0	-59.8	-158.5	-158.5	-59.8
TR3	G'TG1	-55.4	173.0	49.2	164.4	43.4	-34.4	61.3
TR4	GGG1	54.9	59.9	46.7	-57.2	170.3	-27.7	76.3
TR5	G'TG2	-59.4	-165.9	65.1	52.2	174.7	-98.0	-79.4
TR6	G'TG'1	-56.0	-167.9	-53.8	47.9	-81.9	41.8	166.5
TR7	G'TG3	-58.9	-164.3	73.9	52.1	173.9	-86.8	-168.9
TR8	GG'G'1	61.3	-67.7	-56.1	-53.8	-165.4	50.9	171.3
TR9	GGG2	56.3	64.6	46.8	-159.4	-44.7	-27.0	74.3
TR10	GTT1	49.3	162.2	170.1	64.9	-33.9	60.4	-77.0
TR11	TG'T1	-164.8	-66.9	-165.8	-71.1	69.7	-167.1	74.7
TR12	TG'T2	-165.5	-68.6	-164.6	-70.0	69.2	-167.3	167.2
TR13	GTT2	73.0	-168.1	-178.9	-171.2	-84.1	178.2	-93.0
TR14	GTG3	72.4	-163.5	63.9	-169.4	-81.1	175.6	37.5
TR15	GTT3	57.4	167.7	170.0	-58.7	165.6	-143.1	167.0
TR16	GTT4	58.3	173.7	177.0	-60.2	167.0	-152.3	77.1
TR17	GTG4	52.4	174.5	37.3	60.5	-37.1	-27.3	-165.7
TR18	TGT1	-179.3	53.0	-179.3	175.9	-81.7	-81.7	175.9

^a $\varphi_1 = \text{O-1-C-1-C-2-O-2}$; $\varphi_2 = \text{C-1-C-2-C-3-C-4}$; $\varphi_3 = \text{O-3-C-3-C-4-O-4}$; $\varphi_4 = \text{H-O-1-C-1-C-2}$; $\varphi_5 = \text{H-O-2-C-2-C-1}$; $\varphi_6 = \text{H-O-3-C-3-C-4}$; $\varphi_7 = \text{H-O-4-C-4-C-3}$.

Table 5. Relative electronic energies (E_{elec}), enthalpies (H), Gibbs energies (G) and equilibrium populations (P) for the B3LYP/6-311++G(d,p) optimized structures of the low-energy conformers of L-threitol

Conformer	Label	E_{elec} ^a /kJ mol ⁻¹	H (298.15 K)/Hartree	G (298.15 K)/Hartree	P (%) ^b
TR1	GTG1	0.00	-459.3166381	-459.3590901	28.5 (1)
TR2	GTG2	0.90	-459.3164272	-459.3591192	29.4 (1)
TR3	G'TG1	8.19	-459.3140763	-459.3585268	15.7 (2)
TR4	GGG1	10.55	-459.3129664	-459.3567799	2.5 (2)
TR5	G'TG2	12.07	-459.3125536	-459.3572331	4.0 (2)
TR6	G'TG'1	12.44	-459.3126113	-459.3577638	7.0 (2)
TR7	G'TG3	13.34	-459.3123189	-459.3573984	4.7 (2)
TR8	GG'G'1	14.28	-459.3120445	-459.3576560	6.2 (2)
TR9	GGG2	15.43	-459.3111615	-459.3551560	0.4 (2)
TR10	GTT1	17.80	-459.3102277	-459.3549182	0.3 (2)
TR11	TG'T1	19.82	-459.3097960	-459.3542405	0.2 (2)
TR12	TG'T2	20.38	-459.3095882	-459.3541827	0.2 (2)
TR13	GTT2	21.04	-459.3094182	-459.3551117	0.4 (2)
TR14	GTG3	22.42	-459.3087923	-459.3533388	0.1 (2)
TR15	GTT3	22.73	-459.3086193	-459.3547518	0.3 (2)
TR16	GTT4	24.17	-459.3082279	-459.3531964	0.1 (2)
TR17	GTG4	25.17	-459.3076562	-459.3528167	0.0 (2)
TR18	TGT1	26.01	-459.3072703	-459.3515333	0.0 (1)

^a Electronic energies relative to the TR1 conformer ($E_{\text{elec}} = -459.4798351$ Hartree).

