may play a role were also discussed.

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Registry No. **1a**, 34627-92-4; **1b**, 115977-82-7; **1c**, 115977-78-1; **1d**, 115977-81-6; **1e**, 115977-79-2; **1f**, 115977-80-5; **1g**, 115977-83-8; **1h**, 115977-84-9; **4**, 3032-92-6; **5**, 75867-40-2; **6**, 536-74-3; **7**, 34627-90-2; **9**, 115977-86-1; **10**, 2170-06-1; **11**, 3989-14-8; **12**, 75867-41-3; cuprous iodide, 7681-65-4; bis(triphenylphosphine)palladium(II) chloride, 13965-03-2; iodobenzene, 591-50-4; biphenyl, 92-52-4; 1,2-diethynyltetramethyldisilane, 54773-31-8; ethynylmagnesium bromide, 4301-14-8; chloropentamethyldisilane, 1560-28-7; 1,2-dichlorotetramethyldisilane, 4342-61-4.

Rotational Barriers. 4. Dimethoxymethane. The Anomeric Effect Revisited

Kenneth B. Wiberg* and Mark A. Murcko†

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511.
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Abstract: The conformational energy map for the rotamers of dimethoxymethane has been calculated using both the 3-21G and 6-31G* basis sets with complete geometry optimization in each case. Higher level calculations including electron correlation also have been performed on selected rotamers. At larger torsional angles, the map has approximate 4-fold symmetry, and this symmetry may be used to quantify the difference in the interactions in the (+sc, −sc) and (+sc, +sc) regions. Large changes in bond angles were found, and the dipole moment also changed considerably on C–O bond rotation. Calculations on equatorial and axial 2-methoxytetrahydropyran show that the axial form is favored by 1.33 kcal/mol, in fair agreement with experiment. Calculations also were carried out on the two lowest energy forms of 1,1-dimethoxyethane and on five forms of methyl propyl ether. Consideration of all these data indicates that the anomeric stabilization in dimethoxymethane is much greater than in sterically more congested systems, but the stabilization of 1,1-dimethoxyethane is similar to that of 2-methoxytetrahydropyran and other acetals.

Molecular modeling is of increasing importance in many areas of chemistry. The most commonly used method, molecular mechanics,[1] requires a knowledge of potential functions for bond length distortion, bond angle distortion, rotation about single bonds, nonbonded interactions, and atomic charges. Whereas the first two of these may be obtained from vibrational spectroscopy, the latter three frequently present experimental problems.

We have begun an analysis of rotational barriers and have presented information concerning barriers to rotation adjacent to carbonyl groups.[2-4] Here, it was possible to show that the barrier had three components: (a) dipole–induced dipole stabilizing interaction between the carbonyl and an adjacent alkyl group; (b) the 3-fold barrier characteristic of the unsubstituted compound (e.g. acetaldehyde, acetone, or acetic acid); (c) in some of the rotamers a gauche or syn repulsive interaction between the substituents attached to the carbonyl.

We now address the more general case of rotational barriers in the absence of unsaturated groups. Recently, we have studied rotational isomerism in alkanes,[5] 2-haloethanols,[6] and 1,2-dihaloethanes,[7] and in each case found that good agreement with experiment could be achieved with ab initio methods. In general, it is necessary to employ split-valence basis sets augmented by polarization functions and to correct for electron correlation.[8] Compounds in which the anomeric effect is found are of particular interest with respect to rotational barriers. This effect was first uncovered in studies of α-methyl glucosides in which it was found that the methoxy group preferred an axial orientation,[9] despite the contrary observation in the cyclohexane series.[10,11] Many experimental studies have shown that this is a general effect and also have shown that the axial C–O bond is longer than one in an equatorial position by $\sim$0.1 Å.[12]

A number of theoretical studies have been carried out in order to provide an explanation for this effect. Some semiempirical methods do not reproduce the gauche preference and bond length alterations. For instance, it was found that extended Hückel and MINDO/2 did not predict the correct global minimum for dimethoxymethane (DMM).[13] On the other hand, ab initio methods at all levels do reproduce the unusual anomeric geometries.[14,15] In one of the more comprehensive studies, Pople et al.[15] studied the rotamers of DMM using a 60° grid and the rigid rotor approximation with the 4-31G basis set. Their results were conveniently expressed with a contour plot showing the change

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† Present address: Merck, Sharp, and Dohme Research Laboratories, West Point, PA 19486.

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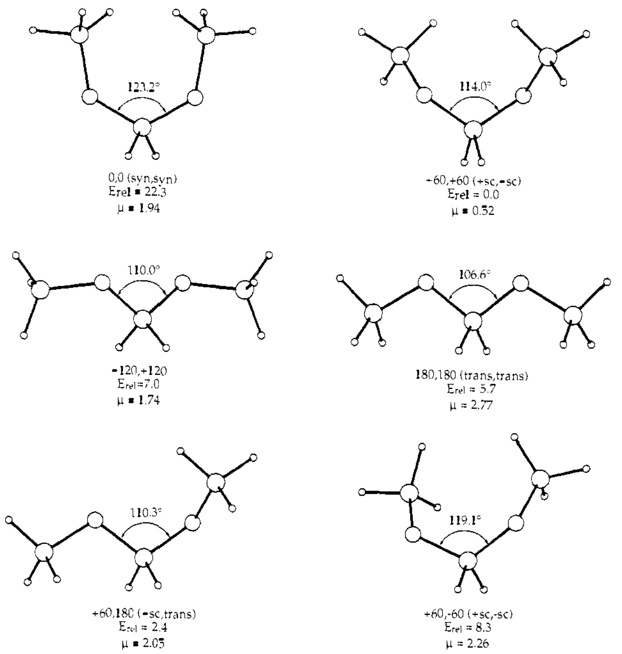

Figure 1. Some rotamers of dimethoxymethane. The relative energies and dipole moments were obtained using the 6-31G* basis set. Note that the global minimum was found at (67°, 67°) and was 0.4 kcal/mol lower in energy than (+60°, +60°).

in energy as a function of the two C–O–C–O dihedral angles, which clearly shows the preference for the rotamer having dihedral angles of (+60°, +60°) about the two CH_2–O bonds. They proposed an interaction between an oxygen lone pair and the adjacent carbon–oxygen bond, which is geometrically favored in the above rotamer. It is commonly referred to as (+sc, +sc) (sc = syn-clinal = torsional angle of 60 ± 30°; Figure 1).

Intuitively, one might expect that rotamers having $\tau_1 = \pm 170°$ and $\tau_2 = \pm 170°$ should all have approximately the same energies since they are far from the orientations at which the anomeric effect is found and lack close methyl–methyl interactions. Thus, at large torsional angles, a plot of energy vs torsional angles should have approximately 4-fold symmetry. However, this is not found in the published data.

