Theoretical study on the stereochemistry of bis(methylthio)methane, a model of dithioacetal segment in thiosaccharides

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The stereochemistry of bis(methylthio)methane, a model of dithioacetal segment in thiosaccharides, was studied by the semiempirical quantum chemical methods. PCILO method was applied for calculation of the conformational map of rotation around the central C—S bonds. The geometry of stable conformations *sc*,*sc*, *sc*,*ap*, and *ap*,*ap* was optimized by MNDO method. The ratio of individual conformers in the isolated molecule, calculated on the basis of MNDO energies, was 78 : 21 : 1. Influence of a solvent was calculated by the procedure, which involved contributions of electrostatic and dispersion interactions and a cavity term. Contribution of electrostatic interactions was shown to be the most conformationally dependent. Populations of conformers in dilute solutions depend on a solvent character and the proportion of conformers with the antiperiplanar positions of the methyl groups increases with the increasing polarity of solvent. In methanol, for example, the proportion of conformers is already 57 : 40 : 3, and in water 31 : 59 : 10; while *sc*,*ap* conformer was shown to be the most stable. Comparison with the oxygen analogues revealed that both anomeric and exoanomeric effects in dithioacetal segment are lower than in acetal one.

Изучена стереохимия бис(метилтио)метана, модели дитиоацетального фрагмента в тиосахаридах. Изучение проводилось полуэмпирическими квантово-химическими методами. Метод PCILO был применен для расчета конформационных схем вращения вокруг центральной C—S связи. Геометрия стабильных конформаций *sc*,*sc*, *sc*,*ap* и *ap*,*ap* была оптимизирована методом MNDO. Соотношение индивидуальных конформеров в изолированной молекуле, вычисленное на основе энергий MNDO, было 78 : 21 : 1. Влияние растворителя было рассчитано с помощью процедуры, учитывающей вклады электростатических и дисперсионных взаимодействий, а также кавитационный вклад. Показано, что сильнее всего зависят от конформации вклады электростатических взаимодействий. Соотношение конформеров в разбавленных растворах зависит от природы растворителя, причем количество конформера с антиперипланарным расположением метильных групп возрастает с ростом полярности растворителя. В метаноле, например, соотношение конформеров уже 57:40:3, а в воде 31:59:10, причем показано, что *sc*,*ap* конформер является наиболее стабильным. Сравнение с кислородными аналогами показало, что как аномерный, так и экзоаномерный эффект в дитиоацетальном фрагменте слабее, чем в ацетальном.

Study of conformational behaviour of dimethoxymethane (DMM), $CH_3OCH_2OCH_3$ using the quantum chemical methods [1—6] was very useful. The analysis of calculated results enabled to better understand the preference of synclinal (*sc*) position over the antiperiplanar one (*ap*) in the rotation around C—O bond and explained the reasons of changes in the geometry with the change of conformation of C—O—C—O—C segment. The above properties of the acetal grouping of atoms are considered to be a demonstration of anomeric or exo--anomeric effects. The latter were observed for the first time in saccharides, where they are very important in determining the conformations of a glycosidic bond. It was shown later that both effects may be found in other groups of compounds, in which the oxygen atom is substituted by another heteroatom. The substitution of the oxygen atoms in DMM with sulfur leads to its sulfur analogue bis(methylthio)methane (BMTM), $CH_3SCH_2SCH_3$, which is the model of structural moieties occurring in thiosugars. It is assumed on the basis of experimental data that the magnitude of anomeric effect is lower in sulfur derivatives than in the oxygen ones. A complete, theoretical conformational analysis of BMTM has not been made thus far. Energies of individual BMTM conformers [7, 8] have only been calculated and the stability of conformers depended on the calculation method used. On the basis of vibration analysis of BMTM [9] can be assumed the presence of at least three conformers synclinal—synclinal *sc*,*sc*, synclinal—antiperiplanar *sc*,*ap*, and antiperiplanar—antiperiplanar *ap*,*ap* in the gaseous and liquid states. *Ohsaku* [9] assumes the following order of stability *sc*,*sc* > *sc*,*ap* > *ap*,*ap*. *Exner et al.* [10, 11] studied the conformations around C—S bonds in dithioacetals by measuring a dipole moment and Kerr constant. It is evident from their results that *sc*,*ap* is the most stable conformer in benzene and carbon tetrachloride. In this work we studied the conformational surface of BMTM and the stability of BMTM conformers in solvents of various polarity using semiempirical quantum chemical methods. The results obtained were compared with the oxygen analogue of dimethoxymethane and with experimental data.

