Conformational Analysis of 2-Methoxytetrahydropyran in Relation to the Anomeric Effect

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Abstract: Conformational energies of 2-methoxytetrahydropyran, a model compound for methyl aldopyranoside, are computed using semiempirical energy expressions. The free-energy difference ΔG_{e-a} between the equatorial and axial conformers and the dipole moment $\langle\mu^2\rangle^{1/2}$ for an equilibrium mixture are calculated, the extra stabilization energy ΔE associated with the gauche C–O$\not\subset$C–O arrangements being treated as a variable. The observed values of $\Delta G_{e-a} = 0.7$–0.9 kcal mol^{-1} and $\mu = 1.20 \pm 0.05$ D are both satisfactorily reproduced at a value of $\Delta E = 1.1$ kcal mol^{-1}, thus leading to a preference for the axial conformer. The stabilization energy of the same magnitude has been estimated for the gauche conformation about a C–O bond in polyoxymethylene (POM) chain in the preceding paper. This strongly suggests that the anomalous preference for gauche conformations found in POM is related in its origin to the "anomeric effect" known in carbohydrate chemistry.

It has been known for a long time in carbohydrate chemistry that the 2-alkoxy substituent on pyranosides show a tendency to occupy the axial position in opposition to what might be expected from steric effects.[1] Recent studies on a variety of related compounds[2] lead to a general rule: "Oxane rings substituted in the 2-position by electron-withdrawing groups (X) are more stable in an axial conformation". In an axial form, the conformation of the bond sequence C–O–C–X is gauche around the central O–C bond. As pointed out by Jeffrey, Pople, and Radom,[3] this so-called "anomeric effect" apparently possesses some common aspects with the conformational characteristics of dimethoxymethane[4] and therefore with those of POM.[5,6] They may be related to each other with regard to their origin.

In the preceding paper,[7] attempts were made to elucidate the extra stabilization energies associated with the gauche conformation about C–O and C–C bonds bearing oxygen atoms as substituents. Conformational energy of a gauche state for a bond taken relative to the trans was estimated by two methods:[6] (1) from semiempirical energy calculations in consideration of van der Waals interaction between nonbonded atoms, torsional potential intrinsic to a bond, and electrostatic interaction between partial electronic charges assigned to atoms, and (2) by adjusting conformational energies to reproduce the experimental values of the unperturbed dimension and dipole moment. The difference between the two energy parameters thus derived is defined as the "extra" stabilization energy characteristic of the bond in consideration. The extra energy estimated for the bond sequence C–O–C–O in POM was ca. 1.1 kcal mol^{-1}. Calculations are extended in this paper to the conformational equilibrium of 2-methoxytetrahydropyran, a model compound for methyl aldopyranoside, to investigate the correlation with the anomeric effect.

Pierson and Runquist[8] studied the axial–equatorial equilibrium of various 2-alkoxytetrahydropyrans by means of NMR coupling constants. De Hoog et al.[9] concluded from NMR and dipole moment measurements that the alkoxy group prefers the axial orientation to the extent of 0–1 kcal mol^{-1}, depending upon the bulkiness of the alkyl group and the solvent system employed in the experiment. Lemieux et al.[10] synthesized 4,4,5,5-tetradeuterio-2-methoxytetrahydropyran and $S(+)$-2-methoxytetrahydropyran. They studied conformational equilibria by NMR in relation to the optical rotation. All these observations suggest that the free energy difference between the axial and equatorial conformers of 2-methoxytetrahydropyran is in the range 0.7–0.9 kcal mol^{-1} in low dielectric media. These values are in agreement with those estimated by Eliel and Giza[11] from chemical equilibration studies on 2-alkoxy-4-methyl- and 2-alkoxy-6-methyltetrahydropyran. The dipole moment of 2-methoxytetrahydropyran has been found to be in the range 1.20 ± 0.05 D in carbon tetrachloride,[9] benzene,[9,12] and a benzene-dioxane mixture.[13]

