THEORETICAL STUDY OF STEREOCHEMISTRY OF METHOXY(METHYLTHIO)METHANE AS A MODEL OF THIOACETAL SEGMENT IN THIOSACCHARIDES

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The stereochemistry of methoxy(methylthio)methane — a model of the thioacetal segment in thiosaccharides — has been studied by semiempirical quantum-chemical methods. The conformational map of the rotation around the central C—O and C—S bonds has been calculated by the PCILO method. Decomposition of the energy for the rotation around the C—O (C—S) bond (the methyl group being fixed in the antiperiplanar position) in terms of the Fourier series gives the values 7·12 (2·53) kJ mol^{-1} for the respective rotational barrier. The geometry of five stable conformers, whose stability decreases in the order (sc,sc) > (ap,sc) > (sc,ap) > (-ac,sc) > (ap,ap), has been optimized by the MNDO method. Ratio of the individual conformers in an isolated molecule calculated on the basis of the MNDO energies is 92 : 5 : 2 : 1 : 0, the mean dipole moment being $3{\cdot}6 \cdot 10^{-30}$ Cm. The solvent effect has been calculated by a method involving electrostatic and dispersion interactions and cavity contribution. Population of the conformers in diluted solutions depends on nature of the solvent, proportion of the antiperiplanar positions being increased with increasing polarity. The calculated ratios of the conformers are 85 : 8 : 3 : 4 : 0 and 63 : 14 : 7 : 16 : 0 in acetonitrile and water, respectively. The calculated values of the Gibbs energies have also been used for assessment of magnitude of anomeric and exo-anomeric effects in α- and β-1-thiopyranosides and α- and β-5-thiopyranosides.

In our previous papers[1-3] we studied the conformational properties of dimethoxymethane (DMM) $CH_3OCH_2OCH_3$ and bis(methylthio)methane (BMTM) $CH_3SCH_2.SCH_3$ and effects of various solvents on stability of their conformers. The present communication deals with stereochemical study of methoxy(methylthio)methane (MMTM) $CH_3OCH_2SCH_3$ in isolated state and in diluted solution by semiempirical quantum-chemical methods. Methoxy(methylthio)methane represents a structural transition between dimethoxymethane and bis(methylthio)methane and can also serve as a model of thioacetal segment in the glycosides in which the ring or glycosidic oxygen is substituted by sulphur. If position of methyl group (during rotation around one of the central bonds C—O (C—S) in MTMM is fixed in antiperiplanar or synclinal position, the rotation around the other central bond C—S (C—O) characterizes the rotation around C(1)—S(1) (C(1)—O(1)) bonds in β- or α-D-1-thiopyranosides (5-thiopyranosides) (Fig. 1). The molecules containing a 1,3-dioxa segment are characterized by distinct stabilization of the synclinal position as compared with the anti-

⌊MMT/

periplanar position, which is called anomeric or *exo*-anomeric effect. These effects are smaller in 1,3-dithia segment. One of the aims of investigation of stereochemistry of methoxy(methylthio)methane was thus determination of changes in geometry and magnitude of the anomeric and exo-anomeric effects due to substitution of oxygen atom by sulphur in the acetal segment.

RESULTS AND DISCUSSION

The model and calculation method. The potential energy of rotation around the central bonds C—O and C—S in methoxy(methylthio)methane, characterized by the angles Θ and Φ, respectively (Fig. 1), was studied by the PCILO semiempirical

