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Ab Initio Molecular Orbital Calculation of Carbohydrate Model Compounds. 3. Effect of the Electric Field on Conformations about the Glycosidic Linkage

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The effect of the electric field on the conformational behavior of model compounds for glycosidic linkages, 2-methoxytetrahydropyran (MTHP) with axially and equatorially oriented methoxy groups has been investigated by the *ab initio* molecular orbital method. The geometry of rotamers about the glycosidic C–O bond was determined by gradient optimization at the 6-31G* level. The potential of rotation about the glycosidic C–O bond has been calculated using the 6-31+G* basis set in an electric field. The 6-31G* optimized geometries were used to calculate energy differences between the AGT, ATG, AGG, EGT, ETG, and EGG conformers with 6-31G*, 6-31+G*, 6-31+G**, 6-311++G*, and MP2/6-31G* basis sets. The electric field has been applied in various directions and strengths. The calculations revealed that strong electric fields influence the topology of the rotational potential energy. At all levels of theory, the electric field has shown to have a significant effect on the relative energies of conformers. This effect is so pronounced that in fields of $E_x = 0.01$, $E_x = -0.01$, and $E_z = -0.01$ au the axial–equatorial equilibrium is reversed. Whereas in gas-phase axial MTHP is preferred by 1.08 kcal/mol, in the presence of these fields, contrary to the anomeric effect, equatorial MTHP is favored by 1.63, 1.14, and 3.48 kcal/mol, respectively. Electric fields also influence the relative stability of conformers in both MTHP anomers. In the field of $E_y = -0.01$ au, the TG conformers are found to be favored over GT in both anomers, contrary to the exo-anomeric effect which prefers the GT conformers. All larger basis sets give relative energies which agree fairly well with the 6-31+G* results. These results suggest that strong external fields present on membrane surfaces might considerably influence conformational equilibria around the glycosidic linkages of carbohydrate portions of membrane glycoconjugates and thus their overall shape. They also imply that conformations not found in gas-phase or solution equilibria might be of importance in the biological activity of membrane bound molecules.

Introduction

Glycoconjugates located at the outer leaflet of the cell membrane are involved in many biological functions, among others, in cell adhesion, recognition events, and immunological protection.^{1,2} The functions of glycoconjugates are primarily determined by the sequence and conformation of the carbohydrate moiety. Therefore, an understanding of the three-dimensional structure and dynamics of oligosaccharides at the cell surface is of considerable importance. The inner surface of a typical biological membrane contains negative charges which produce a potential of the order of 10^{-2} V. Thus, near the surface of biological membranes electric field gradients of the order of 10^7 V/m are common,³ and local electric fields may be even stronger, of the order of 10^{10} V/m. For example, the electric field at 5.6 Å from the ion of a single charge is 5×10^{10} V/m. Transitions leading to changes in sign of these large fields are frequently observed. It is well recognized that such changes will be accompanied by conformational and other effects in the membranes. Calculations on small molecules in electric fields by semiempirical^{4–6} and *ab initio*⁷ methods have shown that the properties of molecules are considerably influenced by the electric field. This is manifested by a reorganization of the electron distribution, resulting in a change

in the geometry of a molecule and by a reorientation of a molecule with respect to the direction of the electric field.

Three-dimensional structure of oligosaccharides is primarily determined by the conformations about the glycosidic linkage. The conformational behavior of the glycosidic linkage is controlled by a balance of many different interaction energies, of intra- and intermolecular origin. A strong electric field may lead to a critical shift of this balance, thus resulting in significant conformational changes. Obviously the structural characterization of the oligosaccharide moieties of membrane glycoconjugates requires knowledge of the extent of field-induced conformational changes. Moreover, these conformational changes are of great interest for an understanding of the functions of glycoconjugates which act as membrane surface receptors for proteins involved in many physiological and pathological processes.

Due to difficulties in obtaining direct experimental data, there is very little knowledge of how external electric fields influence the conformation of oligosaccharides. Therefore, we have undertaken a detailed theoretical investigation on the effect of external electric fields on the potential of rotation about the glycosidic linkage, on the relative stability of conformers, and on the magnitude of the anomeric and exo-anomeric effects using *ab initio* self-consistent-field molecular orbital method. Because of the extensive computational resources needed for

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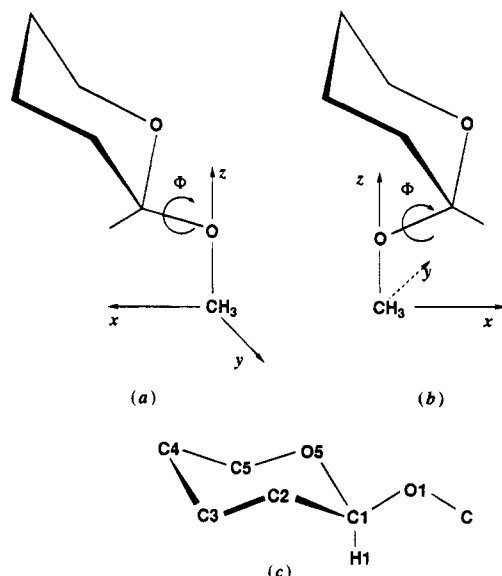


Figure 1. Orientation of the (a) equatorial and (b) axial 2-methoxytetrahydropyran with respect to the coordinate systems and (c) the labeling of the atoms.

these calculations, we have used a widely accepted model for the glycosidic linkage, 2-methoxytetrahydropyran in both the axial and equatorial forms.

Model and Computational Procedures

The axial (AMTHP) and equatorial (EMTHP) forms of 2-methoxytetrahydropyran (MTHP) were chosen as models to study the effect of external electric fields upon the conformational properties of α - and β -glycosidic linkages.