Structural Data

The molecular structure of 2-methoxytetrahydropyran is depicted in Figure 1. Rao and Kewley[14] suggested from the microwave analysis that the only stable conformation of tetrahydropyran ring in the range −40 to 30 °C is a chair form. Bond lengths, bond angles, and dihedral angles given in Figure 1 were selected with reference to the x-ray crystallographic data on β-maltopyranoside (Chu and Jeffrey[15]) and on methyl β-D-ribopyranoside (James and Stevens[16]). For simplicity, the geometry of the ring was taken to be symmetrical for the plane bisecting the bond angle $\angle C_6$–O_1–C_2 and $\angle C_3$–C_4–C_5. Geometrical parameters of the tetrahydropyran ring for the axial and equatorial conformers were taken to be identical except that the signs of dihedral angles are opposite to each other. Shortening of the anomeric C_2–O_7 bond by ca. 0.2 Å in the equatorial conformer has been found from the x-ray analysis on various glycopyranosides.[15-18] In the following calculations unless otherwise noted, a value of 1.38 Å was adopted for this conformer. A value of 1.10 Å was used for the length of all C–H bonds. All angles $\angle$CCH were assumed to be 110° and angles $\angle$OCH for the terminal methyl group were fixed at 109.5°.

Conformational Energy Calculations

Following the procedure set forth in the preceding paper,[7] a threefold intrinsic potential with a barrier of 1.8 kcal mol^{-1} was assigned to rotations around the C_2–O_7 bond. Nonbonded interactions were computed using the Buckingham 6-exponential energy function for each pair of interacting atoms. Parameters required in the expression were taken from Table II of the preceding paper.[7]

Electrostatic interactions were assessed[19] by assigning partial charges to atoms C_6, O_1, C_2, O_7, and C_8 using the observed dipole moment of tetrahydropyran (1.7 D)[14,20] and a previously adopted value (1.2 D)[7,20] for open-chain analogues. Partial electronic charges thus deduced are 0.225(C_6), −0.45(O_1), 0.38(C_2), −0.31(O_7), and 0.155(C_8), respectively. Corresponding values of bond moments are $\mu_{C_6-O_1} = -\mu_{O_1-C_2}$

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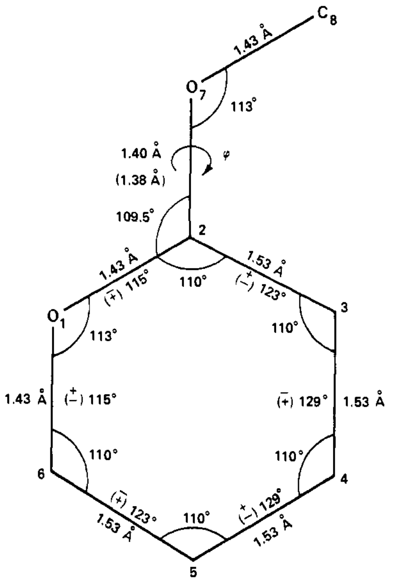

Figure 1. Geometrical parameters for 2-methoxytetrahydropyran. Bond lengths, bond angles, and dihedral angles for the ring conformation are specified. Those in parentheses (bond length C_2–O_7 and signs of dihedral angles) apply to the equatorial conformer. The dihedral angle C_6–O_1–C_2–O_7 is taken to be 125 and −5° for the axial and equatorial conformer, respectively. The configuration thus specified corresponds to the (*R*)-antipode in the absolute notation.

Table I. Calculated Energy Minima ($E_{\min}$ in kcal mol^{-1}, $\varphi_{\min}$ in degrees) for the Axial and Equatorial Conformers

Orientation of bond C_2–O_7	t		g		$\bar{g}$	
	$\varphi_{\min}$	$E_{\min}$	$\varphi_{\min}$	$E_{\min}$	$\varphi_{\min}$	$E_{\min}$
Axial	24	1.38	112	0		>10
Equatorial	24	1.01	113	−0.33	−136	2.45

= 1.55 D, and $\mu_{C_2\text{-}O_7} = -\mu_{O_7\text{-}C_8} = 1.07$ D. A value of 3.0 was used for the effective dielectric constant.[7]

