

# A Molecular Mechanics Treatment of the Anomeric Effect\*

Leif Nørskov-Lauritsen and Norman L. Allinger†

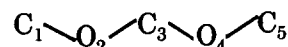
Department of Organic Chemistry, H. C. Ørsted Institute, DK-2100 Copenhagen, Denmark  
Received 18 October 1983; accepted 13 March 1984

The tendency of C—O bond lengths to change as a function of the torsional angles at an acetal carbon has been included in a new version of the molecular mechanics program MM2(82), based on the observed behavior of molecules of this class as indicated by *ab initio* calculations and experimental structural data. The experimental geometries and energies are reasonably well reproduced.

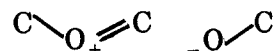
The molecular mechanics or empirical force field method has been widely used for determining molecular structures and energies during the last several years.<sup>1,2</sup> Hydrocarbons and most of the common types of monofunctionalized molecules can be treated with reasonable accuracy and reliability.<sup>3</sup> For polyfunctional molecules the results are generally also quite good if the functions are separated by three or more carbons, but molecules that contain close or adjacent functional groups have not been studied in much detail. Since the interactions between close functional groups are likely to be strong, the results for molecules containing such an organization are not expected to be very good at present. We are currently making an effort to better deal with the interactions between close functional groups, and the present article is concerned with one special interaction of this class which occurs when geminal oxygens (or other electronegative atoms) are present.

This particular pattern of functionalization leads to what is usually called the *anomeric effect*, because it was first recognized as something peculiar to the anomeric carbon (C—1) of sugars.<sup>4</sup> The observation was that an axial methoxyl at the anomeric carbon tended to be more stable than its equatorial counterpart, contrary to the results expected from steric effects. The anomeric effect has been studied theoretically in considerable detail and can be quantita-

tively summarized as follows. The



structure has an important kind of resonance form:



which involves donation of a lone pair of electrons on one oxygen into the carbon oxygen bond region as shown, with a bond breaking and removal of negative charge by the other oxygen. For this resonance to be most effective, the lone pair on O—2 must lie in the plane defined by atoms 2—3—4 (assuming tetrahedral hybridization). If the lone pair lies out of the latter plane, the resonance is suppressed. There are two lone pairs on each oxygen, so the effect needs to be considered for each of the four different lone-pair–oxygen combinations. While the usual steric interactions are minimized by having the torsion angles about the 2—3 and 3—4 bonds either 60° or 180° (+  $V_3$  torsional term), this resonance effect leads to the most effective energy lowering when those angles are 90° (−  $V_2$  torsion term). In addition, the dipole–dipole interactions in the molecule (which in the MM2 program are between the C—O bonds and the O-lone pairs) will try to orient so as to minimize the electrostatic repulsion of the system. The above was all understood and parametrized for in the original version of the MM2 program. Similar effects involving amine nitrogen or halogen occur and were or can be parametrized for similarly. Thus reasonable dihedral angles and energies can be calculated with MM2. There are, however, some unsatisfactory details resulting from this calculation which involve the central O—C—O angle and the bond lengths.

\*Presented at the Molecular Mechanics Symposium, Indianapolis, Indiana, June 23–24, 1983.

†Permanent address: Department of Chemistry, University of Georgia, Athens, GA 30602. Correspondence should be directed to this author at this address.

The O—C—O angle for dimethoxymethane was calculated (MM2) as 114.1° specifically to fit the electron diffraction value (114.3°).<sup>5</sup> Application of the original MM2 force field to a variety of compounds containing geminal oxygens gave calculated angles that were systematically higher than the experimental ones by 2°–4°. This is a significant discrepancy that has now been studied in detail (see below).

In addition, the bond lengths of the C—O bonds in such compounds show a wide variation not accounted for in MM2. In the structure shown, the resonance illustrated lengthens the 2—3 bond and shortens the 3—4 bond, and since this lengthening/shortening is a function of the dihedral angles at 2—3 and 3—4, quite different results are expected (and found) in real molecules, depending on the values of the dihedral angles. The variation may be as much as about

0.030 Å. With MM2, a C—O bond has a fixed value for  $l_0$ , and no torsion–stretch interactions were included, so the observed result of the anomeric effect on bond length was not reproduced. Jeffrey and co-workers have described an adjustment that can be made in MM1<sup>6</sup> which permits good bond lengths to be calculated for the different classes of bonds as they occur in gauche–gauche, anti–gauche, or anti–anti structures that are found in carbohydrates. A similar procedure could be applied to MM2. However, we preferred to develop a more general scheme which would be automatic and applicable to all classes of torsion angle. A straightforward but difficult way (in a programming sense) to account for this interaction would be to use a torsion–stretch interaction term in the force field. The difficult part comes from the first and second derivatives, which must be calculated and programmed for

**Table I.** Anomeric parameters to be added to MM2(82) (ref. 3).

<u>Bending Parameters</u>			
Angle	k	$\phi_0$	Type <sup>a</sup>
O-C-O	0.46	99.9	1
O-C-O	0.46	97.0	2
O-C-O	0.46	102.2	3
<u>Torsion Parameters</u>			
Angle	V <sub>1</sub>	V <sub>2</sub>	V <sub>3</sub>
O-C-O-C	-0.17	-1.20	0
O-C-O-LP <sup>b</sup>	0	0.50	-0.20
<u>Anomeric stretching parameters</u>			
Parameter	Value		
k	0.010 Å		
c	1.3		
d	0.0085 Å		
<u>Heat Parameters</u> (kcal/mol)			
Number	Structure	Parameter	Strainless Parameter
13	O-CH <sub>2</sub> -O	-3.941	-3.527
14	O-CHR-O	-9.886	-6.626
15	O-CR <sub>2</sub> -O	-13.134	-8.560

<sup>a</sup>Types 1, 2, and 3 contain 0, 1, or 2 hydrogens, respectively, on the central carbon.

<sup>b</sup>LP indicates lone pair of electrons.

