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1,4-INTERACTIONS IN MOLECULAR MECHANICS CALCULATIONS OF ETHERS[1]

ULRICH BURKERT
Universität Konstanz, Fachbereich Chemie, Postfach 7733, 7750 Konstanz, West Germany

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Abstract—Van der Waals and electrostatic interactions are found to be insufficient for the calculation of conformational energies of ethers by molecular mechanics. Low order torsional potential functions must be added for the potential about C–O bonds. A onefold term necessary for the CCOC-fragment is interpreted to be a substitute for gauche interactions present in CCCC-, but missing in CCOC-fragments. For the COCO fragment the anomeric effect must be included explicitly as another torsional energy term, but no such term is required to stabilize the gauche conformation for OCCO. With the resulting ether force field the geometries and energies of model compounds, many of them 1,3-dioxanes, are calculated with good accuracy.

Empirical force field calculations (molecular mechanics) have become a powerful instrument for conformational analysis which is applied extensively and with increasing precision and reliability to the determination of structure and energy as well as other properties of hydrocarbons.[2] For obvious reasons the extension of hydrocarbon force fields to include the most frequent heteroatoms like the halogens, nitrogen, oxygen, sulfur, etc. is highly desirable, and systematic work to this end has been reported for many elements. This extension is found hardly problematic when carbon is replaced by silicon[3] or divalent sulfur,[4] but replacement of hydrogen by halogen, especially fluorine, has earlier caused considerable problems.[5] These problems are in part due to an inadequate treatment of electrostatic interactions in early force fields, usually these are neglected in hydrocarbon force fields, and are handled in halide force fields by dipole–dipole or Coulomb charge interactions. Even more severe difficulties arise when the model of molecular mechanics, which assumes that the molecular potential is determined in principle by bond length and angle restoring forces and nonbonded interactions, is insufficient, because orbital interaction effects of a completely different nature than the molecular mechanics nonbonded interactions play an important part. Such effects, mainly within the four-atom fragment defining a torsion angle, have been described in the theoretical literature,[6–12] and were found important in molecular mechanics calculations for example of vicinal difluorides.[13]

Oxygen occurring in organic molecules at a terminal position in carbonyl compounds has been dealt with in molecular mechanics successfully,[14] but the results of ether force fields has been less satisfactory. For some time the van der Waals potential[15,16] and electrostatic interactions[16] were thought to be calculated inadequately only in earlier force fields, calculations which we have performed on a larger set of compounds containing all the typical structural elements of saturated mono and diethers show however, that other interactions than can be handled by van der Waals and electrostatic potentials are indeed significant in ethers. In our opinion this finding contributes not only important new parameters, which will be found to be necessary in every ether force field, but also shows the general significance of the related interactions for more qualitative discussions of ether conformations.

RESULTS AND DISCUSSION

Monoethers. One of the basics of conformational analysis of hydrocarbons is the *gauche/anti* conformational equilibrium of the CCCC fragment in n-butane and methylcyclohexane. For ethers two fundamental units must be distinguished, the CCCO fragment occurring in n-propanol and 5-alkyl-1,3-dioxanes, and the CCOC fragment of ethyl methyl ether and 2-methyl-1,3-dioxanes. We have reported earlier an extension of Allinger's 1973 hydrocarbon force field MMI[17] for ethers, which was parameterized to give correct geometries for simple ethers, and the van der Waals potential of oxygen was adjusted to fit the experimental energies of the conformations of 5-alkyl-1,3-dioxanes.[18] In these calculations no molecules showing a *gauche/anti* equilibrium of the CCOC fragment were studied. The conformational energies of ethyl methyl ether 1, and 2- and 4-methyl-1,3-dioxanes 2 and 3 (Table 2) are considerably larger than in the related hydrocarbons (for example n-butane: 4.0 kJ mol^{-1}),[20] and this is usually explained by the increased van der Waals repulsion between the two ends of the fragment because of the shorter C–O bonds and the smaller COC bond angles.[21] We found however that our earlier force field[16] gives for these conformational energies values amounting to only about 50% of the experimental values. The discrepancy at first seems to originate from an inadequacy of the MMI van der Waals parameters for C and H, because the Me–Me repulsion in 1 and the transannular repulsions in 2 and 3 are calculated less hard than required to obtain the correct conformational energies. These parameters are known to differ very much from those of most other force fields, with the van der Waals parameters of Allinger's MM2 hydrocarbon force field, which are very similar to those of most other force fields,[22] we obtained however nearly the same results. We conclude that in these two force fields, and propably in all other hydrocarbon force fields when extended to ethers, there must be an additional interaction in the CCOC fragment than the methyl...methyl van der Waals repulsion in 1 or the transannular repulsion in 2 and 3 which was neglected earlier.