In order to see if this might be associated with the use of the rigid rotor approximation, we have repeated the calculations. A 30° grid for the dihedral angles was employed along with the 3-21G basis set and complete geometry optimization. The results of our calculations are presented graphically in Figure 2a. It can be seen that the expectation of approximate 4-fold symmetry at large dihedral angles is borne out by the calculations. In order to highlight the differences between the adjacent quadrants, we have taken the upper left and lower right quadrants of Figure 2 and have rotated them by 90° to give a completely symmetrical pattern (Figure 2b). This was then subtracted from Figure 2a, giving the difference plot (Figure 2c). A strong effect is clearly localized in this plot. Either there is a stabilizing effect in the (+60°, +60°) region, a destabilizing effect in the (+60°, −60°) area, or some combination of the two.

We know in other cases that the 3-21G basis set is not adequate to represent the polarization of atomic orbitals in the presence of an electric field, such as that which might be generated by C–O dipoles.[16] When the 3-21G data were reexamined using a 60° grid, the results were essentially the same as for a 30° grid. Therefore, we have repeated the calculation using the 6-31G* basis set, but at a 60° grid. Whereas a 30° grid required optimization of the structures of 43 rotamers, a 60° grid required the study of only 13 rotamers. This smaller number made it practical to use the more flexible basis set, which usually gives results in good agreement with experimental data.[17]

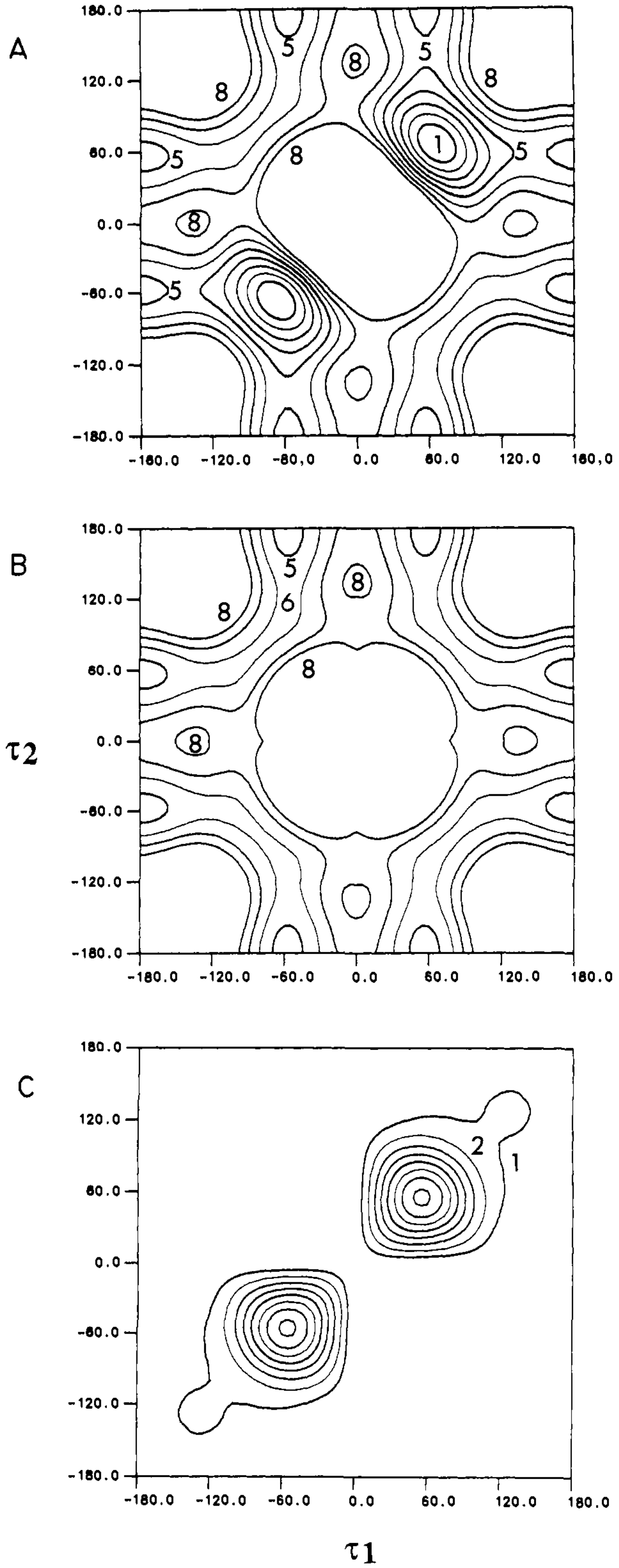

Figure 2. (A) Energy of dimethoxymethane as a function of the torsional angles—3-21G basis set. The relative energies are given in kilocalories per mole. (B) Upper left and lower right quadrants rotated 90°. (C) Figure 2A minus Figure 2B showing the locus of the anomeric effect. The contours are spaced at 1 kcal/mol intervals, and the inner contour is at −8 kcal/mol relative to the plateau.

The 6-31G* energies are summarized in Table I. A contour plot of the energies as a function of dihedral angle is shown in Figure 3a. Figure 3b corresponds to Figure 2c for the 3-21G basis set. Again, it is seen that the anomeric effect is localized

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Table I. Calculated Energies of Dimethoxymethane Conformers, 6-31G* Basis Set

a. Relative Energies (kcal/mol)

	τ_1						
τ_2	-180°	-120°	-60°	0°	60°	120°	180°
-180°	5.66	6.25	2.42	7.08	2.42	6.25	5.66
-120°	6.25	7.01	3.32	8.00	3.96	7.92	6.25
-60°	2.42	3.32	0.00	11.06	8.27	3.96	2.42
0°	7.08	8.00	11.06	22.33	11.06	8.00	7.08
60°	2.42	3.96	8.27	11.06	0.00	3.32	2.42
120°	6.25	7.92	3.96	8.00	3.32	7.01	6.25
180°	5.66	6.25	2.42	7.08	2.42	6.25	5.66

b. Energies of (+60°, +60°) Rotamer and Stationary Points (hartrees and kcal/mol)

τ_1	τ_2	energies	
60.0	60.0	267.954 08	0.00
180.0	65.3	267.950 35	2.34
67.3	67.3	267.954 67	-0.37