<sup>c</sup>See Appendix for details on input format.

the energy minimization. We have therefore used an approximation which we believe to be a good one, which gives the desired effect as follows. Instead of using the ordinary value of  $l_0$  for the C—O bond, this value is redetermined for bonds involved in the anomeric effect according to the equation below. Once having the new value of  $l_0$ , the calculation is carried out in the usual way, and the tedious torsion–stretch interaction problem is avoided. As suggested by the resonance form, the value of  $l_0$  is reduced to give a new natural bond length ( $l'_0$ ) by

$$l'_0 = l_0 + \Sigma \delta l$$

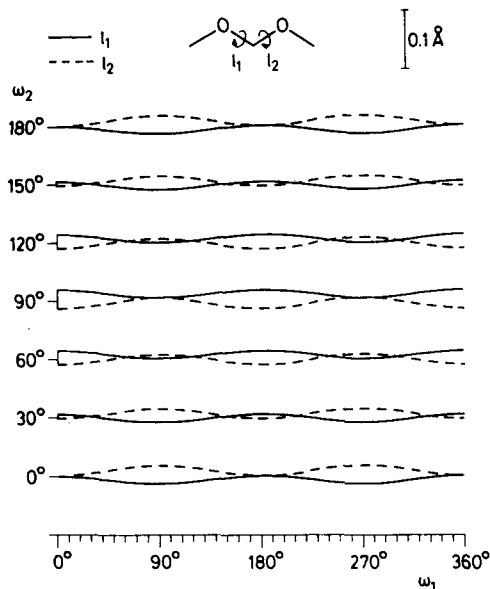
where for the 2, 3 bond, for example,

$$\delta l_{2,3} = \frac{k}{2} [1 + \cos(2\omega_{2,3})] - \frac{ck}{2} [1 + \cos(2\omega_{3,4})] + d_{2,3}$$

and the summation is over each of the electron pairs on  $O_2$ . The optimum constants settled on are given in Table I. A plot of  $l_0$  variations as a function of  $\omega_{2,3}$  and  $\omega_{3,4}$  is shown in Figure 1. The effect of the double bond lengthening is slightly greater (factor of 1.3) than the effect of shortening. There is also an overall shortening (the constant  $d$ ).

The constant  $d$  deserves special comment, as it is an example of an effect that has not been previously recognized to our knowledge, which we will call the "electronegativity effect." Briefly, if an electronegative atom is attached to a given bond, that bond will be shortened. The effect is greater for fluorine than for chlorine or oxygen, and is in the opposite direction for silicon, which is electropositive. The latter case has been worked out by M. Frierson,<sup>7</sup> and is included in the program MM2(82). The others will be discussed in subsequent publications and included in later versions of MM2.

Having decided what formalism was to be used, it was next necessary to decide on the experimental data to be fit. The electron diffraction study by Astrup<sup>5</sup> on dimethoxymethane seemed to provide the key data. We have always fit the MM1 and MM2 force fields to electron diffraction (or neutron diffraction) data in so far as possible. These techniques locate the positions of the atomic nuclei. Microwave spectra measure something different, and the numbers obtained are not quite comparable.<sup>8</sup> But when the force field is used in practice, one usually ends up comparing the calculations to x-ray data, as these are

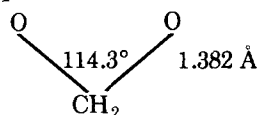


**Figure 1.** Variation of  $l_0$  as function of  $\omega_1$  for fixed values of  $\omega_2$ . Note the symmetry about  $\omega_1 = 90^\circ$  (and  $180^\circ$ ),  $\omega_2 = 90^\circ$ , and  $\omega_1 = \omega_2$  [i.e. no distinction between syn and anti or gauche(+) , gauche(+) and gauche(+), gauche(-)].

far more plentiful. X-rays measure the positions of electron density, which are not quite the same as the nuclear positions. Room-temperature x-ray data will typically give radial bond lengths<sup>9</sup> that are significantly too short, because of the vibrational motions of the molecule in the lattice (unless specific correction for this motion is made). Low-temperature data are much more accurate. In the case of C—O bonds, the lone pairs offset the center of electron density about oxygen so as to make the apparent bond length larger by about 0.004 Å if ordinary data are used.<sup>10</sup> If only data with high-scattering angles are used, this error is reduced by perhaps half (since high-angle data emphasizes the density of the 1s electrons). Small errors in bond angles are also introduced by this factor (a few tenths of a degree), but we will ignore these. In the calculations referred to in the present work neutron diffraction quantities are our standard, and experimental values from x-ray data will be corrected as indicated above before comparisons are made. In cases where the authors have made corrections for thermal (rigid body) motion we have adopted these corrections.

A single peak in an electron diffraction radial distribution function may correspond to two (or more) different atomic distances. To resolve these one utilizes the longer range part of the pattern, but the 1, 3 distance, for example, is determined by two bond lengths and an angle. Compensating

errors in these quantities can give a model that will fit very well the observed distribution function and that may nevertheless be an inaccurate structure. The parts of the Astrup structure of immediate interest are shown. Van Alsenoy et al.<sup>11</sup> have pointed out



that the C—O bond for which Astrup gives a length of 1.382 is much too short to be consistent with his *ab initio* calculations, and he suggests that this bond is longer (and the bonds to methyl shorter so as to keep the average as the experimental value). We agree that such a qualitative change is desirable to bring the values we ultimately calculate into agreement with the x-ray data. We can almost fit to her average C—O value ( $r_a = 1.407$  Å, which would make  $r_g = 1.410$  Å). Our value is 1.417 Å. She quotes an unpublished value by Andreassen and Bauer of 1.413 Å for the bond length (apparently  $r_a$ ). Accordingly, we feel our value is in fair agreement with experiment here. However, if one accepts that the C—O bond lengths are somewhat too short in the Astrup structure, then the O—C—O (114.3°) angle must also be too big (keeping the O···O distance the same). The error is substantial, and our calculated value (111.6°) gives close to the same experimental O···O distance [2.338 vs. 2.320(17), respectively]. These calculated values reproduce the x-ray data and *ab initio* calculations quite well, while the Astrup structure cannot be well fit. It appears, however, that our calculated structure (possibly with further small adjustments) would also give a radial distribution function close to what Astrup observed. As with other previously discussed cases we feel that here again the radial

distribution function does not contain enough information to choose between two structures (or, in this case, probably a range of structures), and the structure found by standard methods is in fact not very accurate.

