

# Conformational Analysis of Cyclohexane-1,2-diol Derivatives and MM3 Parameter Improvement†

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The positions of the equilibria between the diequatorial and diaxial conformers of *trans*-1,2-dimethoxycyclohexane (2) and *trans*-2-methoxycyclohexanol (3) have been measured accurately by  $^{13}\text{C}$  n.m.r. spectroscopy at  $-80^\circ\text{C}$  in a series of solvents ranging from non-polar pentane to highly polar methanol. The equilibria favour the diequatorial conformers under all conditions but the extent increases with solvent polarity and is greater for (3). Improved parameters for the OCCO torsional term in MM3(94) have been developed ( $V_1$ ,  $V_2$ , and  $V_3$ , 3.0,  $-2.5$ , 1.25, respectively) by comparison with conformational data for (2) and 1,2-dimethoxyethane (1). Application of the modified parameters to a number of examples demonstrates marked improvement for ethers. These examples include 1,2-dimethoxypropane, for which n.m.r. spectra in ( $\text{D}_{12}$ )cyclohexane have been analysed and those from the gas phase reevaluated. Lesser improvement was achieved for systems having intramolecular hydrogen bonding. *Ab initio* results for rotation about the C5–C6 bond in pyranosides are satisfactorily reproduced but experimental results favour the *gg* and *tg* rotamers over the *tt* rotamer considerably more than calculated.

## Introduction

Biological recognition of cells is often mediated by the cell-surface oligosaccharides in glycoproteins or glycolipids. The conformation adopted by the carbohydrate segment is a critical factor in this recognition. Therefore, it is highly desirable to accurately model the conformations adopted by the carbohydrates to enable the development of mimics for medicinal purposes.<sup>1</sup> The molecular mechanics program MM3<sup>2</sup> is considered to be the state of the art for modelling organic molecules in the gas phase.<sup>3</sup> Allinger *et al.* first detailed the MM3 force field for alcohols and ethers, including ethylene glycol derivatives in 1990,<sup>4</sup> and a recent reevaluation of the part of the force field for compounds containing the OCCO unit is incorporated in MM3(94).<sup>5</sup>

We had initially used MM3(89) and MM3(92) to study the chair–boat conformational equilibria of derivatives of 1,6-anhydro- $\beta$ -D-glucopyranose and found the agreement obtained less than satisfactory.<sup>6</sup> Much of the parameter development for OCCO-containing molecules for MM3 was based on *ab initio* results for 1,2-dimethoxyethane (1), a molecule for which the experimental evidence about the populated conformations varied widely with the phase on which the measurement was made and on the technique that was used.<sup>7,8</sup> The

acquisition of additional accurate experimental data for molecules in which the relative populations of conformers can be measured unambiguously is desirable for force-field development. In addition, similarity to carbohydrate structures was also important for our purposes. *trans*-1,2-Dimethoxycyclohexane (2) and *trans*-2-methoxycyclohexanol (3) are molecules which meet these requirements, and conformational results for them are reported here in a variety of solvents. In addition, this paper describes the development and testing of improved parameters for MM3 for molecules incorporating the OCCO unit.

## Results and Discussion

### *Experimental Determination of Conformational Stability*

*trans*-1,2-Dimethoxycyclohexane (2) with the methoxy carbons labelled with  $^{13}\text{C}$  was prepared by reacting the dianion of *trans*-cyclohexane-1,2-diol with ( $^{13}\text{C}$ )methyl iodide.

In order to ensure that accurate intensities were obtained from  $^{13}\text{C}$  n.m.r. peak areas and to obtain information about molecular aggregation, carbon relaxation times were measured on non-degassed samples

†Dedicated to Professor Stephen J. Angyal.

**Table 1.**  $^{13}\text{C}$  n.m.r. chemical shifts and relaxation times for *trans*-1,2-dimethoxycyclohexane<sup>A</sup> conformers (2e) and (2a)

Carbon atoms	Diequatorial (2e)			Diaxial (2a)			
	$\delta^B$ (ppm)	$T_1^A$ (s)	$T_1^B$ (s)	$T_1^C$ (s)	$\delta^B$ (ppm)	$T_1^B$ (s)	$T_1^C$ (s)
C1, C2	83.6	13.3		2.7	75.8		2.9
C3, C6	30.1	6.2		1.1	23.9		<sup>D</sup>
C4, C5	24.2	6.2		0.90	19.9		0.71
OMe	56.9	13.5	0.90	3.3	55.7	1.19	3.3

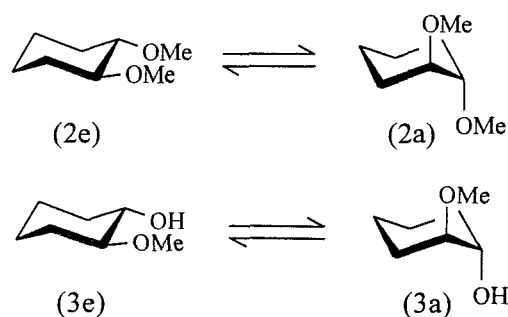
<sup>A</sup> For a 0.5 M solution in ( $\text{D}_6$ )acetone at 293 K. <sup>B</sup> For a 0.5 M solution in ( $\text{D}_6$ )acetone at 193 K. <sup>C</sup> For a 0.5 M solution in pentane at 193 K. <sup>D</sup> Could not be measured because of signal overlap.

in ( $\text{D}_6$ )acetone and in pentane by using the inversion recovery sequence. These are listed in Table 1. After removal of multiplicity effects, relaxation times ( $T_1$ ) for all cyclohexane carbons in a particular solvent at a particular temperature are nearly identical. This pattern is consistent either with motion about an axis joining the midpoints of the C1-C2 and C4-C5 bonds or with isotropic motion. The former motion might be observed if aggregates were formed through alignment of either C-O bond moments or molecular dipoles in associated molecules. If such association did occur, it would be most important in the least polar solvents at low temperature. It would also be much more important for the diequatorial than the diaxial conformer because of the much larger molecular dipole in the former conformer and because steric effects would disfavour association in the latter. However, the  $T_1$  values are nearly identical for the same carbons of the two conformers in pentane at  $-80^\circ\text{C}$ . Thus, this evidence indicates that molecules of (2) are not strongly aggregated in solution and motion of these conformers of (2) is probably close to isotropic.

The position of the equilibrium depicted in Fig. 1 between the diequatorial and diaxial conformations was measured at  $-80^\circ\text{C}$  by deconvolution of the  $^{13}\text{C}$  n.m.r. signals of the methoxy carbons of the  $^{13}\text{C}$ -labelled sample of (2) recorded under conditions where peak areas are directly proportional to the amount of compound present. Results are reported in Table 2. The position of this equilibrium had been measured previously<sup>9</sup> in carbon disulfide and in dichloro( $\text{D}_2$ )methane and

the current results are in excellent agreement with the previous measurements, which are also given in Table 2.

To further rule out aggregation effects, the effect of the concentration of  $^{13}\text{C}$ -labelled (2) on the position of the equilibrium was evaluated in pentane at  $-80^\circ\text{C}$ . Percentages of diequatorial conformer found by deconvolution of the  $^{13}\text{C}$ -labelled methoxy carbons were: 57.1, 57.3, 55.4 and 56.2% in 0.250, 0.125, 0.0625 and 0.031 M solutions, respectively. It was concluded that the position of the equilibrium was not influenced by concentration and, therefore, that aggregation effects could be neglected.

**Fig. 1.** The equilibria between the diequatorial (e) and diaxial (a) conformations of *trans*-1,2-dimethoxycyclohexane (2) and *trans*-2-methoxycyclohexanol (3).

The equilibrium favoured the diequatorial conformer (2e) in all solvents with percentages of this form ranging from 57–95% with more polar solvents favouring this more polar conformer to a greater extent. Solvent effects on conformational equilibria have been studied extensively<sup>10–12</sup> and have been related to the dipole and quadrupole moments of the conformers. Evaluation of such terms for (2) is difficult because the several methoxy rotamers (see later) will each have different dipole and quadrupole moments, and their individual populations are unknown. Plots of the  $\Delta G^\circ$  values against various measures of solvent polarity, including  $(\epsilon-1)/(2\epsilon+1)$ , only gave correlations with  $r$  values  $>0.9$  against  $E_T$ <sup>12</sup> ( $r = 0.96$ ) and  $\epsilon$  ( $r = 0.95$ ), when either the room temperature or  $-80^\circ\text{C}$   $\epsilon$  values were used, and only if the value for dichloromethane was omitted.