Technically, such insufficiencies of force fields can be relieved by adding torsional energy terms. Usually the only term of the Fourier expansion of a general torsional potential function

$$V_{tor} = \frac{1}{2}V_1(1-\cos\omega)+\frac{1}{2}V_2(1+\cos 2\omega) + \frac{1}{2}V_3(1-\cos 3\omega)+\cdots$$

used in hydrocarbon force fields and also in the earlier ether force fields[15,16] is the V_3 term, correcting for the part of the rotation barrier not covered by van der Waals repulsions and interpreted as bond–bond repulsion. A large V_2 term was necessary for calculations of vicinal difluorides,[13] and small V_1 and V_2 terms[13,23] were employed in Allinger's MM2 hydrocarbon force field.[22] In the same way a large V_1 term may be employed to stabilize the CCOC anti arrangement, or a V_2 term to stabilize 90° torsion angles over periplanar arrangements, and thereby increase the *gauche*/*anti* energy difference in 1, and the related conformational energies of 2 and 3. In our force field we prefer a V_1 term (Table 1), which was adjusted to fit the conformational energy of 2. With the thus modified force field excellent agreement of calculated and experimental energies is obtained also for 1 and 3 (Table 2).

For a rationalization of this unusually large V_1 torsional energy term, we recall the observation of Wertz and Allinger that *gauche* interactions of hydrogens are a major factor in their calculations of conformational energies.[17] The high energy of the *gauche* form of n-butane, earlier ascribed exclusively to the 1,4-Me–Me repulsions, was found to be caused at least in part by the interactions of the hydrogens on the methylene groups. It is also known that the relative weight of these interactions depends on the parameterization of the C and H van der Waals potentials,[13,22–26] that they may however not be neglected altogether. In the CCCO fragment these interactions are identical to those in the CCCC fragment, but not so in the CCOC fragment. We find the reason for the low energies calculated for 1–3 to be related to these interactions. In our force field 1,4-interactions of lone pairs are excluded by definition,[16] so there are essentially no 1,4-interactions from the methylene hydrogens in 1 along the central bond which would correspond to *gauche* hydrogen interactions. The repulsion of the oxygen lone pairs and the methylene hydrogens in 1, which is minimized at $\omega = 180°$, is therefore a plausible explanation of the V_1 term. Indeed the conformational energies calculated for 1–3 by Allinger and Chung with their force field allowing 1,4-interactions of (hard and large) lone pairs[15] are higher than the values calculated with our earlier force field neglecting such interactions,[16] they amount however only to about 60% of the experimental values. A rationalization of a V_2 term is less obvious, and for this reason a V_1 term was used exclusively, although a small V_2 term may be useful in the future to further refine the torsional potential.