The calculated structures for the conformations of dimethoxymethane obtained in the present work are summarized in Table II. The O—C—O angle shows a large calculated conformational dependence, from 111.7° in the gauche, gauche (SC, SC) to 106.4° in the anti-anti (ap, ap). This is mainly a result of van der Waals repulsion. Interestingly, the internal C—O bonds are almost the same length in the gauche, gauche and anti, anti conformations (1.413 and 1.410 Å, respectively), but in the anti, gauche conformation, the former is 1.425 and the latter 1.398 Å, respectively). These values are in reasonable agreement with the relative values deduced by Schäfer from *ab initio* calculations, and the gauche, gauche (the only conformation for which experimental data are available) is calculated to be in marginal agreement with Astrup's data. Now we can compare our calculated structures for a wide variety of compounds which have geminal oxygens with available data, mostly from structures determined by x-ray crystallography.

The original (1977) version of MM2 does not allow for the anomeric effect on bond lengths (although this could be remedied as described by Jeffrey), and it gives O—C—O angles based on the original Astrup structure which are too large (by about 2° for the gauche, gauche structure, 3° for anti, gauche and 4° for anti, anti). This can be corrected in MM2 by using smaller values for both  $\Theta_0$  and  $k_\theta$  for this angle (see Table II). These changes also require small adjustments in the heat of formation calculation (in the structure increments for O—C—O).

Table II. Structures for the dimethoxymethane conformations.

FEATURE	+sc, +sc		+sc, ap		ap, ap	
	MM2 (82)	AB INITIO <sup>a</sup>	MM2 (82)	AB INITIO <sup>a</sup>	MM2 (82)	AB INITIO <sup>a</sup>
CH <sub>3</sub> -O	1.422	1.426	1.421, 1.422	1.419, 1.425	1.422	1.421
O-CH <sub>2</sub>	1.413	1.400	1.425, 1.398	1.410, 1.386	1.410	1.397
O-C-O	111.7	112.4	109.3	109.5	106.4	105.9
C-O-C	112.8	114.5	111.9, 112.8	114.9, 114.3	119.0	114.0
C-O-C-O	72.9	62.4	175.0, 73.0	179.4, 57.4	180.0	180.0

<sup>a</sup>The 4-21G *ab initio* values are corrected by adding  $-0.023$  Å to give the  $r_g$  values [an average of the recommended (ref. 12) corrections  $-0.019(3)$  to  $-0.027(4)$ ].

The newer (1982) version of MM2 [called MM2(82)<sup>3</sup>] has the necessary bond length correction equation in the program, but the required parameters were not yet known when the program was released, and were all entered as zeros. Hence to incorporate all of this material in MM2(82), the information in the Appendix must be read in with the input data in the usual way.

There are some inconsistencies in the experimental data that we are not able to resolve. The standard structures from which we normally fit the force field come from electron diffraction data on small molecules in the gas phase, and more recently, from an occasional neutron diffraction structure from a crystal. These methods locate the atomic nuclei and measure similar quantities (not exactly the same because of different methods of averaging over the vibrational motion); x-ray data are on the whole closely similar to neutron data, except for special cases such as location of hydrogen or oxygen, where there are large and small differences, respectively, between the positions of the nuclei and the centers of electron density. In the case of C—O bonds discrepancies remain. The C—O bond lengths found for ethers apart from those involved in the anomeric effect seem to be on the average about 0.010 Å longer by good, high quality, corrected low temperature x-ray data than by electron diffraction. Since these bond lengths

in simple ethers were originally fit in the MM2 program to electron diffraction values, the experimental values quoted in the present work from x-ray data are longer. On the other hand, the anomeric effect has been fit to x-ray data (the only available data), and when the calculated value is compared with the single available experimental value from electron diffraction the calculated value is too large. Why these systematic differences exist is uncertain, and hopefully more high quality data and a fuller understanding of the problems involved will permit resolution of the difficulty in the future.

In the process of fitting the bond lengths, and in reoptimizing the other anomeric parameters, including the O—C—O angles that MM2 did not deal with very well, we first examined dimethoxymethane. There are found in the calculations three conformations, *GG*, *AG*, and *AA*, and the torsional potential function about the C—O—C—O bond has the  $V_1$  and  $V_2$  parts chosen to yield a reasonable energy difference between these. The  $V_3$  term was carried over from the C—C—O—C bond of ethers. While the energy differences between the conformers are not known accurately here<sup>14</sup> (only the *gauche*, *gauche* is seen experimentally by electron diffraction), the stability of the *gauche*, *gauche* isomer must be at least 1 kcal/mol greater than the others; the final value decided was arrived

**Table III.** Calculated and experimental data for the compounds studied. Values marked with a trailing + or - represent differences (calc - exp).