**Table 2.** Conformational equilibria for *trans*-1,2-dimethoxycyclohexane

Solvent	$\epsilon$ values		Percentage diequatorial <sup>B</sup> (2e)	$\Delta G^\circ$ (kJ/mol) <sup>C</sup>	$\Delta G^\circ$ (kJ/mol) lit. <sup>B,D</sup>
	25°C	$-80^\circ\text{C}^A$			
Pentane	1.8	2.0	57.2( $\pm 1.0$ )	0.50( $\pm 0.08$ )	—
( $\text{D}_8$ )Toluene	2.4	2.7	72.0( $\pm 1.0$ )	1.51( $\pm 0.08$ )	—
$\text{CS}_2$	2.6	2.9	65.6( $\pm 1.0$ )	1.05( $\pm 0.08$ )	1.17
( $\text{D}_8$ )Tetrahydrofuran	7.6	10.1 <sup>E</sup>	67.2( $\pm 1.0$ )	1.13( $\pm 0.08$ )	—
$\text{CD}_2\text{Cl}_2$	8.9	15.0	95.0( $\pm 1.0$ )	4.7 ( $\pm 0.3$ )	4.44
( $\text{D}_6$ )Acetone	20.7	32.5	80.0( $\pm 1.0$ )	2.22( $\pm 0.08$ )	—
( $\text{D}_4$ )Methanol	32.7	54	90.2( $\pm 1.0$ )	3.5 ( $\pm 0.2$ )	—

<sup>A</sup> Calculated from data in 'CRC Handbook of Chemistry and Physics' 66th Edn, pp. E50–52 (CRC Press: Boca Raton, Florida, 1985). <sup>B</sup> For 0.5 M solutions at  $-80^\circ\text{C}$ . <sup>C</sup> For the equilibrium (2e)  $\rightleftharpoons$  (2a). <sup>D</sup> Ref. 9. <sup>E</sup> Temperature dependence adjusted by using slope for dimethyl ether.

Table 3. Conformational equilibria for 2-methoxycyclohexanol

Solvent	$\epsilon$ values		Percentage diequatorial (3e)	$\Delta G^\circ$ A,B (kJ/mol)
	25°C	-80°C <sup>C</sup>		
Pentane	1.8	2.0	89.8	3.5(±0.2)
(D <sub>8</sub> )Toluene	2.4	2.7	95.2	4.8(±0.4)
CS <sub>2</sub>	2.6	2.9	96.5	5.3(±0.5)
(D <sub>8</sub> )Tetrahydrofuran	7.6	10.1 <sup>D</sup>	93.9	4.4(±0.3)
CD <sub>2</sub> Cl <sub>2</sub>	8.9	15.0	>99	>7
(D <sub>6</sub> )Acetone	20.7	32.5	97.1	5.6(±0.6)
(D <sub>4</sub> )Methanol	32.7	54	97.3	5.8(±0.6)

<sup>A</sup> For 0.5 M solutions at -80°C. <sup>B</sup> For the equilibrium (3e)  $\rightleftharpoons$  (3a). <sup>C</sup> Calculated from data in 'CRC Handbook of Chemistry and Physics' 66th Edn, pp. E50-52 (CRC Press: Boca Raton, Florida, 1985). <sup>D</sup> Temperature dependence adjusted by using slope for dimethyl ether.

It is well known that aromatic solvents often appear to be more polar than predicted by their  $\epsilon$  values in plots of this type.<sup>12,13</sup> For the plot of  $\Delta G^\circ$  values against  $\epsilon$  (-80°C values), the correlation coefficient ( $r$ ) improved from 0.95 to 0.987 when the value for toluene was omitted. The equation for this plot was  $\Delta G^\circ = 0.0524\epsilon + 0.617$ . Also, chlorinated solvents often deviate from plots of conformational energies against  $\epsilon$  but the extent of deviation is larger here than previously noted.<sup>12,13</sup>

The equilibria of *trans*-2-methoxycyclohexanol (3) were measured by the same technique in the same solvents on unlabelled samples. Results are presented in Table 3. The diequatorial conformer was stabilized to a greater extent for (3) than for (2) in all solvents. At low concentrations (<0.002 M) in carbon tetrachloride or carbon disulfide, i.r. spectroscopy has shown that, at room temperature, (3) exists as a mixture of the intramolecularly hydrogen-bonded diequatorial conformer and a minor non-hydrogen-bonded form.<sup>14</sup> It seems likely that at the higher concentrations used here aggregates will be important, particularly in non-polar solvents as they are for other ethers with hydroxy groups on adjacent carbons.<sup>15-17</sup> The effect of solvent polarity on the equilibria supports this idea; plots against  $\epsilon$  or  $E_T$  are not nearly as linear as for (2) and also show a lessened dependence on solvent polarity. For instance, when the  $\epsilon$  values at -80°C are used, and the values for toluene and dichloromethane are omitted,  $\Delta G^\circ = 0.0169\epsilon + 0.483$ , with  $r = 0.73$ . Presumably this plot includes the effect of erratic lessening of aggregation as solvent polarity increases.

#### Parameter Development

Parameter development was based on conformational stabilities of compounds (1) and (2). The ambiguous experimental evidence as to which of the many different conformations of 1,2-dimethoxyethane (1) are populated was recently summarized by Fuchs and his coworkers.<sup>7,8</sup> Conformers of (1) are shown in Fig. 2. Because the experimental results are inconsistent, it was decided to use the energy difference between the *aaa* and *aga* conformations from high level *ab initio* calculations as one of the primary pieces of

information for parameter development. Fuchs and his coworkers<sup>7</sup> obtained 0.76 kJ/mol for *aaa*  $\rightleftharpoons$  *aga* using an MP2/6-311+G(3df)//6-311+G(3df) method, Murcko and DiPaola obtained 0.79 kJ/mol using an MP2/6-311+G(df)//6-31G\* method,<sup>18</sup> and Jaffe *et al.* obtained 0.42 kJ/mol using MP2/D95+(2d,f,p) and suggest that

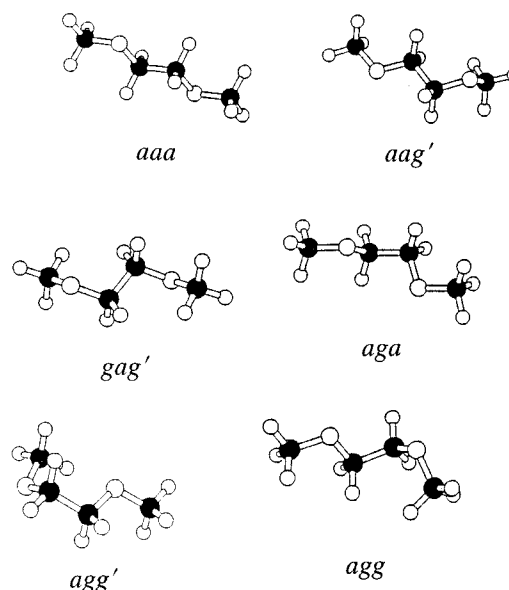


Fig. 2. ATOMS diagrams of the most populated rotamers of 1,2-dimethoxyethane (1).

Table 4. Relative energies of 1,2-dimethoxyethane conformers

Rotamer [mult.] <sup>B</sup>	$\Delta H^\circ$ (kJ/mol)	$\Delta S^\circ$ (kJ/mol K)	$\Delta G^\circ$ (298 K) (kJ/mol)	$\Delta E^\circ$ (lit.) <sup>A</sup> (kJ/mol)
<i>aaa</i> [1]	0.00	0.00	0.00	0.00
<i>aag</i> [4]	7.36	19.4	1.59	5.98
<i>aga</i> [2]	4.14	5.23	2.59	0.58
<i>agg'</i> [4]	9.03	15.9	4.31	0.96
<i>agg</i> [4]	12.3	18.9	6.74	6.32
<i>gag'</i> [2]	14.6	16.6	9.71	12.9
<i>gag</i> [2]	14.4	9.20	11.6	13.1
<i>ggg'</i> [4]	16.9	17.1	11.8	7.78
<i>ggg</i> [2]	20.1	3.46	19.1	6.86
<i>g'gg'</i> [2]	<sup>C</sup>	<sup>C</sup>	<sup>C</sup>	10.1

<sup>A</sup> From D95+(2df,p) level *ab initio* calculations; see ref. 13.

<sup>B</sup> Multiplicity refers to the number of equivalent rotamers.

<sup>C</sup> This conformation was not a minimum when the modified MM3(94) force field was used.

the actual difference is probably in the 0.4–0.8 kJ/mol range.<sup>19,20</sup> The lack of electron correlation during geometry optimization for all of these calculations may mean that the actual energy difference between these two conformers has not been duplicated by calculation yet.

The difference in stability between the diequatorial and diaxial conformers of (2) in pentane at  $-80^\circ\text{C}$  listed in Table 2 was the other primary piece of information used for parameter development. Rotamers of (2) are shown in Fig. 3.