Method of calculation

BMTM molecule in *ap*,*ap* conformation is depicted in Fig. 1. First of all, we investigated rotation around the central C—S bonds characterized by Θ and Φ angles. The methyl groups were in staggered position, in which H-8 and H-11 atoms were oriented antiperipla-

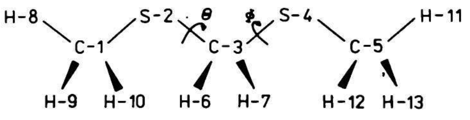

Fig. 1. Schematic depicting of BMTM molecule in *ap*,*ap* conformation ($\Phi = \Theta = 180°$) together with numbering of atoms.

nar towards the C-3 atom. The two-dimensional energetical map (Θ, Φ) was calculated by the PCILO [12] semiempirical quantum chemical method with the rigid BMTM geometry. We applied the following geometrical parameters obtained as the mean values from the X-ray structures of thiosugars [13], bond length C—S 180 pm, bond angles C—S—C and S—C—S 99.6° and 112.6°, respectively. The bond length of C—H was taken as 110 pm and bond angles S—C—H 109.5°. The geometries of the stable conformations were optimized by MNDO quantum chemical method [14]. MNDO energy was used as the energy of isolated molecule in calculation of the solvent effect. The solvation Gibbs energy is, in this approach, composed of three terms, *i.e.* of cavity G_{cav}, electrostatic G_{el}, and dispersion G_{disp} terms, and was described in detail in our preceding papers [15, 16].

Results and discussion

Energies of individual BMTM conformations, obtained by rotation around the central C—S bonds and calculated by PCILO methods, are depicted in the form of two-dimensional contour map of conformational energies in Fig. 2. In the calculation, we used the constant values of bond angles and bond lengths and changed only the values of dihedral angles Θ, Φ in the interval of 10°, in the vicinity of minima by 5°. The absolute minimum corresponds to the conformation, in which one methyl group is rotated from the antiperiplanar position by 115 degrees. For symmetrical reasons, this conformer is fourfold degenerated and lies in the range of *sc*,*ap*, -*sc*,*ap*, and *ap*, ∓ *sc* conformations. The values of angles in *sc* position are ±65° and in *ap* position 180°. The further minimum with energy higher by 0.41 kJ mol^{-1} corresponds to *ap*,*ap* conformation. For symmetrical reasons, the latter minimum is again twice degenerated. It lies in the area of *sc*,*sc* or -*sc*,-*sc* conformers having the angle values $\Theta = \Phi = \pm 65°$. These conformers have the energy higher by 3.4 kJ mol^{-1} than the total minimum.

The geometry of these conformers was optimized using MNDO method. The results characterizing stability, geometry; and the charge distribution in the individual minima are presented in Table 1. In contrast to PCILO calculation with the constant geometry, *sc*,*sc* conformer is the most stable one having the angle values $\Theta = \Phi = 73.8°$. Conformer *sc*,*ap* with $\Theta = 75.8°$, $\Phi = 180°$ and the corresponding symmetrical structures have the energy higher by 5 kJ mol^{-1}. The least

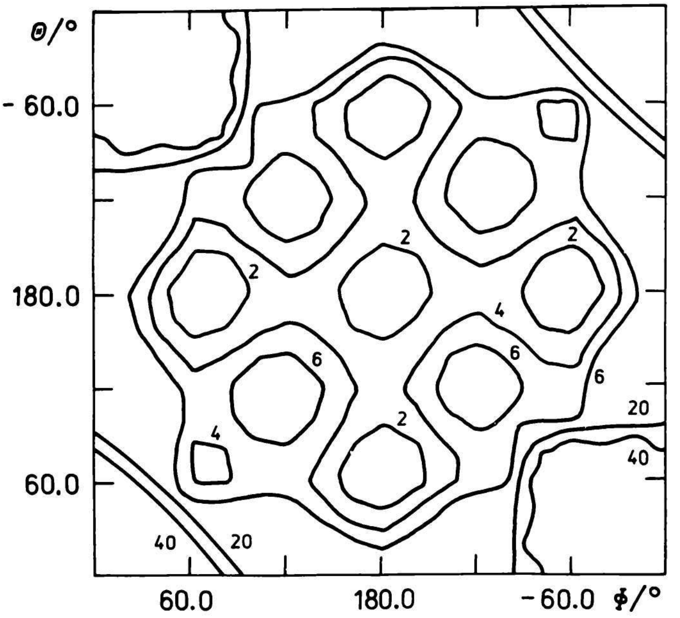

Fig. 2. Map of the relative BMTM conformational energies of rotation around the central C—S bonds calculated by PCILO method (contours: energy/(kJ mol^{-1})).