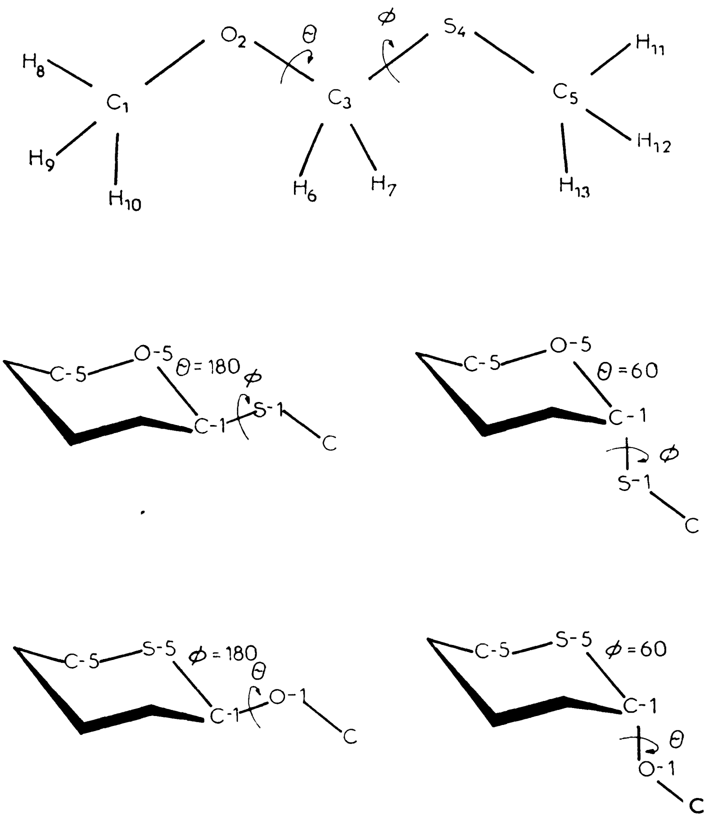

FIG. 1

Schematic representation of methoxy(methylthio)methane — a model compound for methyl β-D- and methyl α-D-1-thiopyranosides and 5-thiopyranosides quantum-chemical method[4]. For the calculation of two-dimensional map the methyl hydrogen atoms were in staggered position, and the geometry was constant. For the calculations of the map and its cross sections the angles were varied by 10° and 5° intervals, respectively. The following geometry parameters were used: bond length C_1—O_2 = 143, C_3—O_2 = 141, C—S = 180, and C—H = 110 pm; bond angle COC = 112, OCS = 112, CSC = 99·6, and HCO = HCS = 109·46°. The geometry of the stable conformers obtained by the PCILO method was optimized by the MNDO semiempirical quantum-chemical method using the Davidon–Fletcher–Powell algorithm for energy minimization[5,6]. The energies thus obtained were used as energies of the isolated molecule in the calculation of solvent effect. The Gibbs solvation energy, in this approach, is composed of three contributions: cavity (G_{cav}), electrostatic (G_{elst}), and dispersion (G_{disp}), and it was described in our previous reports[7,8] giving also all necessary solvent parameters for calculation of the individual contributions. The parameters characterizing the individual MMTM conformers were calculated by the MNDO method except for the refractive index for which the value 1·4432 of ethoxy(ethylthio)methane[9] was used.

Map of conformational energies. As in MMTM there are two axes of internal rotation connected with rotational isomerism, we have five possible conformers: antiperiplanar-antiperiplanar (ap,ap), antiperiplanar-synclinal (ap,sc), synclinal-antiperiplanar (sc,ap), synclinal-synclinal (sc,sc), and -synclinal-synclinal (-sc,sc), the two terms relating to the rotations around the C—O (Θ angle) and C—S (Φ angle) bonds, respectively. Out of these conformers the (ap,ap) only is non-degenerated, whereas each of the other conformers is twice degenerated. The map of conformational energies calculated by the PCILO method for an isolated MMTM molecule and obtained by rotation around the C—O and C—S bonds is given in Fig. 2. The map shows nine minima corresponding (due to symmetry reasons) to the five above-mentioned conformers. In DMM and BMTM, whose (sc,ap) conformers are identical with (ap,sc), only three different conformers were found, the fourth structure (-sc,sc) being not connected with any energy minimum at the hypersurface for sterical reasons. In MMTM the energy minimum is observed in the region close to this conformer and corresponding to (-ac,sc). The PCILO method predicts the (sc,sc) or (-sc,-sc) conformers to be the most stable, their methyl groups being oriented at opposite sides with respect to the O—C—S plane. The further conformer of the (ap,sc) or (ap,-sc) type is less stable by 1·05 kJ mol^{-1}. Then follows the (sc,ap) or (-sc,ap) conformer with the energy higher then that of (sc,sc) by 1·65 kJ mol^{-1}. The (-ac,sc) or (ac,-sc) conformer has the energy higher than the absolute minimum by 3·25 kJ mol^{-1}. The last minimum at the energy hypersurface belong to the (ap,ap) conformer with the energy 5·47 kJ mol^{-1} above the absolute minimum. As the PCILO conformational energies of MMTM were computed with constant geometry, we only used them for qualitative description of the conformational behaviour of the thioacetal segment and for comparison with analogous calculations for dimethoxymethane. For quantitative discussion of the influence of substitution of oxygen atom by sulphur and solvent effect on stability of the conformers, for anomeric and *exo*-anomeric effects we used the energy values calculated by gradient optimization of bond angles and bond lengths in the terms of the MNDO method.

