J. Am. Chem. Soc. **1980**, *102*, 6929-6936

Theoretical Studies on the Conformation of Saccharides. 3. Conformational Properties of the Glycosidic Linkage in Solution and Their Relation to the Anomeric and Exoanomeric Effects[1]

Igor Tvaroška*[2a] and Tibor Kožár[2b]

Contribution from the Institute of Chemistry, Slovak Academy of Sciences, 809 33 Bratislava, and Institute of Neurobiology, Slovak Academy of Sciences, 040 01 Košice, Czechoslovakia.
Received February 8, 1980

Abstract: The conformational equilibria of 2-methoxytetrahydropyran (MTHP), a model for methyl aldohexopyranosides, has been theoretically studied in 16 solvents. The stability of chair conformers of MTHP bearing an axially (A-MTHP) and an equatorially (E-MTHP) oriented methoxyl group has been compared by using the continuum reaction field method in conjunction with quantum mechanical calculation. The energy of the isolated molecule has been calculated by the PCILO quantum chemical method while the geometry of every stable conformer was optimized by taking into account 21 degrees of freedom. The solvation energy consists of electrostatic, dispersion, and cavity terms which have been determined from the calculated properties of the solute and physicochemical properties of the solvents. The effect of the individual contribution to the solvation energy upon the shape of the conformational maps and the potential of rotation around the C(1)–O(1) bond have been investigated. The calculated abundance of A-MTHP and E-MTHP at equilibrium, the average dipole moments, the coupling constants, and the magnitude of the anomeric (AE) and exoanomeric (EAE) effects are in excellent agreement with the experimental data available concerning the equilibrium of 2-alkoxytetrahydropyrans in solution. The calculated environmental dependence of the magnitude of the anomeric and exoanomeric effect is discussed from the point of view of the currently acknowledged nature and importance of these phenomena.

I. Introduction

Owing to the wide occurrence and extreme importance in nature of glycosidically linked substances considerable attention has been currently focused at the properties of the glycosidic linkage not only from the experimental but also from the theoretical point of view. Anomeric and exoanomeric effects have been studied on several acyclic[3-10] and cyclic[11-13] models representing structural segments of saccharides. Quantum chemical methods of various approximation have been used for this purpose. The results of these calculations are consistent with the AE and EAE assumption according to which, during rotations around C–O bonds, synclinal (sc) position is preferred to the antiperiplanar (ap) position. They also reproduce successfully geometrical differences and restricted rotations around the exocyclic C(1)–OR bond as observed by means of X-ray and neutron diffraction studies on methyl glycosides, oligosaccharides, and polysaccharides[7,8,13,14] in their solid state.

In previous works, however, conformational properties of molecules were studied in the free-space approximation, and, therefore, these results are inapplicable to many chemical and biochemical processes where glycosidically linked substances act in solution. Our recent study concerning the effect of the medium[15] (carbon tetrachloride and water) upon conformational properties of dimethoxymethane indicated qualitatively that in highly polar solvents ap conformations may be preferred. Also, it has been shown by analyses of NMR coupling constants[16-20] of various 2-alkoxytetrahydropyrans that at the equilibrium the population of the axial conformer depends upon the solvent used in the experiments. It follows from these observations that the difference in the free energy between A-MTHP and E-MTHP ranges from 3.0–3.9 kJ/mol in low dielectric media to 0.2 kJ/mol in water which corresponds, respectively, to 77–83 and 52% occurrence of A-MTHP. In other words, an increase of the medium polarity results in the increased abundance of ap forms of MTHP.

In this work a method is presented by means of which it is possible to take into account the effect of media upon the conformational properties of glycosidic structures. The method is consistent with the basic philosophy, elaborated by Sinanoglu et al.[21] and applied for the first time by Beveridge et al.,[22] considering the solvent as a dielectric continuum. It differs from previous works that used a continuum model in the means of expressing the individual contributions to the solvation energy. The relationships between the results obtained for an isolated molecule, the calculated geometry of the conformers, and the comparison with the geometry of the corresponding saccharides in the crystalline state were discussed in our previous work.[13] Here, we focus our attention on a comparison of the theoretical results taking into account solvent effects with experimental data on the conformational equilibrium of MTHP. The effect on individual contributions upon the change of the conformational equilibrium of MTHP, compared with an isolated molecule, will also be analyzed. On the basis of free energies calculated for individual conformers, the molar fractions of MTHP conformers x_i, average dipole moment μ, and coupling constants $^3J_{HH}$ and $^3J_{CH}$ in various

---

(1) For parts 1 and 2 of this series, see ref 12 and 13.

(2) (a) Institute of Chemistry. (b) Institute of Neurobiology.

(3) G. A. Jeffrey, J. A. Pople, and L. Radom, *Carbohydr. Res.*, **25**, 117–131 (1972).

(4) G. A. Jeffrey, J. A. Pople, and L. Radom, *Carbohydr. Res.*, **38**, 81–95 (1974).

(5) I. Tvaroška and T. Bleha, *J. Mol. Struct.*, **24**, 249–259 (1975).

(6) I. Tvaroška and T. Bleha, *Tetrahedron Lett.*, 249–252 (1975).

(7) D. G. Gorenstein and D. Kar, *J. Am. Chem. Soc.*, **99**, 672–677 (1976).

(8) G. A. Jeffrey, J. A. Pople, J. S. Binkley, and S. Vishveshwara, *J. Am. Chem. Soc.*, **100**, 373–379 (1978).

(9) S. Vishveshwara, *Chem. Phys. Lett.*, **59**, 30–32 (1978).

(10) S. Wolfe, M.-H. Whangbo, and D. J. Mitchell, *Carbohydr. Res.*, **69**, 1–26 (1979).

(11) Yu. A. Zhdanov, R. M. Minyaev, and V. I. Minkin, *J. Mol. Struct.*, **16**, 357–364 (1973).

(12) T. Kožár and I. Tvaroška, *Theor. Chim. Acta*, **53**, 9–19 (1979).

(13) I. Tvaroška and T. Kožár, in preparation.

(14) S. Perez and R. H. Marchessault, *Carbohydr. Res.*, **65**, 114–120 (1978).

(15) I. Tvaroška and T. Bleha, *Collect. Czech. Chem. Commun.*, **45**, 1883–1895 (1980).

(16) G. O. Pierson and O. A. Runquist, *J. Org. Chem.*, **33**, 2572–2578 (1968).

(17) C. B. Anderson and D. T. Sepp, *Tetrahedron*, **24**, 1707–1716 (1968).

(18) E. L. Eliel and C. A. Giza, *J. Org. Chem.*, **33**, 3754–3758 (1968).

(19) A. J. de Hoog, H. R. Buys, C. Altona, and E. Havinga, *Tetrahedron*, **25**, 3365–3375 (1969).

(20) R. V. Lemieux, A. A. Pavia, J. C. Martin, and K. A. Watanabe, *Can. J. Chem.*, **47**, 4427–4439 (1969).

(21) O. Sinanoglu in "Molecular Association in Biology", B. Pullman, Ed., Academic Press, New York, 1968, p 427–445.

(22) D. L. Beveridge, M. M. Kelly, and R. J. Radna, *J. Am. Chem. Soc.*, **96**, 3769–3778 (1974).