stable is *ap*,*ap* conformer with $\Theta = \Phi = 180°$, and with the energy of 11 kJ mol^{-1} over *sc*,*sc*. Comparison with the preceding energy calculations of individual conformers is given in Table 2. It reveals a qualitative agreement of MNDO conformational energies with *ab initio* calculation in STO-3G base [8]. It should be mentioned here that *ab initio* calculation was performed with standard parameters, except S—C—S angle, for which the authors used the values 114.6° for *sc*,*sc*, 112.5° for *sc*,*ap*, and 110.4° for *ap*,*ap* conformers, which were obtained by optimizing the methanedithiol geometry [8]. The order of stability is also in accordance with the experimental data of vibration analysis [7]. Similarly, the chain of polymer analogue, polythiomethylene, forms a helical structure in a solid state with dihedral angle of approximately 66°, *i.e.* it corresponds to *sc*,*sc* conformer of BMTM [9, 17]. The energy difference between BMTM conformers is a little lower than in the case of dimethoxymethane, where on the basis of measurement of dipole moment, *Uchida et al.* [18] found that *sc*,*ap* and *ap*,*ap* conformers had the energy higher by 7.1 kJ mol^{-1} or 14.2 kJ mol^{-1} than *sc*,*sc* conformer. Likewise, calculation using CNDO/2 method with the constant geometry led to the energetical difference of 9.9 kJ mol^{-1} and 13.7 kJ mol^{-1}, respectively [1].

The values of charges (Table 1) point to the dependence of electron distribution on the conformation of dithioacetal structure. A dipole moment of the given

Table 1

Values of MNDO energy E, ionization potential I, net charges Q, and geometrical parameters of stable conformers of bis(methylthio)methane

Parameter	Conformer		
	sc,sc	*sc,ap*	*ap,ap*
$E/(\text{kJ mol}^{-1})$	−94038.20	−94033.20	−94027.10
I/eV	10.15	10.16	10.12
$Q(\text{C-1})/(10^3\,e)$	45.2	38.2	31.0
$Q(\text{S-2})/(10^3\,e)$	−145.0	−136.9	−91.8
$Q(\text{C-3})/(10^3\,e)$	12.5	6.4	−2.5
$Q(\text{S-4})/(10^3\,e)$	−145.0	−99.4	−91.8
$Q(\text{C-5})/(10^3\,e)$	45.2	36.8	31.0
$r(\text{C-1—S-2})/\text{pm}$	173.6	173.5	173.6
$r(\text{S-2—C-3})/\text{pm}$	173.4	173.9	173.6
$r(\text{C-3—S-4})/\text{pm}$	173.4	173.9	173.6
$r(\text{S-4—C-5})/\text{pm}$	173.6	173.7	173.6
$\alpha(\text{C-1—S-2—C-3})/°$	108.5	107.0	106.2
$\alpha(\text{S-2—C-3—S-4})/°$	115.9	110.3	105.5
$\alpha(\text{C-3—S-4—C-5})/°$	108.5	108.3	106.2
$\Theta/°$	73.8	180.0	180.0
$\Phi/°$	73.8	75.8	180.0

Table 2

Comparison of the calculated relative energies of stable conformers of bis(methylthio)methane

Method	$\Delta E_i/(\text{kJ mol}^{-1})$			Ref.
	sc,sc	*sc,ap*	*ap,ap*	
MCNDO (*spd*)	0.0	78.3	147.4	[7]
MCNDO (*sp*)	11.6	4.4	0.0	[7]
STO-3G	0.0	4.23	7.36	[8]
PCILO	3.41	0.0	0.41	This paper
MNDO	0.0	4.99	11.05	This paper