A better representation of the character of rotation around the C—O and C—S bonds in MMTM is given in Fig. 3 which shows the sections through the conformational hypersurface involving all the minima. They are curves of relative energies (with respect to the energy of the (sc, sc) conformer) for the rotation around the C—O or C—S bonds, that angle being kept constant which characterizes the rotation around the other bond. The solid lines describe the rotation around the C—O bond

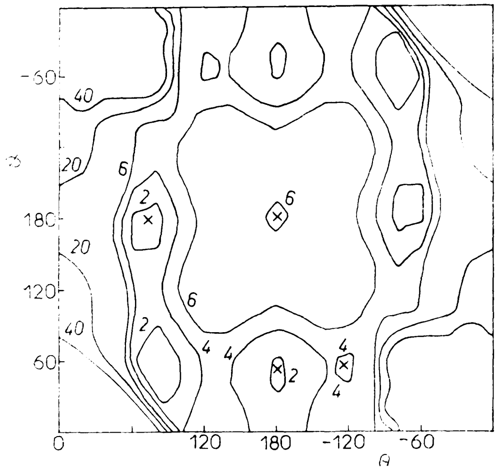

FIG. 2

Map of relative conformational energies of rotation around the central C—O and C—S bonds in methoxy(methylthio)methane calculated by the PCILO method (the energy contours are in kJ mol^{-1}). The cross denotes positions of the five minima

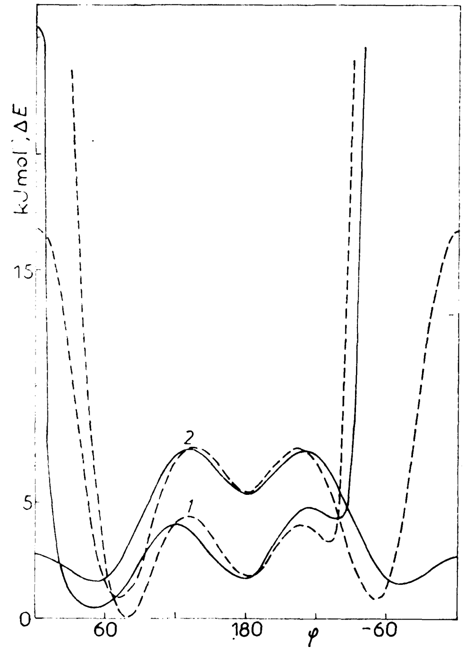

FIG. 3

Cross sections of the potential energy hypersurface of rotations around the C—O bond (solid line) with $\Phi = 60°$ (curve *1*) and $\Phi = 180°$ (curve *2*) and around the C—S bond (dashed line) with $\Theta = 60°$ (*1*) and $\Theta = 180°$ (*2*) calculated (in kJ mol^{-1}) by the PCILO method for methoxy(methylthio)methane (the value of the Φ angle being fixed at 60 or 180°) and correspond to the model of rotation in α- and β-D-5-thiopyranosides. The dashed curves describe the rotation around the C—S bond (the value of the Θ angle being fixed at 80° or 180°), modelling thus the rotation in α- and β-D-1-thiopyranosides. The courses of the rotational energy are similar to those of hydroxymethanethiol $HOCH_2SH$ calculated by the *ab initio* method in the STO-3G base[10]. With respect to the substitution of methyl group by hydrogen, of course, the energy differences between the individual conformers are different. Figure 3 indicates different character of the rotations around the C—S and C—O bonds which suggests different conformational behaviour of the glycosidic bond in 1-thio- and 5-thiosaccharides. When compared with dimethoxymethane, the rotational barriers of methoxy(methylthio)methane in synclinal position are greater, this difference being more distinct in the case of the C—O bond. On the contrary, the barriers to the transition from synclinal to antiperiplanar position are smaller. In contrast to DMM, MMTM shows a minimum in the (-ac, sc) region which is more stable than the (ap, ap) conformer. When expressing the potential energy curve of the rotation for Θ or Φ = 180° in terms of the Fourier series $V(\varphi) = V_1/2\ (1 - \cos \varphi) + V_2/2\ (1 - \cos 2\varphi) + V_3/2\ (1 - \cos 3\varphi)$, we obtained the following values of the coefficients V_i (in kJ mol^{-1}): For the rotation around the C—O bond $V_1 = -3{\cdot}94$, $V_2 = -9{\cdot}26$, $V_3 = -7{\cdot}12$. For the rotation around the C—S bond $V_1 = 5{\cdot}45$, $V_2 = 0{\cdot}31$, $V_3 = -2{\cdot}53$. The values of the V_3 coefficient characterize the values of the intrinsic torsional potential around the given bond and can be used in calculations of the conformational energies by the potential methods. In DMM the coefficient V_3 calculated from the CNDO curve[11] of the rotation has the value $-3{\cdot}8$ kJ mol^{-1}.