Table 1. Force field parameters[a)]

Stretching

Bond	k_s (mdynA^{-1})	l_0 (A)
C–O	5.36	1.406
O–lone pair	4.60	0.50

Bending

Angle	k_b (mdyn rad^{-2})	θ_0
C–O–C	0.80	104.10
C–C–O	0.56	109.10
O–C–O	0.56	107.50
O–C–H	0.43	107.50
C–O–lp	0.35	103.26
lp–O–lp	0.24	140.00

Torsion[b,c)]

Atoms	V_1	V_2	V_3
CCCO	0.0	0.0	0.53
CCOC	2.075	0.0	0.66
OCCO	0.0	0.0	0.53
COCO	0.0	−1.80	0.66
OCCH	0.0	0.0	0.53
COCH	0.0	0.0	1.98

van der Waals[d)]

Atom	r_0 (A)	(kcal mol^{-1})
O	1.65	0.046
lone pair	1.50	0.003

[a)] All calculations were performed with the MMI program of Allinger, and the 1973 hydrocarbon parameters.[17] For easier implementation all parameters are given in units of A and kcal. The potential functions are given in Ref. 17. [b)] The V_3 term is ignored for $\omega > 60°$, if V_1 and V_2 are zero, otherwise it is included for all values of ω. [c)] All torsional constants involving lone pairs are zero. [d)] 1,4-Interactions of lone pairs are not calculated.

The geometry of the *anti* form of ethyl methyl ether has been determined by microwave spectroscopy,[27] and it agrees well with our calculated structure (Table 3). An electron diffraction study of this molecule has also been published,[28] and from a shoulder in the radial distribution curve corresponding to the gauche C_{me}–C_{me} nonbonded distance the CCOC torsion angle in the *gauche* conformation was inferred to be much larger than in n-butane, where it is 65°. This quantity is however highly correlated with the bond angles, for which an average value of *gauche* and *anti* form was obtained only. According to the force field calculation the COC bond angle hardly opens up in the *gauche* conformation, but the CCO angle does considerably, which is also reflected in the differences between microwave and electron diffraction bond angles (Table 3). The observed C_{me}–C_{me} distance can therefore also be obtained with a much small torsion angle as calculated with our force field (Table 3, $r_{C..C}$(calc) = 302 pm, ED: 306.6 pm). To confirm the result of the molecular mechanics calculation, we performed quantum mechanical *ab initio* calculations with the 4-31G basis,[29] with the geometries for *gauche* and *anti* ethyl methyl ether obtained from the molecular mechanics calculation, and with a geometry for which the torsion angle was fixed at the value of 80° by the method of Wiberg and Boyd,[29] and the rest of the internal coordinates fully optimized by molecular mechanics (Table 3).

The V_1 torsional energy parameter for the CCOC fragment hardly has any effect on the conformational energies calculated for compounds with the CCCO fragment in a *gauche*/*anti* conformational equilibrium. The energies calculated for 5-alkyl-1,3-dioxanes are practically the same as before[16] (Table 2). Other compounds which show a conformational equilibrium of obtained for the 5-Me group of 2,5-dimethyltetrahydropyran **8** agrees with the experimental value for 2-carbmethoxy-5-methyltetrahydropyran.[30] For n-propanol, the simplest compound with the CCCO fragment, the available experimental information is not conclusive: vibrational and NMR data indicate prevailance of the *anti* form,[31] but a microwave study gave an enthalpy difference of 1.2 ± 0.6 kJ mol^{-1} in favor of *gauche*.[32] The calculations gives a preference for the *anti* form (Table 2). A conventional calculation of conformational energies adding *gauche* energy increments would predict identical energies for the equatorial and axial conformers of 4,4,5- and r-4,5,t-6-trimethyl-1,3-dioxane **10** and **11**, because the additional *gauche* CCCC interaction present in the equatorial isomer (2 CCCC *gauche* vs 1 *gauche* and 1 *anti* in the axial form) balances out with the conformational energy of the 5-Me group in 5-methyl-1,3-dioxane (2 CCCO *gauche* in the axial vs 2 *anti* in the equatorial isomer).[33] Our molecular mechanics calculation indicates a preference for the equatorial 5-Me group close to the experimental values. The axial conformers are less stable than the equatorial forms because of the flattening of the CCC region observed in all 1,3-dioxanes. The repulsion of the axial 5-Me and the equatorial 4-Me groups is stronger than in *gauche* butane, because the CCCC torsion angle is considerably smaller than there. In **10** the equatorial Me group cannot even relax to relieve this van der Waals strain, but in **11**, where the buttressing second Me group on C-4 is missing, the C-4 can escape some of the van der Waals repulsion by a bending deformation.