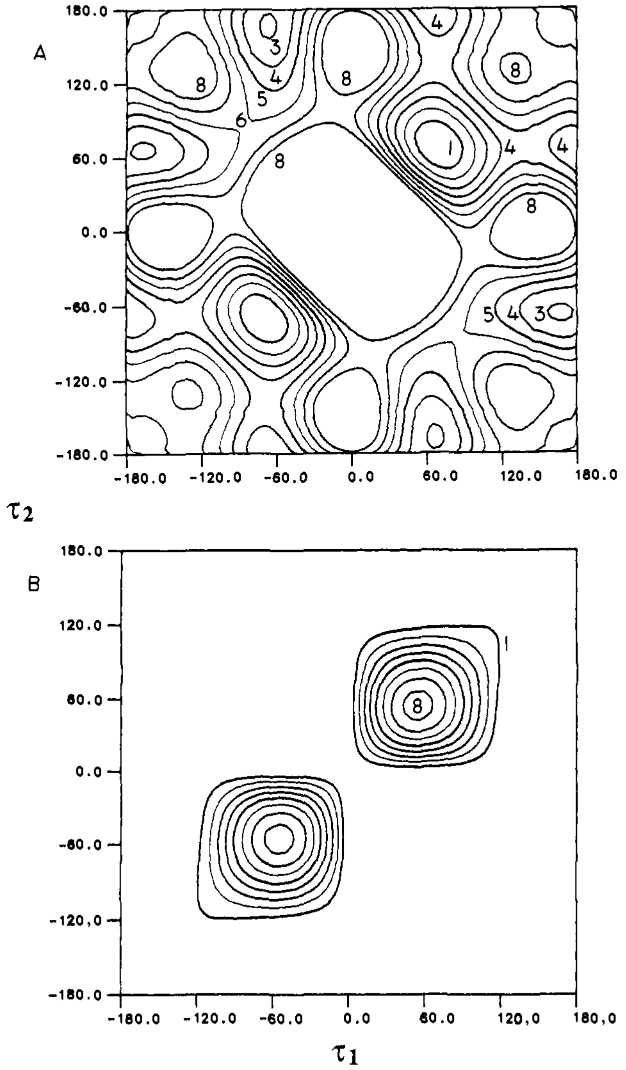

Figure 3. (A) Energy of dimethoxymethane as a function of the torsional angles—6-31G* basis set. The relative energies are given in kilocalories per mole. (B) Figure 3A minus the equivalent of Figure 2B showing the locus of the anomeric effect calculated at the 6-31G* level. The contours are spaced at 1 kcal/mol intervals, and the inner contour is at -8 kcal/mol relative to the plateau.

in a small range of dihedral angles. The relative energies are in some cases significantly different from those obtained using the 3-21G basis. This is quantified in Figure 4, which gives the difference between the 3-21G and 6-31G* relative energies. The effect is most pronounced at the corners of the map, with dihedral angles of (180°, 180°). Here the 6-31G* relative energy is more than 4 kcal/mol lower than at the 3-21G level. Also, at the 3-21G level, the (0°, 180°) conformer is more stable than the all-trans (180°, 180°) species. This is difficult to reconcile with the eclipsing interaction in the (0°, 180°) form, which must be destabilizing. Again, the 6-31G* results are more reasonable, with the (0°, 180°) form now higher in energy than the (180°, 180°) rotamer by more than 1 kcal/mol.

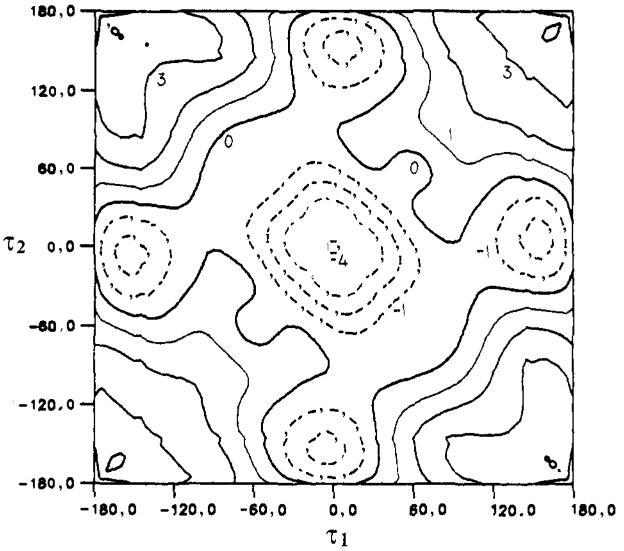

Figure 4. Difference between the 6-31G* and 3-21G energy maps given in Figures 2A and 1A. The energies are given in kilocalories per mole, and positive values indicate lower 6-31G* energies as compared to 3-21G.

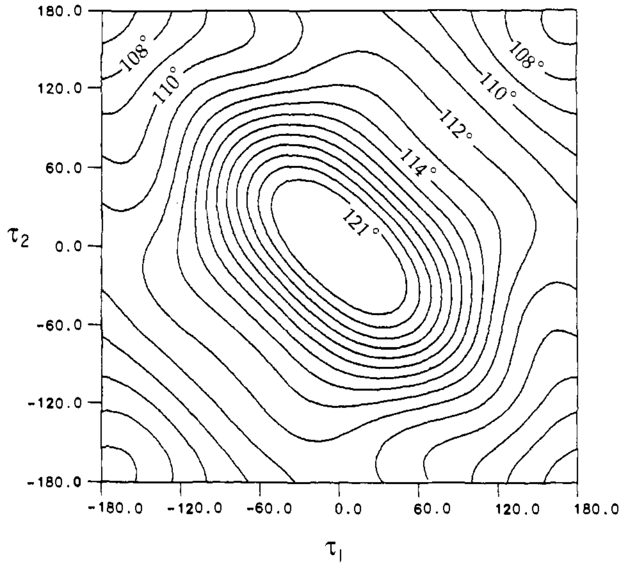

Figure 5. O–C–O bond angles in dimethoxymethane as a function of the dihedral angles.

The variation in geometrical parameters for the set of rotamers also is of interest. These data are given in Table II. The C–O–C and O–C–O bond angles are plotted as a function of the torsional angles in Figures 5 and 6, and the CH_2–O and O–CH_3 bond lengths are plotted as a function of the torsional angles in Figures 7 and 8. The C–O–C angle is taken from the side of the molecule containing τ_1, as is the CH_3–O bond. The CH_2–O bond chosen is the one about which rotation occurs in τ_1. It is clear that there are pronounced geometric changes as rotation occurs, with angles varying by up to 17° and lengths varying by up to 0.04 Å. Clearly, the rigid rotor approximation leads to considerable errors in this case.

