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Bioactive Four-Membered Heterocyclic Compounds: The Anti → Syn Interconversion in Dithietane-1,3-dioxide

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The anti-dithietane-1,3-dioxide → syn-dithietane-1,3-dioxide isomerization reaction has been theoretically studied on the frame of MO theory both in the gas phase and in solution. In the gas phase the anti (II_a) ↔ syn (II_s) equilibrium is slightly displaced to the anti isomer formation. The syn concentration ([Syn]) is ca. 36% in the gas phase, whereas in low polarity solvent, such as carbon tetrachloride, [Syn] is ca. 63%. In medium-high polarity solvents like acetonitrile and dimethyl-sulfoxide the [anti]/[syn] ratio is ca. 0.37.

Key Words: dithietane-1,3-dioxides; ab initio calculations; anti-syn interconversion.

INTRODUCTION

Organosulfur compounds are found in a large number and diverse locations. In living creatures they are found in certain amino acids, enzymes, vitamins, RNA components, antibiotics, secretions of defensive systems, and a number of natural food such as garlic, cabbage, mustard, onions, asparagus, truffles, cauliflower, mushrooms, coffee, and pineapple. Substituted-1,3-dithietanes directly attached to cephalosporins produce an increase in the activity of this beta-lactam antibiotics agent (*1*), whereas as 2-ylidene (YH439) derivative inhibits the mutagenicity and tumorigenicity of vinyl carbamate in liver (*2*), and hence it has been proposed as a new hepatoprotective agent (*3*).

Block *et al.* (*4,5*) have prepared a series of *S*-oxides of 1,3-dithietane. Progressive oxidation of dithietane leads to mono, di, tri, and tetraoxides whose relevant structural features have been recently reported (*6*). Oxidation of dithiethane-1-oxide with *m*-$ClC_6H_4CO_3H$ in dichloromethane at 0°C produces a mixture of the anti and syn isomers of dithietane-1,3-dioxides, whereas the preparation of dithietane-1,1-dioxide (vicinal isomer) requires a selective and mild oxidation with $KmnO_4$, $MgSO_4$ in

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acetone at −30°C. Theoretical calculations at different levels of theory (*6*) show that the vicinal isomer is ca. 33 kcal/mol more stable than the anti and syn isomers. This result is in keeping with the experimental fact that it is easier to produce a sulfone than a sulfoxide. In fact to prepare the anti and syn forms requires a more drastic oxidizing agent such as *m*-chloro peroxobenzoic acid.

Theoretical calculations on the anti ↔ syn equilibrium in the gas phase at the HF/6-31G** level (*6*) show that the anti isomer is slightly favored (by ca. 0.27 kcal/mol) over the syn. The [anti]/[syn] ratio is 1.6 with a syn concentration of ca. 39%. Due to different dipole moments of the anti and syn isomers, one can expect that solvents of low and medium-high polarity such as carbon tetrachloride ($\varepsilon = 2.228$), acetonitrile ($\varepsilon = 36.64$), and dimethylsulfoxide ($\varepsilon = 46.70$) would exert a large influence on the anti ↔ syn interconversion. In the present work we have calculated the gas phase thermodynamics and energetics at the MP2/6-31G** geometries as well as the effect of the above mentioned solvent on the anti → syn interconversion reaction.