Methoxycyclohexane **12** is a molecule in which the CCCO fragment determines the energy difference of equatorial and axial conformations, and the CCOC fragment defines the rotameric position of the exocyclic chain. Both the equatorial and the axial conformations are calculated to favor the unsymmetrical geometry (by 8.7 and 23.7 kJ mol^{-1}), the equilibrium of equatorial and axial forms is faithfully reproduced (Table 2).

Di- and polyethers. No problems are expected for the application of the force field to diethers with oxygens

Table 2. Conformational energies of some ethers (in kJ mol^{-1})

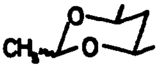
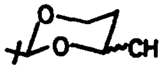
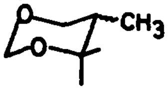
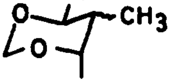
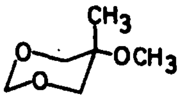
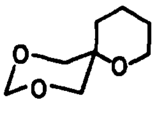
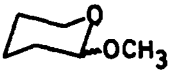
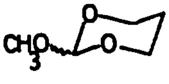
Compound	fav.	H_{calc}	H_{exp}	G_{exp}	Ref.
1 $CH_3CH_2OCH_3$	anti	7.3	6.2±0.8		a
				5.1±1.1	b
2 	eq	16.6	16.6		c
3 	eq	11.6		11.7	d
4 	eq	3.5	3.5		e
5 	eq	2.7	3.2		e
6 	eq	6.7	6.8		e
7 	eq	7.0	6.8		e
8 	eq	4.3 ($R=CH_3$)		5.3 ($R=COOCH_3$)	f
9 $CH_3CH_2CH_2OH$	anti	0.9	anti -1.2±0.6		g h
10 	eq	5.2		6.0	i,j
11 	eq	4.2		2.5	j
12 	eq	2.6		2.5	k

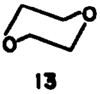
Table 2. (*Contd*).

Compound	fav.	H_{calc}	H_{exp}	G_{exp}	Ref.
16 	eq	5.5		4.4 (C_6H_{12})	l
17 	O eq	4.0		1.2 (ether)	m
18 	O eq	2.9		1.54, 1.0 (ether)	n
19 	ax	4.6	4.5		o
20 $CH_3OCH_2OCH_3$					
g^+g^+		0.0			
ga		7.7			
g^+g^-		10.9			
aa		16.2			
21 	ax	2.1		2.5 (ether?)	d

[a] T. Kitagawa and T. Miyazawa, *Bull. Chem. Soc. Jap*. 41, 1967 (1968), [b] Ref. 28, [c] Ref. 21, [d] E. L. Eliel, *Acc. Chem. Res*. 3, 1 (1970), [e] E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc*. 88, 5347 (1966), *Ibid*. 90, 3444 (1968), F. G. Riddell and M. J. T. Robinson, *Tetrahedron* 23, 3417 (1967), [f] Ref. 30, [g] Ref. 31, [h] Ref. 32, [i] Ref. 33, [j] K. Pihlaja and P. Äyräs, *Suomen Khemistilehti* B42, 65 (1969), [k] J. A. Hirsch, in *Topics in Stereochemistry* (Edited by N. L. Allinger and E. L. Eliel), Vol. 1, p. 223. Wiley, New York (1967), [l] Ref. 35, [m] E. L. Eliel and R. M. Enanoza, *J. Amer. Chem. Soc*. 94, 8072 (1972), [n] Ref. 45, [o] A. J. de Hoog, H. R. Buys, C. Altona and E. Havinga, *Tetrahedron* 25, 3365 (1969).

separated by at least three C atoms. Diethers with the OCCO (glycol ether) and COCO (acetal) fragments deserve, however, special attention.