The calculations were carried out using GAUSSIAN 92,⁸ and standard basis sets were used.⁹ The rotation around the glycosidic linkage is described by the angle Φ , and a 30° grid was used to calculate the potential energy of rotation. The geometry of the MTHP conformers was determined by a complete gradient geometry optimization at the 6-31G* level, except for the dihedral angle Φ , which was kept fixed. In order to localize the minimum on the rotational curve, the final refinement was carried out without freezing the dihedral Φ . The energy of each point on the potential energy curve was then calculated with the 6-31+G* basis set. The 6-31+G**/6-31G* basis set has been suggested as suitable for calculations with carbohydrate derivatives on the basis of *ab initio* calculations of halogen derivatives of tetrahydropyran.¹⁰ The conformational energies of MTHP calculated with this basis set were found to be similar to the energies calculated with the 6-311++G**//6-31G* basis set.¹¹ Next, single-point calculations were performed for the six conformers of MTHP using 6-31G*, 6-31+G*, 6-31+G**, 6-311++G*, and MP2/6-31G* basis sets.

The effect of the electric field was calculated for each conformer at the 6-31+G* level, using routines in the GAUSSIAN 92 program. The magnitude of the field was varied over a range from 0.0001 to 0.01 au (5×10^7 to 5×10^9 V/m). In order to investigate the influence of field direction, the electric field was applied in six different orientations, namely, along the three coordinate axes x , y , and z , with the field in both the positive and negative directions. The orientation of the MTHP anomers in the coordinate system and the labeling of the atoms of interest are shown in Figure 1. The conformational equilibrium of MTHP is illustrated in Figure 2, which shows three staggered orientations for rotation about the glycosidic bond in both the axial and equatorial forms of MTHP. These are referred to as AGT, ATG, AGG, EGT, ETG, and EGG. In this

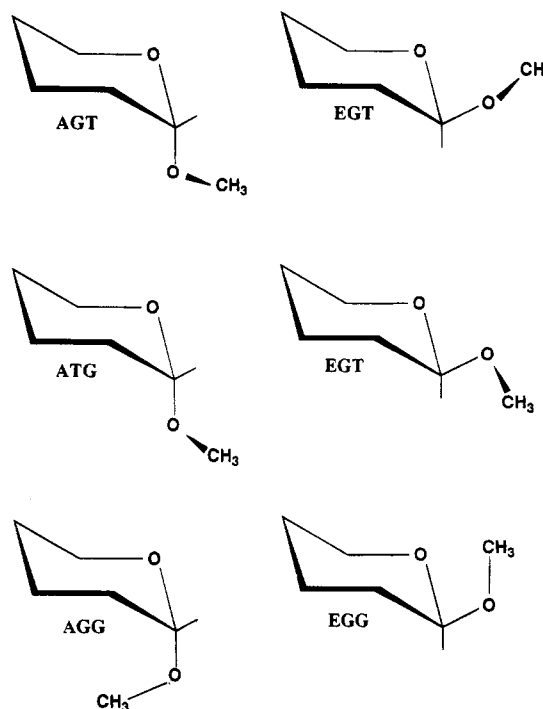


Figure 2. Schematic representation of the AGT, ATG, AGG, EGT, ETG, and EGG conformers of 2-methoxytetrahydropyran.

notation, the description of the anomeric form is stated first, then the torsion angle $\Phi = \Phi[\text{O5}-\text{C1}-\text{O1}-\text{C}]$, and finally the torsion angle $\Theta = \Theta[\text{C2}-\text{C1}-\text{O1}-\text{C}]$. In this way, for example, AGT means that the methoxy group is in the axial position (A) and the angles Φ and Θ are close to those in the *sc* or *gauche* (G) and *ap* or *trans* (T) conformations, respectively. The calculations were carried out at the University of Toronto on an HP370 computer.

Results and Discussion

Effect of the Electric Field on the Calculated Conformational Energies around Glycosidic C—O Bond. It has been demonstrated on small molecules⁴⁻⁷ that the electric field considerably influences the structure of the molecule and the orientation with respect to the direction of the electric field. In order to evaluate the effect of the field strength on the potential energy of rotation around the C—O glycosidic linkage, the energy, as a function of torsion angle Φ , was calculated at three different intensities (0.0001, 0.001, and 0.01 au) and in both directions along the axis z . The *ab initio* data, obtained at the 6-31+G**/6-31G* level without external electric field, are compared to the results with the presence of field in Figures 3 and 4.

First, one can notice that the calculated potential energy profiles for 0.0001 au are almost identical with the profiles calculated without the electric field. The stability of conformers around the glycosidic linkage starts to change when the field strength is increased, and the deviations from the gas-phase curve without an applied field become quite large at an intensity of 0.01 au. These deviations depend on the orientation of the external electric field and are different in both anomers as can be seen from a comparison Figures 3 and 4. Below we discuss only the results obtained with an external electric field of 0.01 au.

When an electric field is applied to a molecule with a permanent dipole moment μ , the molecule will try to align in the direction of the field vector \mathbf{E} with a corresponding energy of $-\mu \cdot \mathbf{E}$. In our model, MTHP molecule is fixed in the