0002-7863/80/1502-6929$01.00/0

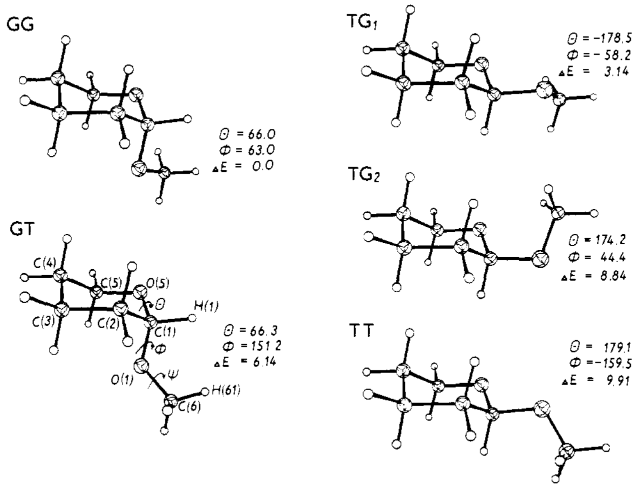

Figure 1. Molecular structure and numbering of the atoms in the most stable MTHP conformers resulting from the rotation around the glycosidic linkage. The notation of conformers follows from θ and Φ values (gauche = G, trans = T) which characterize the conformation of the C(5)-O(5)-C(1)-O(1)-C(6) segment. The relative energy values, ΔE (in kJ/mol), for an isolated molecule were calculated by the PCILO method.

solvents will be determined. Finally, the effect of solvents upon the magnitude of the anomeric and exoanomeric effect will be discussed.

II. Model and Method of Calculation

For a study on the effect of solvents upon conformational properties of the glycosidic linkage, 2-methoxytetrahydropyran was chosen as the model compound. The five most stable MTHP conformers in the $^4C_1$ conformation are shown in Figure 1. The molecular geometry of these conformers was obtained by optimalization of 21 internal geometrical parameters, using the PCILO method.[23] The shape of the ring and calculated internal geometrical parameters have been previously discussed in detail.[13] (Cartesian coordinates for all MTHP conformers will be sent upon request.) The notation of the individual conformers is based on the values of the dihedral angles θ and Φ describing the conformation of the acetal segment C(5)-O(5)-C(1)-O(1)-C(6) in MTHP.[12] In this way, e.g., GG means that the angles θ and Φ are close to those in an sc or gauche (G) conformation etc. The rotation around the glycosidic linkage is described by angles Φ and Ψ, and the angle θ determines an axial or equatorial orientation of the methoxyl group.[12] We have studied the effect of the solvent upon the conformational properties of glycosidic linkage in A-MTHP and E-MTHP by means of two-dimensional Φ and Ψ conformational maps and sections through them which were calculated in the interval 10°. Individual conformations of MTHP needed for calculations of the conformational energy maps have been constructed for an A-MTHP molecule in its $^4C_1$ form and for E-MTHP in the corresponding $^1C_4$ form.[12] Due to the symmetry of MTHP for a given anomer (A-MTHP or E-MTHP) the change of $^4C_1$ form to $^1C_4$ form results merely in opposite sign of the angle Φ. For example, the TG$_1$ conformer in the $^4C_1$ and $^1C_4$ forms shows $\Phi = -58.2°$ and $\Phi = +58.2°$, respectively. In view of a great amount of calculations, when the conformational maps were constructed, constant geometry was used which for A-MTHP and E-MTHP corresponded to the optimized geometries GG and TG$_1$, respectively. When the equilibrium distribution of MTHP conformers was evaluated quantitatively, the geometry corresponding to the optimized geometry of every individual conformer was used.

When the continuum model is used, the total conformational free energy of the solute (the parameters that characterize the solute will be noted by an index u) in a particular solvent (index v) is divided into the free energy of the solute molecule in the free-space approximation G_u and intermolecular solvent–solute interactions G_{solv}.

$$G = G_u + G_{solv} \qquad (1)$$

The intrinsic free energy of the isolated solute molecule in a given conformation has been calculated by the semiempirical PCILO method.[23] Here we made an implicit assumption that we compare conformations whose rotational entropy differences are not significant.

For solvent–solute interactions the free energy, G_{solv}, can be partitioned into the contributions in eq 2, where G_{cav} is a term

$$G_{solv} = G_{cav} + G_{elst} + G_{disp} + G_{spec} \qquad (2)$$

representing the energy required in a given solvent to create a solvent cavity of sufficient size to accommodate a solute molecule and G_{elst}, G_{disp}, and G_{spec} characterize the contributions of electrostatic, dispersion, and specific interactions of the solute molecule with the solvent. We shall assume in this work, as usual when using a continuum model, that specific interactions are conformationally independent, i.e., that G_{spec} is a constant which does not effect the conformational equilibrium of MTHP. Specific interactions, however, will be important when such absolute energetical values are compared, as for instance the enthalpy of solution etc. For the other three terms in eq 2 several approximations, based on a procedure proposed by Sinanoglu[21] and used by Beveridge,[20] have been described in the literature (see ref 15 and papers cited therein). In this work, as briefly described below, the individual members in eq 2 will be expressed in a somewhat different way.

At a temperature T and a pressure P the calculation of the free energy required for the formation of a cavity (see eq 3) is based

$$G_{cav} = \left\{-\ln(1-y) + \left(\frac{3y}{1-y}\right)R_a + \left[\frac{3y}{1-y} + \frac{9}{2}\left(\frac{y}{1-y}\right)^2\right]R_a^2 + \frac{yP}{kT}\right\}RT \qquad (3)$$

on an expression taken from the Scaled Particule Theory (SPT) which has been successfully used in studies of thermodynamical properties of aqueous and nonaqueous solutions,[24] where $y = 4\pi\rho a_v^3/3$ is the reduced number density and $R_a = a_u/a_v$ is a ratio of the radii of the hard sphere solute molecule (a_u) and of the solvent molecule (a_v) such that the cavity radius, a, is $a_u + a_v$. Constants R and k are common gas and Boltzmann's constants.

The electrostatic energy, G_{elst}, of the solute–solvent interactions was calculated according to Onsanger's theory of the reaction field as applied by Abraham.[25] The first two terms in eq 4 are the

$$G_{elst} = kx/(1 - lx) + 3hx/(5 - x) + bf[1 - \exp(-bf/16RT)] \qquad (4)$$

result of calculating the solute electric field including both the dipolar and quadrupolar contributions and the solute polarizability, and the third member is a so-called direct polar term obtained by a generalized integration of the solute dipolar and quadrupolar interactions with the solvent dipoles, where $k = \mu_u^2/a^3$, $h = q_u^2/a^5$ and $l = 2(n_u^2 - 1)/(n_u^2 + 2)$ and where μ_u, q_u, and n_u are solute dipole moment, quadrupole moment, and refractive index, respectively, $b = 4.35(T/300)^{1/2}(2^{3/2}/r_{uv}^3)(k + ha^2/r_{uv}^2)^{1/2}$, and parameter r_{uv} is the average distance of the separation of the molecules of the solvent from the solute molecule defined as the radius of the cavity divided by $2^{1/2}$, i.e., $r_{uv} = a/2^{1/2}$. The only parameter in eq 4 that characterizes the solvent is the dielectric constant, ϵ, which occurs in $x = (\epsilon - 1)/(2\epsilon + 1)$ and also in $f = [(\epsilon - 2)(\epsilon + 1)/\epsilon]^{1/2}$ for $\epsilon > 2$; when $\epsilon \leq 2$, $f = 0$.

The free energy of dispersion interactions takes into account both attractive and repulsive nonbonding interactions. A simplified

---

(23) S. Diner, J. P. Malrieu, F. Jordan, and M. Gilbert, *Theor. Chim. Acta*, **15**, 100–110 (1969).