In OCCO fragments a *gauche* effect has been proposed to cause dimethoxyethane[34] to prefer the *gauche* conformation,[8] which is, however, contradictory to the known preference of 5-methoxy-1,3-dioxanes for the equatorial (OCCO *anti*) conformation.[35] Although the application of a V_2 torsional energy term has been recommended for glycol ethers,[13] in the present work no low periodicity torsional energy term was employed for the OCCO fragment. Lacking an experimental value for the rotation barrier in a glycol ether, the same V_3 parameter was used for CCCC and OCCO (Table 1). For the central C–C bond of glycol ethers a "normal" length of 152.3 pm was found for 1,4-dioxane by electron diffraction,[36] but much shorter one are observed in X-ray structures of ethylene glycol diesters[37,38] and macrocyclic polyethers (mostly between 148 and 150 pm). At least part of this foreshortening seems to be an artificial effect of thermal (torsional) motions in the crystal,[39] although even in a recent low temperature X-ray study of a macrocyclic polyether short bonds of 149.8 pm were found.[40] The geometries calculated for some model compounds, 1,4-dioxane 13, 1,4,6,8-tetraoxaspiro(4,5)undecane 14, and 5-hydroxy-5-isopropyl-1,3-dioxane 15, deviate from experimental structures in the



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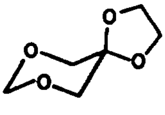

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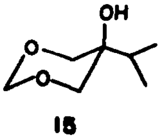


15

Table 3. Geometries and energies of ethyl methyl ether conformations

	This study anti	This study gauche	This study 80°	microwave[27)] r_s (anti)	el.diff.[28)] r_a (mixture)
r(C-C)	1.533	1.531	1.531	1.520	1.520
r(C_{methyl}-O)	1.416	1.415	1.415	1.404	1.413
r($C_{methylene}$-O)	1.420	1.417	1.418	1.415	1.422
C-O-C	111.9	112.4	112.3	111.8	111.9
C-C-O	108.7	113.8	113.2	108.1	109.4
C-C-O-C	180	71.2	80.0		84±6
<u>ab initio</u> energies					
absolute (au)	-192.81877	-192.81526	-192.81511		
relative (kcal)	0.0	9.2	9.6		

bond lengths usually by less than 1.5 pm, with one deviation of 2.2 pm, in the bond angles by 1–2°, and in the torsion angles by less than 2°. No systematic "foreshortening" of the experimental vs the calculated (O)C–C(O) bonds is found. The ring of 13 is calculated to be less flattened than the cyclohexane ring, but while in our study the COC angle is small and the CCO angle is large, the electron diffraction structure[36] shows the inverse. A derivative of 14, which contains additional rings attached to the 5-membered ring, was investigated by X-ray diffraction.[41] Only in the conformation of the 5-membered ring major differences are found, which cannot be surprising, because the additional rings present in the molecule studied experimentally have a large influence on the pseudorotationally mobile dioxolane ring. In the calculated structure of 15 the OH hydrogen is in the plane bisecting the 1,3-dioxane ring, forming a bifurcated hydrogen bond,[42] whereas in the crystal the compound is intermolecularly H-bonded.[43] In the calculated structure the OH group is therefore bent towards the ring oxygens.

Of the few data available about the conformational equilibria of glycol ethers and analogous compounds, the most reliable are the conformational energies of 5-alkoxy-1,3-dioxanes, which exhibit a much stronger solvent dependency than the energies of 5-alkyl-1,3-dioxanes. Experimental values for 5-t-butyl-1,3-dioxane range from 5.7 kJ mol^{-1} (in cyclohexane) to 7.2 kJ mol^{-1} (in acetonitrile),[44] but for 5-methoxy-1,3-dioxane values from 4.4 kJ mol^{-1} (in hexane) and 3.4 kJ mol^{-1} (in ether) down to 0.04 kJ mol^{-1} (in acetonitrile) are found.[35] Our calculations refer to the isolated molecule in the gas phase, which we compare to the experimental energies in the least polar solvent.