^b Numbers in parentheses correspond to the degeneracy degree of conformers.

bonds taking place between vicinal OH groups. The two middle hydroxyl groups act simultaneously as proton donors and proton acceptors. A rather similar structure regarding hydrogen bonding is exhibited by the ER6 conformer, which has a GG'G' backbone conformation.

The conformers ER7 and ER8 present a GG'G conformation characterized by a hydrogen bond system consisting of two hydrogen bonds between the terminal OH groups and their vicinal OH groups and a third one between OH groups 1 and 3 (ER7) or 2 and 4 (ER8).

The energy of the conformers is not determined exclusively by the backbone and the hydrogen bonding sys-

tem because conformers defined by similar structures regarding these features have significantly different electronic energies. Several other factors can influence the energy of the conformers. One of those is concerned with the role of the OH groups in the hydrogen bonds. Most of these groups participate in these bonds as proton donor, proton acceptor or as proton donor and acceptor simultaneously. In a few cases the same group is a double proton acceptor. The latter case is always accompanied by an increase in energy. For example, ER1 and ER20 have similar backbones and hydrogen bonding systems, but the energy of the latter is about

10 kJ mol⁻¹ higher than that of the former. The main structural difference between the two conformers lies in the doubly proton acceptor character of O-3-H in ER20. This effect is observed provided an OH group acts as double proton acceptor. It is quite likely that this type of hydrogen bonding discourages the adaptation of the acceptor site of the group to the preferred hydrogen bonding orientation.

Enthalpy, entropy and Gibbs energy are thermodynamic functions widely used to understand physical and chemical processes. The values for these functions at 298.15 K were calculated and the results obtained are listed in Table 2. For a better visualization, these data are represented graphically in Figure 2. While *H* increases gradually with the electronic energy, with a few small variations, *S* oscillates around a constant mean value with pronounced positive and negative deviations. Regarding the behaviour observed for these functions, *G* shows a general tendency to increase as the electronic energy increases, but with deviations high enough to change the sequence of the conformers relative to that given by the electronic energy. The entropy differences among the conformers, responsible for their different ranking according to either the enthalpy or the Gibbs energy, are mainly due to the vibrational component and are very sensitive to the structure, to hydrogen bonding in particular. In fact, the lower entropy conformers are the ones that exhibit three hydrogen bonds, with the strongest of these connecting the terminal OH groups. The opposite behaviour is observed for the conformers with only two weak hydrogen bonds, which tend to present higher entropy values, caused by their greater flexibility. ER26 is the structure with the highest entropy, making it the third most stable conformer, despite its high-enthalpy value. The entropic effects on the Gibbs energy are responsible for the order of stability of the most significant conformers of erythritol, ER4 being the most stable, followed by ER10, ER6 and ER26. The lowest electronic energy conformer (ER1) is the fifth most populated. Although the formation of strong hydrogen bonds is a crucial factor to minimize the energy of a molecule, it can be also responsible for lowering the entropy and thus its stability by means of the Gibbs energy. This can change the order of stability of conformers at room temperature for molecules whose potential energy surfaces present local minima with small energy differences.

3.2. L-Threitol

Like erythritol, the lower energy conformers of L-threitol are stabilized by intramolecular hydrogen bonds. The optimized structures of the four lowest energy conformers are presented in Figure 3 and a summary of the structural hydrogen bonding parameters for these conformers is given in Table 6.

Table 6. Hydrogen-bond parameters for the four lowest energy conformers of L-threitol

Conformer	H-bonds	<i>d</i> (O···H)/Å	<i>α</i> (O-H···O)/deg
TR1	O-1-H···O-3	2.05	134
	O-4-H···O-2	2.05	134
	O-2-H···O-1	2.17	117
	O-3-H···O-4	2.17	117
TR2	O-3-H···O-1	1.96	144
	O-2-H···O-4	1.96	144
	O-1-H···O-2	2.37	104
	O-4-H···O-3	2.37	104
TR3	O-2-H···O-1	2.21	112
	O-3-H···O-4	2.20	116
	O-4-H···O-2	2.01	132
TR4	O-1-H···O-2	2.36	104
	O-3-H···O-4	2.17	118
	O-4-H···O-1	1.89	148