Molecular mechanics force fields evaluate the energy of a conformation as the sum of a number of classical terms;<sup>21</sup> those for non-bonded energy, bond compression and stretching, electrostatic effects, bond-angle bending, stretch-bend and bend-bend cross terms, and torsional effects are included in the MM3 force field. Most of the parameters required for each of the terms in this calculation have been well tested for MM3 and cannot be changed without major implications for the rest of the force field. In fact, the OCCO torsional term is the one term that can be used to improve the agreement for the molecules considered here without influencing the performance of the force field for other types of molecules.

The equation for torsional energy in MM3 is given as

$$E_{\text{TOR}} = \frac{V_1}{2}(1 + \cos\omega) + \frac{V_2}{2}(1 - \cos 2\omega) + \frac{V_3}{3}(1 + \cos 3\omega) \quad (1)$$

where  $V_1$ ,  $V_2$  and  $V_3$  (in kcal/mol)<sup>†</sup> are torsional parameters and  $\omega$  is the torsional angle.

New torsional parameters for the OCCO moiety were produced by systematic adjustment of each of the parameters ( $V_1$ ,  $V_2$  and  $V_3$ ) until satisfactory energy differences were obtained between the *aaa* and *aga* conformers of 1,2-dimethoxyethane and the diequatorial and diaxial conformers of *trans*-1,2-dimethoxycyclohexane. Further fine tuning of the parameters was performed by adjusting the  $V_3$  term until a reasonable value of the heavy atom torsional angles in 1,4-dioxan was obtained ( $60.8^\circ$ ). The standard parameters give  $59.9^\circ$ ,<sup>5</sup> and the electron diffraction value is  $57.9^\circ$ .<sup>22,23</sup> The energies obtained for the various rotamers of (1) and (2) are summarized in Tables 4 and 5. The free energies shown in Tables 4 and 5 were calculated by using the unmodified (other than the new parameters for the OCCO torsional term) MM3(94) program with the default dielectric constant of 1.5. Unless otherwise noted, the energies in Tables 4 and 5 are for the equilibria in which *gauche* OCCO conformations are converted to *anti* conformations at 298 K. The initial structures for

input into MM3 were obtained with PCMODEL. Then, either through modification of the PCMODEL files or by MM3 dihedral driving of the MeOCC torsional angle, input files of all unique rotamers were created. The final energies of all conformers were obtained by using full matrix Newton Raphson minimization and none had imaginary i.r. frequencies. All saddle points had one imaginary frequency.

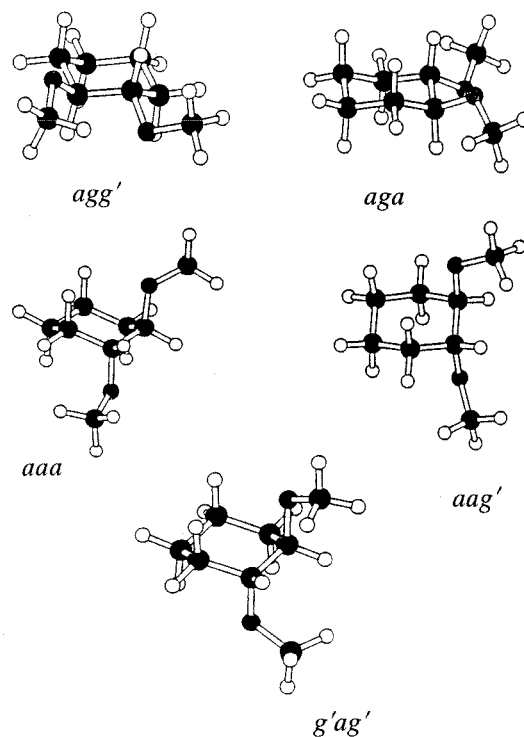


Fig. 3. ATOMS diagrams of the most populated rotamers of *trans*-1,2-dimethoxycyclohexane (2).

Table 5. Relative energies of *trans*-1,2-dimethoxycyclohexane conformers

Rotamer [mult.] <sup>A</sup>	$\Delta H^\circ$ (kJ/mol)	$\Delta S^\circ$ (kJ/mol K)	$\Delta G^\circ$ (193 K) (kJ/mol)
<i>agg'</i> [4]	1.30	7.36	-0.13
<i>aga</i> [2]	0.00	0.00	0.00
<i>aag'</i> [4]	3.68	9.04	1.92
<i>aaa</i> [2]	2.85	-2.31	3.30
<i>g'ag'</i> [2]	4.18	-2.79	4.73
<i>agg</i> [4]	13.0	9.46	11.1
<i>g'gg</i> [4]	15.0	7.53	13.6
<i>ggg</i> [2]	24.2	-6.36	25.4
<i>aag</i> [4]	33.9	7.36	32.5
<i>gag'</i> [4]	34.4	7.20	33.0
<i>gag</i> [2]	54.4	-14.6	57.3
<i>g'gg'</i> [2]	B	B	B

<sup>A</sup> Multiplicity refers to the number of equivalent rotamers.

<sup>B</sup> This conformation was not a minimum when the MM3(94) force field was used.

<sup>†</sup> 1 kcal = 4.184 kJ.

MM3(94) calculates entropies for molecules by using statistical mechanics from the vibrational spectra calculated by the MM3 program. The entropies for each of the rotamers were corrected for symmetry, optical isomerism, and internal rotation in cases where the MM3 program does not give the correct answers.† The internal rotation correction was calculated from tables produced by Pitzer and Gwinn.<sup>25</sup> This procedure gave a value of  $14.93 \text{ J mol}^{-1} \text{ K}^{-1}$  for the rotation of a methoxy group at 298 K. The enthalpies of formation and corrected entropies were determined relative to the lowest energy rotamer of a given OCCO conformation. These values were then used to determine  $\Delta G^\circ$  values for the rotameric equilibria and hence equilibrium constants and rotamer mole fractions. The mole fractions ( $x_i$ ) could then be used to calculate the entropy of mixing

$$S_{\text{mix}} = -R \sum_i^n x_i \ln x_i \quad (2)$$

due to the different rotamers for a given OCCO conformation, where  $n$  is the number of rotamers considered. After the most populated rotamers of each OCCO conformation and their entropy of mixing were determined, their enthalpies and entropies were then used to obtain the free energy difference between the two conformers.

The new  $V_2$  and  $V_3$  are fairly similar to the old values ( $-2.50$  and  $1.25$  versus  $-2.00$  and  $1.90$ , respectively). The major change in the parameters is the large increase in the size of the  $V_1$  term from  $0.50$  originally to  $3.00$  which is necessary to make the diequatorial conformation of (2) less stable relative to the diaxial conformation. Large  $V_3$  terms improve the geometry but they decrease the *gauche* preference of (1). It is possible to obtain excellent agreement with the experimental energy differences for both (1) and (2) by making the  $V_3$  term negative but the geometries obtained for these molecules become extremely poor. The source of the *gauche* preference for (1) therefore must lie in the  $V_2$  term. In the original MM3(94) parameters, the large  $V_3$  parameter determines the geometry while the lack of a substantial  $V_1$  term allows for duplication of the *gauche* preference. Introduction of a much larger  $V_1$  term counteracts much of the *gauche* effect obtained through the  $V_2$  term. The parameters obtained here are similar to those proposed in 1993 by Tsuzuki<sup>24</sup> for MM2 where a  $V_1$  term with a value of  $3.964$  was determined from high level *ab initio* results on 1,2-dimethoxyethane including minima and saddle points for rotation. Tsuzuki obtained a rotational barrier of  $39.77 \text{ kJ/mol}$  for dimethoxyethane at the MP3/6-311+G//HF/6-311+G\* level; the calculated value using the new parameters was in excellent agreement at  $40.3 \text{ kJ/mol}$ . The value obtained using the standard MM3(94) parameters was considerably lower,  $32.5 \text{ kJ/mol}$ .

During the parameterization, it was noticed that, when the parameters stabilized the *aga* conformation of (1) sufficiently, then the diequatorial conformer of (2) was overstabilized. This observation must arise from small deficiencies in either the hydrocarbon or the ether part of the MM3(94) force field but the precise source of the problem cannot be determined easily. The parameters obtained are a compromise in that they reproduce the *gauche* preference of (1) as much as possible without overstabilizing the diequatorial conformation of (2). For 1,2-dimethoxyethane, a '*gauche* effect'<sup>26</sup> is observed experimentally in that the OCCO *gauche* conformers are more favoured in the gas and liquid phases<sup>27</sup> than would be expected for n-hexane.