C1 - O2 - C3 - O4 - C5				
# COMPOUND, COMMENT	OBS	EXP	MM2	MM282
1 DIMETHOXYMETHANE <i>anti,anti</i> Ab initio: L. Schaefer et al., <i>J. Mol. Struct.</i> <b>86</b> (1981) 111. C-O bond lengths corrected by -0.0230 Å. Energy (E) is relative to most stable isomer (kcal/mol <sup>-1</sup> )	O2-C3	1.3971	0.0285 +	0.0133 +
	C1-O2	1.4210	0.0003 +	0.0008 +
	O-C-O	105.9	3.97 +	0.50 +
	C-O-C	114.0	2.02-	2.09-
	E	?	3.38	4.03
2 DIMETHOXYMETHANE <i>anti,gauche</i>	O2-C3	1.4098	0.0148 +	0.0154 +
	C3-O4	1.3863	0.0393 +	0.0117 +
	C1-O2	1.4193	0.0017 +	0.0018 +
	O4-C5	1.4257	0.0043-	0.0037-
	O-C-O	109.5	2.60 +	0.24-
	C1-O2-C3	114.3	2.23-	2.45-
	C3-O4-C5	114.9	2.86-	2.16-
	C1-O2-C3-O4	179.4	3.5-	4.4-
	O2-C3-O4-C5	57.4	14.2 +	15.6 +
	E	?	1.62	1.98
3 DIMETHOXYMETHANE <i>gauche(+),gauche(+)</i> Gas electron diffraction: E.E. Astrup, <i>Acta Chem. Scand.</i> <b>27</b> (1973) 3271. $r_s$ = C-O (average) = 1.407(3) Å $r_s$ (O2-C3) = 1.396 Å, $r_s$ (C1-O2) = 1.423 Å	O2-C3	1.3996	0.0252 +	0.0133 +
	C1-O2	1.4261	0.0049-	0.0045-
	O-C-O	112.4	1.87 +	0.75-
	C-O-C	114.5	2.19-	1.75-
	C-O-C-O	62.4	7.7 +	10.5 +
	E	0	0.0	0.0
11 TETRAMETHOXYTETRAMETHYL- 1,4-CYCLOHEXADIENE <i>anti,anti</i> X-ray diffraction at 100 K (Mo, 0.81 Å <sup>-1</sup> ) M.G. Ettlinger et al., <i>Acta Cryst.</i> <b>B38</b> (1982) 3107. Non-exact symmetry averaged. C-O correction (LP deformation) -0.002 Å. C(11)-O(7)-C(3)-O(8)-C(12)	O2-C3	1.4291(10)	0.0116 +	0.0038-
	C1-O2	1.4228(11)	0.0039-	0.0022-
	O-C-O	98.95(5)	4.32 +	0.69 +
	C-O-C	115.00(7)	0.03-	0.69-

Table III. (continued from previous page)