conformer can be considered a sum of vectors of dipole moments of C—S—C segments and thus it depends on the mutual orientation of these two groups. The highest dipole moment belongs to *ap,ap* conformer ($\mu = 10.49 \times 10^{-30}$ C m), where both segmental dipole moments are oriented parallelly, the smallest one belongs to *sc,sc* conformation ($\mu = 0.3 \times 10^{-30}$ C m), where they are oriented almost antiparallelly. In the third *sc,ap* conformer, the dipole moment has a value of 8.03×10^{-30} C m. The charge distribution on the central carbon C-3 and on the sulfur atoms S-2 and S-3 is most influenced by the change of conformation. In *ap,ap* conformation, C-3 is negative and by each rotation of the methyl group from *ap* to *sc* position it becomes more positive. On the contrary, sulfur atoms are the most negative in *sc,sc* conformation and the least negative in *ap,ap* conformation. These changes may be explained on the basis of analogy with the delocalization interactions of the lone electron pairs of oxygen atoms in DMM [19]. In *ap,ap* conformation, the lone pairs of sulfur atoms are in such an arrangement that their delocalization, *i.e.* the charge transfer from a sulfur lone pair to antibonding orbitals on the central methylene group is the highest one and the carbon is, therefore, the most negative one. Rotation of the methyl groups into *sc* positions decreases possibility of delocalization and thus the back donation of electrons from the oxygen lone pairs is lower than in *ap* position. Conformational dependence of delocalization interactions will also reflect the changes of geometry of the dithioacetal segment (Table 1). The most pronounced changes are in the bond angle S—C—S. The lowest value has the angle S—C—S in conformer *ap,ap*, 105.5°, where delocalization of the lone pairs is the highest one; the highest value has in *sc,sc*, 115.9°, where delocalization of the lone pairs is the lowest one. It has the value of 110.3° in conformer *sc, ap*. Similar changes have been observed in the acetal segment in DMM, where the angle O—C—O has the following values 104.6°, 110.0°, and 114.9° [19], or in pyranosides, too [20]. It should be mentioned here that the values of dihedral angles Θ, Φ are higher in BMTM conformers than in *sc,ap* in DMM (35°), in comparison with 74° in BMTM. Likewise, the dihedral angle of *sc,sc* conformer is 60° in DMM and 76° in BMTM.

On the basis of conformational energies and dipole moments of the individual BMTM conformers (Table 1) we calculated their proportion in equilibrium and the mean dipole moment. The results revealed 78.3 % proportion of *sc,sc* conformer, 20.8 % of *sc,ap*, and a negligible 0.9 % population of *ap,ap* conformer. In such a composition of conformers, the mean dipole moment is 3.7×10^{-30} C m. It is obvious that the preceding values characterize only an isolated molecule and they cannot be applied for more polar environment. Therefore, we used the procedure [15, 16] for calculating Gibbs energies of the individual conformers in fourteen solvents of various character. Parameters characterizing solvents are given in our previous papers [15, 16]. The parameters of BMTM conformers were calculated using MNDO method with the exception of refractive index $n_D = 1.5322$ [21]. In Table 3, the results are given in the form of relative Gibbs energies, mole fractions, and the mean dipole moment. Comparison of relative energies reveals that with the increasing solvent polarity decrease energy differences between the conformers. They were 5 kJ mol^{-1} and 11 kJ mol^{-1} in the isolated state while in water only 0.1 kJ mol^{-1} and 2.8 kJ mol^{-1}. Changes in the proportion of conformers are not simple, but reflect also specific properties of individual solvents. For example,

Table 3

Calculated relative, with respect to *sc,sc*, Gibbs energies ΔG_i and mole fractions x_i of bis(methylthio)-methane conformers at 298.2 K with the mean dipole moment in isolated state and in solution

	$\Delta G_i/(\text{kJ mol}^{-1})$		x_i			$\langle\mu\rangle 10^{30}/\text{C m}$
	sc,ap	*ap,ap*	*sc,sc*	*sc,ap*	*ap,ap*	
Isolated molecule	5.0	11.1	78.3	20.8	0.9	3.7
Hexane	4.6	10.6	75.4	23.6	1.0	4.0
1,4-Dioxan	4.3	10.1	73.0	25.8	1.2	4.3
Carbon tetrachloride	4.5	10.4	74.6	24.3	1.1	4.0
Benzene	4.5	10.3	74.5	24.3	1.2	4.0
Carbon disulfide	4.3	10.0	73.0	25.7	1.3	4.3
t-Butylamine	4.1	9.7	71.3	27.3	1.4	4.4
Chloroform	3.8	9.2	68.7	29.7	1.6	4.7
Pyridine	3.4	8.6	65.0	33.0	2.0	5.0
Acetone	3.5	8.6	65.9	32.1	2.0	4.7
Ethanol	3.2	8.1	63.0	34.6	2.4	5.0
Methanol	2.6	7.0	56.8	39.8	3.4	5.3
Acetonitrile	2.9	7.6	60.0	37.2	2.8	5.3
Dimethyl sulfoxide	3.2	8.1	63.0	34.6	2.4	5.0
Water	0.1	2.8	30.8	59.2	10.0	7.0

