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NEW SUPRAMOLECULAR HOST SYSTEMS. 2[1]. 1,3,5,7-TETRAOXADECALIN, 1,2-DIMETHOXYETHANE AND THE *GAUCHE EFFECT* REAPPRAISED. THEORY *VS*. EXPERIMENT.

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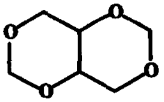
Abstract. *The three 1,3,5,7-tetraoxadecalin diastereomers (***1, 2** *&* **3***), core moieties of new host and macromolecular systems , were calculated "ab initio" and analysed in terms of their fragment-components, C-O-C-O-C and C-O-C-C-O-C with their stereoelectronic effects, namely the "anomeric effect" and "gauche effect", respectively. The inadequacy of split valence basis sets and of molecular mechanics (MM2, MM3) calculations (in reproducing relative stability and structural parameters) was resolved by using high level basis sets and electron correlation. The origins and consequences of the "gauche effect" were critically discussed and reparametrization of the MM3 force field for C-O-C-C-O-C containing systems, provided a reliable computational tool for the target* cis-*1,3,5,7-tetraoxadecalin system and other O-C-C-O containing systems.*

INTRODUCTION

We have shown[1] that the 1,3,5,7-tetraoxadecalin (1,3,5,7-TOD) system, a building-block in a series of new macromolecular host compounds, shows peculiar behaviour concerning the structure, spectroscopy and relative stability of its three possible isomers *trans* (**1**), *cis*-O-inside (**2**) and *cis*-O-outside (**3**). We have examined[1] certain static and dynamic aspects of their behavior in the crystal (X-ray diffraction) and in solution (NMR). Much insight could also be gained by considering the TOD system as built of two 4,5-condensed 1,3-dioxane rings, since the latter ring system had been thoroughly studied; we have performed such an analysis and discussed its results[1].

However, in our quest for a good computational (molecular mechanics) tool for reproducing the structural features and relative stabilities in the TOD stereochemical manifold, we have found MM3 (and MM2) only partly satisfying. Thus, while MM3 calculated the right relative stability for the *cis*-TOD couple, namely, *cis*-O-inside (**2**) more stable than *cis*-O-outside (**3**), it failed to support the inference from fragment analysis based on experimental results on substituted 1,3-dioxanes, that the *trans* isomer (**1**) is the most stable one in the TOD manifold. Neither did it reproduce well all the experimentally established structural parameters[1]. This inconsistency had to be understood and resolved.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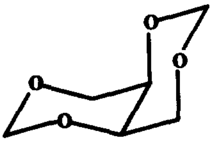
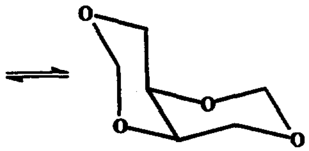
1,3,5,7-**TOD**

(9*S*)-*trans* (**1**)



(9*R*)-*cis*-O-inside (**2**)



(9*R*)-*cis*-O-outside (**3**)

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A more fundamental analysis of the 1,3,5,7-tetraoxadecalin (TOD) system is possible by realising that it is actually made up of C-O-C-O-C and C-O-C-C-O-C atomic sequences. These dihetero moieties are known to exhibit well known stereoelectronic effects: C-O-C-O-C the *anomeric effect* and C-O-C-C-O-C the *gauche effect.*

The *anomeric effect*[2-5], which was initially observed in carbohydrates, where it means the preference of a pyranose for the axial anomeric OR (**5**) over the equatorial one (**4**), is observed in general R-O-C-O-R moieties by the fact that conformers having an O-lone-pair (*lp*) antiperiplanar to the adjacent O-R bond gain special stability, due to delocalization of the *lp* into the adjacent $\sigma^*_{C\text{-}O}$ orbital, hence a preference of *gauche* (*g*) forms over *anti* (*a*) ones. In valence bond terms this corresponds to the double bond - no bond resonance **5** ↔ **5'** or the negative hyperconjugation concept[4]. Thus, for the basic C-O-C-O-C (dimethoxymethane) moiety (Figure 1), the order of increasing stability is $aa < ag < gg$[†]; as to the particular g^+g^- conformation, although the requirements for a stabilizing double anomeric effect are met, the strong steric, non-bonded 1,5 interaction destabilizes it to less than *ag*, unless this interaction is removed, as f.ex. in 1,3-dioxane. Indeed, the latter with its built in g^+g^- geometry and corresponding anomeric effect is considerably more stable than the isomeric 1,4-dioxane[4]. Both MM2[5-7] and MM3[8] have been satisfactorily parametrized for the *anomeric effect.*