MM3 treats solvent effects by altering the bulk dielectric constant. In the equation in which the electrostatic energy is calculated, the summation of the energies arising from the interactions of the bond moments is divided by the dielectric constant. Thus, most of the changes occur as the dielectric constant changes from  $1.5$  to  $10 \text{ C}^2/(\text{N m}^2)$ . The preference for the diequatorial conformer of (2) was calculated to increase with increasing solvent polarity as observed but the changes did not match the observations well; at a dielectric constant of  $2.9$  ( $\text{CS}_2$ ,  $-80^\circ\text{C}$ ),  $\Delta G^\circ$  was  $3.3 \text{ kJ/mol}$  ( $1.5 \text{ kJ/mol}$  observed), at  $10.1$  (tetrahydrofuran,  $-80^\circ\text{C}$ ),  $\Delta G^\circ$  was  $3.6 \text{ kJ/mol}$  ( $1.1 \text{ kJ/mol}$  observed), and at  $54.0$  (methanol,  $-80^\circ\text{C}$ ),  $\Delta G^\circ$  was  $3.7 \text{ kJ/mol}$  ( $3.5 \text{ kJ/mol}$  observed).

#### Applications of the New Parameters

Some applications of the new parameters ( $3.00$ ,  $-2.50$  and  $1.25$  for  $V_1$ ,  $V_2$  and  $V_3$ , respectively) are found in Tables 6–11. The new parameters give considerably improved agreement with experiment when compared with results obtained by using the standard values present in MM3(94). Equilibria between the *cis*- and *trans*-diastereomers of 2-isopropyl-5-methoxy-1,3-dioxan (4) (see Fig. 4 and Table 11) have been studied in numerous solvents by Eliel, Abraham, and coworkers.<sup>10,13,28</sup> The experimental values for  $\Delta G^\circ$  for this equilibrium going from axial to equatorial (or *g,g* to *a,a*) in non-polar solvents like n-hexane, cyclohexane, or  $\text{CCl}_4$  are large and negative ( $-4.4$ ,  $-4.3$ , and  $-3.8 \text{ kJ/mol}$ , respectively) as was calculated here by using the modified parameters. The standard MM3(94) parameters overstabilize the *gauche* conformation and as a result give a small positive energy difference. Abraham and coworkers<sup>10</sup> developed a solvation model that evaluated the interaction between calculated conformer dipole and quadrupole moments and the solvent, and hence obtained the gas phase energy difference for the equilibrium. The results from the modified parameters fit the gas phase value ( $-5.2 \text{ kJ/mol}$ )<sup>4</sup> slightly better than the solution value.

† See ref. 24 for a discussion with application to 1,2-dimethoxyethane (1).

The results are similar for the conformational equilibrium of 1,2-dimethoxy-2-methylpropane (5) (see Fig. 5 and Table 6). The experimental values were determined by  $^{13}\text{C}$  n.m.r. spectroscopy in cyclohexane.<sup>29†</sup> The standard MM3(94) parameters overcompensate for the *gauche* effect resulting in the excessive favouring of the *gauche* conformation. The new parameters favour the *anti* conformation slightly for (1), in good agreement with the experimental result.

As can be seen in the last column of Table 6, the new parameters do not stabilize the *gauche* conformations of 1,2-dimethoxypropane (6) (see Fig. 5) sufficiently to match the reported<sup>30</sup> experimental results. However, there is considerable uncertainty about the experimental determination of the conformational mixture present for (6), which was calculated from  $^3J_{\text{H,H}}$  values from gas phase n.m.r. spectra of the derivative of (6) with the methoxy groups deuterated.<sup>30</sup> The experimental spectrum pictured in Figure 3 of that paper,<sup>30</sup> which shows the ABC part of the ABCX<sub>3</sub> pattern, should contain 30 distinct lines but only 12 broadened peaks are apparent. Also clearly visible in the experimental spectrum but not reproduced in the simulated spectra were bulges on the inside and outside of the two large central peaks of the BC part of the pattern. The broadness of the lines and the inaccuracy of the simulation cast doubt on the coupling constants obtained.<sup>30</sup>

To obtain more reliable values for the coupling constants of (6), a  $^1\text{H}$  n.m.r. spectrum in ( $\text{D}_6$ )cyclohexane (0.08 M) was recorded at 500 MHz. The resulting ABCX<sub>3</sub> pattern was then analysed with the iterative

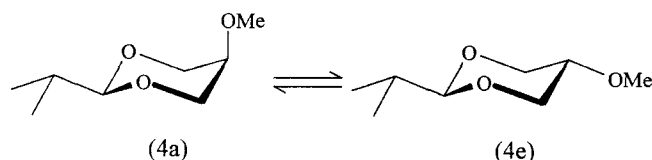


Fig. 4. Equilibrium of 2-isopropyl-5-methoxy-1,3-dioxan (4).

program LAMES8.<sup>31</sup> The final iteration included 110 of the 123 transitions and 99.9% of the total intensity. Fig. 6 shows the agreement achieved and the results of this analysis are found in Table 7. Note that we have used the conventional labeling for the spin system (e.g., the highest frequency is labelled A), not the system used previously.<sup>30</sup> The previous analysis had  $^3J_{\text{AB}} > ^3J_{\text{AC}}$  by 1.3–1.8 Hz at different temperatures. In the current results,  $^3J_{\text{AB}}$  is equal to  $^3J_{\text{AC}}$  within the calculated uncertainty. Simulation of the gas phase spectrum by using the coupling constants obtained for the ( $\text{D}_{12}$ )cyclohexane solution and chemical shifts from the gas phase spectrum reproduced the 345 K spectrum shown very well including the bulges evident on the central peaks that were not reproduced in the original simulation.<sup>30</sup>

The new coupling constants were then used to determine the fractions of each conformer present in solution by using the following equations:

$$^3J_{\text{AB}} = f_a ^3J_{\text{AB}(a)} + f_g ^3J_{\text{AB}(g)} + f_{g'} ^3J_{\text{AB}(g')} \quad (3)$$

$$^3J_{\text{AC}} = f_a ^3J_{\text{AC}(a)} + f_g ^3J_{\text{AC}(g)} + f_{g'} ^3J_{\text{AC}(g')} \quad (4)$$

$$1 = f_a + f_g + f_{g'} \quad (5)$$

where the  $f$  values are the mole fractions of the three conformations, A is the methine proton, and B and C

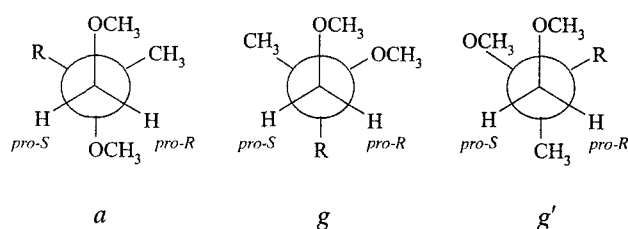


Fig. 5. Conformers of 1,2-dimethoxy-2-methylpropane (5) (R = CH<sub>3</sub>) and 1,2-dimethoxypropane (6) (R = H). Note that for (5) the *gauche* conformations  $g$  and  $g'$  are identical.

Table 6. Relative free energies (kJ/mol) of 1,2-dimethoxy-2-methylpropane (5) and 1,2-dimethoxypropane (6) conformers

Compound	Conformer	$\Delta G^\circ$ (exp.) <sup>A</sup>	$\Delta G^\circ$ (exp.) <sup>B</sup>	$\Delta G^\circ$ (exp.) <sup>C</sup>	$\Delta G^\circ$ Standard MM3(94)	$\Delta G^\circ$ New MM3(94)
(5)	OCCO <i>a</i>		0.0 <sup>D</sup>		3.8	0.0
	OCCO <i>g</i>		2.2 <sup>D</sup>		0.0	1.2
	OCCO <i>g'</i>		2.2 <sup>D</sup>		0.0	1.2
(6)	OCCO <i>a</i>	0.0	0.0 <sup>E</sup>	0.0	0.0	0.0
	OCCO <i>g</i>	3.4	3.7 <sup>E</sup>	1.6	0.8	5.9
	OCCO <i>g'</i>	-2.1	0.0 <sup>E</sup>	0.5	-2.6	2.2

<sup>A</sup> In the gas phase (Miyajima, T., Hirano, T., and Sato, H., *J. Mol. Struct.*, 1984, **125**, 97). <sup>B</sup> From data in ( $\text{D}_{12}$ )cyclohexane. <sup>C</sup> In ( $\text{D}_{12}$ )cyclohexane by using coupling constants derived from the equation of Haasnoot, C. A. G., DeLeeuw, F. A. A. M., and Altona, C., *Tetrahedron*, 1980, **36**, 2783. <sup>D</sup> From Abe, A., and Tasaki, K., *J. Mol. Struct.*, 1986, **145**, 309. <sup>E</sup> Derived by using coupling constants from Miyajima, T., Hirano, T., and Sato, H., *J. Mol. Struct.*, 1984, **125**, 97.