(24) R. A. Pierotti, *Chem. Rev.*, **76**, 717–726 (1976).

(25) R. J. Abraham and E. Bretschneider in "Internal Rotation in Molecules", W. J. Orville-Thomas, Ed., Academic Press, London, 1974, Chapter 13.

Table I. Physicochemical Parameters[24,28,31,32] of Pure Solvents Used for Calculations of G_{solv} According to Equations 2-5

solvent	ϵ	a_v, pm	y	$10^6 V_v$, m^3/mol	n_v	$10^{30}\alpha_v$, m^3/mol	I_v, eV
p-dioxan	2.21	201.5	0.262	78.90	1.4202	11.45	9.13
carbon tetrachloride	2.24	269.0	0.506	97.09	1.4574	10.49	11.47
benzene	2.28	263.0	0.513	89.40	1.4979	10.32	9.24
carbon disulfide	2.64	226.2	0.483	60.65	1.6241	8.57	10.08
tert-butylamine	4.43	279.0	0.620	88.40	1.3761	9.63	8.64
chloroform	4.81	195.0	0.226	82.73	1.4429	8.47	11.42
fluorobenzene	5.42	265.5	0.453	94.30	1.4684	10.28	9.20
tetrahydrofuran	7.58	234.0	0.420	76.90	1.4072	7.92	9.42
1-octanol	10.34	334.0	0.593	158.42	1.4275	16.14	10.00
pyridine	12.40	214.0	0.322	76.70	1.5075	9.55	9.30
acetone	20.70	239.5	0.468	74.05	1.3560	8.67	9.69
ethanol	24.55	218.0	0.445	58.69	1.3594	5.13	10.49
methanol	32.70	185.5	0.395	40.73	1.3265	3.26	10.84
acetonitrile	37.50	212.0	0.455	52.86	1.3416	4.41	12.20
dimethyl sulfoxide	46.68	246.5	0.530	71.30	1.4773	7.99	9.01
water	78.30	138.5	0.371	18.07	1.3325	1.47	12.60

formulation, based on a combination of London disperse equation and Born-type repulsion, can be derived following the work of Birge et al. (eq 5),[26] where α and I are molecular polarizability

$$G_{\mathrm{disp}} = -(1 - \delta)K_r\tfrac{3}{2}N_v\alpha_u\alpha_v\left(\frac{I_uI_v}{I_u + I_v}\right)r_{uv}^{-6} \qquad (5)$$

and ionization potentials. The value of the semiempirical constant K_r ranges from 0.2 to 0.7, and in our calculations the representative value 0.5 was used. The proportionality constant $(1 - \delta)$ converts energy to free energy. Halicioglu and Sinanoglu[27] have found that this proportionality is fairly constant (0.564) for both polar and nonpolar solvents. The number N_v of the nearest-neighbor solvent molecules surrounding the given conformer of a solute molecule was calculated for each conformer by dividing the effective volume of the accessible shell by the volume of the solvent molecule (eq 6). The effective radii of the solvents, a_{ef}, are defined

$$N_v = [(a_u + 2a_v)^3 - a_u^3]/a_{ef}^3 \qquad (6)$$

by the molar volume of the solvent molecule, V_v (Table I), $a_{ef}^3 = 3V_v/4\pi N_A$, where N_A is Avogadro's number.

All parameters characterizing the conformation of the solute molecules in eq 2–6, except $n_u = 1.4402$,[28] were calculated values. The radius of the hard-sphere solute was calculated from the surface, obtained from the geometry of the individual conformers optimized by the PCILO method by using a modified Herman's program.[29,30] The contribution of hydrogen atoms was incorporated into that of carbon atoms by enlarging the van der Waals radii of the latter to 200 pm. In this way about 75% of CPU time was saved while the difference in the hard-sphere solute diameter values did not exceed 3%. The application of the described program is justified by the fact that the calculation of the molecular surface according to program MOLAREA[29] (QCPE program No. 225) required in the case of MTHP longer CPU time than did the calculation of the energy by the PCILO method. In the applied simplification the change of the orientation of the hydrogen atoms, resulting from the rotation of the methyl group characterized by the angle Φ, has no effect upon the cavity radius. However, due to the symmetry of the methyl group this change is negligible and does not affect the results obtained. The dipole and quadrupole moments were calculated by the PCILO method from the electron distribution, and the ionization potential was approximated by the energy of the highest occupied localized molecular orbital. The center of the spherical cavity was located always in the center of gravity of the molecule and the coordinate axes were oriented in the direction of the main axes of inertia moment. Since the quadrupole moment depends upon the choice of a particular coordinate system, it was always related to this coordinate system.

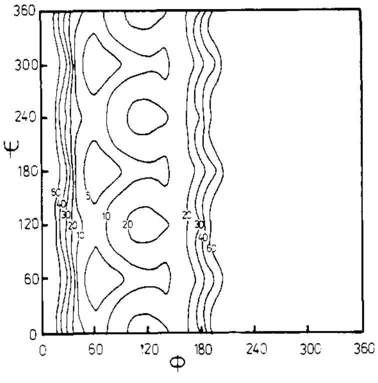

Figure 2. Conformational energy map of the total free energy, *G*, for A-MTHP–carbon tetrachloride (in kJ/mol).

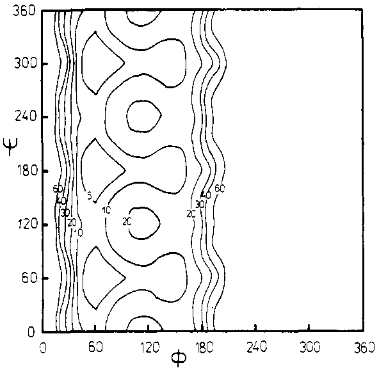

Figure 3. Conformational energy map of the total energy, *G*, for A-MTHP-water (in kJ/mol).

The calculations of G_{solv} have been carried out for a set of 16 representative solvents of different properties. The studied solvents include all those in which the conformational properties of 2-alkoxytetrahydropyrans have been experimentally studied.[16-20] The individual physicochemical parameters of solvents used in the calculations of G_{cav}, G_{elst}, and G_{disp} according to eq 2–6 were taken from the literature[24,28,31,32] and are given in Table I.

III. Results and Discussion

The Effect of Solvents upon (Φ, Ψ) Conformational Energy Maps. Figures 2 and 3 show contour conformational energy maps of A-MTHP in two selected solvents of considerably different

---

(26) R. R. Birge, M. J. Sullivan, and B. E. Kohler, *J. Am. Chem. Soc.*, **98**, 358–367 (1976).

(27) T. Halicioglu and O. Sinanoglu, *Ann. N.Y. Acad. Sci.*, **158**, 308–317 (1969).

(28) "Handbook of Chemistry and Physics", 55th ed., CRC Press, Cleveland, Ohio, 1974.

(29) R. B. Herman, *J. Phys. Chem.*, **76**, 2754–2759 (1972).

(30) S. C. Valvani, S. H. Yalkowsky, and G. L. Amidon, *J. Phys. Chem.*, **80**, 829–835 (1976).

(31) J. A. Riddick and W. B. Bunker, "Organic Solvents", 3rd ed., Wiley-Interscience, New York, 1970.

(32) A. A. Liabastre, Ph.D. Thesis, Georgia Institute of Technology, 1974.