The MNDO *structure of the conformers.* Energy, geometry, and electron distribution of the individual minima optimized by the MNDO method are presented in Table I. The stability order of the conformers is the same as in the PCILO method, however, the energy differences are not. The highest energy is connected with the plane antiperiplanar arrangement of the C—O—C—S—C skeleton – the (ap,ap) conformer with the energy greater than the overall minimum by 17·2 kJ mol^{-1}. This minimum corresponds to the (sc,sc) conformer formed from (ap,ap) by rotation around the C—O and C—S bonds by about 101° and 112°, respectively. Interestingly, the values of Θ and Φ angles of the rotation around the C—O and C—S bonds are not the same, the higher value being (surprisingly) that of the Θ angle characterizing the rotation around the C—O bond. This fact can also be observed with further conformers, (ap,sc) and (sc,ap), whose energies are higher than that of (sc,sc) by 7·2 and 9·6 kJ . . mol^{-1}, respectively. Even after the optimization there remained another one in the region (-ac,sc) with the energy lower than that of (ap,ap) conformer by 5·6 kJ mol^{-1}. Taking into account the differences between methoxy(methylthio)methane and hydroxymethanethiol, we can compare quantitatively our results with the *ab initio*

(STO-3G) calculations[10]. The relative energies of hydroxymethanethiol conformers (sc,ap), (ap,sc), and (ap,ap) (related to (sc,sc)) calculated by the *ab initio* method with the optimized C—O and C—S bonds and O—C—S angle are 4·86, 11·8, and 16·6, respectively, being 2·76, 9·79, and 14·1 kJ mol^{-1}, respectively, in the case of standard geometry. The authors do not give the energy of the fifth conformer, although from the sections through the conformational map it follows that there exists a (-sc,sc) conformer whose energy is higher than that of (sc,sc) by about 8 kJ . . mol^{-1}.

The calculated values of the central C—S bond length fall within the region 175·5 to 184·6 pm observed with thiosaccharides[12]. The $S\text{-}CH_3$ bond lengths is shorter by about 1·5 – 4 pm. The both C—O bonds have the same length within the interval 138·0 to 142·9 pm observed with glycosides[13]. The OCS bond angle shows similar coupling with conformation of the thioacetal segment to that observed with DMM and BMTM[3,14] and is connected with the conformational dependence of interaction of lone electron pairs[14]. Lower values of this angle are seen in the conformations with antiperiplanar positions, *i.e.*, those corresponding to β anomeric configurations and, on the contrary, its values increase with synclinal orientations corresponding to α anomeric configuration in D series of thiosaccharides.

TABLE I

Values of MNDO energy E (in kJmol^{-1}), dipole moment (in 10^{30} Cm), ionisation potential I (in eV), net charges Q (in 10^3 e) and selected geometrical parameters (angles in degrees, lenghts in pm) of stable conformers of methoxy(methylthio)methane

Values	(sc,sc)	(ap,sc)	(sc,ap)	(—ac,sc)	(ap,ap)
E	—102 106·76	—102 099·58	—102 097·18	—102 096·08	—102 089·32
I	10·20	10·11	10·10	10·14	10·04
μ	3·0	7·4	7·9	9·7	10·0
$Q(C_1)$	217·2	221·4	216·0	220·3	219·3
$Q(O_2)$	—351·6	—358·3	—331·5	—345·8	—335·5
$Q(C_3)$	203·5	195·3	211·9	201·2	198·8
$Q(S_4)$	—207·8	—139·5	—199·3	—170·0	—118·0
$Q(C_5)$	54·9	45·5	50·0	41·8	33·0
$r(C_1—O_2)$	138·5	139·2	138·2	138·7	138·9
$r(O_2—C_3)$	140·7	140·5	140·7	140·5	140·6
$r(C_3—S_4)$	176·2	175·0	177·2	176·1	176·1
$r(S_4—C_5)$	173·4	173·5	173·3	173·2	173·5
$\alpha(C_1—O_2—C_3)$	121·4	120·1	121·5	121·6	119·6
$\alpha(O_2—C_3—S_4)$	114·5	110·4	110·6	112·4	105·9
$\alpha(C_3—S_4—C_5)$	109·0	109·1	106·4	109·4	105·4
Θ	79	176	79	—116	180
Φ	68	63	182	84	180