We also have relaxed the dihedral angles in order to obtain the geometry of the global minimum. For this purpose, both the 6-31G* and 6-31+G* basis sets were used. The latter was included because the addition of diffuse functions (indicated by +)

Table II, Geometric Data for Dimethoxymethane, 6-31G* Basis Set

	τ_1						
τ_2	-180°	-120°	-60°	0°	60°	120°	180°
			a. Methylene-Oxygen Bond Lengths				
-180°	1,3755	1.3743	1.3684	1.3816	1.3684	1.3743	1.3755
-120°	1,3841	1.3829	1.3767	1.3917	1.3769	1.3842	1.3841
-60°	1,3879	1.3884	1.3819	1.3970	1.3849	1.3885	1.3879
0°	1.3856	1.3847	1.3816	1.3968	1.3816	1.3847	1.3856
60°	1.3879	1.3885	1.3849	1.3970	1.3819	1.3884	1,3879
120°	1,3841	1.3842	1.3769	1.3917	1.3767	1.3829	1.3841
180°	1.3755	1.3743	1.3684	1.3816	1.3684	1.3743	1.3755
			b. Methyl-Oxygen Bond Lengths				
-180°	1,3932	1.3966	1.4011	1.4027	1.4011	1.3966	1.3932
-120°	1.3926	1.3962	1.3998	1.3997	1.3971	1.3957	1.3926
-60°	1.3931	1.3969	1.4002	1.3955	1.3951	1.3969	1.3931
0°	1.3943	1.3981	1.4016	1.3933	1.4016	1.3981	1.3943
60°	1,3931	1.3969	1.3951	1.3955	1.4002	1.3969	1.3931
120°	1.3926	1.3957	1.3971	1.3997	1.3998	1.3962	1.3926
180°	1.3932	1.3966	1.4011	1.4027	1.4011	1.3966	1.3932
			c. C-O-C Angle Changes[a]				
-180°	113.99	116.47	115.35	119.55	115.35	116.47	113.99
-120°	113.83	116.54	115.04	119.23	115.66	116.78	113.83
-60°	114,04	116.41	115.12	123.57	121.39	116.97	114.04
0°	113.89	116.60	119.32	128.70	119.32	116.60	113.89
60°	114.04	116.97	121.39	123.57	115.12	116.41	114.04
120°	113.83	116.78	115.66	119.23	115.04	116.54	113.83
180°	113,99	116.47	115.35	119.55	115.35	116.47	113.99
			d. O-C-O Angle Changes				
-180°	106.60	108.26	110.26	111.43	110.26	108.26	106.60
-120°	108.26	109.97	112.03	113.14	112.34	110.51	108.26
-60°	110,26	112.03	113.98	118.72	119.11	112.34	110.26
0°	111.43	113.14	118.72	123.21	118.72	113.14	111.43
60°	110.26	112.34	119.11	118.72	113.98	112.03	110.26
120°	108.26	110.51	112.34	113.14	112.03	109.97	108.26
180°	106.60	108.26	110.26	111.43	110.26	108.26	106.60

[a] τ_1 is closer to the COC angle.

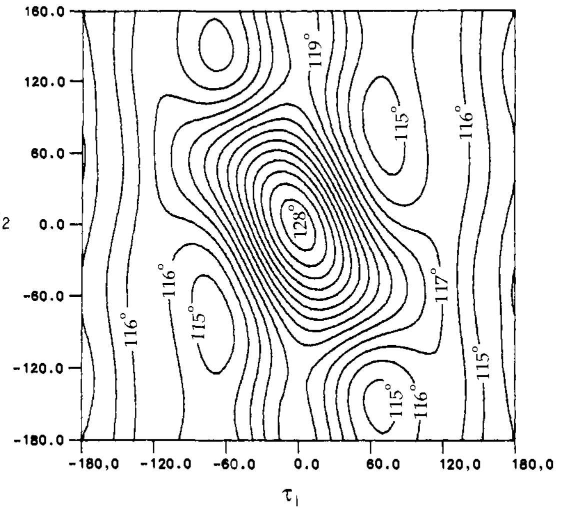

Figure 6. C-O-C bond angles in dimethoxymethane as a function of the dihedral angle. The C-O-C angle is taken from the side of the molecule containing τ_1.

might improve the description of the oxygen lone pairs.[18] Both geometries are given in Table III. The C-O-C-O dihedral angle opened up from 67.3 to 68.4, but other geometric parameters changed by smaller amounts. It is worthwhile to compare our calculated structure to that determined experimentally, also given in Table III. The (60°, 120°) and (60°, 180°) conformers both are calculated to be at least 2 kcal/mol above the global minimum and therefore will not significantly influence the energy or geometry. Thus the calculated geometry for the global minimum is directly comparable to the experimental value. An electron diffraction study found the O-C-O angle to be 114.3°, while the

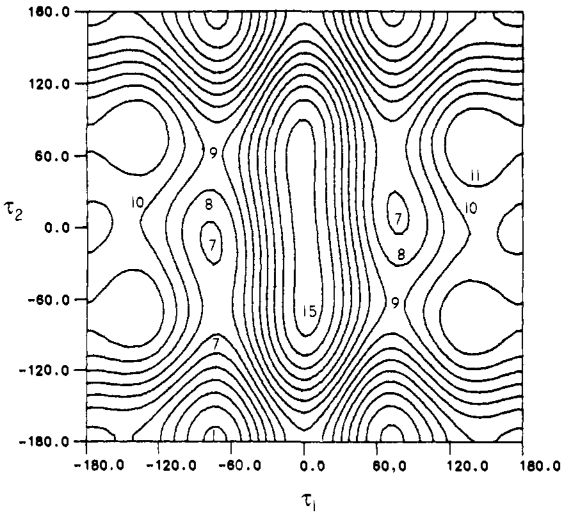

Figure 7. CH_2-O bond lengths in dimethoxymethane as a function of dihedral angle. The C-O bond chosen is the one about which rotation occurs in τ_1. Contour 1 corresponds to 1.368 Å, and the contours are spaced by 0.002 Å.