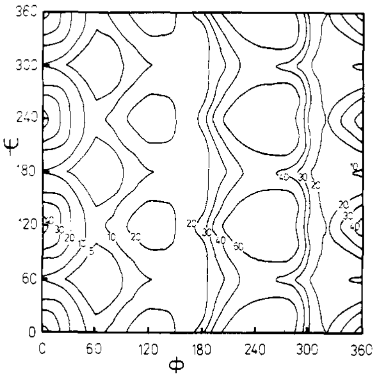

Figure 4. Conformational energy map of the total free energy, G, for E-MTHP–carbon tetrachloride (in kJ/mol).

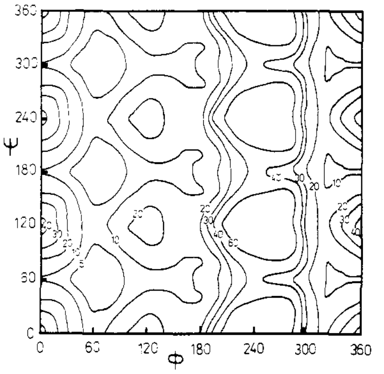

Figure 5. Conformational energy map of the total free energy, G, for E-MTHP–water (in kJ/mol).

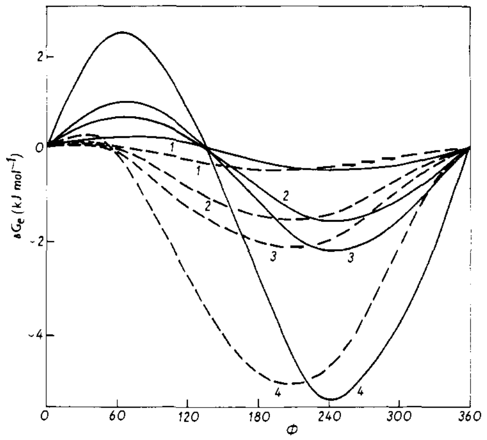

Figure 6. A section through conformational maps ($\Psi = 60°$) of electrostatic interactions, G_{elst} (in kJ/mol), for A-MTHP (full line) and E-MTHP (broken line) in (1) carbon tetrachloride, (2) acetone, (3) acetonitrile, and (4) water.

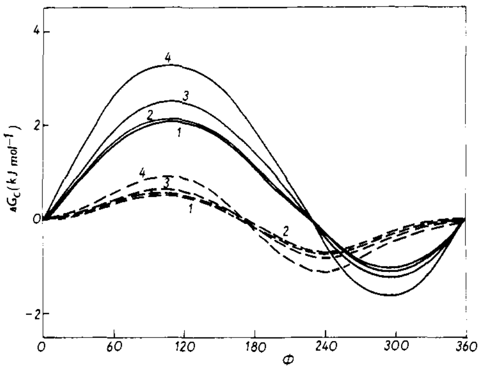

Figure 7. A section through conformational maps ($\Psi = 60°$) of cavity energies, G_{cav} (in kJ/mol), for A-MTHP (full line) and E-MTHP (broken line) in (1) carbon tetrachloride, (2) acetone, (3) acetonitrile, and (4) water.

character, carbon tetrachloride and water. The symmetry of the conformational surface in the direction of the coordinate Ψ, in both solvents and similar to the case of an isolated MTHP molecule, is caused by the symmetry of the rotating methyl group. The minima at 60, 180, and 300° in the direction Ψ can, therefore, be explained in terms of threefold rotation barriers around O(1)–C(6) bonds, and the same is valid for the maxima at 0, 120, and 240°. The same properties, as far as the symmetry is concerned, were observed also for conformational maps in all other solvents investigated. In addition to this general feature of all the maps, the one of A-MTHP indicates a considerably restricted rotation around the C(1)–O(1) bond. This is demonstrated by a narrow range of angle Φ (35–160°) in which the conformations are in the energy interval of 20 kJ/mol over the total minimum. The other conformations are of higher energy and, from sterical reasons, are unfavorable. In the range of (ap, sc) conformations, i.e., the GT conformer, a rather flat course of the energy of about 10 kJ/mol higher than that of the GG conformer can be observed for CCl_4 as the solvent. For water (Figure 3) the MTHP conformation map differs from the one in Figure 2 mainly in the range of (ap, sc) conformations. The GG conformer still remains the overall minimum but the number of conformations in the (ap, sc) range with the energy 10 kJ/mol over the GG conformer is considerably higher than that encountered in nonpolar carbon tetrachloride.

Figures 4 and 5 show the effect of solvents (CCl_4 and H_2O) in the case of E-MTHP. The obvious feature here, in contrast to the maps for A-MTHP, is a greater complexity of the two-dimensional conformational surface in the Φ direction, indicating the possibility of three ranges of energy minima (sc, sc), (ap, sc), and (−sc, sc), corresponding to TG_1, TT, and TG_2 conformers (Figure 1). The global minimum is the TG_1 conformer. The region of conformers of the relative energy 20 kJ/mol relative to the global minimum is considerably wider than that in the case of A-MTHP. In the case of water as the solvent the energies in the neighborhood of TG_2 and TT conformers are again lower.

A close look upon the shape and the change of the conformational maps (Figures 2–5) and the comparison with maps for an isolated MTHP molecule[13] shows only a relatively small alteration of the character of the maps as a result of the change of the solvent. The conformational maps of MTHP in solution preserve the symmetry of the maps observed for an isolated molecule in the direction of angle Ψ and show a limited rotation in the direction of angle Φ. In the latter case, however, with the increased polarity of the solvent the accessibility of the conformational space increases as well. The global minima in solution are the same as those for an isolated molecule, and they can be identified with the GG and TG_1 conformers which are, most frequently, found in crystal structures of mono- and polysaccharides.[7,8,13,14] The solvent effect manifests itself mainly in the change of energies of the individual stable conformers. Although it is obvious that the quantitative character of the conformational maps is influenced by the use of fixed geometries, they show that the GT and TT conformers are stabilized by the increased dielectrical constant of the solvent. The small changes in the shape of the maps and the role of the individual contributions of the solvation energy upon the change of the conformational behavior of MTHP in various solvents will be better understood after a detailed analysis of their conformational dependences.

The Importance of G_{solv} Contributions and Their Conformational Dependence. Molecular characteristics of MTHP depend only slightly on the rotation of the hydrogen atom of the methyl group (the value of angle Ψ). Therefore, when the conformational dependence of the individual contributions to G_{solv} (eq 3–5) and their relative importance are analyzed, it is easier to consider sections through conformational maps of the individual terms. Figures 6–9 show the course of the solvation energy and its individual contributions according to eq 3–5 for four selected solvents (CCl_4 = curve 1, acetone = curve 2, acetonitrile = curve 3, and water = curve 4).

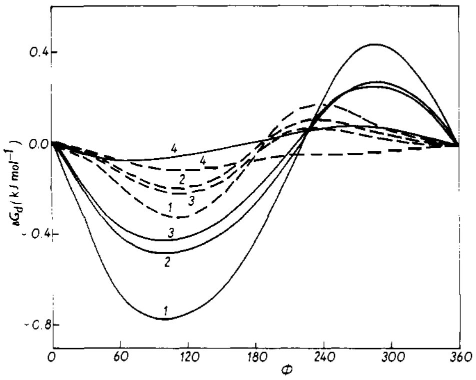

Figure 8. A section through conformational maps ($\Psi = 60°$) of dispersion interactions, G_{disp} (in kJ/mol), for A-MTHP (full line) and E-MTHP (broken line) in (1) carbon tetrachloride, (2) acetone, (3) acetonitrile, and (4) water.