Turning to the *gauche effect,* it represents the tendency of an X-C-C-Y moiety (X,Y = electronegative atoms or groups) to alleviate or even revert the butane (C-C-C-C) preference for the *anti* over the *gauche* conformation (Figure 1). This has been established long ago, both by experiment and calculation[9-36]. Wolfe and coworkers[9] have defined the issue, which had been observed in various forms in earlier studies[10-33], and subsequent publications[24-33] and reviews[34-36]. The extent of the phenomenon and its origins, however, are the matter of some controversy and results of earlier and contemporary work will be critically discussed below, *vis-à–vis* our own computational studies.

The TOD relative stability problem could, hence, be approached also *via* the above molecular entities and the corresponding stereoelectronic effects. Clearly, the reported and often conflicting data concernig the *gauche effect* and systems affected by it needed to be sorted out and rectified, as much as possible, before solving our own problems. This implies also addresing the question of the origin and manifestations of the *gauche effect.* Hence, we set out to resolve this puzzle by judiciously decomposing the TOD molecules into the molecular components with measurable energetic and structural manifestations, calculating them and the large TOD system using MO methods at adequately high level of theory and analysing the nature, magnitude and consequences of the stereoelectronic effects therein. Finally, we aimed at reparametrizing MM3 to the point of reproducing as accurately as possible the relative stabilities and structural parameters of the small units and, of course, the large TOD systems and other systems of interest.

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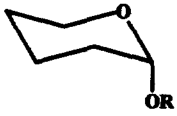

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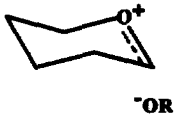
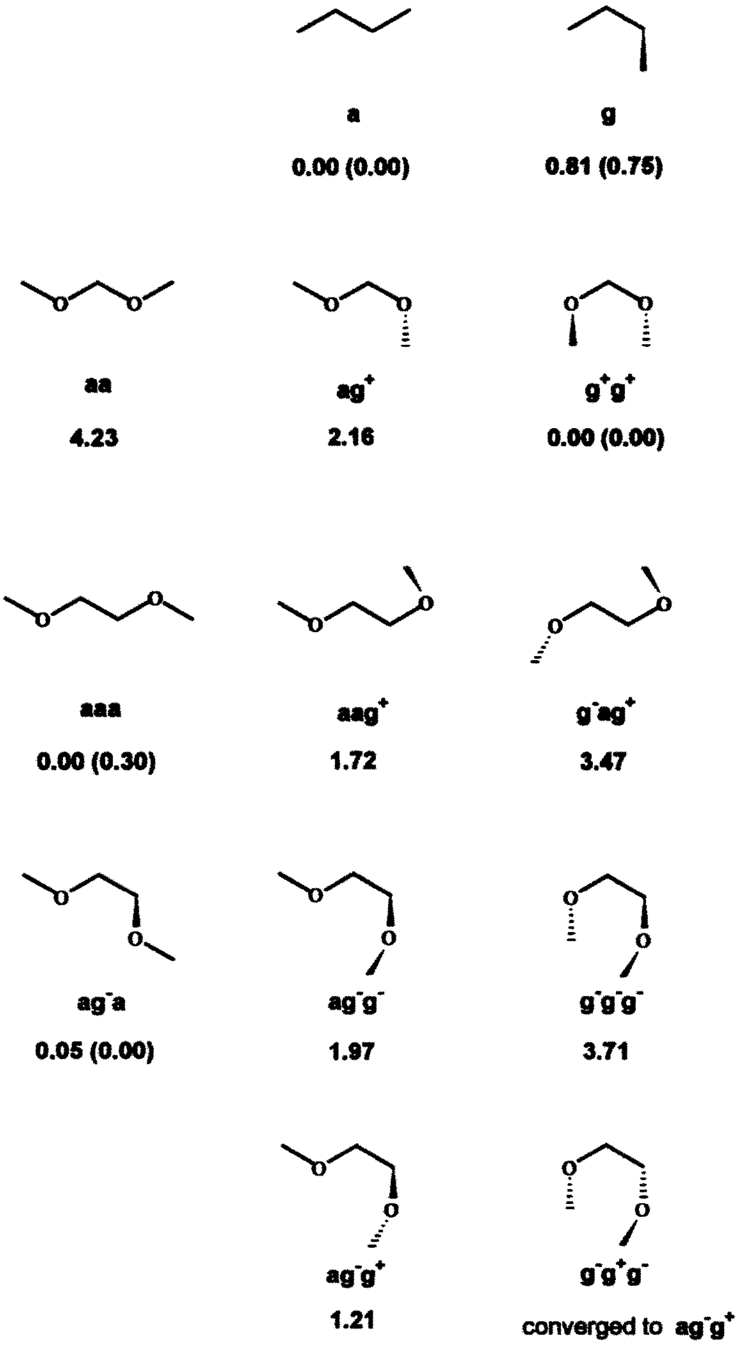