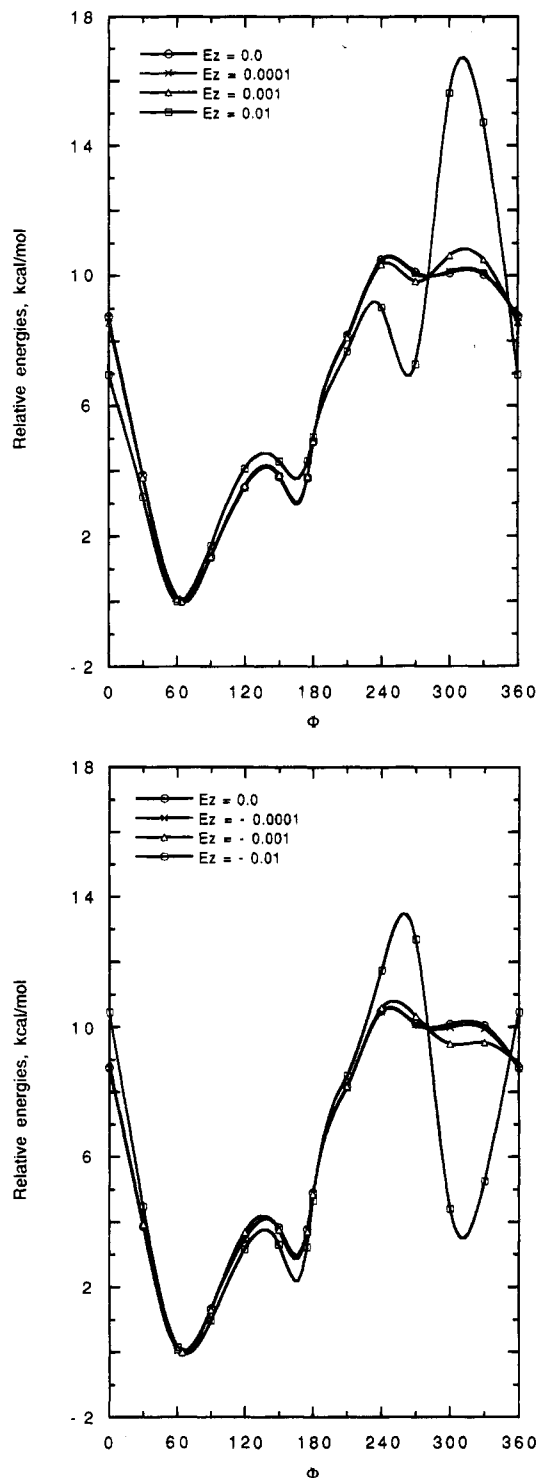


Figure 3. *Ab initio* 6-31+G*//6-31G* potential energy of rotation about C1–O1 glycosidic linkage (Φ) for axial 2-methoxytetrahydropyran in an external electric field with intensity (a, top) $E_z = 0.0, 0.0001, 0.001$, and 0.01 au and (b, bottom) $E_z = 0.0, -0.0001, -0.001$, and -0.01 au.

coordinate system (Figure 1) with the carbon atom of the methyl group placed at the origin and with the outer C–O bond oriented along the z axis. Therefore, MTHP can undergo only reorientations associated with the rotation around the C–O glycosidic linkage. The dipole moment of MTHP depends mainly on the conformation of the segment C5–O5–C1–O1–C. Since the atoms C–O1–C1 are in the xz plane, the dipole moment associated with this segment also lies in this plane. Rotation about the C1–O1 bond changes the orientation of the dipole moment of the C5–O5–C1 group and determines the total

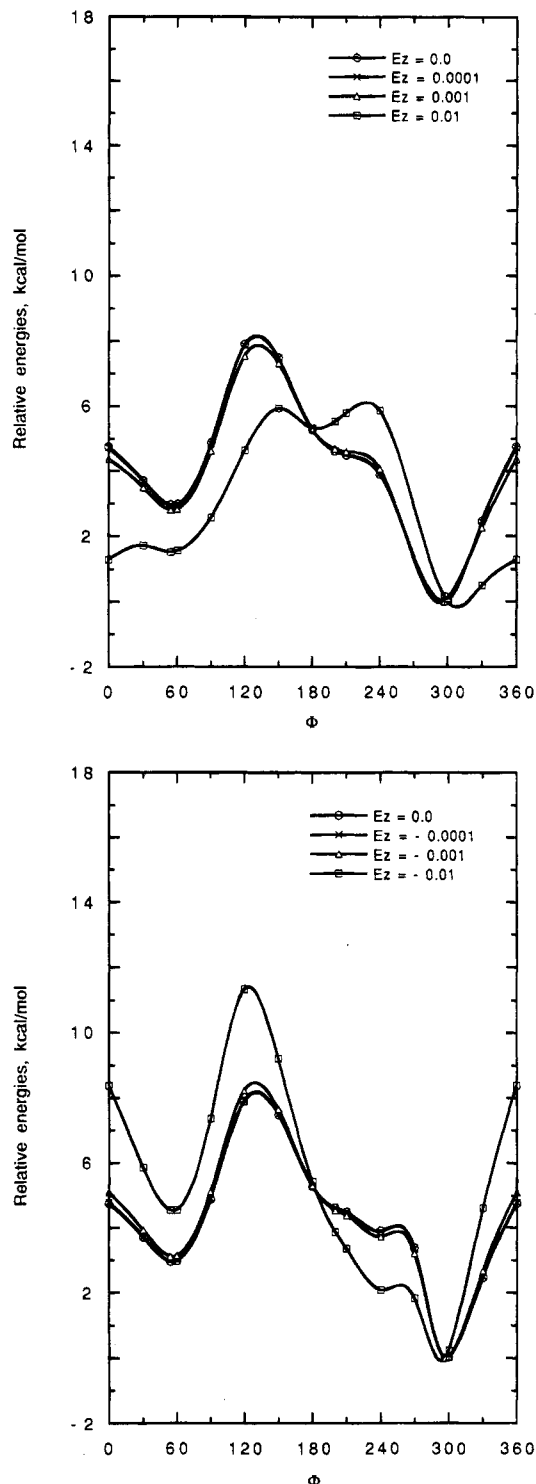


Figure 4. *Ab initio* 6-31+G*//6-31G* potential energy of rotation about C1–O1 glycosidic linkage (Φ) for equatorial 2-methoxytetrahydropyran in an external electric field with intensity (a, top) $E_z = 0.0, 0.0001, 0.001$, and 0.01 au and (b, bottom) $E_z = 0.0, -0.0001, -0.001$, and -0.01 au.

dipole moment of MTHP. Therefore, the magnitude and directionality of the dipole moment of MTHP continuously change with rotation around the C1–O1 bond. The extent of stabilization of a given conformation in the presence of the external electric field depends on the magnitude of its dipole moment and on the cosine between the field direction and the dipole moment axis; the maximum occurs when the dipole is parallel to the field. This simplified model implies that stabilization of a particular conformer will depend on the orientation of the electric field.