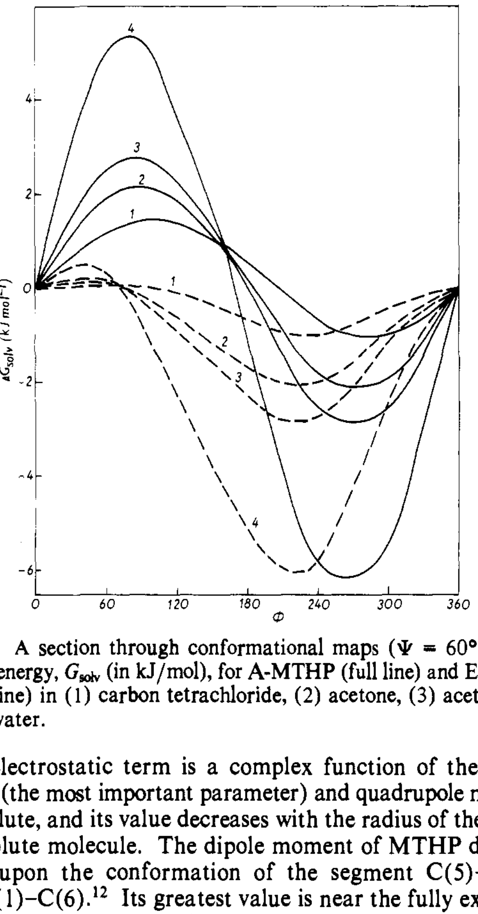

Figure 9. A section through conformational maps ($\Psi = 60°$) of the solvation energy, G_{solv} (in kJ/mol), for A-MTHP (full line) and E-MTHP (broken line) in (1) carbon tetrachloride, (2) acetone, (3) acetonitrile, and (4) water.

The electrostatic term is a complex function of the dipole moment (the most important parameter) and quadrupole moment of the solute, and its value decreases with the radius of the cavity of the solute molecule. The dipole moment of MTHP depends greatly upon the conformation of the segment C(5)–O(5)–C(1)–O(1)–C(6).[12] Its greatest value is near the fully extended form of this segment, i.e., for the TT conformer $\mu_{\mathrm{TT}} = 3.18$ D (1 D = 3.33×10^{-30} mAs), and the smallest value is for the GG conformer, $\mu_{\mathrm{GG}} = 0.28$ D. For the other conformers (GT, $\mathrm{TG_1}$, and $\mathrm{TG_2}$) the values of the dipole moments are similar, $\mu_{\mathrm{GT}} = 2.17$ D, $\mu_{\mathrm{TG_1}} = 2.13$ D, and $\mu_{\mathrm{TG_2}} = 2.36$ D. The electrostatic term follows approximately the conformational dependence μ_i with the rotation Φ (Figure 6). Since the highest values of dipole moments are observed for conformations in the range of ap values of Φ, these conformations will be in cases of the orientation of the methoxyl group in MTHP the most stabilized ones, and the stabilizations will be proportional to the increasing dielectrical constant of the solvent. In the case of $\mathrm{CCl_4}$ the stabilization is almost negligible, but for water the difference in the stabilization of the individual conformers amounts up to 8 kJ/mol. The stabilization of the conformations by electrostatic interactions is most pronounced in the range of $\Phi = 240°$ (Figure 6). These conformations are, however, due to the very unfavorable steric repulsion between the methyl group and methylene groups at C(2), C(3), and C(5). The explanation of this stabilization is rather simple. In these conformations the methyl group is very close to the ring and the overlapping of the atomic spheres characterized by van der Waals radii results in considerably smaller volume of these conformations, compared with the other ones. Since μ_i of these conformations are comparable with μ_i of GT, $\mathrm{TG_1}$, $\mathrm{TG_2}$, and TT conformers, in these regions the stabilization by electrostatic interactions will be most pronounced.

The cavity term (eq 3) depends on the ratio of the size of solvent and solute molecules and on the density of the solvent. In a given solvent this contribution is exclusively a function of the conformational dependences of the radius of the solute cavity. The cavity radia (expressed in pm) for the solute conformers are as follows: $a_{\mathrm{GG}} = 333.76$, $a_{\mathrm{GT}} = 334.12$, $\alpha_{\mathrm{TG_1}} = 335.05$, $a_{\mathrm{TG_2}} = 333.62$, and $a_{\mathrm{TT}} = 334.74$. Since the molecular volumes of conformers having the methyl group in the region of $\Phi = 240°$ are smaller (331–332.5 pm), these conformers will also be stabilized by the cavity term. The absolute value of this contribution to the solvation energy increases in the order: carbon tetrachloride, acetone, acetonitrile, water. The increase of the value of the cavity term corresponds to the magnitude of the surface tension of the solvent, commonly used in an alternative mode of calculation of the cavity term also used in our work on DMM.[15] The conformational dependence of the cavity term is about 5 kJ/mol (Figure 7).

Compared with the changes of the terms discussed above the conformational changes of dispersion interactions (Figure 8) are negligible. For the sake of clarity, in Figure 8 the scale of the energy ordinate is enlarged by the factor of 5, compared with those in Figures 6 and 7. The most pronounced change in the dispersion free energy is 1.2 kJ/mol in carbon tetrachloride and its course is opposite with respect to that of the cavity and electrostatic terms. In the case of other solvents the conformational dependence of this term of the solvation energy is less pronounced.

Since the dispersion term shows but a little conformational dependence, the determining factors of the conformational dependence of the solvation energy (Figure 9) are the effects of G_{elst} and G_{cav} contributions. The final dependence, however, results from the balance of all three contributions, although each of them contributes with a different weight proportion to the total energetical sum. In water the maximum change of the solvation energy is up to 11 kJ/mol. The final stabilization is most pronounced in the case of those conformers ($\Phi \approx 240°$) that are very unfavorable from the sterical point of view. Although compared to the sc orientations the stabilization in the case of water amounts to 11 kJ/mol, it is insufficient to overcome the considerable high energy of these conformations in the isolated state due to the steric repulsion. It decreases, however, the barrier separating the ap and sc conformers during the rotation around the C(1)–O(1) bond.

The Comparison of the Calculated Values with the Experimental Data for the Conformational Equilibrium of MTHP. Discussed above were the effect of solvents upon the conformational maps and the importance of the individual terms of the solvation energy upon the equilibrium of MTHP. For this purpose sections (for $\Psi = 60°$) through (Φ, Ψ) conformational maps were used. In the literature there is a relatively large number of data describing the equilibrium in various solvents of axial and equatorial forms of alkoxytetrahydropyrans.[16–20] Now, the experimental data obtained for the molar fraction of the axial form at the equilibrium, x_{A}, dipole moments, μ_i, and coupling constants, $^3J_{\mathrm{HH}}$ and $^3J_{\mathrm{CH}}$, will be compared with the calculated values based on the energies of the five most stable MTHP conformers (Figure 1), GG, GT, $\mathrm{TG_1}$, $\mathrm{TG_2}$, and TT, in their optimized geometry. The molar fractions (or probability of occurrence) of the ith conformer of MTHP were calculated according to the standard expression given in eq 7, where G_i is the free energy of the i conformer calculated

$$x_i = 100 \exp(-G_i/RT)/Q_\alpha \tag{7}$$

according to eq 2 and Q_α is the partition function of conformers MTHP, A-MTHP or E-MTHP (according to n in the summation n = 5, 2, or 3, respectively, given by eq 8). The free-energy