5'

[†] a = *anti*; g^+= *gauche*$^+$; g^-= *gauche*$^-$; $g = g^+$ or g^-.

Figure 1. Relative conformational energies (kcal/mol) of n-butane, dimethoxymethane and 1,2-dimethoxyethane as obtained by MM3 calculations and experiment (in parenthesis).



METHODOLOGY

MO *ab initio* calculations using RHF methods with various basis sets and electron correlation energy corrections were performed with Gaussian-90[37]. Molecular mechanics calculations were performed using MM3-92[38]. Semi-empirical calculations, with MOPAC 6.0[39]. Force constants were obtained by the GAMESS program[40]. Bond paths and path angles were derived by the AIMPAC set of programs[41]. Electron density maps were calculated from the *ab initio* results using the MOLDEN program[42]. All calculations were performed on a DEC 5000/200 work-station.

RESULTS AND DISCUSSION

To begin with, we calculated all 1,3,5,7-tetraoxadecalin (TOD) stereoisomers *ab initio*, using the 3-21G basis set[37], which had successfully performed in our previous studies of the *anomeric effect*[5b,7]. Unexpected results were obtained (Figure 2 and Table 8 - *vide infra*), in that the *cis*-O-outside isomer **3** is assigned considerable preference over **2**!, in flagrant disaccord with both experimental findings and molecular mechanics calculations[1]. This made our plight for a reliable computational approach more compelling than ever.

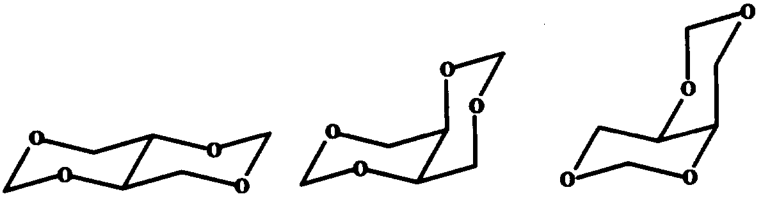
In principle, the TOD system can be regarded as being constructed of the following fragments: C-C-C-C (butane), C-O-C-O-C (dimethoxymethane - DMM) with its *anomeric effect* and C-O-C-C-O-C (1,2-dimethoxyethane - DME) with its *gauche effect*. A judicious fragment analysis thereof should enable one to evaluate the relative energies of **1**, **2** and **3**. All possible and unique conformations of the above molecular units are depicted in Figure 1, along with their relative energies, as calculated by MM3 and endorsed by experiment, whenever possible. The DMM energy and geometry values are reliable since MM3 is well parameterized for the *anomeric effect*[8] (following our own MMP2[5,6] modification, MM2-AE[5b,7]). The C-O-C-O-C (*anomeric*) fragments are **intraannular** and conformationally constant within the entire TOD series, namely, in the g^+g^- geometry[†]; therefore, they can be disregarded in the comparative analysis of relative energies (but not, of course, of structural parameters). In contrast, the C-O-C-C-O-C fragments are **interannular** and vary with each diastereomeric form, namely, 2x(*aag*)+(g^+ag^-) in **1**, 2x(*agg*)+(*ggg*) in **2** and 3x(*gag*) in **3**. There is no reliable experimental information on DME in any particular conformation, although it is quite clear that the *aaa* and *aga* forms are of lowest enthalpy. In our case we had to rely on molecular mechanics and we chose MM3, although its results had to be regarded with reservation, since Allinger et al. themselves remarked in their MM3 paper on ethers[6b]: "for 1,2-dimethoxyethane.... satisfactory agreement between theoretical and experimental data could not be obtained for any single conformer". Finally, the C-C-C-C moiety is also interannular, namely, *a* in **1** and **2**, *g* in **3**. The butane values have been taken from both experiment and calculation[43].