†The experimental details for this determination have only been published in a thesis: Sasanuma, Y., M.Sc. Thesis, Tokyo Institute of Technology, 1982 (reference 6 in our ref. 29).

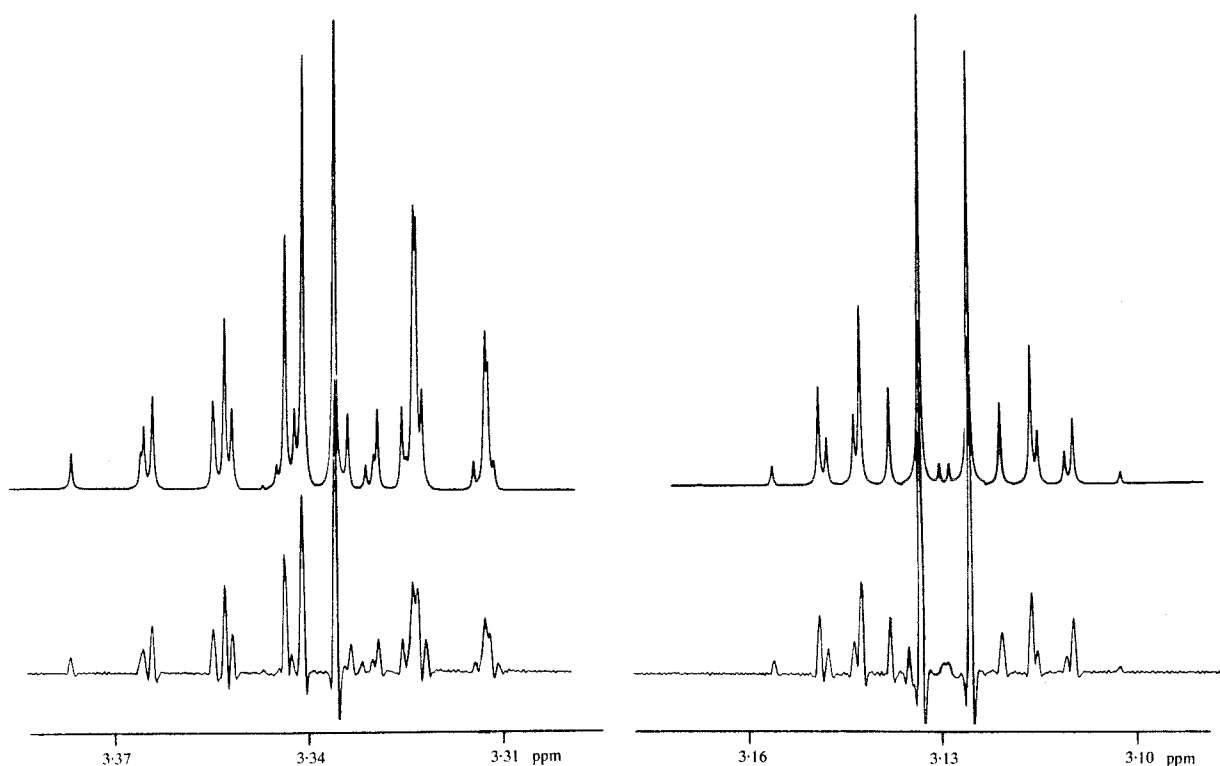


Fig. 6. Top: simulation of the ABCX<sub>3</sub> pattern in the 500 MHz <sup>1</sup>H n.m.r. spectrum of 1,2-dimethoxypropane in (D<sub>12</sub>)cyclohexane (0.08 M); on the left, the AB portion; on the right, the C portion. Bottom: the experimental spectrum; on the left, the signals of the methine proton H<sub>2</sub> and the *pro-S* H<sub>1</sub> proton (in the *R* enantiomer); on the right, the signal of the *pro-R* H<sub>1</sub> proton. The heights of the left and right portions are not on the same scale.

Table 7. N.m.r. (500 MHz) data for 1,2-dimethoxypropane in (D<sub>12</sub>)cyclohexane (0.08 M)<sup>A</sup>

Proton(s)	Chemical shifts (ν) <sup>B</sup>		Coupling constants (Hz)		
	Frequency (Hz)	Uncertainty	<i>J</i>	Coupling	Uncertainty
A (methine)	1673.37	0.024	<sup>3</sup> <i>J</i> <sub>AB</sub>	5.53	0.037
B ( <i>pro-S</i> )	1664.52	0.023	<sup>3</sup> <i>J</i> <sub>AC</sub>	5.55	0.034
C ( <i>pro-R</i> )	1565.57	0.023	<sup>3</sup> <i>J</i> <sub>AX</sub>	6.27	0.021
X <sub>3</sub> (Methyl)	530.33	0.014	<sup>2</sup> <i>J</i> <sub>BC</sub>	-9.41	0.037

<sup>A</sup> Data were obtained from iterative fitting with LAME8.<sup>31</sup>

<sup>B</sup> The chemical shifts of the methoxy groups

were 1638.41 and 1626.43 Hz.

are the *pro-S* and *pro-R* methylene protons, respectively, in the *R* enantiomer of (6). Miyajima *et al.* used 9.1 Hz as the value for both *anti* couplings and 2.6 Hz for all *gauche* couplings. These values were taken from n.m.r. studies on the conformationally hindered 1-methoxypropan-2-ol.<sup>32</sup> When these values were used with the new experimental coupling constants, the populations of the *a*, *g'*, and *g* conformers were 45, 45 and 10%, respectively.

Haasnoot *et al.*<sup>33</sup> have developed an equation for calculating vicinal coupling constants involving terms for both torsional angles and electronegativities of the substituents. The H-C-C-H torsional angles for the three conformers were obtained from the MM3(94) results. These angles and the Huggins electronegativities<sup>34</sup> for the substituents were used to calculate all <sup>3</sup>*J*<sub>H,H</sub> values for each conformation with the help of a computer program incorporating the equation.† The torsional angles and coupling constants obtained are shown in Table 8.

† We thank Dr J. S. Grossert for a copy of this program.

These new coupling constants were then used to obtain the rotamer mole fractions from equations (3)–(5), above. The populations of the *a*, *g'* and *g* conformers derived were 42.5, 35.2 and 22.3%, respectively.

Table 8. Calculated torsional angles<sup>A</sup> and coupling constants<sup>B</sup> for 1,2-dimethoxypropane conformers *a*, *g* and *g'*

	<i>a</i>	<i>g</i>	<i>g'</i>
θ <sub>AB</sub>	63.2°	-50.2°	168.4°
θ <sub>AC</sub>	-177.9°	67.7°	-72.8°
<sup>3</sup> <i>J</i> <sub>AB</sub>	4.70 Hz	1.48 Hz	9.10 Hz
<sup>3</sup> <i>J</i> <sub>AC</sub>	10.48 Hz	1.96 Hz	1.86 Hz

<sup>A</sup> From MM3 calculations. <sup>B</sup> From the equation of Haasnoot *et al.*<sup>33</sup> by using the calculated geometry.

The relative free energies of the conformers from both sets of coupling constants are found in Table 6.

The results obtained from both approaches agree with the order of conformational energies obtained by using the new parameters but not that obtained with the standard parameters. The best agreement is with the relative stabilities obtained from the coupling constants calculated from the equation of Haasnoot *et al.*<sup>33</sup> However, for this molecule, the *anti* conformation is somewhat overstabilized.

The relative stabilities of the conformations of the 1,3,5,7-tetraoxadecalin (7) isomers shown in Fig. 7 potentially provide excellent tests of OCCO torsional parameters because they contain three OCCO units that adopt different geometries in each conformer. Three chair-chair conformers need be considered: the OCCO units are present in two *aag* and one *gag'* arrangements in the *trans*-diastereomer (7t); in the *O*-inside conformer (7ci) of the *cis*-diastereomer, they are in two *agg* and one *ggg* arrangements; while in the *O*-outside conformer (7co), they are in three *gag* arrangements (see Table 9). Unfortunately, there are no good experimental data for this system. Fuchs and coworkers<sup>7</sup> suggest that (7t) is more stable than (7ci) based on fragment analysis and demonstrate that (7ci) is the only populated conformation for the *cis* isomer. They have performed MP2/6-31G\*//6-31G\* calculations on these conformations that confirm the above stability order. The standard MM3(94) parameters yield the wrong stability order, where (7t) is 7.7 kJ/mol less stable than (7ci), when the *ab initio* calculations indicate that it is 2.5 kJ/mol more stable. Our results (Table 9) are in the same order as the *ab initio* results and (7co) is similarly by far the least stable, although the differences are considerable.