$$Q_\alpha = \sum_{i=1}^{n} \exp(-G_i/RT) \tag{8}$$

Table II. Calculated Molar Fractions x_i of GG, GT, TG_1, TG_2, and TT MTHP Conformers (for $T = 298.2$ K) and the Comparison of the Calculated and Experimental Molar Fractions x_A of the Axial MTHP Conformer in the Isolated State and in Solution

solvent	x_{GG}	x_{GT}	x_{TG_1}	x_{TG_2}	x_{TT}	x_A(calcd)	x_A(exptl)
isolated MTHP	70.80	5.95	19.95	2.00	1.30	76.75	
p-dioxan	67.44	6.63	21.80	2.34	1.79	74.07	77[f]
carbon tetrachloride	69.70	6.22	20.29	2.22	1.57	75.92	83,[a] 82,[b] 77.3,[c] 80,[d] 80.2[e]
benzene	69.58	6.31	20.25	2.27	1.58	75.90	82,[a] 82,[b] 80[d]
carbon disulfide	68.76	6.47	20.67	2.36	1.74	75.23	80[a]
tert-butylamine	69.32	6.66	19.78	2.51	1.74	75.98	
chloroform	63.38	7.35	24.17	2.68	2.42	70.73	71,[a] 78,[b] 77[d]
fluorobenzene	66.47	6.81	22.28	2.46	1.98	73.28	
tetrahydrofuran	64.42	7.27	23.31	2.68	2.31	71.69	
1-octanol	67.71	6.66	21.36	1.84	2.43	74.37	
pyridine	61.50	7.70	25.12	2.88	2.80	69.20	
acetone	62.59	7.65	24.16	2.91	2.69	70.24	72[a]
ethanol	60.70	8.01	25.10	3.09	3.09	68.72	65.5,[c] 67.9[e]
methanol	55.94	8.89	27.40	3.57	4.20	64.83	69,[a] 62.5,[c] 67.3,[e] 69,[f] 67[g]
acetonitrile	58.65	8.39	26.07	3.32	3.57	67.04	68,[a] 65,[b] 64.3,[c] 65,[d] 67,[e] 65[f]
dimethyl sulfoxide	61.18	7.98	24.69	3.12	3.03	69.16	74[a]
water	35.74	12.03	34.05	5.66	12.52	47.77	52[a]

[a] From equilibration studies of 2-methoxytetrahydropyran.[20] [b] From equilibration studies of 2-methoxytetrahydropyran.[19] [c] From equilibration studies of 6-methyl-2-methoxytetrahydropyran.[18] [d] From equilibration studies of 2-ethoxytetrahydropyran.[18] [e] From equilibration studies of 4-methyl-2-methoxytetrahydropyran.[18] [f] From equilibration studies of 4-methyl-2-methoxytetrahydropyran.[17] [g] From equilibration studies of 6-methyl-2-methoxytetrahydropyran.[17]

difference $\Delta G_{\alpha-\beta}$ between states α and β was then calculated according to eq 9, and the averages quantities A were calculated

$$\Delta G_{\alpha-\beta} = RT \ln (Q_\beta/Q_\alpha) \tag{9}$$

from the values $A(i)$ (where $A = \mu^2$, ${}^3J_{CH}$, ${}^3J_{CH}$, and ${}^3J_{HH}$) by general equation 10. Table II shows the calculated values of the

$$A = \sum_{i=1}^{n} x_i A(i) \tag{10}$$

molar fractions of the five MTHP conformers x_i, the molar fraction of A-MTHP ($x_A = x_{GG} + x_{GT}$) in the isolated state and in 16 solvents, and the comparison with the experimental values x_A for alkoxytetrahydropyrans.[16-20] As can be seen, particularly when the scattering of the experimental values is realized, the calculated values are in an excellent agreement with the experimental data obtained for a number of solvents of diverse character. Although the results indicate an increased abundance of the more polar E-MTHP conformer, x_E, with the increasing solvent polarity (represented by ϵ), the dependence is not a simple one. The proposed means of incorporating the solvent effect takes into account also such fine effects as the much more pronounced effect of chloroform on the decrease of x_A compared with other solvents of similar polarity and, reversely, a relatively weak effect of highly polar solvent dimethyl sulfoxide compared with less polar solvents.[20] While this special behavior of chloroform, noted also in the case of other glycosides, has been explained in the literature by specific interactions of the solvent, namely, the formation of intermolecular hydrogen bonds, no explanation has been offered for the case of dimethyl sulfoxide.[20] It can be concluded from the comparison of the individual contributions to the solvation energy of the individual conformers that the behavior mentioned above is caused by the electrostatic term. When the stabilization of the given conformer by the electrostatic term is compared in different solvents of, at least approximately, the same dielectric constant, the only parameter responsible for the change of stabilization is a_v. It can be seen when a_v values for Me_2SO are compared with those for solvents of similar polarity (Table I, see for example CH_3CN) that the value a_v in Me_2SO is higher. Since a high power of a_v member is in the denominator of the expression for G_{elst}, the stabilizing electrostatic interactions of conformers in E-MTHP will be less pronounced and, thus, the axial conformer will be more abundant. The situation is completely different in the case of chloroform. Here, a_v is smaller and E-MTHP is more abundant, which follows from higher values of electrostatic stabilization of the equatorial conformer. The different effect of the two solvents is caused, therefore, by their better or worse ability to approach the molecule of a solute and form in this way a greater or smaller reaction field which better stabilizes more polar MTHP conformers.

The experimental data describing the equilibrium of the two chair forms of MTHP are based largely upon the measured coupling constants ${}^3J_{HH}$ between the hydrogen atoms at C(2) and the hydrogen atom at C(1) (see eq 11), where J_A and J_E are

$${}^3J_{HH} = x_A J_A + (1 - x_A) J_E \tag{11}$$

coupling constants for the axially and equatorially oriented alkoxy groups. Each coupling constant is a sum of two coupling constants, according to the orientation of three hydrogen atoms at C(1) and C(2) (see eq 12), where the indexes e and a denote the equatorial

$$J_A = J_{ea} + J_{ee} \qquad J_E = J_{aa} + J_{ae} \tag{12}$$

and axial orientation of hydrogen atoms at C(1) and C(2). The following values (in hertz) were used by Lemieux et al.[20] for the analysis of an equilibrium composition: $J_{aa} = 9.9$, $J_{ae} = 1.9$, $J_{Ea} = 3.9$, and $J_{ee} = 1.4$. Table III shows the ${}^3J_{HH}$ values calculated by using the just shown data, for MTHP in different solvents, and their comparison with the experimental values.[20] As expected on the basis of the excellent agreement of x_A values, for these parameters there is also a reasonable agreement between experimental and calculated values.