Magnitude of dipole moment of the given conformer is – in principle – determined by mutual orientation of the two (C—O—C and C—S—C) segment dipoles. From analogy with dimethyl ether and dimethyl sulphoxide, the above segments can be ascribed the dipole values 5·3 . 10^{30} and 4·8 . 10^{30} Cm, respectively, which can be used for qualitative comparison with the calculated dipole moments. In the (ap,ap) conformer the dipoles of the both segments lie parallel and the dipole moment is maximum (10 . 10^{30} Cm). This value agrees with the qualitative assessment from the vector resultant of the above-mentioned segment dipoles. Every rotation of the methyl group from ap to sc position lowers the net dipole moment, the lowest value (3 . 10^{30} Cm) being that of the (sc,sc) conformer. In accordance with the electronegativity difference the oxygen atom is more negative that sulphur. All three carbon atoms carry positive charges, that at S—CH_3 carbon atom being more negative. In analogy with DMM, delocalization of the lone electron pairs is greatest in (ap,ap) and smallest in (sc, sc) conformer[14]. Hence, in the (ap,ap) conformation oxygen and sulphur should have the lowest negative charges, and the central carbon atom should have the smallest positive charge, and, on the contrary, sulphur and oxygen atoms of the (sc,sc) conformation should be the most negative, and the carbon atom should have the most positive charge. Table I shows the existence of this coupling between the charge distribution of the O—C—S segement and its conformation, though not as distinct as in DMM and BMTM because of electronegativity difference between oxygen and sulphur.

Solvent effects on the conformation equilibria. The calculated energies of the individual conformers of the isolated MMTM molecule indicate that the equilibrium ratio of the four conformers: (sc,sc), (ap,sc), (sc,ap), and (-ac,sc) is 92 : 5 : 2 : 1, whereas the fifth conformer – (ap,ap) – is absent. Table II gives the calculated effects of medium on the conformation equilibrium for 13 solvents, and the values presented show that population of the individual MMTM conformers depend on nature of the medium. Increasing solvent polarity increases the proportion of the conformers with higher dipole moment, *i.e.* those with antiperiplanar orientation of the methyl groups. In contrast to DMM and BMTM, however, the population of (ap,ap) conformer will not reach 1 per cent even in water. This fact is due to the great energy difference in the isolated state which cannot be lowered by the solvent stabilization, although it is the greatest of all the conformers. Analysis of the individual contributions to the solvation energy shows that the contribution of electrostatic interactions exhibits the greatest conformational dependence. This situation is identical to that of DMM and BMTM, the electrostatic solvent–solute interactions being decisive for the changes in the conformer proportions accompanying the changes of medium, and the other two contributions (cavity and dispersion) affect the total balance but insignificantly.

Direct comparison of the calculated equilibrium composition with experimental

TABLE II

The calculated relative, with respect to (sc,sc), Gibbs energies ΔG (in kJmol^{-1}) and molar fractions x_i of methoxy(methylthio)methane conformers at 298·2 K with mean dipole moment (in 10^{30} Cm) in isolated state and in solution

Values	ΔG_i				x_i					$\langle\mu\rangle$
	(sc,ap)	(—ac,sc)	(ap,sc)	(ap,ap)	(sc,sc)	(sc,ap)	(—ac,sc)	(ap,sc)	(ap,ap)	
Isolated molecule	9·6	10·7	7·2	17·5	91·8	1·8	1·2	5·0	0·0	1·1
Hexane	9·5	10·3	7·1	17·3	91·3	2·0	1·4	5·2	0·0	1·1
1,4-Dioxane	9·5	10·1	7·1	17·3	91·2	2·0	1·6	5·2	0·0	1·1
Tetrachloromethane	9·5	10·1	7·1	17·4	91·2	2·0	1·6	5·2	0·0	1·1
Benzene	9·4	10·0	7·0	17·2	90·9	2·0	1·6	5·4	0·0	1·0
Carbon disulfide	9·4	9·8	7·0	17·2	90·8	2·0	1·7	5·4	0·0	1·1
Chloroform	9·0	9·3	6·7	16·5	89·5	2·4	2·1	6·0	0·0	1·2
Pyridine	8·7	8·8	6·5	16·0	88·3	2·6	2·5	6·4	0·0	1·2
Acetone	8·7	8·7	6·4	16·0	88·0	2·6	2·6	6·7	0·0	1·2
Ethanol	8·3	8·1	6·1	15·5	86·2	3·0	3·3	7·4	0·0	1·2
Methanol	7·7	7·2	5·6	14·6	83·0	3·7	4·6	8·7	0·1	1·3
Acetonitrile	8·0	7·6	5·8	15·1	84·5	3·4	3·9	8·1	0·1	1·3
Dimethyl sulfoxide	8·3	8·1	6·1	15·5	86·2	3·0	3·3	7·4	0·1	1·2
Water	5·4	3·4	3·7	11·1	62·6	7·1	15·9	14·1	0·4	1·8