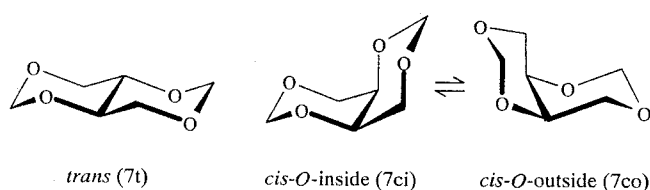


Fig. 7. 1,3,5,7-Tetraoxadecalin conformers.

Table 9. Stabilities ( $\Delta H^\circ$ ) of 1,3,5,7-tetraoxadecalin conformers (kJ/mol)

Source	<i>trans</i> (7t)	<i>cis</i> -in (7ci)	<i>cis</i> -out (7co)
<i>Ab initio</i> MP2/6-31G*//6-31G* <sup>7</sup>	0.0	2.5	19.6
Standard MM3(94)	0.0	-7.7	20.8
New MM3(94)	0.0	7.2	28.3

Fuchs and coworkers also developed new parameters for MM3(92) in which the  $V_2$  term is increased to  $-1.5$  and a conformationally dependent bond-shortening of the central bond in the OCCO unit is introduced. Here, MM3(94) was altered to allow treatment of some carbon atoms differently than the rest and a

new carbon type was defined to allow introduction of different parameters for desired carbon atoms only. The modified program gave results identical to those of the unmodified program when the parameters were identical. However, the suggested<sup>7</sup> alteration of the torsional parameters did not give improved results for *trans*-1,2-dimethoxycyclohexane. During parameter development, alterations of the equilibrium default CC bond lengths in a conformationally dependent manner as detailed above were also evaluated. The results were mixed; 0.2 kJ/mol worse for (1) and 0.4 kJ/mol better for (2). Thus, this approach with its added complexity was not pursued further.

The relative stability of rotamers about the C5-C6 bond in hexopyranosides has attracted considerable attention because of its importance in the conformations of biologically significant 1,6-linked oligosaccharides.<sup>35,36</sup> This feature of carbohydrates has been very difficult to successfully model.<sup>36</sup> A model compound for this conformational problem, *cis*-2-methoxy-6-methoxymethyltetrahydropyran (8), has recently been studied by *ab initio* methods at the HF/6-31G\* level.<sup>37</sup> Results are compared with the enthalpy differences among the three exocyclic rotamers (see Fig. 8) calculated by MM3 in Table 10. Raising the level of calculation to the MP2/6-311+G(3df)//6-311+G(3df) caused the greater stability of the *aaa* conformer of 1,2-dimethoxyethane with respect to the *aga* conformer to decrease to 0.79 from 5.86 kJ/mol.<sup>7</sup> It is expected that the same effect would apply to (8). Correction of the difference between the *anti* and *gauche* conformations of (8) obtained from the 6-31G\* calculations<sup>37</sup> for this elevation in level of theory brings the MM3 results using the new parameters into almost exact agreement with the *ab initio* results as shown in Table 10. The standard MM3 parameters do not perform well for this molecule.

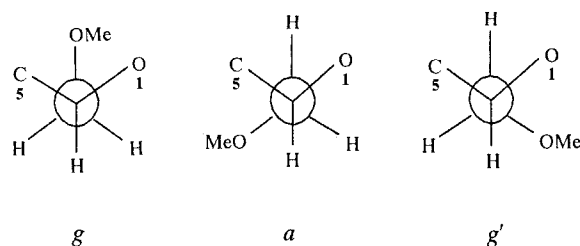


Fig. 8. Newman projections of the exocyclic rotamers for *cis*-2-methoxy-6-methoxymethyltetrahydropyran (8).

Table 11 summarizes the agreement obtained in the comparison of the experimental results for ethers with the MM3(94) results using the new parameters. It is evident that the agreement is excellent, much better than for the old parameters.

#### Systems with Significant Hydrogen Bonding

In addition to the factors considered for the ethers, intramolecular hydrogen bonding is important in



Table 10. Relative enthalpies (kJ/mol) of *cis*-2-methoxy-6-methoxymethyltetrahydropyran (8)

Conformer	$\Delta H^\circ$ <sup>A</sup> (exp.)	$\Delta H^\circ$ <sup>B</sup> (exp.)	$\Delta H^\circ$ Standard	$\Delta\Delta H^\circ$ MM3(94)	$\Delta H^\circ$ New MM3(94)	$\Delta\Delta H^\circ$ <sup>C</sup> New MM3(94)
OCCO <i>a</i>	0.00	0.00	0.00		0.00	
OCCO <i>g</i>	7.5	2.5	-2.8	-5.3	2.0	0.5
OCCO <i>g'</i>	9.7	4.7	1.1	-3.6	6.4	-1.7

<sup>A</sup> HF/6-31G\*.<sup>37</sup> <sup>B</sup> Low level *ab initio* results<sup>37</sup> corrected by 5.0 kJ/mol for the difference between the *aaa* and *aga* conformers of 1,2-dimethoxyethane at this level of theory and at the highest level reported,<sup>7</sup> including MP2 electron correlation. <sup>C</sup> With respect to the corrected enthalpies.

Table 11. Conformational energies (kJ/mol) of diethers containing OCCO units

Compound	$\Delta G^\circ$ (exp.)	$\Delta G^\circ$ Standard	$\Delta\Delta G^\circ$ MM3(94)	$\Delta G^\circ$ New MM3(94)	$\Delta\Delta G^\circ$ New MM3(94)
1,2-Dimethoxyethane	-0.4 to -0.8 <sup>A</sup>	2.7	3.3	-2.0	-1.4
1,2-Dimethoxyethane (rotational barrier)	39.8 <sup>B</sup>	32.5	7.3	40.3	-0.5
<i>trans</i> -1,2-Dimethoxycyclohexane	0.46 <sup>C</sup>	7.7	7.2	1.8	1.3
1,2-Dimethoxy-2-methylpropane	-2.2 <sup>D</sup>	3.8	6.0	-1.2	1.0
1,2-Dimethoxypropane	1.6 <sup>E</sup>	0.8	0.8	5.9	4.3
	0.5 <sup>F</sup>	-2.6	-3.1	2.2	1.7
2-Isopropyl-5-methoxy-1,3-dioxan	-4.4 <sup>G</sup>	1.8	6.2	-8.0	-3.6
	-5.2 <sup>H</sup>	1.8	7.0	-8.0	-2.8
1,3,5,7-Tetraoxadecalin	2.5 <sup>I</sup>	-7.7	10.2	7.2	4.7
	19.6 <sup>J</sup>	20.8	1.2	28.3	8.7
<i>cis</i> -2-Methoxy-6-methoxymethyltetrahydropyran	2.5 <sup>K</sup>	-2.8	-5.3	2.0	0.5
	4.7 <sup>L</sup>	-8.6	-3.6	6.4	-1.7
			5.1 <sup>M</sup>		2.6 <sup>M</sup>

<sup>A</sup> For the equilibrium *aga*  $\rightleftharpoons$  *aaa* by *ab initio* methods, see text. <sup>B</sup> By an MP3/6-311+G//HF/6-311+G\* calculation.<sup>24</sup>  
<sup>C</sup> For the equilibrium (2e)  $\rightleftharpoons$  (2a) in pentane at -80°C. <sup>D</sup> For the equilibrium *g*  $\rightleftharpoons$  *a* in cyclohexane.<sup>29</sup>  
<sup>E</sup> For the equilibrium *a*  $\rightleftharpoons$  *g* in (D<sub>12</sub>)cyclohexane, see text. <sup>F</sup> For the equilibrium *a*  $\rightleftharpoons$  *g'* in (D<sub>12</sub>)cyclohexane, see text.  
<sup>G</sup> For the equilibrium (4a)  $\rightleftharpoons$  (4e) in hexane.<sup>10</sup> <sup>H</sup> For the equilibrium (4a)  $\rightleftharpoons$  (4e) corrected to the gas phase.<sup>10</sup>  
<sup>I</sup> For the equilibrium *trans*  $\rightleftharpoons$  *cis*-in calculated at the MP2/6-31G\*//6-31G\* level,<sup>7</sup> see text. <sup>J</sup> For the equilibrium *trans*  $\rightleftharpoons$  *cis*-out calculated at the MP2/6-31G\*//6-31G\* level,<sup>7</sup> see text.  
<sup>K</sup> For the equilibrium *a*  $\rightleftharpoons$  *g* calculated at the HF/6-31G\* level,<sup>37</sup> corrected for polarization and electron correlation, see text. <sup>L</sup> For the equilibrium, *a*  $\rightleftharpoons$  *g'* calculated at the HF/6-31G\* level,<sup>37</sup> corrected for polarization and electron correlation, see text. <sup>M</sup> Average  $|\Delta\Delta G^\circ|$ .