The quantitative determination of the population of individual conformers in the axial (GG, GT) and in the equatorial (TG_1, TG_2, TT) form of MTHP is, however, not possible by using the data gathered in the literature. De Hoog et al.[19] assume, on the basis of a linear relationship between the coupling constants and the squares of the dipole moments in the nonpolar solvents (CCl_4 and benzene), that only two (or three) conformations predominate in the mixture, namely, GG ($\mu_{GG} = 0.87$ D) for the axial MTHP form and TG_1 (and TG_2) ($\mu_{TG_1} = \mu_{TG_2} = 2.18$ D) for the equatorial MTHP form. The relatively high μ_{GG} and the value obtained from the linear relationship between μ^2 and ${}^3J_{HH}$ indicate, in view of the very small dipole moment value of the GG conformers calculated by the PCILO method ($\mu_{GG} = 0.28$ D), that at least a small percentage of a GT conformer, having a higher dipole moment ($\mu_{GT} = 2.17$ D), must be present. We assume that the above-mentioned dipole moments are more likely to correspond to the dipole moments of A-MTHP and E-MTHP forms of MTHP than to the moments of GG and TG_1 conformations. This assumption is confirmed by dipole moments of these forms as well as the mean dipole moment of MTHP we calculated for CCl_4 and benzene (Table III), which all are in an excellent agreement with the values found experimentally[19] for CCl_4 ($\mu = 1.21$ D) and benzene ($\mu = 1.23$ D). Lemieux et al.[20] have found that solvents affect optical rotation of molecules bearing a fixed axially oriented methoxyl group, the effect being, except for water, rather small.

Table III. Calculated Dipole Moments μ (in D),[a] Proton–Proton Coupling Constants,[b] $^{3}J_{HH}$, and Carbon (CH_3)–Proton (Anomeric) Coupling Constants,[c] $^{3}J_{CH}$ (in Hz), of the Axial (Index A) and Equatorial (Index E) MTHP Form, and the Mean Value of These Parameters in Various Solvents at 298.2 K

solvent	μ(A)	μ(B)	μ	$^{3}J_{HH}$	$^{3}J_{HH}$(exptl)	$^{3}J_{CH}$(A)	$^{3}J_{CH}$(E)	$^{3}J_{CH}$
isolated MTHP	0.67	2.24	1.23	6.81		3.22	3.74	3.34
p-dioxan	0.71	2.26	1.30	6.99		3.27	3.80	3.40
carbon tetrachloride	0.69	2.25	1.26	6.86	6.4	3.24	3.80	3.37
benzene	0.69	2.25	1.26	6.86	6.5	3.24	3.81	3.38
carbon disulfide	0.70	2.26	1.28	6.91	6.6	3.25	3.83	3.40
tert-butylamine	0.71	2.26	1.27	6.86		3.26	3.90	3.41
chloroform	0.76	2.27	1.39	7.20	7.2	3.32	3.84	3.47
fluorobenzene	0.72	2.26	1.32	7.04		3.28	3.82	3.42
tetrahydrofuran	0.75	2.27	1.37	7.14		3.31	3.86	3.46
1-octanol	0.71	2.26	1.30	6.97		3.27	3.83	3.41
pyridine	0.78	2.28	1.42	7.30		3.35	3.87	3.51
acetone	0.77	2.28	1.40	7.23	7.1	3.34	3.90	3.50
ethanol	0.80	2.29	1.44	7.33		3.36	3.93	3.54
methanol	0.85	2.32	1.54	7.59	7.3	3.44	4.00	3.64
acetonitrile	0.82	2.30	1.48	7.44	7.4	3.40	3.96	3.58
dimethyl sulfoxide	0.79	2.29	1.43	7.30	7.0	3.36	3.94	3.54
water	1.12	2.46	1.94	8.70	8.4	3.86	4.34	4.11

[a] $1\ D = 3.33 \times 10^{-30}$ mA s. [b] $^{3}J_{HH}$ were calculated by using the parameters $^{3}J_{aa} = 9.9$, $^{3}J_{ae} = 1.9$, $^{3}J_{ea} = 3.9$, and $^{3}J_{ee} = 1.4$ Hz[20]. [c] $^{3}J_{CH}$ were calculated by using the parameters $^{3}J_{CH}(GG) = 2.94$, $^{3}J_{CH}(GT) = 6.6$, $^{3}J_{CH}(TG_1) = 3.04$, $^{3}J_{CH}(TG_2) = 9.59$, and $^{3}J_{CH}(TT) = 5.5$ Hz determined according to the equation[34] $^{3}J_{CH} = 11 \cos^2 \Phi^H$.

Based on these measurements, they assume that in the case of 2-deoxy-α-D-pyranosides at equilibrium there is another conformer (GT) present. When analyzing the dipole moments in benzene, they use the same distribution among the conformers of one form (axial or equatorial) as between these forms.[20] The values of coupling constants $^{3}J_{CH}$ (between ^{13}C-aglyconic carbon atom and the anomeric hydrogen atom) make it possible to determine the population of individual conformers around the C(1)–O(1) bond in glycosides, particularly since the Karplus type relationship between vicinal ^{13}C and ^{1}H atoms has been established. Lemieux et al.[33,34] expressed this relationship as $^{3}J_{CH} = 11 \cos^2 \Phi^H$, where $\Phi^H = \Phi[H(1)\text{–}C(1)\text{–}O(1)\text{–}C(6)]$ in MTHP. The same authors have also synthesized a series of alkyl α- and β-D-glycopyranosides enriched with ^{13}C at the aglyconic carbon position. For methyl glycosides the $^{3}J_{CH}$ observed were 3.6 and 4.3 Hz respectively for α and β anomers. For ethyl and cyclohexyl glycosides the same values were 3.9 and 4.4 and 3.8 and 4.2 Hz, respectively, while water was the solvent of the measurement.[34] In the calculated geometries of GG, GT, TG_1, TG_2, and TT conformers of MTHP the values for Φ^H are as follows: 58.88, 39.26, 58.31, 158.99, and −44.97°. With use of the above-mentioned Karplus-type equation for $^{3}J_{CH}$, the following values were calculated (in hertz): $^{3}J_{CH}(GG) = 2.94$, $^{3}J_{CH}(GT) = 6.60$, $^{3}J_{CH}(TG_1) = 3.04$, $^{3}J_{CH}(TG_2) = 9.59$, and $^{3}J_{CH}(TT) = 5.51$. By the use of these values, we have calculated $^{3}J_{CH}$ for A-MTHP and E-MTHP and the mean value for MTHP in a particular solvent (Table III). It can be seen that in all cases the coupling constants for E-MTHP, $^{3}J_{CH}(E)$, (i.e., the β-anomer in pyranosides), are considerably larger (by about 0.5 Hz) than those for A-MTHP (i.e., the α-anomer). The difference in the coupling constant values is preserved also for measurement in more polar solvents where their absolute value decreases. The values $^{3}J_{CH}$ calculated for individual MTHP forms in water are close to those calculated for α and β alkyl D-glucopyranosides and suggest the correctness of the calculated abundance of A-MTHP and E-MTHP conformers. Our theoretical results make it possible to determine quantitatively the population of the five conformers in an equilibrium mixture of MTHP in various solvents. At the same time, the calculated x_i values emend the previous qualitative conclusions on the basis of optical rotation measurements, correlations of dipole moments with proton coupling constants, and $^{3}J_{CH}$ coupling constants observed with alkyl D-glycopyranosides. The abundance of the more polar conformer GT of A-MTHP in nonpolar solvents is less than 8% ($x_{GT} = 6.2\%$ in carbon tetrachloride). It increases with the increasing solvent polarity and reaches its maximum in water, 12.03%, which corresponds to about 26% of the axial form. The abundance of the TT conformer in E-MTHP is similar. In nonpolar solvents it does not exceed 7% ($x_{TT} = 1.6\%$ in carbon tetrachloride) and, again, it is most abundant in water, 12.5%, which corresponds approximatively to 24% of the equatorial form. It is worth mentioning that in water the TT conformer is somewhat more stable than GT and TG_2 conformers, i.e., the order of stability of the conformers is GG > TG_1 > TT > GT > TG_2.