Conformational energies were calculated as a function of the rotation angle around the C_2–O_7 bond, values of φ being defined by the relative position of the O_7–C_8 bond with respect to the O_1–C_2 bond in a conventional manner.[6] We define rotational isomeric states located at approximately $\varphi = 0$, $\pm(2\pi/3)$ as t, g, and $\bar{g}$, respectively, using the notation introduced by Flory et al.[21] for vinyl polymer systems. In the $\bar{g}$ state, the C_8-methyl group is syn to both the O_1 atom and C_3-methylene group. The conformational energies, expressed relative to the g state of the axial conformer, are plotted in Figure 2. Locations of energy minima and the associated energies are summarized in Table I. In agreement with the previous calculations,[7] the g state is more stable by ca. 1.3 kcal mol^{-1} than the corresponding t state in both axial and equatorial conformers. In the $\bar{g}$ state, the C_8-methyl group is sterically interacting with both the O_1 atom and C_3-methylene group: In particular, additional interactions between C_8-methyl and methylene groups at C_4 and C_6 become prohibitively high (>10 kcal mol^{-1}) in the axial conformer. The energy difference of −0.33 kcal mol^{-1} between the most stable (g) forms of the axial and equatorial conformer indicates that electrostatic attraction (−0.5 kcal mol^{-1}) which favors the axial orientation is overcome by the higher steric repulsion (0.8 kcal mol^{-1}). The result of calculations which leads to a lower energy for the equatorial orientation about the C_2–O_7 bond is apparently at variance with the experimental observations.[8-11]

As suggested from the analysis on the POM system,[7] calculations carried out in this manner underestimate the energy difference between the trans and gauche state for the bond sequence C-O-C-O. Conformational energies given in Table I may be corrected for such an effect by adding an extra energy ΔE for each occurrence of a trans C-O-C-O arrangement. Thus

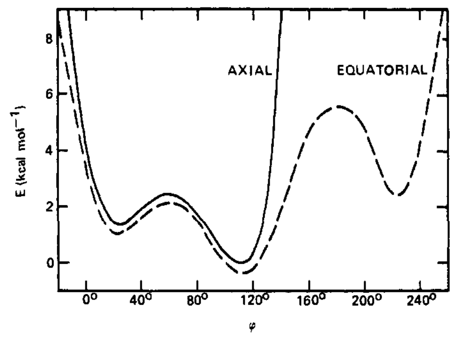

Figure 2. Conformational energies of 2-methoxytetrahydropyran calculated as a function of rotation angles about the bond C_2–O_7. Energies are expressed relative to the g state of the axial conformer.

$$\begin{aligned} E_t^{ax} &= 1.38 + \Delta E_1 \\ E_t^{eq} &= 1.01 + \Delta E_1 + \Delta E_2 \\ E_g^{eq} &= -0.33 + \Delta E_2 \\ E_{\bar{g}}^{eq} &= 2.45 + \Delta E_2 \end{aligned} \qquad (1)$$

where the superscripts specify the orientation of the C_2–O_7 bond. The correction factors ΔE_1 and ΔE_2 represent those required for the moiety O_1–C_2–O_7–C_8 and C_6–O_1–C_2–O_7, respectively. Since ΔE_1 appears only in the less populated species, its contribution should be minor compared to that from ΔE_2. In the following treatment, therefore, no distinction was made between these two ΔE's.

Free Energy Difference between the Axial and Equatorial Conformers

Let us define the statistical weight parameter for a given molecular conformation as

$$\sigma = \exp(-E/RT) \qquad (2)$$

where E is the conformational energy given in Table I and eq 1. The free energy difference $\Delta G_{e\text{-}a}$ was calculated for a given value of ΔE according to the expression

$$\Delta G_{e\text{-}a} = RT \ln \left[\left(\sum_s \sigma_s \right)_{ax} \Big/ \left(\sum_s \sigma_s \right)_{eq} \right] \qquad (3)$$

where s denotes the rotational states t, g, and $\bar{g}$ defined for the C_2–O_7 bond, and subscripts to parentheses specify the orientation of the bond. Results are plotted as a function of ΔE in Figure 3. The observed values of $\Delta G_{e\text{-}a}$ are 0.7–0.9 kcal mol^{-1} in nonpolar solvents.[8-11,22] As indicated by the heavy line in the figure, they are reproduced in the range ΔE = 1.05–1.25 kcal mol^{-1}. At ΔE = 1.1 kcal mol^{-1}, the fraction of the axial conformer corresponds to 78%.