determining conformational stabilities for both 1,2- vicinal methoxy alcohols<sup>14,38</sup> and carbohydrates. The parameters developed here were used to calculate  $\Delta G^\circ$  values for 2-methoxyethanol (9) and *trans*-2-methoxycyclohexanol (3). The results are compared with *ab initio* results and experimental results in Table 12. Microwave<sup>39</sup> and i.r. data<sup>40-42</sup> are available for (9), and two groups, Lii and Allinger<sup>5</sup> and Gil and Teixeira-Dias,<sup>41</sup> have performed high level calculations on (9). Four conformers are considered to have significant populations, namely the *aaa*, *aag*, *ggg'* and *agg'* conformers. The *agg'* and *ggg'* conformers contain intramolecular hydrogen bonds. Lii and Allinger obtained a value of 8.45 kJ/mol for the equilibrium *agg'*  $\rightleftharpoons$  *aaa* at the 6-31G\*\* level.<sup>5</sup> Gil and coworkers' calculation at the MP2/6-31G\* level gave 14.6 kJ/mol for this equilibrium, but they pointed out that the *anti* conformations become destabilized at higher levels of theory and that a second *gauche* conformer, the *ggg'*, is intermediate in stability between the *agg'* and conformers with the OCCO unit *anti*.<sup>41</sup> However, several i.r. studies indicate that even the highest level *ab initio* calculations overestimate the *anti-gauche* energy difference; in dilute solution in non-polar solvents,  $\Delta H^\circ$

for equilibria between the hydrogen-bonded (OCCO *gauche*) and non-hydrogen-bonded conformers was measured as 7.5 $\pm$ 1.0,<sup>40</sup> 9.2 $\pm$ 2.0,<sup>42</sup> and 7-10 kJ/mol.<sup>41</sup>  $\Delta G^\circ$  values should be less because the hydrogen-bonded conformers are more restricted.

The calculated value for (9) with the new parameters was considerably smaller than either the best *ab initio* results or results from MM3(94) with standard parameters. This arises from the large  $V_1$  term, which, as for 1,2-dimethoxyethane (1), reduces the stability of the *gauche* conformer. The difference between the results for (9) from the standard parameters and the new parameters are about the same as for (1). The value obtained for the O-C-C-O torsional angle in the *agg'* conformer was 66.3° from MM3(94) with the new parameters, in comparison to Lii and Allinger's value of 62.1°,<sup>5</sup> and the microwave value of 57(3)°.<sup>39</sup> The HOCC torsional angle was 54°, larger than the uncertain microwave<sup>39</sup> value, 45(5)°. Not surprisingly, the new parameters give moments of inertia that are farther from the microwave values than the standard parameters<sup>5</sup> do:  $I_x$  6.3716 (1.4% off),  $I_y$  31.3277 (2.4%),  $I_z$  34.4532 (1.3%).

Table 12. Conformational energies (kJ/mol) of 2-methoxyethanol derivatives

Compound	$\Delta G^\circ$ (exp.)	$\Delta G^\circ$ Standard MM3(94)	$\Delta G^\circ$ New MM3(94)
2-Methoxyethanol (9)	14.6 <sup>A,B</sup> 7.5 <sup>A,C</sup>	6.9	1.7
2-Methoxyethanol (9)	6.3 <sup>D</sup>	7.6	7.8
<i>trans</i> -2-Methoxycyclohexanol (3)	3.51 <sup>E</sup>	14.9	9.3

<sup>A</sup> For the equilibrium  $agg' \rightleftharpoons aaa$ . <sup>B</sup> From MP2/6-31G\*///6-31G\* calculations.<sup>41</sup> <sup>C</sup> From dilute solutions by i.r. spectroscopy.<sup>40</sup> <sup>D</sup> For the equilibrium  $agg' \rightleftharpoons ggg'$  from MP2/6-31G\*///6-31G\* calculations.<sup>41</sup> <sup>E</sup> For the equilibrium (3e)  $\rightleftharpoons$  (3a) from current results in pentane at  $-80^\circ\text{C}$ .

Table 13. Relative energies (kJ/mol) of hydroxymethyl rotamers in methyl  $\alpha$ -D-glucopyranoside (10), methyl  $\alpha$ -D-galactopyranoside (11) and methyl 4-deoxy- $\alpha$ -D-glucopyranoside (12) in water

Compound	Rotamer	$\Delta G^\circ$ (exp.) <sup>36</sup>	$\Delta G^\circ$ <sup>A</sup>	$\Delta G^\circ$ Standard MM3(94)	$\Delta G^\circ$ New MM3(94)
(10)	<i>gg</i>	0.00	0.0	0.00	0.00
	<i>gt</i>	0.33	0.09	-3.14	-1.8
	<i>tg</i>	>10	2.36	5.77	0.17
(11)	<i>gg</i>	3.85		5.21	6.15
	<i>gt</i>	0.0		0.0	0.0
	<i>tg</i>	5.29		6.69	1.51
(12)	<i>gg</i>	0.45		2.59	3.05
	<i>gt</i>	0.0		0.0	0.0
	<i>tg</i>	9.95		6.65	1.38

<sup>A</sup> By *ab initio* calculations at the MP2 6-31G(d) level on  $\alpha$ -D-glucopyranoside.<sup>43</sup>

*trans*-2-Methoxycyclohexanol (3) has been studied with Fourier-transform i.r. techniques.<sup>14</sup> These showed that intramolecular hydrogen bonding was important at low concentrations in non-polar solvents but the results were not quantitative. In order to obtain accurate data regarding this equilibrium (see Fig. 1), compound (3) was synthesized, and low temperature n.m.r. spectra were measured in various solvents and analysed as for (2). The results are listed in Table 3. Because it was not possible to measure the equilibria at low concentrations, the species on which the equilibria were measured were probably aggregates. In agreement with this conclusion, <sup>1</sup>H n.m.r. spectra of (3) at  $-80^\circ\text{C}$  were broad in CS<sub>2</sub> and tetrahydrofuran.

The standard MM3(94) parameters are very poor in duplicating the experimental energy difference between conformers (3e) and (3a). The new terms give significantly better agreement but the deviation is still large (5.8 kJ/mol). However, the direction of the deviation is opposite to that for (9), that is, the conformer with the OCCO unit *gauche* where hydrogen bonding is possible is now calculated to be more stable than observed experimentally.

Rotation about the C5-C6 bond in hexopyranosides was studied for methyl  $\alpha$ -D-glucopyranoside (10), methyl  $\alpha$ -D-galactopyranoside (11) and methyl 4-deoxy- $\alpha$ -D-xylo-hexopyranoside (12), and the results are compared with those from experimental studies<sup>36</sup> and MP2 6-31G(d) *ab initio* studies<sup>43</sup> in Table 13 (see Fig. 9). Free energy differences between rotamers were obtained by modifying the enthalpy differences between pairs of most stable C6-O6 rotamers for the entropy of mixing contributions from the other C6-O6 rotamers. The MM3 calculations were performed at a

dielectric constant  $\epsilon$  of 80, similar to that of water, the solvent from which the n.m.r. data are taken. A large  $\epsilon$  value removes any intramolecular hydrogen bonding but does not duplicate the steric effects or electrostatic effects of solvation of the various hydroxy groups. For (10), the results are fairly similar to those of the high level *ab initio* studies.<sup>43</sup> For all three compounds, the *tg* conformer is calculated by MM3 with the modified parameters to be much more stable than observed in water.<sup>36</sup>

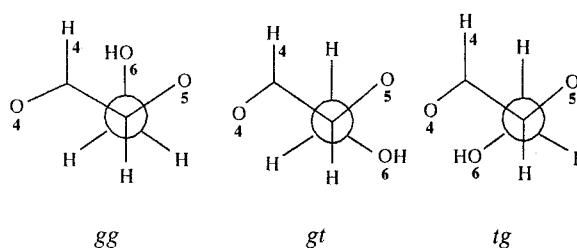


Fig. 9. C5-C6 rotamers for D-glucopyranosides (10). For D-galactopyranosides (11), H4 and O4 exchange positions. For (12), O4 is replaced by an H.