COMPUTATIONAL METHODS

Standard *ab initio* calculations, in the framework of molecular orbital theory, were performed using the GAUSSIAN 94 and 98 codes (*7*). The initial anti and syn gas phase geometries were taken from Ref. *3*. Geometry optimizations were carried out at the MP2/6-31G** level. The energy calculations were carried out using various basis sets in order to observe the effect of including both polarization and diffuse functions as well as electron correlation at the Moller–Plesset theory in the frozen core approximation. To estimate the free energy changes of isomerization, the energies calculated at the MP2/6-311++G** level were used. The solute–solvent interactions were taken into account using Tomasi's polarizable continuum model (PCM) (*8*) modified by Wiberg *et al.* to produce the isodensity polarizable continuum model (IPCM) (*9,10*). IPCM calculates the electric field analytically, and the cavity is defined upon an isosurface of the total electron density calculated at the level being used. Thus, in IPCM the cavity is uniquely defined from the electronic environment and just the isosurface level (i.e., charge density) needs to be specified. It is worth noting that this method calculates the eñectrostatic terms only. Dispersion and cavitation contributions were not included in the present calculations. Since structural parameters change very little in going from the gas phase to solution in these compact molecules, no large effect on solvation energies, in relative terms, can be expected (*7,8*). The solvation free energies ΔG°_s were calculated from $\Delta G^\circ_s = (E_{soln} = \Delta G^\circ_{gas})$, whereas the free energies in solution (G°_{soln}) were derived from $G^\circ_{soln} = \Delta G^\circ_{gas} + \Delta G^\circ_s$ (*12*).

RESULTS AND DISCUSSION

Figure 1 shows the optimized structures at the MP2/6-31G** level of the anti **(II_a)** and syn **(II_s)** isomeric forms of dithietane-1,3-dioxide as well as the parent compound dithietane **(I)**. Selected bond distances and angles for **I, II_a,** and **II_s** are given in Table 1. Dithietane possesses a planar structure with all ring bond distances ca. 1.828 A, whereas the internal angles having a carbon as a central atom are ca. 96° (α). Those having sulfur as central atom as ca. 84° (β). Since $\alpha + \beta = 180°$, the molecule has a regular parallelogram geometry. The anti and syn isomers of dithietane-1,3-doxide are puckered. In fact, the S1C2S3C4 angles are −26.31 and −23.11° for **II_a** and **II_s**,