Root-Mean-Square Dipole Moment

The root-mean-square dipole moment for an equilibrium mixture was calculated according to the standard expression

$$\langle \mu^2 \rangle^{1/2} = \left(\sum_i \sigma_i \mu_i^2 \Big/ \sum_i \sigma_i \right)^{1/2} \qquad (4)$$

where each μ_i denotes the dipole moment for a given molecular conformation (Table I) calculated by assigning bond dipoles given above. Here the summation is taken over all species in equilibrium. Results are also plotted against ΔE in Figure 3. The experimental values[9,12,13] (1.20 ± 0.05 D) are reproduced

Table II. Effect of Alkyl Groups on the Dipole Moment of 2-Alkoxytetrahydropyrans

-OR	$\Delta G_{e\text{-}a}$ (obsd),[a] kcal mol^{-1}	μ, D	
		Calcd	Obsd[a]
-OCH_3	0.89	1.07[b]	1.21
-$OCH(CH_3)_2$	0.65	1.25[c]	1.33
-$OC(CH_3)_3$	0.41	1.45[d]	1.44

[a] Observed in CCl_4 at 25 °C; ref 9. [b] Calculated for $\Delta\varphi = 8°$. [c] $\Delta\varphi = 15°$. [d] $\Delta\varphi = 20°$

in the range $\Delta E = 0.95\text{-}1.1$ kcal mol^{-1} (heavy broken line). The magnitude of ΔE thus obtained is in good agreement with that derived from the equilibrium data. Dipole moments of axial and equatorial conformers at $\Delta E = 1.1$ kcal mol^{-1} are 0.60 and 2.21 D, respectively.

Discussion

In an axial form, the bond C_2-O_7 is disposed in the gauche orientation with respect to the bond O_1-C_6 as well as C_3-C_4. As described in the preceding paper,[7] an extra stabilization energy of 0.2-0.3 kcal mol^{-1} is required for a gauche conformation of the bond sequence C-C-C-O in order to reproduce the observed values of unperturbed dimension and dipole moment of poly(tetramethylene oxide). However, this does not necessarily mean that the contribution from the C_4-C_3-C_2-O_7 moiety is as large as this amount. Such effects may not be additive. The good agreement in ΔE values found from the analyses on POM[7] and 2-methoxytetrahydropyran indicates that the major contribution to the anomeric effect arises from the bond sequence C_6-O_1-C_2-O_7. Owing to such effect, the POM chain prefers strongly a helical conformation in succession of either . . . g^+g^+ . . . or . . . g^-g^- . . . .

In the preceding analysis, the bond length C_2-O_7 was taken to be 1.38 Å in the equatorial conformer, being shorter by 0.02 Å than that in the axial counterpart.[30] Adoption of an identical value (1.40 Å) for both conformers lowers the conformational energies E_s^{eq} (s = t, g, $\bar{g}$) by 0.15 kcal mol^{-1} (see Table I). Correspondingly, the value of ΔE which reproduces experimental values of $\Delta G_{e\text{-}a}$ and μ increases by an amount of similar magnitude. The effect arising from this source is minor compared to experimental uncertainties.