For 5-methoxy-2-t-butyl-1,3-dioxane 16 two Me rotamers must be considered for both the equatorial and axial isomer. Again unsymmetrical conformations are highly favored, by 10.5 and 9.4 kJ mol^{-1} for the equatorial and axial isomer, respectively. From dipole moments a preference of 3.3 kJ mol^{-1} for the unsymmetrical conformation was obtained for the axial isomer in benzene solution.[45] Because of the electrostatic repulsion of the O atoms in the ring and the Me group, the axial conformation of 16 is more destabilized than that of 5 (Table 2). The conformational energies of 5-methoxy-5-methyl-1,3-dioxane 17 and 2,4,7-trioxaspiro(5,5)undecan 18 show the large influence of the solvent. Finally the conformations of dimethoxyethane were calculated. In the literature this molecule has usually been treated as being in an equilibrium of only two conformations (*gauche* and *anti* about the central bond), although 10 conformations are feasible. Detailed molecular mechanics calculations have been reported by Podo *et al.* with a force field which was not tested on other molecules.[46] Our calculations agree that the $g^+g^-g^+$ form is not a stable conformation, but is converted during energy minimization to other conformations. We also agree on the ranking of the stabilities of all conformations, the all-*anti* form is most stable, and the aga form second (Table 4). In our calculation the energy difference of aaa and aga is however much larger than in Podo's, and the high degeneracy of the aga from is not sufficient to populate this conformer more than the most stable aaa form. For the two-state equilibrium we calculate a Gibbs energy difference of 0.5 kJ mol^{-1} in favor of *anti* conformations, while Podo *et al.* calculated a preference of 1.1 kJ mol^{-1} for *gauche*.[46] In solution both families of conformations are very similarly populated, depolarized Raleigh scattering and ^{1}H NMR data indicate a slight preference for *gauche* (about 1 kJ mol^{-1}),[34] while vibrational data are less decisive.[46]

Although for most of the molecules studied the experimental data point to a smaller preference for the OCCO *anti* arrangement than we calculate, this is such a small energy increment that it is difficult to decide whether it is due to solvent effects or an electronic

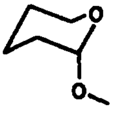
Table 4. Conformational energies and conformer populations of dimethoxyethane

Conformation	rel. energy[a)] (kJmol^{-1})	Population %
aaa	0.0 (0.0)	45.6
aag	7.3 (4.4)	9.5
g^+ag^-	10.0 (9.0)	0.1
g^-ag^-	15.3 ([illegible].4)	0.3
aga	2.[illegible] (0.5)	37.7
$g^-g^-g^+$	1[illegible].7 (12.0)	1.0
$g^-g^-g^-$	15.6 (9.0)	0.2
ag^-g^+	10.6 (6.9)	[illegible].5
ag^-g^-	9.5 (4.8)	4.0

[a)] In brackets: values of Ref. [46].

"*gauche* effect". At present we see no justification to add any low periodicity torsional energy terms, which might only be in the order of 0.1 kJ mol^{-1}.