data is not possible. Structurally similar to MMTM are 2-alkylthiotetrahydropyranes for which data are available[15] about influence of medium on the axial-equatorial equilibrium. In this case we compare the conformer proportions with changes of the Θ angle (C—O bonds) from synclinal to antiperiplanar position. From the NMR measurements[15] it follows that 2-methylthiotetrahydropyrane in non-polar solvent (CCl_4) exists in the axial form (about 69%), corresponding to the (sc,sc) and (sc,ap) conformers of MMTM, and in the equatorial form (about 31%), corresponding to the (ap,sc) and (ap,ap) conformers of MMTM, the dipole moment being $5{\cdot}1 \,.\, 10^{30}$ Cm. In methanol and acetonitrile the proportion of axial form decreases to 54 and 50%, respectively. Table II reveals that the (sc,sc) conformer is much more populated in MMTM than it would be in the cyclic analogue, which can be due, at least partially, to the presence of the ring and its interactions with the methylthio group.

Anomeric and exo-anomeric effects. The values of the Gibbs energies given in Table II for various solvents enable an assessment of magnitude of the anomeric and *exo*-anomeric effects in thioglycosides. For the present purpose and with respect to the crude approximation we shall use the following energy differences (Fig. 1) for determination of values of the anomeric (AE) and exo-anomeric effects (EAE). For the anomeric effect in 1-thioglycosides $AE_1 = \Delta G(\text{ap,sc}) - \Delta G(\text{sc,sc})$, in 5-thioglycosides $AE_5 = \Delta G(\text{sc,ap}) - \Delta G(\text{sc,sc})$. For the exo-anomeric effect in 1-thioglycosides (different values must be considered for the α and β anomeric configurations[7]) $EAE_1^{\alpha} = \Delta G(\text{sc,ap}) - \Delta G(\text{sc,sc})$, $EAE_1^{\beta} = \Delta G(\text{ap,ap}) - \Delta G(\text{ap,sc})$, and for 5-thioglycosides $EAE_1^{\alpha} = \Delta G(\text{ap,sc}) - \Delta G(\text{sc,sc})$, $EAE_2^{\beta} = \Delta G(\text{ap,ap}) - \Delta G(\text{sc,ap})$. Values of the anomeric and *exo*-anomeric effects can be calculated very simply from values of Table II. Magnitude of AE in 1-thioglycosides decreases from 7·2 (the isolated molecule) to 3·7 (in water). The corresponding change for 5-thioglycosides is from 9·6 to 5·4 kJ mol^{-1}. The analogous change of EAE in 1-thioglycosides in α configuration is from 9·6 to 5·4, in β configuration from 10·3 to 7·4, in 5-thioglycosides in α configuration from 7·2 to 3·7, and in β configuration from 7·9 to 5·7 kJ mol^{-1}. Hence, the character of solvent effect on magnitude of the anomeric and *exo*-anomeric effects is, qualitatively, the same as that observed with 2-methoxytetrahydropyrane[7]. Therefore, it can be stated that in the case of thioacetal segment, too, the electrostatic solute-solvent interactions act against the intramolecular electrostatic interactions and, hence, weaken magnitude of the two effects.

As the AE and EAE values were determined from an acyclic model and, for simplicity, the most stable conformer of the given form of thiosaccharides only was considered, the above values only represent a qualitative assessment of the real values of thioglycosides. For a more quantitative comparison of influence of the substitution of oxygen atom by sulphur in the glycosides on magnitude of the anomeric and *exo*-anomeric effects, as well as further consequences for their conformational behaviour, it will be necessary to study the cyclic analogues.

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