The global minimum, TR1, has a GTG backbone structure with four hydrogen bonds, two of them involving vicinal OH groups (O-2-H···O-1 and O-3-H···O-4) and the other two involving non-vicinal OH groups (O-1-H···O-3 and O-4-H···O-2). Since this conformer has C₂ symmetry, the hydrogen bond between the hydroxyl groups 1 and 2 is equivalent to that connecting OH groups 3 and 4, and the same happens with the other two bonds, established between OH groups 1 and 3 and between 2 and 4. As shown in Figure 3, this conformer can be described as a cyclic structure of intramolecular hydrogen bonds, in which all hydroxyl groups act simultaneously as proton donors and acceptors, forming two five-membered rings (containing vicinal OH groups) and two six-membered rings (containing non-vicinal OH groups). The TR2 conformer has the same backbone, an electronic energy close to that of TR1 and a similar hydrogen bond system. Their main difference lies in the inversion of the four OH groups orientation (see Fig. 3), which leads to a weakness of the hydrogen bonds between vicinal groups and a strengthening of the other two hydrogen bonds. From TR1 to TR3, an increase of about 8 kJ mol⁻¹ for *E*_{elec} is observed. The most important difference between these conformers lies in the O-1-C-1-C-2-O-2 dihedral, which is gauche anticlockwise in the latter and gauche clockwise in the former. This conformational change disrupts the hydrogen bond cyclic scheme exhibited by TR1 and reduces the number of hydrogen bonds from four to three.

It is worth noting that TR3, TR5 and TR7 are identical in terms of backbone type and hydrogen bond systems, and so similar energy values may be expected for the three conformers. In fact, the energy values for TR5 and TR7 are, respectively, 3.9 and 5.2 kJ mol⁻¹ above that for TR3. The difference between these three structures lies in the role of the hydroxyl group as proton acceptor. While for TR3, the O-1-H group acts only

as proton acceptor, the O-3-H group acts only as proton donor and the others act simultaneously as donors and acceptors, for TR5 and TR7 one hydroxyl (O-2-H) is donor and double acceptor. As mentioned before, this situation discourages hydrogen bond directions relative to the preferred orientations.

TR4 is the only conformer with an intramolecular hydrogen bond between terminal OH groups, originating a very compact cyclic structure. Its geometry is characterized by a seven-membered ring (H-O-4-C-4-C-3-C-2-C-1-O-1) condensed with two five-membered rings on each end (H-O-1-C-1-C-2-O-2 and H-O-3-C-3-C-4-O-4). This cyclic form, with a very efficient geometric arrangement of internal hydrogen bonds, is a stabilizing factor.

The values for the thermodynamic properties at 298.15 K calculated for each conformer are given in Table 5 and represented in Figure 4. The order of the conformers given by the enthalpy is identical to that based on the electronic energy. The pattern for the enthalpy increase shows a small variation from TR1 to TR2 and a pronounced one from TR2 to TR3. From this conformer to TR18, this property increases with smaller and regular variations.

As already observed for erythritol, entropy values are scattered around a mean. However, unlike the *meso* form, the conformational distribution given by the enthalpy is not significantly changed by the entropy. Indeed, the three most stable conformers regarding enthalpy are in the same order with respect to the Gibbs energy. For TR1 and TR2, their particularly strong ring-like hydrogen bond network is responsible for their exceptional low values of both enthalpy and entropy. On the other hand, TR3 enthalpy difference to TR1 and TR2 is attenuated by its relatively high entropy. The relative population calculated from the Gibbs en-

ergy indicates that the first three conformers represent 74% of the structure of L-threitol in the gas phase.

4. Concluding remarks

Polyfunctional compounds with a flexible backbone chain give rise in the gas state to a diversity of conformations with significant energy differences from one compound to another. Structure and energy differences are worthy of consideration even for molecules as similar as those of isomers.