C1 - O2 - C3 - O4 - C5					
#	COMPOUND, COMMENT	OBS	EXP	MM2	MM282
12	ETHYLENEGLUCOPYRANOSE <i>anti,anti</i> Xray at 120 K (Mo, 0.71 Å <sup>-1</sup> ): R. Norrestam et al., <i>Acta Cryst. B37</i> (1981) 1689. No hydrogen-bonding to ether oxygens. MM2 model compound: 1,4,5-trioxadecalin. C-O correction (LP deformation) = -0.002 Å. C(6)-O(5)-C(10)-O(4)-C(3)	O2-C3 C3-O4 C1-O2 O4-C5 O-C-O C1-O2-C3 C3-O4-C5	1.411(2) 1.403(2) 1.436(2) 1.443(2) 105.2(1) 111.2(1) 109.1(1)	0.0148+ 0.0217+ 0.0149- 0.0219+ 4.81+ 0.61+ 1.54+	0.0025- 0.0042+ 0.0116- 0.0202+ 0.01+ 0.11- 0.67+
21	2,10-DIOXATRICYCLO(4.4.4.0)TETRADECANE <i>anti,gauche</i> , Xray at 96 K (Mo, 0.86 Å <sup>-1</sup> ): J.D. Dunitz et al., <i>Acta Cryst. B38</i> (1982) 1241. Bond lengths corrected by +0.002 Å to account for thermal motion. C-O correction (LP deformation) = -0.002 Å. C(9)-O(10)-C(1)-O(2)-C(3)	O2-C3 C3-O4 C1-O2 O4-C5 O-C-O C1-O2-C3 C3-O4-C5 C1-O2-C3-O4 O2-C3-O4-C5	1.438(1) 1.412(1) 1.432(1) 1.432(1) 105.1(1) 115.5(1) 115.0(1) 178.2(1) -62.8(1)	0.0053- 0.0232+ 0.0116- 0.0117- 2.97+ 0.22+ 0.52- 0.8+ 1.5+	0.0091- 0.0036- 0.0106- 0.0106- 0.38+ 0.51- 0.22+ 1.8+ 0.4+
22	CIS-1,8-DIOXA-4,5-DITHIADECALIN <i>anti,gauche</i> Xray at 100 K (Mo, 0.90 Å <sup>-1</sup> ): L. Nørskov-Lauritsen, unpublished. Bond lengths have been corrected by +0.001 Å for thermal motion. C-O correction (LP deformation) = -0.002 Å. C(7)-O(8)-C(9)-O(1)-C(2)	O2-C3 C3-O4 C1-O2 O4-C5 O-C-O C1-O2-C3 C3-O4-C5 C1-O2-C3-O4 O2-C3-O4-C5	1.4146(12) 1.4023(12) 1.4352(13) 1.4371(12) 107.43(6) 113.47(7) 115.36(6) 169.65(7) 62.28(9)	0.0113+ 0.0260+ 0.0145- 0.0155- 3.67+ 0.08+ 1.34- 3.2- 0.1-	0.0074+ 0.0005+ 0.0140- 0.0146- 1.08- 0.54- 0.20- 3.4- 1.5+
23	TETRAMETHOXYDIMETHYLCYCLOHEXADIENE <i>anti,gauche</i> , Xray at 100 K (Mo, 0.96 Å <sup>-1</sup> ): L. Nørskov-Lauritsen, unpublished. Bond lengths have not been corrected for thermal motion. C-O correction (LP deformation) = -0.002 Å. C(11)-O(7)-C(3)-O(8)-C(12)	O2-C3 C3-O4 C1-O2 O4-C5 O-C-O C1-O2-C3 C3-O4-C5 C1-O2-C3-O4 O2-C3-O4-C5	1.4383(9) 1.4076(9) 1.4217(10) 1.4274(9) 105.36(5) 114.36(5) 116.30(6) 173.0(1) 66.4(1)	0.0045- 0.0296+ 0.0003+ 0.0067- 3.88+ 0.46- 1.09- 4.4+ 1.5+	0.0048- 0.0026- 0.0005+ 0.0060- 0.10- 0.83- 0.22- 4.0+ 4.4+
24	CIS-1,4,5,8-TETRAOXADICALIN <i>anti,gauche</i> Xray at room temp (Mo, film): B. Fuchs et al., <i>J.C.S. Perkin II</i> 1972, 357. Bond lengths corrected for thermal motion by up to +0.011 Å. Non-exact symmetry averaged. C-O correction (LP deformation) = -0.004 Å. C(7)-O(8)-C(9)-O(1)-C(2)	O2-C3 C3-O4 C1-O2 O4-C5 O-C-O C1-O2-C3 C3-O4-C5 C1-O2-C3-O4 O2-C3-O4-C5	1.425(4) 1.404(8) 1.437(5) 1.442(5) 107.7(6) 110.0(7) 113.2(3) 179.5(5) 71.0(5)	0.0016- 0.0213+ 0.0183- 0.0222- 1.83+ 0.86+ 1.72- 0.2+ 1.4-	0.0032- 0.0075- 0.0178- 0.0203- 0.52- 0.01+ 0.95- 0.6- 0.2-
25	EQUATORIAL 2-METHOXYOXANE <i>anti,gauche</i> Averaged crystal structures: G.A. Jeffrey et al., <i>Carbohydr. Res.</i> 25 (1972) 117. C(6)-O(1)-C(2)-O(7)-C(8)	O2-C3 C3-O4 E	1.425 1.383 1.05	0.0009+ 0.0450+ 1.22	0.0013+ 0.0170+ 1.17
31	TETRAMETHOXYCYCLOHEXADIENE <i>gauche(+),gauche(+)</i> Xray -50 °C (Mo 0.68 Å <sup>-1</sup> ): Liebich et al., <i>Acta Cryst. B32</i> (1976) 269. No correction for thermal motion. Non-exact sym- metry averaged. C-O correction (LP deformation) = -0.003 Å. C(11)-O(7)-C(3)-O(8)-C(12)	O2-C3 C1-O2 O-C-O C-O-C C-O-C-O	1.423(3) 1.434(8) 110.6(1) 115.9(2) 62 (?)	0.0121+ 0.0131- 1.39+ 0.53- 6.5+	0.0006- 0.0130- 2.37- 0.00- 9.9+
32	OCTAOXATRICYCLO(6.12.6)EICOSANE <i>gauche(+),gauche(+)</i> Xray 100 K (Mo, 0.70 Å <sup>-1</sup> ): R.B. Jensen, unpublished. No correction for thermal motion. C-O correction (LP deformation) = -0.002 Å. C(1)-O(2)-C(3)-O(4)-C(5)	O2-C3 C3-O4 C1-O2 O4-C5 O-C-O C1-O2-C3 C3-O4-C5 C1-O2-C3-O4 O2-C3-O4-C5	1.417(3) 1.406(2) 1.429(2) 1.430(3) 113.0(1) 112.7(2) 111.9(2) 80.0(2) 71.2(2)	0.0078+ 0.0181+ 0.0032- 0.0070- 0.13- 0.81+ 0.74+ 5.1- 3.6+	0.0037- 0.0068+ 0.0035- 0.0068- 2.67- 1.15+ 1.17+ 4.5- 5.0+
33	AXIAL 2-METHOXYOXANE <i>gauche(+),gauche(+)</i> Averaged structures: G.A. Jeffrey et al., <i>Carbohydr. Res.</i> 25 (1972) 117. C(6)-O(1)-C(2)-O(7)-C(8)	O2-C3 C3-O4 E	1.417 1.407 0	0.0092+ 0.0199+ 0.0	0.0012- 0.0058+ 0.0
34	DIMETHOXYPROPANE <i>gauche(+),gauche(+)</i> Gas electron diffraction: E.E. Astrup et al., <i>Acta Chem. Scand.</i> 29 (1975) 794.	O2-C3 C1-O2 C-C O-C-O C-O-C C-C-C C-O-C-O	1.423(6) 1.423(6) 1.513(8) 117.4(22) 114.0(14) 112.2(29) 52(?)	0.0079+ 0.0022- 0.0322+ 4.21- 0.89+ 4.44- 12.0+	0.0048- 0.0018- 0.0310+ 7.76- 1.60+ 3.95- 17.3+
41	TRANS-1,3,5,7-TETRAOXADICALIN <i>gauche(+),gauche(-)</i> Xray, 100 K (Mo, 0.70 Å <sup>-1</sup> ): Karin Nilsson, unpublished. No correction for thermal motion. C-O correction (LP deformation) = -0.002 Å. C(9)-O(1)-C(2)-O(3)-C(4)	O2-C3 C3-O4 C1-O2 O4-C5 O-C-O C1-O2-C3 C3-O4-C5 C1-O2-C3-O4 O2-C3-O4-C5	1.4182(8) 1.4161(11) 1.4300(9) 1.4391(9) 112.38(6) 109.00(5) 110.98(6) -61.73(8) 62.33(7)	0.0069+ 0.0086+ 0.0102- 0.0154- 0.97+ 0.36+ 0.34- 0.07- 1.03-	0.0040- 0.0020- 0.0100- 0.0148- 0.92- 0.92+ 0.34+ 1.27- 0.17+

Table III. (continued from previous page)