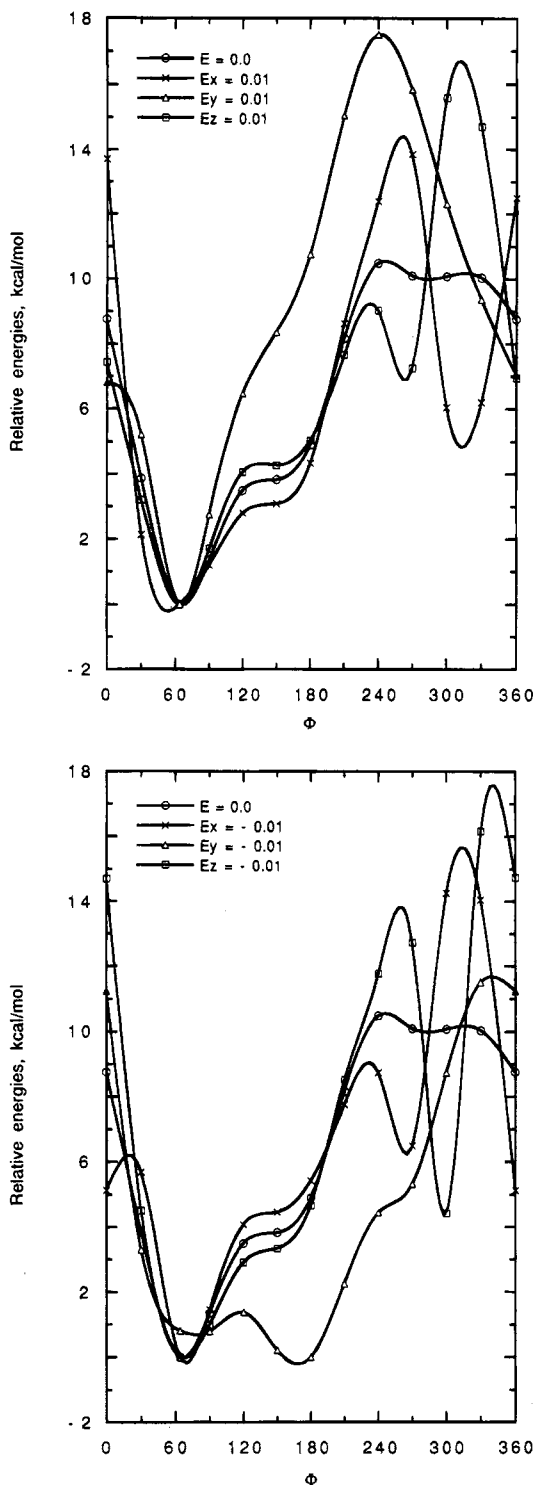


Figure 5. *Ab initio* 6-31+G**/6-31G* potential energy of rotation about C1–O1 glycosidic linkage (Φ) for axial 2-methoxytetrahydropyran in an external electric field with intensity (a, top) $E = 0.0$, $E_x = 0.01$, $E_y = 0.01$, and $E_z = 0.01$ au and (b, bottom) $E = 0.0$, $E_x = -0.01$, $E_y = -0.01$, and $E_z = -0.01$ au.

To see what effect the direction of the external electric field might have on the energy profiles, the energy of rotation around the C1–O1 bond was calculated at six different orientations of the field with a strength of 0.01 au. The pertinent results for the two anomers of MTHP are summarized in Figures 5 and 6. The obvious feature here is the greater complexity of the potential energy profiles compared to those calculated without an applied electric field.

For the axial MTHP (Figure 5), the presence of the external electric field has several interesting consequences. The calcu-

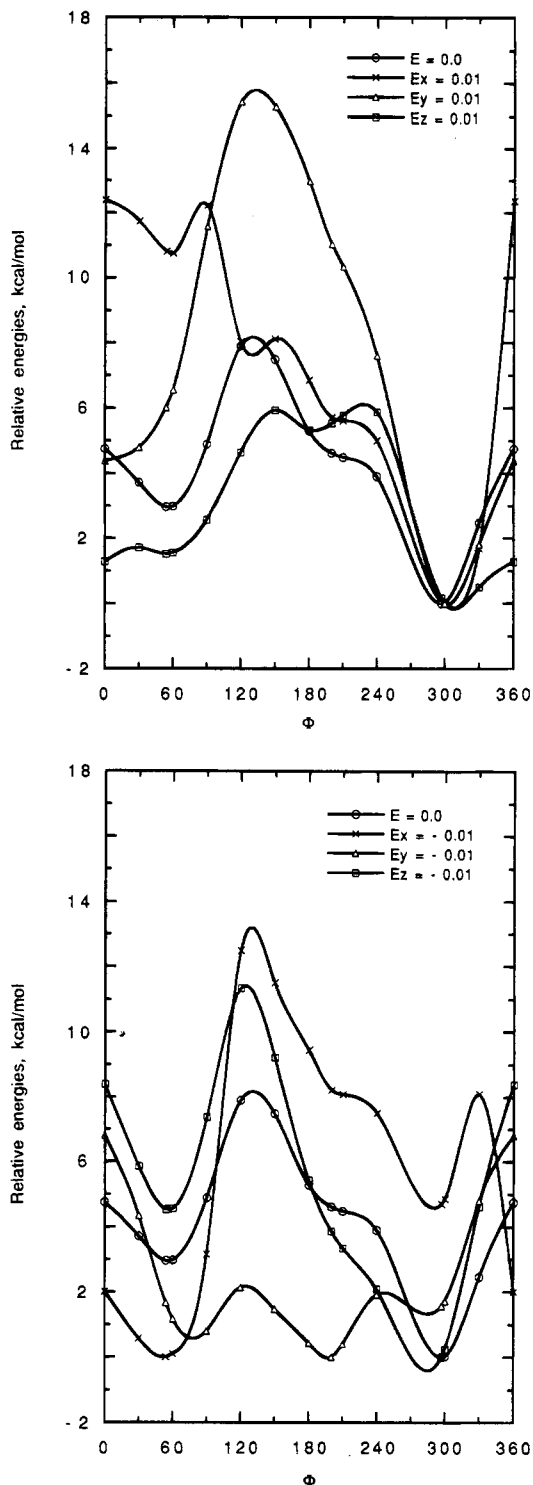


Figure 6. *Ab initio* 6-31+G**/6-31G* potential energy of rotation about C1–O1 glycosidic linkage (Φ) for equatorial 2-methoxytetrahydropyran in an external electric field with intensity (a, top) $E = 0.0$, $E_x = 0.01$, $E_y = 0.01$, and $E_z = 0.01$ au and (b, bottom) $E = 0.0$, $E_x = -0.01$, $E_y = -0.01$, and $E_z = -0.01$ au.