The effect of larger alkoxy substituents -OR in place of the methoxy group has been studied by NMR[8,9] and dipole moment measurements.[9,12] With alkoxy substituents such as R = C_2H_5, n-C_3H_7, or n-C_4H_9, the most important steric interactions take place between the α-methylene group at C_8 and constituent groups of tetrahydropyran ring. Replacement of the methyl group of 2-methoxytetrahydropyran by a methylene should not cause much difference in conformational energies. The observed values of $\Delta G_{e\text{-}a}$ and μ are identical within experimental error to the corresponding properties of 2-methoxytetrahydropyran. When the substituent is branched at the α carbon, steric interactions become more severe.[23] With substituents such as R = $CH(CH_3)_2$ or $C(CH_3)_3$, the lowest energy conformation still appears at the g position ($\varphi_g = (2/3)\pi - \Delta\varphi$) about the C_2-O_7 bond in both axial and equatorial conformers. Larger displacements of energy minima ($\Delta\varphi$ = 10-20°) should be expected,[7] however. According to the NMR coupling constant analysis,[8,9] the free energy difference between the axial and equatorial conformer decreases with the bulkiness of the substituent. Taking these experimental values (listed in the second column of Table II) as the energy difference between the two most stable conformers, values of the dipole moment $\langle\mu^2\rangle^{1/2}$ were calculated and are shown in the third column. The dipole moment increases slightly with the bulkiness of the alkoxy group, in agreement with the observed results shown in the last column of Table II.

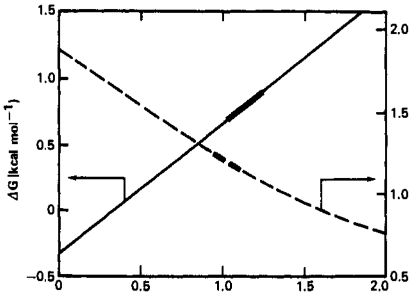

Figure 3. Variation of free energy difference $\Delta G_{e\text{-}a}$ (indicated on the left-hand ordinate) and root-mean-square dipole moment $\langle\mu^2\rangle^{1/2}$ (on the right-hand ordinate) with the extra stabilization energy ΔE. Values were calculated for a temperature of 25 °C. Heavy-line portions represent ranges of ΔE corresponding to $\Delta G_{e\text{-}a}$ = 0.7-0.9 kcal mol^{-1} and μ = 1.15-1.25 D, respectively, in agreement with experiments.

Concluding Remarks

A good agreement in the ΔE value obtained from the analysis on 2-methoxytetrahydropyran and that estimated for POM[7] suggests that these anomeric phenomena arise from a common origin.

Eliel et al.[11,24,25] have extensively studied conformational equilibria for 1,3-dioxane derivatives. When 2-position is substituted by a methoxy group, axial isomers are found to be more stable[11,24] ($\Delta G_{e\text{-}a}$ = 0.4-0.6 kcal mol^{-1}), indicating that the anomeric effect plays an important role. For 5-methoxy derivatives, on the contrary, equatorial conformers are more preferred[25,26] ($\Delta G_{e\text{-}a}$ = −0.8 to −1.0 kcal mol^{-1}). In this conformation, the O-C-C-O arrangements may be identified as "trans". As pointed out by Eliel,[27] this observation contradicts the conclusion drawn from the analysis of polyoxyethylene,[6,7,28] for which the O-C-C-O gauche arrangement was found to be more stable.

Various "gauche oxygen" effects discussed here as well as in the preceding paper[7] are probably related to each other. Similar phenomena are also known with other electronegative atoms such as nitrogen or halogens.[2,29] Conformational analysis along the line presented in this paper will provide useful information regarding the correlation among "anomeric effects" found in a variety of systems.

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(30) K. S. Vijayalakshmi, N. Yathindra, and V. S. R. Rao, *Carbohydr. Res.*, **31**, 173 (1973), estimated the stabilization energy due to the bond shortening to be ca. 0.4 kcal mol^{-1}. This effect should be opposed by the simultaneous increase in the steric interactions.

Electron Impact Studies. C. Doubly Charged Negative Ions[1]

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Contribution from the Department of Organic Chemistry, University of Adelaide, Adelaide, South Australia, 5001. Received August 29, 1975

Abstract: Doubly charged negative ions may be produced in the analyzer region of a conventional mass spectrometer. Evidence is presented which suggests that the formation of the doubly charged ions occurs by the capture process $A^- + e \rightarrow A^{2-}$ and that the ions detected in the mass spectrometer are produced in the electric sector when the sample pressure in that region is greater than 10^{-5} Torr. The most abundant doubly charged molecular anions occur when $n = 3$ or 4 for the series p-NO_2-C_6H_4-$(CH_2)_n$-CO_2R (R = H or Me).