C1 - O2 - C3 - O4 - C5					
#	COMPOUND, COMMENT	OBS	EXP	MM2	MM282
42	OCTAOXATRICYCLO(6.12.6)EICOSANE <i>gauche</i> (+), <i>gauche</i> (-) Xray, 100 K (Mo, 0.70 Å <sup>-1</sup> ) R.B. Jensen, unpublished. No correction for thermal motion. C-O correction (LP deformation) = -0.002 Å C(6)-O(7)-C(8)-O(9)-C(10)	O2-C3 C3-O4 C1-O2 O4-C5 O-C-O C1-O2-C3 C3-O4-C5 C1-O2-C3-O4 O2-C3-O4-C5	1.411(3) 1.407(3) 1.435(3) 1.431(3) 112.2(1) 110.2(1) 110.2(1) 64.9(3) -61.9(2)	0.0107+ 0.0150+ 0.0119- 0.0099- 0.27+ 0.38+ 0.14- 1.8- 1.8-	0.0005- 0.0033+ 0.0117- 0.0095- 1.86- 0.88+ 0.52+ 0.0- 3.4-
43	1,3-DIOXANE (CHAIR) <i>gauche</i> (+), <i>gauche</i> (-) Gas electron diffraction: G. Schultz et al., <i>Acta Chim. Acad. Sci. Hung.</i> <b>83</b> (1974) 331.  Average is mean of 6C-C, 8C-O and 8O-C	O2-C3 C1-O2 O-C-O C-O-C C-O-C-O C-X (av.) E	1.393(25) 1.439(39) 115.0(28) 110.9(15) 58.9 1.446(7) 0	0.0303+ 0.0177- 2.20- 0.82- 4.2+ 0.0069+ 0.0	0.0186+ 0.0174- 4.46- 0.23- 6.2+ 0.0025+ 0.0
44	1,3-DIOXANE (C <sub>2</sub> TWIST) <i>gauche</i> (+), <i>gauche</i> (+)	E	c. 6	5.09	5.08
45	1,3-DIOXANE (C <sub>1</sub> TWIST) <i>gauche</i> (+), <i>gauche</i> (-)	E	?	4.97	4.77
46	1,3-DIOXEPANE (C <sub>2</sub> TWIST CHAIR) <i>gauche</i> (+), <i>gauche</i> (+)	E	?	0.0	0.39
47	1,3-DIOXEPANE (C <sub>1</sub> TWIST BOAT) <i>gauche</i> (+), <i>gauche</i> (-)	E	?	0.04	0.0
48	1,3-DIOXOLANE (C <sub>2</sub> TWIST) <i>syn, syn</i> Minimum energy conformation is envelope.	E	c. 0	0.37	0.52
49	1,3,5-TRIOXANE <i>gauche</i> (+), <i>gauche</i> (-) Gas electron diffraction: A.H. Clark et al. <i>J. Mol. Struct.</i> <b>9</b> (1971) 33. Xray diffraction at 100 K (Mo, film 0.45 Å <sup>-1</sup> ): V. Buseti et al., <i>Acta Cryst.</i> <b>B25</b> (1969) 1191. C-O correction (LP deformation) = -0.004 Å	C-O (ED) C-O (XD) O-C-O(ED) C-O-C(ED) C-O-C-O(ED)	1.411(2) 1.417(6) 111.0(7) 109.2(10) 58.4(7)	0.0130+ 0.0070+ 0.23+ 0.30- 0.1+	0.0004+ 0.0056- 2.34- 0.75+ 2.0+
50	1,3,5,7-TETROXOCANE <i>gauche</i> (+), <i>gauche</i> (-) Xray diffraction at 19 °C (Mo, 0.70 Å <sup>-1</sup> ): Y. Chatani et al. <i>Bull. Chem. Soc. Jap.</i> <b>47</b> (1974) 583. Almost C <sub>4v</sub> symmetry, torsion angles deviate. C-O correction (LP deformation) = -0.004 Å	C-O O-C-O C-O-C C-O-C-O E	1.399(6) 113.8(2) 116.6(6) 84 - 94 1 (?)	0.0240+ 1.32+ 2.72- 90.0 1.94	0.0130+ 1.26- 2.33- 91.7 1.97
51	1,3,5,7,9-PENTOXECANE <i>variable</i> Xray diffraction at 16 °C (Mo, 0.65 Å <sup>-1</sup> ): Y. Chatani et al., <i>Bull. Chem. Soc. Jap.</i> <b>46</b> (1973) 2300. Exact C <sub>2</sub> symmetry. No correction for thermal motion. C-O correction (LP deformation) = -0.004 Å Xray numbering system: O3-C3-O2-C2-O1-C1-O1'-C2'-O2'-C3'	O1-C2 C2-O3 O3-C4 C4-O5 O5-C6 O1-C2-O3 O3-C4-O5 O5-C6-O7 C2-O1-C10 C2-O3-C4 C4-O5-C6 C10-O1-C2-O3 O1-C2-O3-C4 C2-O3-C4-O5 O3-C4-O5-C6 C4-O5-C6-O7	1.407(3) 1.408(2) 1.398(2) 1.416(2) 1.408(2) 110.7(2) 111.7(2) 112.9(2) 115.1(2) 116.0(2) 115.6(2) -69.8 123.4 -84.2 118.7 -72.9	0.0175+ 0.0187+ 0.0293+ 0.0113+ 0.0141+ 3.33+ 1.90+ 0.81+ 1.72- 1.69- 1.76- 1.4- 2.0- 0.1- 2.4+ 1.6+	0.0031+ 0.0092+ 0.0135+ 0.0044+ 0.0022+ 1.06+ 0.68- 1.80- 0.49- 1.29- 1.30- 0.0- 0.2- 2.3- 4.2+ 0.1-
52	TRANS-1,8-DIOXADECALIN <i>anti, anti</i> <i>Cis-trans</i> equilibrium in CCl <sub>4</sub> , ε = 2.228, ΔS assumed to be -RTln2, L. Nørskov-Lauritsen	E	0.2	0.45	0.18

## HEATS of FORMATION

#	COMPOUND, COMMENT	TYPE	EXP	MM2	MM282
61	DIMETHOXYMETHANE	CH <sub>2</sub>	-83.27(±0.14)	-83.61	-82.14
62	1,3-DIOXOLANE	CH <sub>2</sub>	-71.1(±0.2)	-71.50	-71.55
63	1,3-DIOXANE	CH <sub>2</sub>	-80.86(±0.26)	-83.21	-81.86
64	1,3-DIOXEPANE	CH <sub>2</sub>	-82.8(±0.4)	-82.66	-81.80
65	1,3,5-TRIOXANE	CH <sub>2</sub>	-111.32(±0.12)	-116.69	-113.30
66	1,3,5,7-TETRAOXOCANE	CH <sub>2</sub>	-148.24(±0.16)	-152.23	-146.23
67	1,3,5,7,9-PENTOXECANE	CH <sub>2</sub>	-186.38(±0.32)	-189.40	-181.98
68	1,1-DIMETHOXYETHANE	CH	-93.26(±0.31)	-92.66	-92.62
69	2-METHOXYOXANE	CH	-95.5(±0.5)	-96.30	-96.14
70	2,2-DIMETHOXYPROPANE	C	-101.89(±0.50)	-101.86	-101.89