lated profiles, in the presence of a field in directions x and z , look similar to those calculated without a field, except that a new well appears in the region between 240° and 330° (AGG conformer, Figure 2). The deepest minimum appears at 60° , which corresponds to the gauche orientation of the methyl group relative to the ring oxygen and represents the AGT conformer. The relative energies of conformations between 150° and 180° (the ATG conformer) are stabilized about 0.8 kcal/mol by the presence of the field in the positive direction along the x axis (Figure 5a). On the contrary, the opposite direction of field

increases the relative energies of this region about the same amount (Figure 5b). The main difference compared with the "unperturbed" curve occurs in the region between 240° and 330°. These conformers are strongly stabilized by the field, and a deep minimum appears at 300° with a relative energy of 6 kcal/mol for a field along x . In the $-E_x$ field, this minimum is shifted to the orientation with $\Phi = 270^\circ$. Similar results are obtained when field in a direction of the z axis is applied, but in reverse order with respect to the direction of the electric field. Thus, when the field is in the positive z direction, the energy of the ATG (180°) conformer is increased and a deep minimum appears at 270° (AGG), whereas, when the field is in the opposite direction, the relative energy of the ATG conformer is decreased and the AGG minimum is shifted to 300°. Thus, there is a clear similarity in the changes imposed by field in the x and z directions.

Compared with the changes due to the electric field effects discussed above, the influence of the field in the y direction on the rotation around the C1–O1 bond is more pronounced. The calculated profile with the field in the positive direction along y shows only one deep minimum for the ATG conformer at 60°. The conformations between 90° and 240° are strongly destabilized by the electric field, and a high barrier appears at 240°. When an electric field is applied to AMTHP along the negative y axis, the stability of conformers and the topology of the conformational energy curve completely change (Figure 5b). The stabilization is most pronounced in the range 120°–240°. As a consequence, the ATG conformer at 180° becomes the preferred one. The second minimum, the AGT conformer, appears at 60° with an energy 0.8 kcal/mol higher.

For the equatorial form of MTHP, similar effects are observed. Figure 6a shows that, for an electric field in the z direction, the EGG conformer at 60° is stabilized by 1.4 kcal/mol relative to the value with no field. As well, this field stabilized conformations where the methyl group is oriented *ap* to the ring oxygen. Due to this stabilization a new minimum (ETG) appears on the potential energy curve for rotation around the C1–O1 bond at 180°. This minimum is not predicted by the calculations without electric field at the 6-31+G**/6-31G* level. On the other hand, fields in the y and x directions destabilized these regions. In the case of a field applied in the y direction, the destabilization is so pronounced that only one deep well appears on the entire energy profile, at the EGT conformer, and a high barrier appears between 120° and 150°. For the opposite direction of the electric field, as in the case of AMTHP, more pronounced effects are found. In this case, the field in the direction of the $-x$ and $-y$ changes the stability of conformers and the topology of the rotational curve in a such way that for the $-x$ direction the EGG conformer is the preferred species and the EGT conformer has an energy about 4.7 kcal/mol higher. For the $-y$ direction of the field, the lowest-energy conformer is ETG, the next is EGG with an energy of 0.8 kcal/mol, and then the EGT conformer with an energy 1.6 kcal/mol higher than ETG.

An electric field acts in an opposite fashion on nuclei and electrons, in such a way that the electron density is reorganized and forces are induced on the constituent nuclei.⁷ The nuclei will move in response to these forces until an optimal geometry is reached. Since we have used non-field optimized geometries with the torsional angle Φ , as the only flexible geometrical parameter, we can observe only changes connected with conformational changes and with a rearrangement of electron densities. This is illustrated in Figure 7, where the dipole moments of the axial and equatorial forms of MTHP are plotted as a function of the torsion angle Φ for electric fields of $E_y =$