When describing the method of calculation of conformational energies that takes into account solvent effects (section II), we assumed that the conformational dependence of specific interactions is negligible. The very good agreement of calculated data with the experimental values found for various solvents justifies this assumption. To verify further the conformational independence of specific interactions, we have calculated the energies for the system MTHP–water. Our preliminary results showed that although the absolute value of specific interactions (in this case MTHP–water hydrogen bonding) makes an important contribution to the overall solvation energy, it depends only slightly on conformation.

The Effect of Solvent upon the Magnitude of Anomeric and Exoanomeric Effects. The anomeric effect influences the equilibrium between the axial and equatorial forms of MTHP (corresponding to the change of angle θ). In this axial–equatorial equilibrium the axial conformer is, depending upon the medium, more stable to the extent of 0–4 kJ/mol.[16-20] On the other hand, the equilibrium among the conformers within one particular form, i.e., having the alkoxy group oriented either axially or equatorially, depends upon the exoanomeric effect and owing to its operation sc orientation of the alkyl group (angle Φ) is preferred to the ap orientation. Although the importance of the exoanomeric effect for conformational properties has been emphasized,[13,14,33,34] its magnitude in solution has not been determined either theoretically or experimentally. The results of this work make it possible not only to calculate the EAE and AE values but also to quantitatively express the effect of solvent upon the magnitude of both these effects. For the purpose of this investigation we shall define the difference between the free energies of the axial and equatorial MTHP conformers as a theoretical anomeric effect. In evaluating the exoanomeric effect its magnitude in A-MTHP and E-MTHP must be considered separately. It will be given as the difference in free energies of the conformers having the methyl group (angle Φ) in sc and ap positions. The value of both these effects together with experimentally determined values of the anomeric effect calculated from the experimental x_A values are in Table IV. The dependence of the magnitude of the two effects upon the solvent polarity follows the dependence of the composition at the equi-

---

(33) R. U. Lemieux, *Ann. N.Y. Acad. Sci.*, **222**, 915–933 (1973).

(34) R. U. Lemieux, S. Koto, and D. Voisin, *ACS Symp. Ser.*, No. **87**, 18–29 (1979).

Table IV. The Effect of Solvents upon the Anomeric and Exoanomeric Effects (in kJ/mol) at 298.2 K

	anomeric effect		exoanomeric effect	
solvent	calcd	exptl[a]	A-MTHP	E-MTHP
isolated MTHP	2.96		6.14	7.01
p-dioxan	2.60	3.01	5.75	6.45
carbon tetrachloride	2.85	3.0-3.9	5.99	6.61
benzene	2.84	3.4-3.8	5.95	6.58
carbon disulfide	2.75	3.4	5.86	6.41
tert-butylamine	2.86		5.81	6.33
chloroform	2.19	2.2-3.1	5.34	5.97
fluorobenzene	2.50		5.65	6.26
tetrahydrofuran	2.30		5.41	6.00
1-octanol	2.64		5.75	6.35
pyridine	2.01		5.15	5.71
acetone	2.12	2.3-3.0	5.21	5.72
ethanol	1.95	1.5-1.9	5.02	5.48
methanol	1.52	1.3-2.0	4.56	4.95
acetonitrile	1.76	1.4-1.9	4.82	5.23
dimethyl sulfoxide	2.00	2.6	5.05	5.49
water	−0.22	0.2	2.70	2.86

[a] Calculated from the experimental distribution at equilibrium observed with alkoxytetrahydropyrans[17-20] (Table II).

librium, discussed in the previous section. The exoanomeric effect, approximately equal for both chair forms of MTHP, exceeds the anomeric effect by a factor of about 2. Although no experimental data on exoanomeric effect for either axial or equatorial form of alkoxytetrahydropyrans are available, we can assume, on the basis of the comparison of data in Tables II and III with the magnitude of anomeric effect which agree in an excellent way with the experimental data, that the mentioned data provide a true picture of the actual situation. The high value of the exoanomeric effect in nonpolar solvents explains the preferred abundance of sc conformers for the rotation around the glycosidic linkage[14] in the case of polysaccharides in the solid state. It also points out the importance of EAE in affecting the conformational preference of glycosidically linked substances. Although in polar solvents the EAE decreases to about one-third, its value is still sufficient to make the methyl group take preferentially the sc position. For both forms the population of the ap conformer will be less than 30% of the given MTHP form, because these conformations will be destabilized by EAE. On the other hand, in polar solvents on account of the decrease of AE the population of A-MTHP and E-MTHP will level-off, and in water E-MTHP may even be the more abundant form.

It follows from the previous discussion that polar solvents stabilize those conformers that are less stable in an isolated state or in nonpolar solvents. In this way the medium operates against the anomeric and exoanomeric effects. These two effects as they operate in an isolated molecule can be considered as resulting from a balance of intramolecular electrostatic and delocalization interactions.[6] As far as the acetal segment is concerned, the electrostatic interactions prevail at the equilibrium.[6] The shift of the equilibrium, i.e., the preponderance of sc conformers, results actually from the destabilization of ap conformers caused by intramolecular electrostatic interactions. For instance, in the case of the acyclic analogue of MTHP, dimethoxymethane, due to electrostatic interactions the TT conformer is destabilized by about 10 kJ/mol.[35] We have shown by an analysis of the effect of individual solvation energy terms upon the total energy that one of the conformationally most important terms is the contribution of electrostatic interactions stabilizing the ap conformers. In the case of TG and TT conformers in water, the stabilization of the TT conformer, caused by solute–solvent electrostatic interactions, compared with an isolated molecule, amounts to about 4 kJ/mol.

The inter- and intramolecular electrostatic interactions operate in the directions opposite to each other. While the intramolecular interactions are the phenomena responsible for anomeric and exoanomeric effects, the solute–solvent interactions reduce their effects and may even cancel them out. The two important effects that govern conformational properties of glycosidic C–O–C–O–C structures are, thus, a function not only of the intramolecular structure but also of the medium in which they occur.

IV. Summary and Conclusions

The effect of solvents upon the conformational behavior of the glycosidic segment in methoxytetrahydropyran was determined in 16 solvents. The PCILO quantum chemical method was used for calculating the energy of the isolated molecule and the continuum model for the calculation of MTHP interactions with the medium. All parameters calculated on the basis of the proposed continuum model are in excellent agreement with experimental data. In addition to determination of the abundance of axial and equatorial forms of MTHP the obtained results make it possible also to determine the population of other conformers as well as the magnitude of anomeric and exoanomeric effects in various solvents. The calculated values of anomeric and exoanomeric effects in several solvents show the importance of both these effects in determining the conformational properties of glycosidic structures in solution. The exoanomeric effect is particularly important. Its influence, resulting in preference of the sc conformations, although considerably less pronounced, remains preserved even in highly polar solvents, e.g., dimethyl sulfoxide, water, etc. The magnitude of anomeric effect and exoanomeric effect in solution results essentially from the balance of intramolecular electrostatic interactions and solute–solvent electrostatic interactions.

The results obtained justify the use of this method in studies of the solvent effect on more complicated glycosidic structures. The work on oligo and polysaccharides is currently in progress and will be published later.

Acknowledgment. The authors thank Drs. T. Bleha and V. Klimo for their critical and helpful comments on the manuscript.

---

(35) I. Tvaroška and T. Bleha, *Collect. Czech. Chem. Commun.*, **43**, 922–931 (1978).

(36) R. U. Lemieux and S. Koto, *Tetrahedron*, **30**, 1933–1944 (1974).