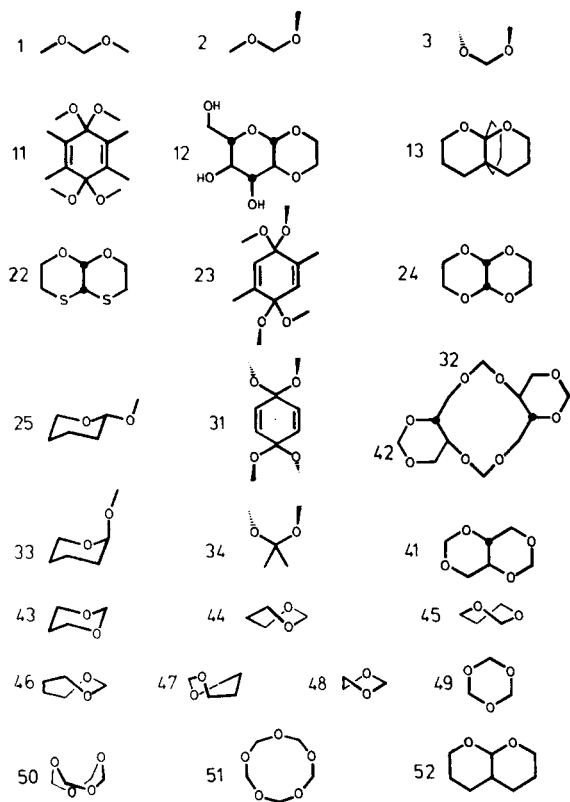


Figure 2. Molecules of Table III.

at by considering 2-methoxytetrahydropyran, where the axial-equatorial equilibrium constant is known<sup>15</sup> and was fit. The  $\Theta_0$  and  $k_\theta$  for the angle O—C—O were chosen to fit the conformers of this molecule, for which the *ab initio* values show quite a range (106°–113°). The available x-ray data on the various molecules listed in Table III was then utilized to refine the adjustable structural parameters. The only

apparent ambiguity at this point was in the C—O—C—O torsional potential. The *ab initio* values for dimethoxymethane were not regarded as sufficiently accurate to fit to, and no structural information was available that permitted specification of the barrier heights. We therefore turned to the heats of formation of the compounds listed in Table III. While most of the compounds contain near gauche structures, and the gauche–anti energy difference is available, the dioxolane molecule provides a key for defining the rest of the torsional potential. It is known to be an almost free pseudorotor,<sup>16</sup> and this fact, together with the heat of formation, fixes pretty well the values of  $V_1$  and  $V_2$ . The heat of formation results are less good than one might like, but they are reasonable. The MM2, MM2(82), and experimental results are all summarized in Table III.

There are a modest number of heats of formation available for acetals. The original MM2 program fit these rather well. As it turned out, the revising downward of the O—C—O angles in the present work has made these heats of formation more difficult to fit. Additionally, the earlier work was fit to a value for the heat of formation of 1,3-dioxane that is now believed to not be the best one. Cox and Pilcher<sup>17</sup> list three values for this compound that spread over 2 kcal/mol, and choose one as the “selected value.” However, an independent redetermination<sup>18</sup> of the value has in fact recently confirmed another one. The most recent value has been chosen as the one to fit in the present work. The average deviation between the calculated and found values in the present

Table IV. Root mean square deviations from experiment for geometrical features of the acetal group.

Feature	Examples	MM2	MM2(82)
O—C—O—C	16 <sup>a</sup>	0.0164 Å	0.0045 Å
O—C—O—C	31 <sup>b</sup>	0.0188 Å	0.0072 Å
O—C—O—C	16 <sup>a</sup>	0.0117 Å	0.0109 Å
O—C—O—C	9 <sup>a</sup>	3.02°	1.45°
O—C—O—C	17 <sup>c</sup>	2.71°	2.56°
O—C—O—C	10 <sup>d</sup>	3.4°	4.5°
O—C—O—C	22 <sup>e</sup>	2.7°	3.5°

<sup>a</sup>High accuracy, low-temperature determinations, (numbers 11, 12, 21, 22, 23, 31, 32, 41, 42).

<sup>b</sup>Including less accurate structure determinations, (24, 25, 33, 34, 43, 46, 47, 48).

<sup>c</sup>Including less accurate ones (24, 34, 43, 46, 47, 48).

<sup>d</sup>Excluding torsion angles in 6-membered rings, (leaves 23, 31, 32, 34, 47, 48).

<sup>e</sup>Including 6-membered rings (21, 22, 24, 41, 42, 43, 46).



work is much larger than we are usually able to achieve. The relatively few available experimental data, and the hygroscopic nature of ethers, plus their now well-known tendency to form peroxides on standing in air, make it difficult to decide how much of the problem is experimental<sup>19</sup> and how much is calculational. The heat of formation data are given in Table III, the geometrical effects of the changes to the MM2 program are summarized in Table IV.

In principle the anomeric effect will occur whenever there is a lone pair of electrons on an atom bound to a second atom, which in turn is bound to a third electronegative atom. Such structures would include ortho esters and geminal polyhalides, for example, and also analogs containing nitrogen, sulfur, or other electronegative atoms. Presumably the method outlined here could be extended to include such cases. It would be necessary to establish the parameters, specifically *k*, *c*, and *d*, separately for each combination of atoms.

## APPENDIX

### Input Data for the MM2(82) Program

The following cards can be read into MM2(82) to incorporate the anomeric effect. First, a changed constants card (9\* in the manual) containing two, two, three, and three in cols. 5, 10, 20, and 40, respectively, indicating that two torsional (9a\*), two stretching or anomeric effects cards (9b\*), three angle cards (9f\*), and three heat-of-formation cards (9h\*) are to follow. The torsional cards in the standard format have for atom types 6—1—6—1 the values for *V*<sub>1</sub>, *V*<sub>2</sub>, and *V*<sub>3</sub> of -0.17, -1.20, and 0.00, and for type 6—1—6—20, 0.0, 0.5, and -0.20, respectively. The first of the two anomeric effect cards has the atom type (6) and the constants *c* and *d* in cols. 21—30 (1.3) and 31—40 (0.0085), respectively. The three angle cards are for atom types 6—1—6 in the usual format with a bending constant of 0.46. The natural angles are 99.9, 97.0, and 102.2 for types 1, 2, and 3, respectively. The three heat-of-formation cards each contain the structural element, the new heat-of-formation parameter, and the strainless heat of formation parameter, as follows: 13, -3.941, -3.527, 14, -9.886, -6.626; 15, -13.134, -8.560.