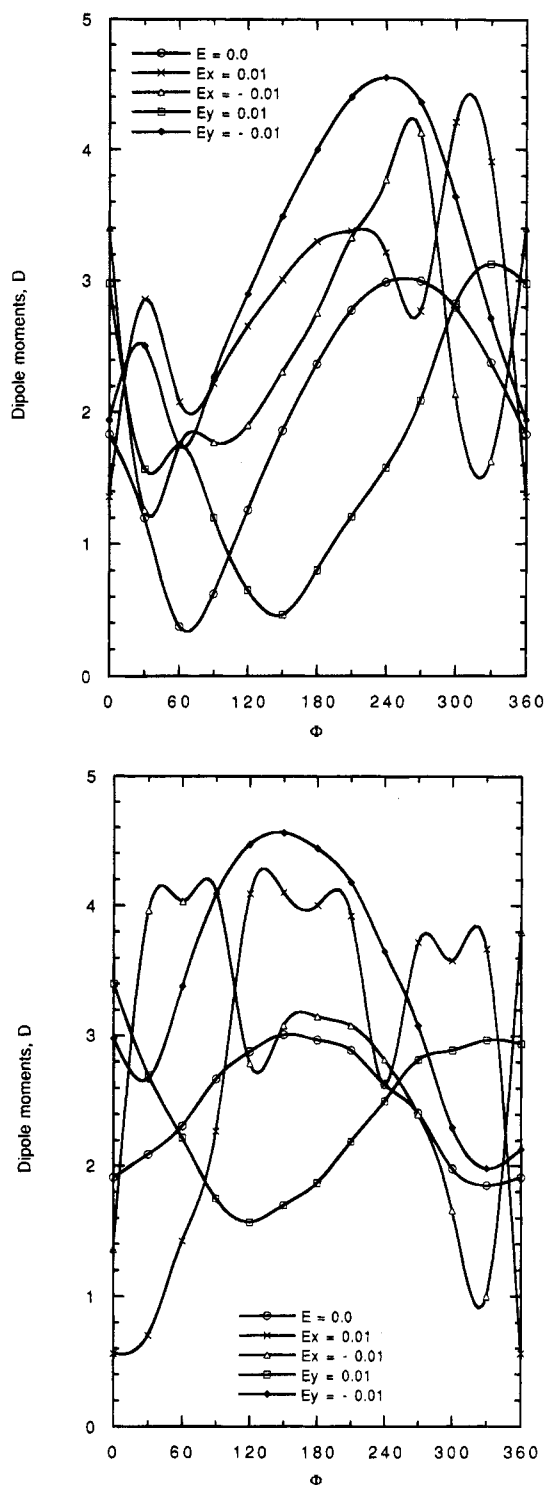


Figure 7. *Ab initio* 6-31+G**/6-31G* calculated dipole moments as a function of rotation about C1–O1 glycosidic linkage (Φ) for (a, top) axial and (b, bottom) equatorial 2-methoxytetrahydropyran in an external electric field with intensity of $E = 0.0$, $E_y = 0.01$, and $E_y = -0.01$ au.

0.01 au and $E_y = -0.01$ au. A comparison of dipole moments under an applied electric field and without field revealed that μ variations reproduce nicely the influence of the electric field on the energy of conformers. For example, with the electric field in the E_y direction, the dipole moments of AMTHP conformations between 90°–270° are lower in comparison with corresponding values without field. These conformers are destabilized by this field. In contrast, when the field is in the opposite directions, the dipole moments of AMTHP conformers with Φ between 90° and 300° are considerably increased, and

TABLE 1: Calculated Influence of the External Electric Field on the Energies of AGT, ATG, and AGG Conformations of the Axial 2-Methoxytetrahydropyran

field		absolute	relative		
direction	intensity (au)	energy (hartrees)	energy (kcal/mol)		
		lowest minimum	AGT	ATG	AGG
E_x	0.0	-383.917 432 2	0.0	4.90 ^a	10.46 ^b
	0.01	-383.921 803 1	0.0	4.32 ^a	6.05
	-0.01	-383.920 487 9	0.0	5.42 ^a	6.49
E_y	0.01	-383.920 855 9	0.0	10.75 ^a	12.30 ^b
	-0.01	-383.922 013 6	0.80	0.0	8.73 ^b
E_z	0.0001	-383.917 442 9	0.0	3.82 ^a	10.06
	0.001	-383.917 587 1	0.0	3.86 ^a	9.81
	0.01	-383.921 855 2	0.0	5.04 ^a	7.26
E_z	-0.0001	-383.917 411 8	0.0	3.80	9.98
	-0.001	-383.917 332 5	0.0	3.75	9.48
	-0.01	-383.919 283 7	0.0	3.31	4.42

^a Conformation at $\Phi = 180^\circ$. ^b Conformation at $\Phi = 300^\circ$.**TABLE 2: Calculated Influence of the External Electric Field on the Energies of EGT, ETG, and EGG Conformations of the Equatorial 2-Methoxytetrahydropyran**

field		absolute	relative		
direction	intensity (au)	energy (hartrees)	energy (kcal/mol)		
		lowest minimum	EGT	ETG	EGG
E_x	0.0	-383.915 705 2	0.0	5.29 ^a	2.96
	0.01	-383.924 526 2	0.0	6.86	10.71
	-0.01	-383.922 307 5	4.72	9.45 ^a	0.0
E_y	0.01	-383.920 709 8	0.0	13.01 ^a	6.01 ^b
	-0.01	-383.920 106 9	1.57	0.0	0.80
E_z	0.0001	-383.915 644 2	0.0	5.29 ^a	2.95
	0.001	-383.915 129 6	0.0	5.30 ^a	2.80
	0.01	-383.913 039 8	0.0	5.33	1.52
E_z	-0.0001	-383.915 762 2	0.0	5.29 ^a	2.98
	-0.001	-383.916 340 2	0.0	5.31 ^a	3.12
	-0.01	-383.924 833 8	0.0	6.01	4.54

^a Conformation at $\Phi = 180^\circ$. ^b Conformation at $\Phi = 60^\circ$.

those conformers are strongly stabilized by a field in this direction. A similar relationship between μ and energy was observed for other orientations of the electric field. A qualitative explanation of the field effects follows from the simplified discussion of the interaction between an electric field and a molecule with a permanent dipole moment given above. The stabilization of a molecule by an applied electric field depends on the magnitude of dipole moment. Therefore, the conformations where reorganization of electron density by the electric field yields larger values of the dipole moment are more stabilized, and *vice versa*. Since the highest values of dipole moments are observed for conformations in the range of Φ values from 150° to 180° , we may expect that these conformers will be the ones most strongly influenced by electric fields.

Stability of the Conformers and Anomeric and Exoanomeric Effects. In the previous section we have demonstrated how strong electric fields influence the topology of the internal rotation potential energy for MTHP. It is interesting to compare the effect of the electric field on the stability of individual conformers and to see how this is reflected in the magnitudes of the anomeric and exoanomeric effects.¹² The calculated relative energies of the staggered conformations are given in Tables 1 and 2. It should be noted that, out of the three possible staggered conformers for axial and equatorial MTHP, only one and two minima, respectively, appear on the gas-phase potential energy curve calculated at the 6-31+G**/6-31G* level.