Table III, Geometric Parameters of the Ground State of Dimethoxymethane

param	6-31G*	6-31+G*	exptl[a]
$r(CH_3$-O)	1.4002	1.4012	1.432
r(O-CH_2)	1.3814	1.3823	1.382
∠(C-O-C)	114.89	115.31	114.6
∠(O-C-O)	113.48	113.49	114.3
τ(C-O-C-O)	67.30	68.40	63.3

[a] By electron diffraction.[19]

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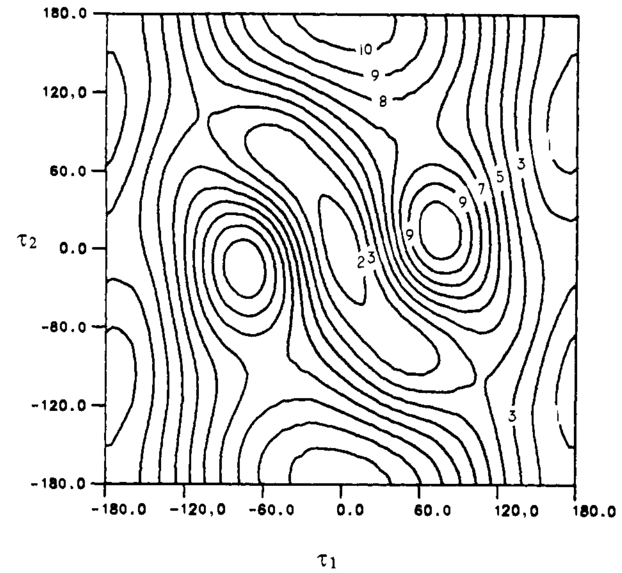


Figure 8. CH_3–O bond lengths in dimethoxymethane as a function of dihedral angle. The C–O bond is taken from the side of the molecule containing τ_1. Contour 1 corresponds to 1.393 Å, and the contours are spaced by 0.001 Å.

outside C–O–C angle was 114.6°.[19] The inside C–O bond length was 1.382 Å while the outside C–O bond was 1.432 Å. The C–O–C–O dihedral angle was 63.3°.[20] The dipole moment in benzene was found to be 0.99 D. All of these agree reasonably well with our results, except for the bond lengths, which are shorter in the calculated structure. This is expected because the ab initio geometry represents a minimum energy structure and fails to account for anharmonicity at the zero-point energy level. A question has been raised concerning the experimental C–O–C bond angle, and a value of 111.6° has been proposed.[21] However, our results provide support for the 114° experimental angle.

To see what effect electron correlation might have on the calculated relative energies, several points were chosen for extended treatment. Full MP4 single-point calculations at the 6-31G* and 6-31+G* levels were carried out on four structures, including the global minimum and three others with dihedral angles of roughly (64°, 117°), (65°, 180°), and (180°, 180°). These results are given in Table IV. Generally, electron correlation raises the relative energies of DMM conformers, while adding diffuse functions to carbon and oxygen (6-31+G*) lowers their relative energies. As has already been noted, the 6-31G* relative energies themselves are significantly lower than the 3-21G results. Thus the effect of increasing basis set size appears to partially cancel the effect of adding electron correlation, and the 6-31G* basis set may provide a reasonable estimate of the relative energies in DMM.

The results of the calculations confirm that the energy changes on bond rotation in DMM are caused by several factors. The changes in bond angles shown in Figures 1, 5, and 6 must in large measure be due to steric interactions. They become large whenever the terminal groups approach each other. The changes in dipole moments such as are shown in Figure 1 will lead to changes in energy. In the gas phase, it is generally found that the rotamer with the larger dipole moment has the larger electrostatic energy, and an increased energy.[7] This effect will be reduced on going to a medium with a higher dielectric constant, and as a result, the populations of various rotamers will change with solvent. Finally, the changes in bond lengths (Figures 7 and 8) probably result from an electronic interaction, and the latter may have an effect on the relative energies. It is not possible at this time to separate the contributions of these terms to the energy differences, and this problem continues to be studied.

Table IV. Effect of Electron Correlation on Calculated Energies of Dimethoxymethane

6-31G* Basis Set

dihedral angles		RHF	MP2	MP3	MP4-(SDTQ)
a. Total Energies (hartrees)					
67.30	67.30	267.954 67	268.695 78	268.727 87	268.762 14
64.38	117.51	267.949 01	268.689 08	268.721 50	268.755 55
65.32	180.00	267.950 35	268.690 27	268.722 72	268.756 67
180.00	180.00	267.945 06	268.684 02	268.716 81	268.750 46
b. Relative Energies (kcal/mol)					
67.30	67.30	0.00	0.00	0.00	0.00
64.38	117.51	3.55	4.20	4.00	4.13
65.32	180.00	2.71	3.46	3.23	3.43
180.00	180.00	6.03	7.38	6.94	7.33

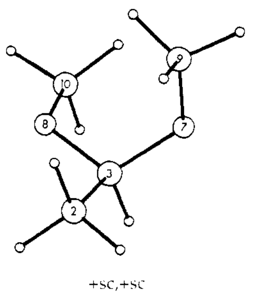
6-31+G* Basis Set

dihedral angles		RHF	MP2	MP3	MP4-(SDTQ)
a. Total Energies (hartrees)					
67.30	67.30	267.961 92	268.714 73	268.745 23	268.782 92
64.38	117.51	267.956 89	268.708 49	268.739 25	268.776 77
65.32	180.00	267.958 09	268.709 44	268.740 28	268.777 63
180.00	180.00	267.952 97	268.702 79	268.734 04	268.770 93
b. Relative Energies (kcal/mol)					
67.30	67.30	0.00	0.00	0.00	0.00
64.38	117.51	3.16	3.92	3.75	3.86
65.32	180.00	2.40	3.32	3.11	3.32
180.00	180.00	5.62	7.49	7.02	7.52

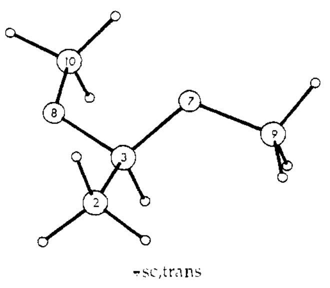
Table V. Calculated Geometries for 1,1-Dimethoxyethane

	(+sc, +sc)		(+sc, 180°)	
	3-21G	6-31G*	3-21G	6-31G*
C2–C3	1.5190	1.5175	1.5168	1.5155
C3–O7	1.4218	1.3916	1.4294	1.3964
C3–O8	1.4207	1.3871	1.4077	1.3760
O7–C9	1.4428	1.4014	1.4341	1.3936
O8–C10	1.4412	1.3995	1.4407	1.3992
C2–C3–O7	113.88	113.98	111.33	111.82
C2–C3–O8	106.39	107.33	106.77	107.51
C3–O7–C9	116.59	117.45	116.29	116.32
C3–O8–C10	115.10	115.24	115.65	115.71
O7–C3–O8	111.23	112.05	108.43	108.74
C2–C3–O7–C9	−59.50	−58.61	85.46	87.59
C2–C3–O8–C10	171.64	168.70	176.09	176.28
O8–C3–O7–C9	60.70	63.53	157.37	153.85
O7–C3–O8–C10	63.83	65.44	56.03	62.48

The next larger acetal is 1,1-dimethoxyethane (DME), which differs from DMM by having one of the methylene hydrogens replaced by a methyl group. DME, with its methyl side chain, is thus a better model for the anomeric effect in acetals, all of which are similarly substituted. The extra alkyl group will raise the steric repulsion in any conformer of DME that has a close contact between methyl and methoxy. Thus, the global minimum (+sc, +sc) should be destabilized relative to the (+sc, trans) form.