chloroform has a higher influence on lowering of energetical differences than it would correspond to its relative permittivity and, on the contrary, DMSO has a smaller effect. Different stabilization of conformers by a solvent is also demonstrated by the change of both their proportion in equilibrium and the mean dipole moment. In the way the energy differences decrease, the abundance of *sc,ap* and *ap,ap* conformers increases in the equilibrium mixture. The *ap,ap* proportion has increased up to 10 % in water and *sc,ap* population is even higher. The reason why *sc,ap* conformer has a higher abundance in water than the *sc,sc* one, although both possess almost the same energy, is the fourfold degeneration of *sc,ap* conformer. The mean dipole moment also increases with the increasing proportion of conformers having a higher dipole moment. In Table 4, the values of solvation energies are presented together with their decompositions into the individual terms calculated for four solvents of various polarity. They enable to better understand the influence of environment on the stability of *sc,ap* and *ap,ap* conformers. Contributions of the dispersion interactions G_{disp} and a cavity term G_{cav} are the highest in magnitude. However, they are almost the same in all three conformers. On the contrary, contribution of the electrostatic interactions G_{el}, which is in its magnitude the smallest one, has a remarkable conformational dependence and its magnitude increases with the relative permittivity ε_r of a solvent. As in denominator of expression for G_{el} [15, 16] a square dipole moment occurs, the

Table 4

Solvation Gibbs energy of stable bis(methylthio)methane conformers in four solvents at 298.2 K and a decomposition into individual components

Solvent	Component of Gibbs energy	G_i/(kJ mol^{-1})		
		sc,sc	*sc,ap*	*ap,ap*
Carbon tetrachloride	G_{el}	−0.01	−0.43	−0.74
	G_{cav}	40.89	40.81	40.71
	G_{disp}	−71.80	−71.81	—71.56
	G_{solv}	−30.92	−31.43	−31.60
Chloroform	G_{el}	−0.03	−1.19	−2.04
	G_{cav}	13.49	13.47	13.43
	G_{disp}	−81.65	−81.69	−81.44
	G_{solv}	−68.19	−69.41	−70.04
Methanol	G_{el}	−0.09	−2.39	−4.06
	G_{cav}	41.03	40.95	40.84
	G_{disp}	−63.49	−63.52	−63.33
	G_{solv}	−22.55	−24.96	−26.55
Acetonitrile	G_{el}	−0.07	−2.06	−3.51
	G_{cav}	45.87	45.77	45.66
	G_{disp}	−65.96	−65.98	−65.77
	G_{solv}	−20.16	−22.27	−23.62

stabilization of conformers raises with the increasing dipole moment, *i.e.* *ap*,*ap* > *sc*,*ap* > *sc*,*sc*. Large differences in dipole moments of conformers are the reason why this contribution determines the whole dependence of solvation energy.

Direct comparison of the equilibrium composition calculated with the experimental BMTM data is not possible. *Exner et al.* [10] studied the conformations of $R^1R^2C(SC_2H_5)_2$ dithioacetals, where R^1 is H or CH_3 and R^2 is CH_3 or aryl, by measuring of dipole moments in benzene. In contrast with our results they reported, in the case of aryl derivatives, that the prevailing conformer was the unsymmetrical *sc*,*ap* conformer. This difference, however, might be caused by the presence of a phenyl group on the central carbon. Further, they were unable to determine the most stable conformation of the aliphatic derivative $(CH_3)_2C(SC_2H_5)_2$, the structure of which is very similar to that of BMTM. Nevertheless, they assume on the basis of substantial differences in the dipole moments with aryl derivatives that the population of conformers is different. Comparison of the experimentally found dipole moment (3.87×10^{-30} C m) with that calculated for a dilute BMTM solution in benzene (4.0×10^{-30} C m) may be regarded as a test of calculated proportions. Good agreement between the values could indicate correctness of the calculated equilibrium composition.

Bis(methylthio)methane is the model compound for dithiopyranosides. The results presented indicate that the magnitude of anomeric effect and thus the difference in the stability of ${}^4C_1$ and ${}^1C_4$ conformations of pyranose ring in dithiopyranosides will be lower than with their oxygen analogues. Likewise, lowering of the magnitude of exoanomeric effect might be the reason for location of the methyl group in the antiperiplanar position in the crystal structure of methyl-1,5-dithio-α-D-ribopyranoside. The solvent effect is similar as in the case of the oxygen analogues, but it is more evident with respect to the lower values of anomeric and exoanomeric effects.

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