The increased bulk of solvated hydroxy groups is one possible cause of the experimentally observed destabilization of the *tg* conformation (see Fig. 9). Hydroxy groups have larger *A* values in hydrogen bond donor solvents, such as alcohols, than in non-polar solvents.<sup>44,45</sup> This effect has been ascribed to the difficulty of solvating the axial rotamer with the H inside the ring,<sup>44</sup> and is equivalent to suggesting that the OH group has increased but variable steric bulk in hydroxylic solvents. If a steric effect of solvation were included, conformations having 1,3-diaxial interactions

would be disfavoured. Such interactions are difficult to evaluate even qualitatively because the extent of solvation is probably different for secondary and primary hydroxyls and may well be different for different rotamers. However, the largest destabilizing effect of solvation should be on conformations with 1,3-OH-OH interactions. The *tg* conformer of (10) has such an interaction and its destabilization results in a better fit of the calculated results to the experimental data. For (11), the *gg* conformation would be destabilized by the 1,3-OH-OH interaction, contrary to the experimental observation.<sup>36</sup>

Experimentally, the importance of such interactions can be evaluated by considering the 4-deoxy derivative of (10) or (11), methyl 4-deoxy- $\alpha$ -D-xylo-hexopyranoside (12), for which data<sup>36</sup> are presented in Table 13. If these interactions were significant, their removal would stabilize the conformation in which they are present, *tg* for (10) and *gg* for (11). For both (10) and (12), the population of the *tg* conformer is too low to be evaluated accurately, so a comparison is not meaningful. The relative stabilities of the *gg* and *gt* conformers can be compared for (11) (*gt* 3.85 kJ/mol more stable) and for (12) (*gt* 0.45 kJ/mol more stable). In this case, the direction of change is consistent with this explanation but the size of the difference in the changes (3.4 kJ/mol) is not sufficient to explain the difference between the calculated and the experimental results, either by MM3 or by the *ab initio* method.<sup>43</sup> In fact, the experimental (3.4 kJ/mol) and MM3 calculated changes (3.1 kJ/mol) are almost the same, suggesting that increased steric bulk of solvated hydroxy groups is not the cause of the difficulty.

It appears that there are specific interactions that either destabilize the *tg* conformer more than predicted or stabilize the *gg* and *gt* conformers. Possible mechanisms for the latter explanation could be either direct hydrogen bonding or hydrogen bonding involving one water molecule acting both as a hydrogen bond donor and as a receptor to complete a seven-membered ring. If this occurred, the 6-*O*-methyl derivative of (10) would be expected to have drastically different rotamer populations; in fact, the observed populations are almost identical to that of (10).<sup>36</sup> Another possible mechanism has one water molecule acting as a hydrogen bond donor to both *gauche* oxygen atoms. If this effect were important, the position of these equilibria would be different in methanol; again, the experimental results in CD<sub>3</sub>OD are almost identical to those in water.<sup>36</sup> There does not appear to be a good explanation for this extra stability of the *O-O gauche* C5-C6 conformers with respect to the *trans* conformer in polar solvents at this time.

## Conclusions

By use of low temperature n.m.r. techniques, the conformational energies for the equilibria between the axial and equatorial conformers of (2) and (3) have been

determined in solvents with a range of polarities. These values were then used in conjunction with theoretical and experimental data for (1) and (10) to determine new OCCO torsional parameters for MM3(94). These new parameters are considerably better than those in the standard MM3(94) parameter set for reproducing experimental results on ethers. The agreement is less satisfactory when reproducing systems involving intramolecular hydrogen bonding. MM3(94) calculations with the new parameters satisfactorily reproduce high level *ab initio* results for C(5)-C(6) rotation for a model compound and for methyl  $\alpha$ -D-glucopyranoside but fail to reproduce experimental results in which the *gg* and *gt* conformers are much more stable than the *tg* conformer.

## Experimental

1,2-Dimethoxyethane was dried and distilled over CaH<sub>2</sub> prior to use. Anhydrous methanol was obtained by reflux and distillation over Mg(OMe)<sub>2</sub>. Cyclohexene oxide, <sup>13</sup>C-labelled methyl iodide, and 1,2-dimethoxypropane were purchased from Aldrich and used without further purification. *trans*-Cyclohexane-1,2-diol was prepared by oxidation of cyclohexene with formic acid and hydrogen peroxide,<sup>46</sup> and was recrystallized twice from ethyl acetate before use. Vacuum distillation and concentration were done under the vacuum produced by a water aspirator.

N.m.r. spectra for identification purposes were measured on a Bruker AMX-250 spectrometer. Proton and carbon assignments were confirmed by means of HETCOR and COSY experiments. Chemical shifts are expressed in ppm relative to internal SiMe<sub>4</sub> (0.03%), or the central line of the solvent, (D)chloroform (77.0 ppm), (D<sub>6</sub>)acetone (<sup>1</sup>H 2.04 ppm, <sup>13</sup>C 29.8 ppm), CD<sub>2</sub>Cl<sub>2</sub> (53.8 ppm), (D<sub>8</sub>)toluene (20.4 ppm), (D<sub>4</sub>)methanol (49.0), or (D<sub>8</sub>)tetrahydrofuran (67.4 ppm). The CS<sub>2</sub> sample was referenced to the CS<sub>2</sub> peak at 192.8 ppm, and the pentane spectrum was referenced to the methyl peak of pentane at 13.7.

N.m.r. samples for conformational analysis (0.5 M, unless otherwise specified) were prepared in 5 mm n.m.r. tubes. The <sup>13</sup>C n.m.r. spectra of labelled *trans*-1,2-dimethoxycyclohexane were measured on a Bruker AMX-400 spectrometer with a 56° pulse, and inverse gated decoupling with a delay time of 5 s. The spectra of *trans*-2-methoxycyclohexanol were measured on a Bruker AC-250 spectrometer, with a 56° pulse and an 8 s pulse delay being used. Temperatures on Bruker AC-250 and AMX-400 spectrometers were maintained with Bruker B-VT 1000 and B-VT 1000E units, respectively. Processing of the spectra including automatic deconvolution (fitting the peaks to a Lorentzian function) was performed by using Bruker software.

### *trans*-1,2-Dimethoxycyclohexane

*trans*-Cyclohexane-1,2-diol (1.98 g, 17 mmol) was dissolved in dry 1,2-dimethoxyethane (35 ml). The solution was stirred and cooled in an ice bath. Excess sodium hydride (1.15 g, 48 mmol) was added slowly over 10 min and the mixture was stirred for 3 h. <sup>13</sup>C-labelled methyl iodide (5.0 g, 35 mmol) was added via a syringe and stirring was continued for 12 h. An equal volume of water (35 ml) was added slowly to avoid frothing and the resulting aqueous solution was extracted with pentane (3×30 ml). The pentane fractions were combined, dried over MgSO<sub>4</sub>, and concentrated. The concentrate was fractionally distilled to obtain *trans*-1,2-dimethoxycyclohexane (0.40 g, 16%) as a clear colourless liquid, b.p. 65–67°C/23 mm (lit.<sup>47</sup> 75°C/33 mm). <sup>1</sup>H n.m.r. (250 MHz, (D<sub>6</sub>)acetone)  $\delta$  1.22, m, 4H, H3<sub>ax</sub>, H4<sub>ax</sub>, H5<sub>ax</sub>, H6<sub>ax</sub>; 1.57, m, 2H, H4<sub>eq</sub>, H5<sub>eq</sub>; 1.87, m, 2H, H3<sub>eq</sub>, H6<sub>eq</sub>; 2.83, m, 2H, H1, H2; 3.32, d, J<sub>C,H</sub> 140 Hz, 6H, methoxy. <sup>13</sup>C n.m.r. (62.9 MHz,

(D<sub>6</sub>)acetone)  $\delta$  82.2, C1,6; 57.0, 2×OMe; 28.9, C2,5; 23.4, C3,4.

#### trans-2-Methoxycyclohexanol

trans-2-Methoxycyclohexanol was made by a literature method<sup>48</sup> and fractionally distilled as a clear colourless liquid, b.p. 80–82°C/24 mm (lit.<sup>48</sup> 72.5–73.2°C/10 mm). <sup>1</sup>H n.m.r. (250 MHz, CDCl<sub>3</sub>)  $\delta$  1.23, m, 4H, H3<sub>ax</sub>, H4<sub>ax</sub>, H5<sub>ax</sub>, H6<sub>ax</sub>; 1.70, m, 2H, H4<sub>eq</sub>, H5<sub>eq</sub>; 1.98, m, 1H, H6<sub>eq</sub>; 2.10, m, 1H, H3<sub>eq</sub>; 2.94, ddd,  $J_{1,2}$  8.85 Hz,  $J_{2,3e}$ , 4.27,  $J_{2,3ax}$  10.68 Hz, H2; 3.11, br s, 1H, OH; 3.40, m, 1H, H1; 3.41, s, 3H, OCH<sub>3</sub>. <sup>13</sup>C n.m.r. (62.9 MHz, CDCl<sub>3</sub>)  $\delta$  23.8, C4; 23.9, C5; 28.2, C3; 32.0, C6; 56.1, OMe; 73.4, C1; 84.8, C2.

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