+sc,+sc



+sc,trans

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Table VI. Calculated Energies for 1,1-Dimethoxyethane[a]

basis set	(+sc, +sc)	(+sc, 180°)	ΔE
3-21G	305.301 29	305.296 39	3.07
6-31G*	306.993 99	306.992 04	1.22
MP2/6-31G*	307.868 44	307.865 84	1.22
MP3/6-31G*	307.909 63	307.907 15	1.56

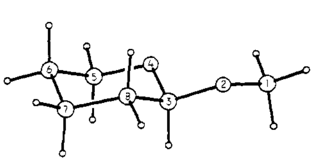
[a] Total energies are given in hartrees, relative energies in kilocalories per mole.

To determine the effect of the increased steric repulsion on the stability of the global minimum, we have carried out some calculations on the (+sc, +sc) and (+sc, trans) forms of DME. 3-21G geometries were first obtained and were followed by optimizations using the 6-31G* basis set. Then, MP3 single-point calculations were carried out at the 6-31G* geometries. The 3-21G and 6-31G* geometries are given in Table V, and all calculated energies are given in Table VI.

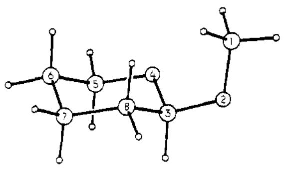
As expected, the (+sc, trans) form is closer in energy to the global minimum (+sc, +sc). The 3-21G calculation again gives a higher relative energy than other basis sets. At the MP3/6-31G* level, (+sc, trans) is about 1.6 kcal/mol above the global minimum, compared to 3.2 kcal/mol for DMM calculated at the same MP3/6-31G* level. More direct evidence for steric destabilization is found in the geometries of the two conformers. In the global minimum, the C2–C3–O7 angle is 113.98° at the 6-31G* level while the C2–C3–O8 angle is 107.33°. Further, the C–O–C–O dihedral angles are smaller than those in DMM, which moves the methyl and methoxy groups apart.

The conformations of dimethoxyethane and related compounds have been studied by Anderson et al.[22] via an examination of the NMR coupling constants along with molecular mechanics calculations. The conclusions are in good accord with those obtained in this study. With the (+sc, trans) form, they estimated a 2° Me–O–C–H torsional angle at the "trans" side. Our calculations suggest a somewhat larger angle, 36°, but still much smaller than the 60° found in the absence of the methyl substituent.

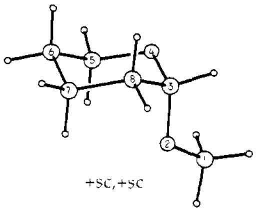
2-Methoxytetrahydropyran (THP) is another important molecule in studies of the anomeric effect. Although on steric grounds one would expect the equatorial conformer to be preferred, variable-temperature NMR equilibrium studies have shown that the axial isomer is indeed favored, with $\Delta G° = 0.89$ kcal/mol in both carbon tetrachloride and benzene solutions.[23] Another NMR study of the pure liquid at 38 °C gave $\Delta G = 0.58 \pm 0.30$.[24] However, recent low-temperature NMR studies by Booth and co-workers suggest that the *enthalpic* difference between the two conformers is practically zero, with the free energy difference coming almost entirely from the entropic term.[25]



trans, -sc



trans, +sc



+sc,+sc

Table VII. Calculated Energies and Geometries for 2-Methoxytetrahydropyran

a. Energies[a]

basis set	equatorial 180°, –sc	equatorial 180°, +sc	axial: +sc, +sc	difference from axial 180°, –sc	difference from axial 180°, +sc
3-21G//3-21G	381.786 43	381.781 61	381.792 33	3.70	6.73
6-31G*//3-21G	383.903 33	383.898 84	383.905 45	1.33	4.15

b. Key Geometrical Parameters (3-21G Basis Set)[b]

param	equatorial 180°, –sc	equatorial 180°, +sc	axial: +sc, +sc
C1–O2	1.4424	1.4435	1.4411
O2–C3	1.4030	1.4091	1.4204
C3–O4	1.4313	1.4035	1.4236
O4–C5	1.4425	1.4428	1.4499
C5–C6	1.5314	1.5317	1.5307
C6–C7	1.5418	1.5413	1.5413
C7–C8	1.5400	1.5411	1.5384
C8–C3	1.5194	1.5268	1.5216
C1–O2–C3	115.63	117.28	115.17
O2–C3–O4	108.75	109.00	111.06
C3–O4–C5	113.81	114.13	114.57
O4–C5–C6	110.21	110.34	110.71
C5–C6–C7	109.74	109.63	109.71
C6–C7–C8	109.78	109.66	109.25
C7–C8–C3	110.13	109.83	109.90
C1–O2–C3–O4	–56.41	43.40	63.63
C1–O2–C3–C8	176.32	78.47	174.64
O2–C3–O4–C5	181.32	175.05	61.51
O2–C3–C8–C7	175.19	179.21	65.68
C3–O4–C5–C6	60.15	60.24	57.15
O4–C5–C6–C7	–55.93	–55.32	–55.55
C5–C6–C7–C8	54.10	54.28	55.83
C6–C7–C8–C3	54.36	55.63	55.60
C7–C8–C3–O4	56.38	57.61	55.72

[a] Total energies are given in hartrees; energy differences are in kilocalories per mole. [b] Bond lengths are given in angstroms; bond angles are in degrees.

The strength of the anomeric effect in THP may be estimated by comparing the axial preference in this system to the value for methoxycyclohexane, which favors the axial by between 0.6[10] and 0.75 kcal/mol.[24] It has been observed[26] that the axial–equatorial free energy differences for many functional groups on tetrahydropyran rings are about 1.5 times the corresponding difference for the cyclohexane derivative. This correction raises the intrinsic equatorial preference of a methoxy group on a tetrahydropyran ring to be ~1.2 kcal/mol. When subtracted from the observed tetrahydropyran value, –0.9, a lower limit on the anomeric effect is seen to be $\Delta G = 2.1$ kcal/mol.[11] The ΔH component might be somewhat smaller.