The structure of the isomers under study is defined mainly by the backbone conformations and by the hydrogen bond system established between the OH groups. For erythritol, a relatively large number of conformers has to be considered to describe its mean gas state structure. The carbon chain of the lowest energy conformers has a clockwise gauche configuration, stabilized by three hydrogen bonds involving all hydroxyl groups and organized in different ways. In contrast, the structure of L-threitol is mainly characterized by a GTG backbone structure, stabilized by a cyclic and symmetrical hydrogen bonding system consisting of four bonds, identical two by two, due to symmetry.

At 298.15 K, entropy differences between the erythritol conformers lead to a sequential order of Gibbs energy different from that given by the electronic energy or the enthalpy. For L-threitol, the differences between the two orderings are only observed for higher energy conformers and are therefore of less importance for the structural characterization of the molecule.

The estimation of total values of thermodynamic quantities weighed by the relative populations may include some uncertainty due to the constraints we were forced to impose by limiting the number of studied conformers. However, the results shown in Table 2 show that every erythritol conformer beyond ER18 have populations not greater than 1%, with the particular exception of the above discussed case of ER26 (8.7%). Special care was taken in ensuring that no important conformer, by comparison with the conformational space of smaller polyols,^{14–16} missed our attention. Thus, we are encouraged to believe that the weighed mean enthalpy (H_{gas}) and Gibbs energy (G_{gas}) of erythritol can be calculated with a reasonable accuracy. Applying Eq. 3 to the data included in Table 2: $H_{\text{gas,erythritol}} = -459.311119$ Hartree, $G_{\text{gas,erythritol}} = -459.356328$ Hartree.

L-Threitol has a much simpler conformer distribution, with greater energy differences among them: the three most stable conformers account for 74% of the overall population and every one beyond TR8 is less than 0.5% of the total. This supports our calculation (even more reliably than for erythritol) of the weighed mean enthalpy (H_{gas}) and Gibbs energy (G_{gas}) of L-threitol, based on the data in Table 5:

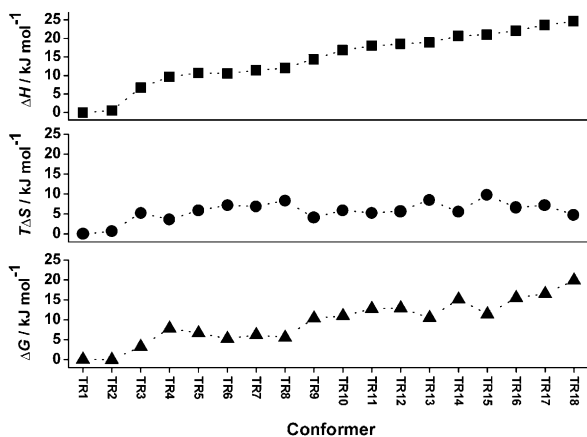


Figure 4. Relative values of H , TS and G of L-threitol conformers at 298.15 K. The reference conformers are TR1 for H and TS , and TR2 for G .

$H_{\text{gas,L-threitol}} = -459.315011$ Hartree and $G_{\text{gas,L-threitol}} = -459.358530$ Hartree.

From these results one can conclude that L-threitol presents lower values for the enthalpy and Gibbs energy than erythritol, in the gas phase. The differences between the values of enthalpy and Gibbs energy observed for the two isomers at 298.15 K are the following: $\Delta H_{\text{gas}} (H_{\text{gas,erythritol}} - H_{\text{gas,L-threitol}}) = 10 \text{ kJ mol}^{-1}$ and $\Delta G_{\text{gas}} (G_{\text{gas,erythritol}} - G_{\text{gas,L-threitol}}) = 6 \text{ kJ mol}^{-1}$.

The differences in these thermodynamic quantities lead to the general conclusion that the study of the gas state plays a key role in the interpretation of the structure of compounds in the condensed matter state. For example, the enthalpy of erythritol and threitol in the liquid or solid states can be determined provided that the enthalpies of vaporization or sublimation are known. The difference of 10 kJ mol^{-1} between the enthalpies of erythritol and threitol in the gas state indicates that the enthalpies of vaporization or sublimation of different compounds cannot be compared without allowing for the difference between the enthalpy of the compound in the gas state.

Acknowledgements

A.J.L.J. acknowledges Fundação para a Ciência e a Tecnologia (FCT), Lisbon, for financial support (Grant SFRH/BD/9110/2002).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.carres.2004.11.018](https://doi.org/10.1016/j.carres.2004.11.018).