For axial MTHP, the AGT conformer is, in agreement with the exoanomeric effect, the lowest energy conformer. It appears that the relative energy of the ATG conformer is in the range

3.3–5.4 kcal/mol, except in a presence of the field along the y axis. For a field $E_y = 0.01$ au, the relative energy of the $\Phi = 180^\circ$ conformer increases to 10.8 kcal/mol. In contrast, for a field in the opposite direction, $E_y = -0.01$ au, the ATG conformer is the preferred one, and the energy of AGT is higher by 0.8 kcal/mol. The AGG conformer is found to be a minimum in the presence of electric fields with the relative energy between 4.4 and 7.3 kcal/mol, except the fields along the y axis where this conformer is not a minimum on the curve of rotation.

For the equatorial MTHP, the lowest energy conformer in the gas-phase calculations is EGT at $\Phi = 297^\circ$, and the next is the EGG conformer at $\Phi = 54^\circ$ with the relative energy of 2.96 kcal/mol. The relative energy of the ETG conformer at $\Phi = 180^\circ$ is 5.29 kcal/mol. The relative energies of these conformers change in the presence of the field. Once again when the electric field is in the $-y$ direction, ETG has the lowest energy, next is the EGG conformer with a relative energy of 0.8 kcal/mol and then the EGT conformer with an energy 1.57 kcal/mol, higher. For $E_x = -0.01$ au field, the EGG conformer is preferred and the energy of EGT is 4.72 kcal/mol. The EGG conformer is also stabilized by a field of $E_z = 0.01$ au, where its energy is decreased by 1.44 kcal/mol in comparison to the value in the gas phase. In contrast, a field of $E_x = 0.01$ au increases the relative energy of this conformer by 7.75 kcal/mol and in the case of $E_y = 0.01$ au, the ETG and EGT conformers disappear. The values shown in Tables 1 and 2 clearly show that the existence of the minima on the curve of rotation, their relative energies, and, therefore, the population of the minima around the glycosidic linkages are strongly dependent on the strengths and direction of the electric field.

Table 3 summarizes the relative energies of the MTHP conformers calculated at the five levels of approximation: 6-31G*, 6-31+G*, 6-31+G**, 6-311++G*, and MP2/6-31G*. The effect of the electric fields on the stability ordering is the same at all levels of theory. However, the energy differences gradually change with the improvement of the basis sets. From Table 3 it can be seen that the use of 6-31+G* basis set yields relative energies of the MTHP conformers close to our largest basis set 6-311++G**. For instance, the relative energy of the EGT conformer for a field of $E_x = 0.01$ au slightly decreases from -1.63 kcal/mol to -1.77 kcal/mol as the basis set is enlarged from the 6-31+G* to 6-311++G**. The electron correlation is also seen to have an effect on the relative energies. When electron correlation at the second-order Moller–Plesset perturbation level using 6-31G* basis set (MP2/6-31G*) is included, the relative energy of the EGT increases to -0.25 kcal/mol. However, it has been shown¹⁰ that this difference decreases by using larger basis sets and by inclusion of the correlation energy at higher level. These features are consistent with previous gas-phase calculations of MTHP.¹¹

The 6-31+G**/6-31G* calculated gas-phase energy difference between the preferred equatorial and axial MTHP conformers is in reasonable agreement with $\Delta G^\circ = 0.89$ kcal/mol, determined from variable-temperature NMR studies of MTHP^{13,14} in both carbon tetrachloride and benzene solutions. Thus, due to the anomeric effect the axial form is favored, though on steric grounds one would expect the equatorial form to be preferred. Absolute energies for the lowest energy conformers of both MTHP forms given in Tables 1 and 2 show that this equilibrium is considerably influenced by the electric field. Calculated energy differences (Table 4) are in the range from -3.48 to 5.71 kcal/mol and reveal that electric fields may even reverse the order of stability of both MTHP anomers. In this case, the electric field operates in a direction opposite to that of the anomeric effect and may even cancel it out.

TABLE 3: Influence of the External Electric Field on the Energies of 2-Methoxytetrahydropyran Conformers Calculated at Different Levels of Theory

field		basis set	absolute energy (hartrees) AGT	relative energy (kcal/mol)				
direction	intensity (au)			ATG ^a	AGG ^b	EGT	ETG ^a	EGG
E_x	0.0	6-31G*	-383.910 032 2	5.02	10.46	1.47	6.86	4.38
		6-31+G*	-383.917 422 9	4.90	10.07	1.08	6.37	4.05
		6-31+G**	-383.935 348 5	4.88	10.10	1.06	6.38	4.02
		6-311++G**	-384.012 520 8	4.77	10.10	0.94	6.32	3.93
		MP2/6-31G*	-385.040 481 3	5.04	10.72	2.07	6.72	4.98
		6-31G*	-383.913 915 7	4.25	6.59	-1.11	5.70	8.95
	0.01	6-31+G*	-383.921 803 1	4.32	6.05	-1.63	5.15	9.10
		6-31+G**	-383.939 778 9	4.29	6.07	-1.67	5.14	9.10
		6-311++G**	-384.017 112 5	4.25	6.14	-1.77	5.10	9.08
		MP2/6-31G*	-385.044 416 4	4.27	7.18	-0.25	6.72	9.00
		6-31G*	-383.913 037	5.70	14.46	3.83	8.73	-0.33
		6-31+G*	-383.920 487 9	5.42	14.24	3.58	8.31	-1.14
E_y	-0.01	6-31+G**	-383.938 461 7	5.42	14.28	3.57	8.32	-1.20
		6-311++G**	-384.015 651 7	5.23	14.22	3.42	8.22	-1.35
		MP2/6-31G*	-385.043 710 2	5.71	14.41	4.13	9.37	0.80
	0.01	6-31G*	-383.913 079 3	10.52	12.45	0.50	13.16	6.17
		6-31+G*	-383.920 855 9	10.75	12.30	0.19	13.07	6.09
		6-31+G**	-383.938 834 2	10.76	12.35	0.18	13.10	6.08
		6-311++G**	-384.016 156 4	10.69	12.44	0.14	13.06	6.06
		MP2/6-31G*	-385.043 56 9	10.01	12.48	1.12	13.42	6.52
		6-31G*	-383.913 207 4	-0.28	8.57	2.44	1.78	2.67
E_z	-0.01	6-31+G*	-383.920 749 2	-0.79	7.93	1.97	0.85	2.08
		6-31+G**	-383.938 700 5	-0.84	7.95	1.94	0.84	2.04
		6-311++G**	-384.015 881 6	-1.00	7.85	1.73	0.74	1.88
		MP2/6-31G*	-385.043 767 3	0.26	9.05	3.02	3.22	3.52
	0.01	6-31G*	-383.914 143 5	5.13	15.72	5.80	11.53	7.30
		6-31+G*	-383.921 863 3	5.04	15.61	5.71	11.33	7.06
		6-31+G**	-383.939 807 9	5.01	15.63	5.70	11.34	7.02
		6-311++G**	-384.017 009 6	4.90	15.55	5.53	11.25	6.86
		MP2/6-31G*	-385.044 669 4	5.08	15.61	5.95	11.94	7.88
		6-31G*	-383.911 725 1	4.81	5.10	-2.80	3.32	1.49
E_z	-0.01	6-31+G*	-383.919 288 3	4.68	4.43	-3.48	2.53	1.06
		6-31+G**	-383.937 248 9	4.66	4.46	-3.51	2.53	1.05
		6-311++G**	-384.014 517 3	4.54	4.53	-3.59	2.50	1.03
		MP2/6-31G*	-385.042 190 6	4.88	5.68	-1.73	4.62	2.10