Since there are experimental data available for THP, it seemed reasonable to attempt calculations on it as well. Unfortunately, the size and lack of symmetry of THP limited us to optimization with the 3-21G basis set and 6-31G* single points carried out at the 3-21G geometries. With the axial form, the (+sc, +sc) conformer is the only low-energy form since the (+sc, trans) rotamer loses much of the anomeric stabilization, and (+sc, –sc) rotamer would place the methyl group over the ring leading to a large steric interaction.[27] In the case of the equatorial form, the lower energy rotamer would be expected to be (180°, –sc), but Fuchs et al.[27] have presented data that suggest that the (180°, +sc) rotamer might have a reasonable energy. Both of these rotamers were studied. The data are given in Table VII. Clearly, the 3-21G basis set gives much larger energy differences than the relatively large 6-31G*. Our best result, 6-31G*//3-21G, has the axial form 1.33 kcal/mol below the (180°, –sc) equatorial form and 4.15 kcal/mol below the (180°, +sc) equatorial form. The effect of using the 3-21G geometry is unknown, but although there

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Table VIII. Calculated Thermodynamic Functions of 2-Methoxytetrahydropyran[a]

	axial	equatorial
zero-point energy	108.98	108.58
$(F - H_0)/T$	−68.55	−68.58
$(H - H_0)/T$	19.40	19.42
S_0	87.75	87.81
C_p	33.60	33.66
zpe + enthalpy	114.76	114.37

[a] Zero-point energy and enthalpy in units of kilocalories per mole; all other quantities in calories per mole Kelvin.

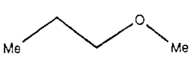
are often systematic changes in bond length on going from 3-21G to 6-31G*, our recent study on compounds containing carbonyl groups has found that the relative energies calculated using the 6-31G* basis set were essentially the same regardless of whether the 3-21G or 6-31G* geometries were used.[4] The possible effect of electron correlation is at present unknown, and the differences in the vibrational frequencies might have a small effect on the relative energies.

In the axial (+sc, +sc) conformer, the two C–O bond lengths at the anomeric center are about equal as expected since both C–O bonds may participate in the anomeric effect. With the equatorial conformer, the bond to the ring oxygen has an approximately 180° torsional angle and so the external C–O bond does not participate in the anomeric effect and is relatively short. The ring C–O bond is now calculated to be unusually long. The two equatorial rotamers generally have similar structural parameters. The major differences are found with the C3–C8 bond to the anomeric center, which is considerably longer in the (180°, +sc) form and with the C1–O2–C3 angle, which is unusually large in the (180°, +sc) form. The C1–O2–C3–C4 torsional angle in the latter is calculated to be 43.4°, considerably smaller than the usual ~60°. This must arise from the greater steric interaction between the methyl group and C8 than with O4.

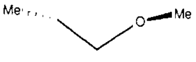
A test of the experimental data is possible using the results of the theoretical calculations. The difference in entropy between the axial and equatorial forms of THP may be calculated if the moments of inertia and the vibrational frequencies are known. The moments of inertia may be obtained from the calculated geometries, and the vibrational frequencies may be estimated using the 3-21G basis set followed by the usual scaling with the factor 0.9. The frequencies have been calculated, and the zero-point energies, enthalpies ($H_{298} - H_0$), heat capacities, and entropies were estimated giving the results shown in Table VIII. Clearly, the calculated entropy difference is not very large and does not support the NMR result[25] that the free energy difference of 0.9 kcal/mol favoring axial THP is entirely due to entropic factors. In fact, combining the ab initio result, 1.33 kcal/mol, with the enthalpies, entropies, and zero-point energies, the calculated ΔH_{298} becomes 0.94 and ΔG_{298} becomes 0.96, the latter number in fortuitously good agreement with experiment.

Various workers have attempted simple methods to quantify the anomeric effect and to estimate the energy differences between isomers. Thus, Deslongchamps[28] and Allinger[21] both give an energy difference of 0.6 for axial and equatorial THP. However, as we have seen, the enthalpic difference may actually be either ~0.0 as the NMR studies indicated[25] or ~1.0, as we calculate here. Thus Deslongchamps' estimate and the MM2 result, both of which are intended to reproduce only the enthalpic difference, should be reconsidered in light of these new findings. In this context, it is worth considering Deslongchamps' and Allinger's estimates of the stability of the several DMM and DME conformers. For DMM, the (+sc, +sc) form is estimated by both methods to be ~1.5 kcal/mol below the (+sc, trans) form. Likewise, DME is found to prefer the (+sc, +sc) rotamer but by only ~0.6 kcal/mol. As the data in Tables III and IV indicate, our calculations give much larger relative energies in both cases.

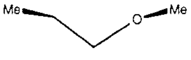
To further explore the strength of the anomeric effect in DMM and related molecules, it is instructive to examine methyl propyl ether (MPE). This molecule contains an electronegative oxygen atom and two C–O bonds on one side and thus will include many of the interactions found in DMM, but it cannot exhibit the anomeric effect. We performed calculations on six rotamers of MPE, as shown below:



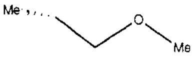
180,180



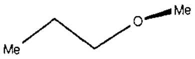
+58,+77



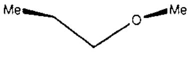
-60,+60



+63,+179



+176,+80



-80,+80

The first number is the C–C–C–O torsional angle, while the second is the C–O–C–C angle. 3-21G- and 6-31G*-optimized geometries were obtained in each case, and *MP*3 single-point calculations were then performed. Key geometric parameters are given in Table IX, while energies are given in Table X.

The geometries should be noted for several reasons. First, the gauche C–O–C–C dihedral angles were actually found to be between 75° and 80° at the both levels of optimization, while the O–C–C–C angles are around 60°. In gauche butane, the C–C–C–C angle is calculated to be ~65°. Second, there is little variation between the CH_3–O and O–CH_2 bond lengths at a given level of theory. In DMM, the O–CH_2 bond is several hundredths of an angstrom shorter than the CH_3–O bond, as is typical for molecules exhibiting the anomeric effect.

The energies in Table X are also worth noting. Contrary to expectations, the (C–O–C–C = trans, O–C–C–C = gauche) form of MPE is found to be the global minimum, 0.36 kcal/mol lower in energy at the MP3/6-31G* level than the all-trans form. The same effect is seen when comparing the (gauche, trans) and (gauche, gauche) forms, which also differ by a small amount, 0.46 kcal/mol, favoring the gauche O–C–C–C component. On the other hand, a trans C–O–C–C fragment is ~1.3 kcal/mol more stable than a gauche orientation. The last two forms of MPE studied were designed to include a 1,5-interaction analogous to the common "syn-gauche" or 1,3-diaxial arrangement. In one case, the two skeletal dihedral angles were fixed at 60° and −60°, and in the other, these angles were fixed at 80° and −80°. This widening of the skeletal dihedral angles is essential if a more realistic relative energy is to be obtained. For instance, in pentane, the form with dihedral angles fixed at 60° and −60° has a calculated energy of 5.4 kcal/mol relative to the trans global minimum, while a relaxed form with angles of roughly 78° and −78° has a relative energy of only 3.6 kcal/mol.[5] A second relaxed form of pentane with dihedral angles of roughly 65° and −95° has about the same energy, 3.3 kcal/mol. For MPE, we could not conveniently find an energy minimum in the (+sc, −sc) region due to large, unstable gradients, so we simply fixed the angles at (+80°, −80°).