References

- Howard, E.; Grigera, J. R. *J. Chem. Soc., Faraday Trans.* **1992**, *88*, 437–441.
- Cohen, S.; Marcus, Y.; Migron, Y.; Dikstein, S.; Shafran, A. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 3271–3275.
- Alvarez, J. G.; Storey, B. T. *J. Androl.* **1993**, *14*, 199–209.
- Storey, K. B.; Storey, J. M. *Annu. Rev. Ecol. Syst.* **1996**, *27*, 365–386.
- Shimada, A. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 325–329.
- Shimada, A. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 330–333.
- Shimada, A.; Higuchi, T.; Fukuyo, M.; Hirotsu, K.; Takusagawa, F.; Shibuya, I.; Iwata, Y.; Koyano, N. *Acta Crystallogr., Sect. A* **1975**, *31*, 178.
- Ceccarelli, C.; Jeffrey, G. A.; McMullan, R. K. *Acta Crystallogr., Sect. B* **1980**, *36*, 3079–3083.
- Jeffrey, G. A.; Huang, D. B. *Carbohydr. Res.* **1992**, *223*, 11–18.
- Kopf, J.; Morf, M.; Zimmer, B.; Haupt, E. T. K.; Jarchow, O.; Köll, P. *Carbohydr. Res.* **1993**, *247*, 119–128.
- Rozenberg, M.; Loewenschuss, A.; Marcus, Y. *Carbohydr. Res.* **1997**, *394*, 183–186.
- Rozenberg, M.; Loewenschuss, A.; Lutz, H.; Marcus, Y. *Carbohydr. Res.* **1999**, *315*, 89–97.
- Reiling, S.; Brickmann, J.; Schlenkrich, M.; Bopp, P. A. *J. Compd. Chem.* **1996**, *17*, 133–147.
- Chelli, R.; Gervasio, F. L.; Gellini, C.; Procacci, P.; Cardini, G.; Schettino, V. *J. Phys. Chem. A* **2000**, *104*, 5351–5357.
- Chelli, R.; Gervasio, F. L.; Gellini, C.; Procacci, P.; Cardini, G.; Schettino, V. *J. Phys. Chem. A* **2000**, *104*, 11220–11222.
- Callam, C. S.; Singer, S. J.; Lowary, T. L.; Hadad, C. M. *J. Am. Chem. Soc.* **2001**, *123*, 11743–11754.
- Jesus, A. J. L.; Rosado, M. T. S.; Leitão, M. L. P.; Redinha, J. S. *J. Phys. Chem. A* **2003**, *107*, 3891–3897.
- Cerius2 (version 3.5), Molecular Simulations Inc., San Diego, CA, 1997.
- Maple, J. R.; Dinur, U.; Hagler, A. T. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 5350–5354.
- Hwang, M.-J.; Stockfish, T. P.; Hagler, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 2515–2525.
- Hohenberg, P.; Kohn, W. *Phys. Rev. B* **1964**, *136*, 864–871.
- Kohn, W.; Sham, L. J. *Phys. Rev. A* **1965**, *140*, 1133–1138.
- Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
- Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100.
- Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
- Stepanian, S. G.; Reva, I. D.; Radchenko, E. D.; Rosado, M. T. S.; Duarte, M. L. T. S.; Fausto, R.; Adamowicz, L. *J. Phys. Chem. A* **1998**, *102*, 1041–1054.
- Guler, L. P.; Yu, Y.-Q.; Kentamaa, H. I. *J. Phys. Chem. A* **2002**, *106*, 6754–6764.
- Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *GAUSSIAN 98*, revision A.9, Gaussian, Inc.: Pittsburgh, PA, 1998.
- Foresman, J. B.; Frisch, A. In *Exploring Chemistry with Electronic Structure Methods*, 2nd ed.; Gaussian: Pittsburgh, PA, 1996; pp 66–69.
- McQuarrie, D. A. *Statistical Thermodynamics*; Harper & Row: New York, 1973.
- Ochterski, J. W. *Thermochemistry in Gaussian*, Gaussian Inc, 2000. http://www.gaussian.com/g_whitepap/white_pap.htm.
- Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48–76.