## References

- U. Burkert and N. L. Allinger, *Molecular Mechanics*, American Chemical Society, Washington, D.C., 1982.
- (a) E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8005 (1973); (b) C. L. Altona and D. H. Faber, *Top. Curr. Chem.*, **45**, 1 (1974); (c) J. D. Dunitz and H. B. Burgi, *MTP International Reviews of Science, Series 2: Chemical Crystallography*, J. M. R. Robertson, Ed., Butterworths, London, 1975, p. 81; (d) N. L. Allinger, *Adv. Phys. Org. Chem.*, **13**, 1 (1976); (e) O. Ermer, *Struct. Bonding (Berlin)*, **27**, 161 (1976); (f) L. S. Bartell, *J. Am. Chem. Soc.*, **99**, 3279 (1977); (g) S. R. Niketic and K. Rasmussen, *The Consistent Force Field*, Springer, Berlin, 1977; (h) A. Warshel, in *Modern Theoretical Chemistry*, Vol. 7, G. Segal, Ed., Plenum, New York, 1978, p. 133; (i) D. N. J. White, in *Molecular Structure by Diffraction Methods*, Chemical Society, London, 1978; Vol. 6, p. 38; (j) O. Ermer, *Aspekte von Kraftfeldrechnungen*, Wolfgang Baur Verlag, Munich, 1981; (k) E. Osawa and H. Musso, *Top. Stereochem.*, **13**, 117 (1982).
- The original version of the MM2 program [MM2(77)] is available from the *Quantum Chemistry Program Exchange*, University of Indiana, Bloomington, Indiana 47401. A later version (which contains only additions and improvements, but gives identical results for any molecules that were treatable by the original version except for compounds subject to the anomeric effect as discussed herein), MM2(82), together with the companion program designed to deal with conjugated systems [MMP2(82)], are available from Molecular Design, Ltd., 1122 B Street, Hayward, CA 94541.
- (a) R. U. Lemieux, *Molecular Rearrangements*, P. de Mayo, Ed., Interscience, New York, 1964; (b) A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, Heidelberg, 1983; (c) Anomeric Effects. Origin and Consequences, Szarek and Horton, ACS Symp. Ser. 87, Washington, D.C., 1979; (d) *Stereoelectronic Effects in Organic Chemistry*, DesLongchamps, Pergamon, New York, 1983.
- E. E. Astrup, *Acta Chem. Scand.*, **27**, 3271 (1973).
- (a) C. Ceccarelli, J. R. Ruble, and G. A. Jeffrey, *Acta Crystallogr.*, **B36**, 861 (1980); (b) G. A. Jeffrey and R. Taylor, *J. Comput. Chem.*, **1**, 99 (1980).
- M. Frierson, unpublished results.
- A. G. Robiette, *Mol. Struct. by Diff. Met.*, The Chemical Society, London, 1973, Vol. I, p. 160.
- Radial in terms of the "riding atom" model: (a) V. Schomaker and K. N. Trueblood, *Acta Crystallogr.*, **B24**, 63 (1968); (b) B. T. M. Willis and A. W. Pryor, *Thermal Vibrations in Crystallography*, Cambridge University Press, (1975).
- (a) G. M. Brown and H. A. Levy, *Acta Crystallogr.*, **B29**, 790 (1973); (b) J. C. Hanson, L. C. Sieker, and L. H. Jensen, *Acta Crystallogr.*, **B29**, 797 (1973).
- C. Van Alsenoy, L. Schafer, J. N. Scarsdale, and J. O. Williams, *J. Mol. Struct. Theochem.*, **86**, 111 (1982).
- L. Schafer, C. Van Alsenoy, and J. N. Scarsdale, *J. Mol. Struct. Theochem.*, **86**, 349 (1982).
- (a) N. L. Allinger, S. H.-M. Chang, D. H. Glaser, and H. Honig, *Isr. J. Chem.*, **20**, 51 (1980); (b) N. L. Allinger and D. Y. Chung, *J. Am. Chem. Soc.*, **98**, 6298 (1976).
- Our calculated values for the dipole moments of the *gg*, *ag*, and *aa* conformations are 0.27, 1.88, and 4.03 D, respectively, with corresponding relative energies of 0.0, 1.97, and 4.03 kcal/mol. These values give a calculated value for the dipole moment of the conformational mixture ranging from 0.55 to 0.89 D over the temperature range 25°–199°C. Because of the usual inaccuracies introduced by atomic polarizations, these values are only rather approximate. The experimental values actually measured (ref. 20) span the range 0.67–1.10 D over this temperature range. These data are consistent with the energy differences we deduced from other data as discussed.
- A. J. De Hoog, H. R. Buys, C. Altona, and E.

- Havinga, *Tetrahedron*, **25**, 3365 (1969).  
H. Booth, T. B. Grindley, and K. A. Khedair, *J. Chem. Soc. Chem. Comm.*, 1047 (1982).
16. R. Davidson and P. A. Warsop, *J. Chem. Soc. Faraday Trans. II*, **68**, 1875 (1972).
  17. J. D. Cox and G. Pilcher, *Thermochemistry of Organic and Organometallic Compounds*, Academic, New York, 1970; J. B. Pedley and J. Rylance, Sussex-N.P.L. Computer Analyzed Thermochemical Data, University of Sussex, 1977.
  18. K. Bystrom and M. Mansson, *Perkin Trans.*, **2**, 565 (1982).
  19. It is not clear from reading some of the earlier articles if the thermochemists were aware of the fact that ethers may form peroxides more or less easily upon exposure to air.
  20. (a) S. Mizushima, Y. Morino, and M. Kubo, *Phys. Z.*, **38**, 459 (1937); (b) T. Uchida, Y. Kurita, and M. Kubo, *J. Polym. Sci.*, **19**, 365 (1956).