Clearly, our calculations indicate there will be a mixture of MPE rotamers present in the gas phase at room temperature. Shimanouchi and co-workers[29] found, by IR and Raman spectroscopy, that MPE exists as a mixture of the (trans, trans), (trans, gauche), (gauche, trans), and (gauche, gauche) forms. ^{13}C NMR studies[30] have been used to determine that the C–O–C–C fragment tends to be trans, while the O–C–C–C segment may be trans or gauche. The microwave spectrum, however, has been analyzed in terms of only the all-trans form.[31]

Our results for MPE may be compared to those for ethyl methyl ether (EME). Here, the trans form is known, both by experiment

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Table IX. Calculated Geometries of Methyl *n*-Propyl Ether (1-Methoxypropane)[a]

	6-31G* Geometric Parameters					
	(180°, 180°)	(77°, 58°)	(80°, 176°)	(179°, 63°)	(60°, −60°)	(80°, −80°)
C1–O2	1.391	1.393	1.393	1.391	1.392	1.393
O2–C3	1.396	1.400	1.399	1.397	1.399	1.400
C3–C4	1.519	1.527	1.526	1.520	1.533	1.530
C4–C5	1.528	1.528	1.529	1.528	1.531	1.531
C1–O2–C3	114.29	115.77	115.87	114.28	119.87	117.92
O2–C3–C4	108.79	113.90	113.47	109.13	119.44	115.70
C3–C4–C5	112.50	112.96	111.97	113.23	119.00	116.58
C1–O2–C3–C4	80.00	77.09	79.65	178.77	60.00	80.00
O2–C3–C4–C5	180.00	58.39	175.66	63.30	−60.00	−80.00

[a] The first number in parentheses is the C–O–C–C dihedral angle, and the second number is the O–C–C–C dihedral angle.

Table X. Calculated Energies for Methyl *n*-Propyl Ether (1-Methoxypropane)

C–O–C–C	O–C–C–C	3-21G	6-31G*	MP2	MP3
		a. Total Energies (hartrees)			
180.00	180.00	230.85745	232.13957	232.83826	232.88209
77.09	58.39	230.85698	232.13717	232.83707	232.80063
79.65	175.66	230.85581	232.13689	232.83609	232.87989
178.77	63.30	230.85849	232.13979	232.83908	232.88266
60.00	−60.00	230.84712	232.12857	232.82845	232.87229
80.00	−80.00	230.85124	232.13257	232.83231	232.87614
		b. Relative Energies (kcal/mol)			
180.00	180.00	0.00	0.00	0.00	0.00
77.09	58.39	0.29	1.51	0.75	0.92
79.65	175.66	1.03	1.68	1.36	1.38
178.77	63.30	−0.65	−0.14	−0.51	−0.36
60.00	−60.00	6.48	6.90	6.16	6.15
80.00	−80.00	3.90	4.39	3.73	3.73

and ab initio calculations, to be at least 1 kcal/mol below the gauche form.[32-35]

It is commonly assumed that the difference in energy between a trans and a gauche O–C–C–C fragment is 0.4 kcal/mol favoring trans.[28] Our results are quite different, however. We find that, at the MP3/6-31G* level, a gauche C–O–C–C fragment is higher in energy by ~1.3 kcal/mol than trans, as is found in EME, but an O–C–C–C fragment *prefers* to be gauche by ~0.4 kcal/mol. In this light, any estimates of relative energies, which consider a gauche O–C–C–C fragment to be destabilizing by 0.4 kcal/mol,[28] should be treated with caution.

We may now attempt to quantify the anomeric effect for DMM. First, the energy difference between the (65°, 180°) and (180°, 180°) rotamers of DMM is obtained. These conformers differ by a single gauche COCO fragment, and the difference E_1 is 3.3 at the 6-31G* level. Second, the energy difference between the (75°, 175°) and (180°, 180°) forms of methyl propyl ether (MPE) is obtained. Here, the gauche torsional angle involves the COCC segment while the OCCC fragment has a 180° torsion. Our calculations indicate that this form of MPE will be less stable than the all-trans form by an amount $E_2 = 1.4$ also at the 6-31G* level. By summing E_1 and E_2 the net stabilization of the "anomeric effect" is seen to be 4.7 kcal/mol. As stated previously, it may be necessary to multiply E_2 by a scaling factor of 1.5 to account for the intrinsic differences between MPE and DMM.[26] This gives a final anomeric stabilization for DMM of 5.4 kcal/mol, much larger than that estimated for THP and other molecules. The simplest explanation for this is the uncrowded nature of the global minimum in DMM relative to all other acetals, which have a central methine rather than a methylene group.

It must be kept in mind that calculations of this kind do not include entropy effects. The absence of such considerations is appropriate where steric and structural factors are under consideration but may give results that do not reproduce experimental findings. While MM2 and other force fields[21,36] often are quite successful at matching experimental data, this may sometimes be the result of fortuitously including entropic factors in the molecular mechanics parameter set. It is desirable to know exactly where such errors occur in order that systematic improvements may be attempted.

Calculations

The calculations were carried out using GAUSSIAN82[37] with the standard basis sets.[38] Initial geometry optimizations were effected using a MicroVAX computer, which was purchased with the aid of a National Science Foundation instrument grant. Most of the 6-31G* optimizations were carried out using a VAX-8600 at the Fairfield University Computer Center, and the larger basis set calculations, post-HF, and vibrational frequency calculations were carried out at the Pittsburgh Supercomputer Center with the aid of a grant from the National Science Foundation Office of Advanced Scientific Computing.

To calculate the enthalpy for each species, $H_{298} - H_0$, the moment of inertia, geometries, and 3-21G frequencies were used in the standard way.[39,40] In calculating the vibrational contribution, however, the frequencies corresponding to methyl rotation were treated separately, using Pitzer's tables.[41]

Acknowledgment. This investigation was supported by the Office of Basic Energy Sciences, Department of Energy, and the National Science Foundation. M.A.M. acknowledges a Connecticut High Technology Scholarship. We thank Fairfield University for a grant of computer time.

Supplementary Material Available: Table of calculated vibrational frequencies of 2-methoxytetrahydropyran (1 page). Ordering information is given on any current masthead page.

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