^a Conformation at $\Phi = 180^\circ$. ^b Conformation at $\Phi = 300^\circ$.**TABLE 4: Influence of the External Electric Field on the Anomeric and Exoanomeric Effects in 2-Methoxytetrahydropyran**

field		anomeric ^a (kcal/mol)	exo-anomeric ^b (kcal/mol)	
direction	intensity (au)		axial	equatorial
E_x	0.0	1.08	4.90	5.29
	0.01	-1.63	4.22	6.86
	-0.01	-1.14	5.42	4.73
E_y	0.01	0.19	10.75	13.01
	-0.01	1.20	-0.80	-1.57
E_z	0.0001	1.13	3.82	5.29
	0.001	1.54	3.86	5.30
	0.01	5.71	5.04	5.33
E_z	-0.0001	1.04	3.80	5.29
	-0.001	0.62	3.75	5.31
	-0.01	-3.48	3.31	6.01

^a Energy difference between the most stable axial and equatorial 2-methoxytetrahydropyran conformers. ^b Energy difference between the GT and TG (or the conformation at $\Phi = 180^\circ$) conformers.

The magnitude of the anomeric effect in MTHP is usually calculated by comparing the free energy difference between the axial and equatorial conformers in this compound to the value for methoxycyclohexane. Here, an application of this definition is impractical since it requires knowledge of the free energy difference for the methoxycyclohexane in the presence of the electric field which is not available. Therefore, for the purpose of this investigation we shall define the difference between the energies of the most stable axial and equatorial MTHP conformers as a theoretical anomeric effect. Positive values of this

difference refer to the preference of the axial form in accordance with the anomeric effect. In evaluating the exoanomeric effect, its magnitude in AMTHP and EMTHP must be considered separately. It will be estimated as the difference in the energies of the GT conformer and the TG conformer. Values of the calculated theoretical values of the anomeric and exoanomeric effects are summarized in Table 4. The dependence of the magnitude of both effects on the electric field follows the dependence of the relative energies discussed above. The exoanomeric effect is larger in the equatorial form, except for a field of $E_x = -0.01$ au. The values in Table 4 show that the effect of electric fields on the exoanomeric effect is not very strong. Its magnitude is similar to the values calculated for the gas phase. Exceptions occur when the fields are in directions along the y axis. For $E_y = 0.01$ au field, the exo-anomeric effect increases in axial and equatorial MTHP to 10.8 and 13.0 kcal/mol, respectively. On the other hand, for $E_x = -0.01$ au, the field decreases the exo-anomeric effect in both forms by 5.70 and 6.86 kcal/mol, respectively. In this latter case, the TG conformers are more abundant forms. Thus, the calculations predict considerable influence of the electric field on the magnitude of the anomeric and exoanomeric effects. The strongest effect is seen at $E_z = -0.01$ au, which stabilizes the equatorial form by 4.56 kcal/mol in comparison with the gas-phase calculated energy, and this form becomes the dominant one. However, fields in the opposite direction increase the anomeric effect and with $E_z = 0.01$ au the anomeric effect becomes 5.71 kcal/mol.

Conclusions

In this paper we have studied the rotation about the glycosidic linkage in the presence of the external electric field by *ab initio* molecular orbital methods at the 6-31+G**/6-31G* level.

We have found from a comparison of the conformational energies calculated in the gas phase with those calculated in the presence of strong electric fields that the potential energy of rotation depends on the direction and strength of the external electric field. Strong electric fields considerably influence the topology of the potential energy curve, the occurrence, and stability of the minima. These effects are so pronounced that with fields of $E_x = 0.01$, $E_x = -0.01$, and $E_z = -0.01$ au the axial-equatorial equilibrium is reversed. For example, whereas in gas phase axial MTHP is preferred by 1.08 kcal/mol, in the presence of these fields, contrary to the anomeric effect, the equatorial MTHP is favored by 1.63, 1.14, and 3.48 kcal/mol, respectively. The relative stability of conformers about the glycosidic linkage in both anomers is also influenced by electric field. For example, TG conformers are found to be favored over GT conformers in both anomers in a field of $E_y = -0.01$ au, contrary to the exoanomeric effect which predicts GT conformers to be more stable. Very similar effects of the electric fields were found at all levels of theory.

These results suggest that strong external fields such as those present at the membrane surface might considerably influence the conformational equilibrium around the glycosidic linkage in carbohydrate parts of membrane glycoconjugates and thus their overall shape. They also imply that conformations not

found in the gas phase or in solution equilibria might be important for the biological activity of these molecules.

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