Stuckey and Kiser[2a] made the first observations of doubly charged negative ions in the gas phase using an omegatron. They reported the formation of O^{2-} and X^{2-} (X = halogen) with lifetimes of 10^{-4} s. This claim was questioned[2b] but later verified.[3,4] Other doubly charged ions have since been reported including H^{2-},[5] and P^{2-}, As^{2-}, Sb^{2-}, Te^{2-}, and Bi^{2-}.[3] Kancerenicius[6] using multiconfigurational approximations calculated the energies and orbitals of doubly-charged ions of the 2nd and 3rd row elements and concluded that such ions (e.g., B^{2-}, C^{2-}, N^{2-}, O^{2-}, Al^{2-}, Si^{2-}, P^{2-}, and S^{2-}) are unstable and cannot exist as free radicals. The only report of a doubly charged negative ion from an organic substrate is that claimed[7] for a dimer of benzo[*cd*]pyren-6-one.

Doubly charged ions should be stable if the additional binding energy due to the second electron exceeds the Coulombic repulsion of the ion. Such ions have however not been observed in the *conventional* negative ion spectra of organic compounds (produced by thermal electron capture[8]), obtained in either of our laboratories[9] or in those of von Ardenne.[8b] This is not surprising, since electron capture by a singly charged anion is unlikely in the ion source because of (a) the low concentration of anions relative to molecules in that region and (b) the short residence time of ions in the source. Simultaneous two-electron capture in the ion source is an even more unlikely process.

Doubly charged cations of small abundance are common in conventional positive ion mass spectra, particularly in those of highly conjugated systems.[10] The production and the study of reactions of doubly charged cations produced by high-energy ion-molecule reactions in the analyzer regions of a double focusing mass spectrometer has been pioneered by Beynon, Cooks, and colleagues.[11] Such reactions include (a) $A^+ + N \rightarrow A^{2+} + N^-$ (an $E/2$ spectrum[12]) and (b) $A^{2+} + N \rightarrow A^+ + N^+$ (a $2E$ spectrum), where A^+ is any positive ion and N is the target gas, generally maintained at a pressure of ca. 10^{-4} Torr in the appropriate collision region.

We suggested previously[13] that it should be possible to produce doubly charged negative ions in the analyzer regions of a mass spectrometer (i.e., a $-E/2$ spectrum), and we chose quinones and dinitrobenzenes to test this proposal. Doubly charged anions were not detected;[14] instead, the charge inversion reaction $M\cdot^- \rightarrow M\cdot^+$ was observed. In retrospect, it is clear that the nonobservance of doubly charged negative ions in the previous study was due to an incorrect choice of substrate molecules.

Our first observation of doubly charged anions was accidental. The collision-induced dissociations[15] of the molecular anions of methyl esters of p-nitrobenzoyl amino acids[16] were being monitored using the negative ion kinetic energy (ike) technique.[17] The negative ike spectra showed strong peaks at ca. $-E/2$, and mass analysis showed that these were due to the respective doubly charged parent anions M^{2-}. This discovery led us to investigate the formation of doubly charged negative ions with a view to determine: (i) the types of molecule which form doubly charged anions, and (ii) the mechanism of formation of such ions.

Results and Discussion

$-E/2$ spectra were measured with an Hitachi Perkin-Elmer RMU 7D spectrometer (modified as previously described[17]) operating at 70 eV using an accelerating potential of 3.6 kV (unless otherwise specified), a sector voltage in the range $-(0.502\text{-}0.512)E$, and a sample pressure of 3-5 $\times 10^{-5}$ Torr measured in the first field-free region of the spectrometer. The doubly charged ions are observed at mass $m_{(A^-)}/4$ for the process $A^- \rightarrow A^{2-}$.[18]

(a) The Formation of Doubly Charged Negative Ions. The type of organic molecule that would be expected to form a