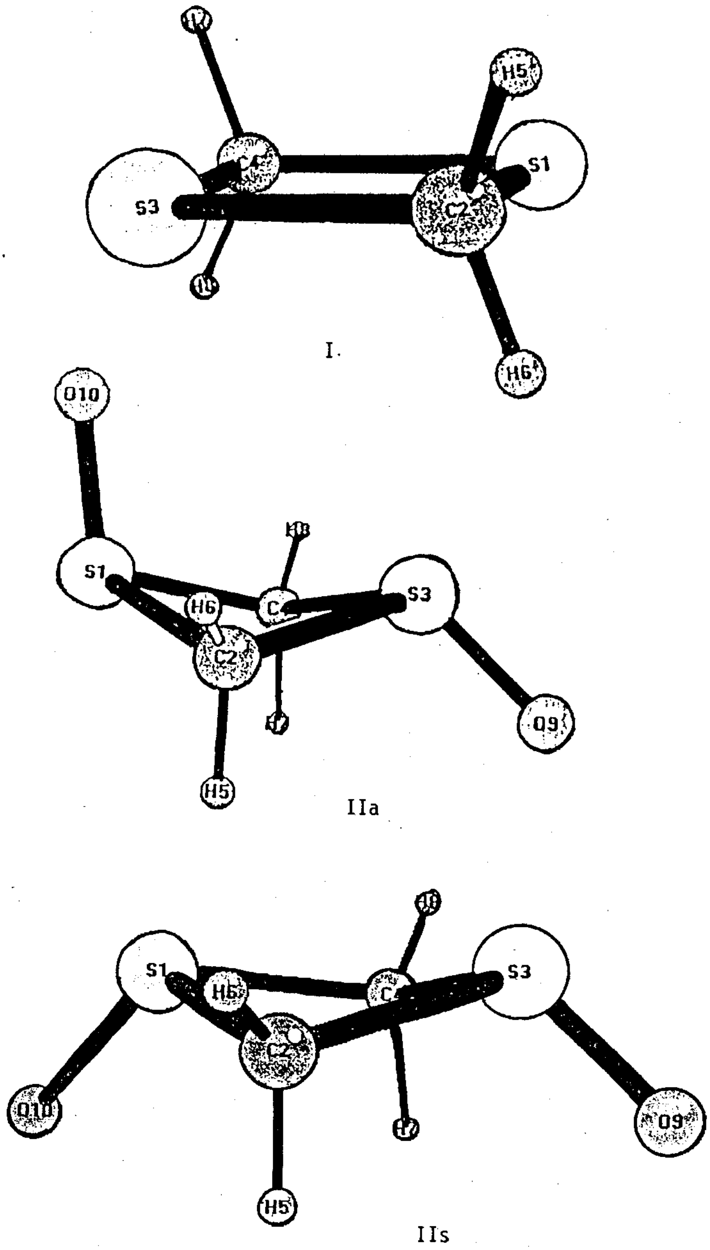

FIG. 1. Dithietane (**I**), anti-dithietane-1,3-dioxide **(II_a)**, and syn-dithietane-1,3-dioxide **(II_s)** optimized structures.

TABLE 1

Calculated Bond Distances (Å) and Angles (degrees) for dithietane **(I),** Anti **(II_a),** and Syn **(II_s)** Isomers of dithietane-1,3-Dioxide[a]

Parameters	**I**	**II_a**	**II_s**
S1 − C2	1.8281	1.8427	1.8424
C2 − S3	1.8280	1.8448	1.8424
S3 − C4	1.8280	1.8448	1.8424
C4 − S1	1.8281	1.8428	1.8424
C2 − H5 (ax)[b]	1.0872	1.0923	1.0929
C2 − H6 (eq)	1.0872	1.0879	1.0873
C4 − H7 (ax)	1.0872	1.0923	1.0929
C4 − H8 (eq)	1.0872	1.0879	1.0873
S3 − O9		1.5009	1.5015
S1 − O10		1.5048	1.5015
S1 . . . S3	2.7124	2.7132	2.7325
C2 . . . C4	2.4515	2.3468	2.3570
<S1C2S3	95.79	94.75	95.73
<C2S3C4	84.22	79.00	79.53
<S1C4S3	95.79	94.75	95.73
<C2S1C4	84.21	79.10	79.53
<H5C2H6	109.74	111.84	111.49
<H7C4H8	109.74	111.84	111.49
<S1C2S3C4	0.01	−26.31	−23.11

[a] Calculated at the MP2/6-31G** level.

[b] Ax, axial; eq, equatorial.

respectively. For the **II_a** isomeric form the S1-C bond distances are slightly different than the S3 − C bond lengths. In the **II_s** these distances are all equal producing a more regular symmetry. In both isomers the C2-H5 and C4-H7 (axial hydrogens) are slightly longer than the C2-H6 and C4-H8 (equatorial hydrogens), whereas in **I** all four C-H distances are identical. This effect is most likely due to the fact that **I** is planar and no hydrogen atoms are neither axially or equatorially positioned. In fact, whereas the H-C-H angles are ca. 111° in **II_a** and **II_s** in **I** are ca. 109°. In both isomers of dithietane-1,3-dioxide the S−O bond distances are ca 1.50 A which is typical of sulfoxide moieties. Analysis of Cartesian displacements vibrational coordinates shows that, the antisymmetric stretching modes lead to a very strong band at 1046 and 1050 cm^{-1} for **II_a** and **II_s**, respectively. The symmetric stretching mode for these species were calculated at 1061 and 1058 cm^{-1}, respectively. These frequency values are lower (by ca. 30 cm^{-1}) than those found in similar heterocyclics containing a single sulfoxide group. In fact in 3-substituted thietane-1-oxide these vibrational modes are detected in the range 1050–1080 cm^{-1} depending on whether the S = O group is cis or trans to the substituent on C3 (*13*). The S1–S3 nonbonded distances are similar for the planar **I** and the puckered **II_a** and **II_S** and hence in these two later structures the C2–C4 must be different. In fact, this distance changes from 2.4515 A in I to 2.3468 and 2.3570 A, respectively. This is a clear consequence of the puckered structure of these isomeric forms; since the sulfur atoms remain at almost the same distance as in the planar parent compound, the carbon atoms must get closer.