The preference of the COCO fragment for the *gauche* conformation is a well-known phenomenon in carbohydrate conformational analysis; an axial O-alkyl group at the anomeric carbon of a pyranose is known to be more stable than the equatorial form, at least definitely more than expected on steric grounds.[47] This "anomeric effect" has found a number of explanations, the classical one being electrostatic interactions of the lone pairs and the C–O bond dipoles.[48] Quantum mechanical arguments, invoking electron back donation from the (p-type) oxygen lone pair orbital into the σ^* molecular orbital of the C–O bond to the exocyclic O atom,[9–12] suggest that the effect stabilizes the conformation with a COCO torsion angle of 90°. None of these interactions is included in our force field, and the anomeric effect is not reproduced in the calculations, unless a torsional energy term, this time standing for the electron back donation, is added. A large V_2 term (Table 1) with energy minima at $\omega = 90°$ and 270° had to be employed to fit the experimental enthalpy difference of equatorial and axial 2-methoxytetrahydropyran 19 (Table 2). The only highly populated conformations are the sterically less hindered conformations A and B, which have the exocyclic COCO fragment in the *gauche* arrangement, a phenomenon known as the *exo*-anomeric effect.[49] A V_2 term has also been used earlier, but was oriented on the (sp^3 hybrid type) oxygen lone pairs, and not on bonds only.[15] Constant terms which are no continuous function of a torsion angle, have also been used.[50]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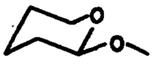
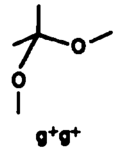
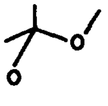
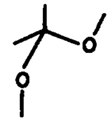

B

In agreement with an electron diffraction study,[51] the most stable conformation of dimethoxymethane 20 was calculated to be the g$^+$g$^+$ form (91% of the equilibrium mixture). The energy gained from the anomeric effect in the g$^+$g$^-$ form is superceded by van der Waals repulsions between the Me groups, and the second most stable conformation is therefore ga, which makes up for 8% of the mixture. Quantum mechanical calculations support this result: CNDO/2 calculates the ga conformation with3.7 kJ mol^{-1} and the aa form with 10.8 kJ mol^{-1} relative to the g$^+$g$^+$ form,[52] *ab initio* calculations (4-31G) with optimized bond lengths give an energy of 9.9 kJ mol^{-1} for ga, 13.4 kJ mol^{-1} for g$^+$g$^-$, and 30.9 kJ mol^{-1} for aa over g$^+$g$^+$.[12] From the temperature dependency of the dipole moment of 21, energies of 8.0 kJ mol^{-1} for ga, and 18.7 kJ mol^{-1} for aa were derived.[52]


g$^+$g$^+$


g$^+$g$^-$


aa


ga

In our calculations no attempts were made to reproduce the slight changes of the (O)C–O bond lengths caused by the anomeric effect.[9,12] In the electron diffraction study of 21 it was not possible to unambiguously decide whether both kinds of C–O distances in this molecule are identical (140.5 pm) or if the central bond is shorter (138.2 pm) than the terminal one (143.2 pm).[51] In our calculations bond lengths of 141.5 and 141.6 pm are obtained. To keep the force field simple, but also because of a lack of more reliable structural data, no correction (as by a torsion-stretch interaction term) has been applied.

The parameters which were developed for acetals can even be transferred to calculate conformational energies of *ortho* ester derivatives. For 2-methoxy-1,3-dioxane we calculate a preference for the axial form in close agreement with the experimental value (Table 2). It seems therefore that the "anomeric effect terms" are roughly additive.

CONCLUSIONS

The parameterization of an ether force fields must account for interactions which are either much weaker in hydrocarbons, such as electrostatic interactions and electron donation effects like the anomeric effect, or which have passed unnoticed for a long time, like the 1,4-interactions of lone pairs. The complete analysis of all torsional interactions of saturated mono- and polyethers given in this paper should help to avoid the use of underparameterized force fields. Low periodicity torsional energy functions have been found necessary for the torsional potentials about the C–O bonds of both monoethers and acetals, standing for 1,4-interactions of a nature not to be handled by van der Waals and electrostatic interactions alone. Such an interaction was however not compulsory for glycol ethers, our force field does therefore not support the existance of a "*gauche* effect" in glycol ethers.[53]

Molecular mechanics as a predictive computational method in conformational analysis becomes obviously less simple when applied to *hetero* systems, because through bond effect which can be neglected in hydrocarbons must be added to bond length and angle restoring forces and nonbonded interactions. With low order torsional terms the method should attain however the same wide scope for *hetero* systems as for hydrocarbons.

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