The relative stabilities of the TOD stereoisomers **1**, **2** and **3**, as estimated from the conformational maps of dimethoxymethane (DMM), 1,2-dimethoxyethane (DME) and *n*-butane in a simple fragment analysis procedure, are given in Figure 2, along with results from direct calculations (*vide infra).*

Scrutiny of the MM3 results in Figure 2 is perplexing: all MM3 calculations of the TOD stereoisomers, be they direct[1] or *via* fragment analysis, indicate the *trans* (**1**) isomer to be less stable than the *cis*-O-inside (**2**) one. While there is no direct experimental (e.g., equilibration or other) way to probe their relative stability, indirect results showed the inverse[1], i.e., the *trans* (**1**)

Figure 2. Relative energies (kcal/mol) of *trans*-, *cis*-O-inside-, and *cis*-O-outside- 1,3,5,7-tetraoxadecalin (TOD) as obtained by fragment analysis, MM3 and *ab initio* calculations

Fragments			
CCCC (MM3)[a,b]	1x(a) 0.0	1x(a) 0.0	1x(g) 0.8
COCOC (MM3)[a,c]	2x(g^+g^-)	2x(g^+g^-)	2x(g^+g^-)
COCCOC:	1x(g^+ag^-)+2x(aag)	2x(ag^+g^-)+1x(ggg)	3x(gag)
(MM3)[a,d]	3.5+3.4=6.9	2.4+3.7=6.1	0.8+9.6=10.4
(MM3-GE)[a,e]	3.5+3.5=7.0	3.6+4.2=7.8	0.8+10.1=10.9



TOD			
Fragment analysis (MM3)[a,d]	0.8	0.0	4.5
MM2-AE[a,c,f]	0.6	0.0	5.3
MM3[a,d,f]	1.1	0.0	5.9
G90 - 3-21G[g]	0.0	4.7	3.5
G90 - 6-31G*[g]	0.0	1.2	4.3
G90 - MP2/6-31G*[g]	0.0	0.6	4.7
Fragment analysis (MM3-GE)[a,e]	0.0	0.8	3.9
MM3-GE[a,e]	0.0	0.5	5.0

a Steric energies.
b Butane (enthalpy differences); cf. Figure 1.
c DMM - the same double anomeric effect in all three isomers; cf. Figure 1.
d DME - gauche effect as treated by MM3; cf. Figure 1.
e Calculated using reparametrized MM3-GE. These two items refer to results described in the last section of this paper.
f Taken from ref. 1.
g *Ab initio* calculations using Gaussian 90 with the indicated basis sets.

isomer is the lowest in energy, as also do *ab initio* calculations (Figure 2). At this point, our conclusion became that the inadequate parametrization of MM3 for the O-C-C-O moiety and for the *gauche effect*, goes a long way in large systems containing multiple such units, in our case TOD.

The task ahead was then, to tackle the DME problem, first *ab initio* at as high a level as needed and then to modify MM3 accordingly, until reasonable energies and geometries are obtained for the DME's, as well as any large systems they take part of, namely TOD's, polyeyhyleneglycol (PEG) systems, crown ethers, etc. The results of *ab initio* calculations at various, ascending levels of theory are given in Table 1; they should be interpreted, of course, together with the known literature data.

An exhaustive search of the available literature[10-33] revealed rather confusing data regarding the conformational preference of 1,2-dimethoxyethane (DME) and Table 2 provides an overview of both such

Table 1. Calculated relative energies (kcal/mol) of the *aaa* and *aga*† conformers of 1,2-dimethoxyethane (DME) (*CF*. Figure 1).

Conformation	*aaa*	*aga*		*aaa*	*aga*
Method		*ab initio*			
Basis set effect			Correlation effect		
3-21G//3-21G	0.00	2.81	MP2/3-21G//3-21G	0.00	1.68
6-31G*//6-31G*	0.00	1.40	MP3/3-21G//3-21G	0.00	1.81
6-311+G(3df)//6-31G*	0.00	0.89	MP4/3-21G//3-21G	0.00	1.65
6-31G**//6-31G**	0.00	1.39	CISD/3-21G//3-21G	0.00	1.81
D95V**//D95V**	0.00	1.30	MP2/6-31G*//6-31G*	0.00	0.60
6-311+G(3df)//6-311+G(3df)	0.00	0.94	MP3/6-31G*//6-31G*	0.00	0.85
CISD/6-31G*//6-31G*	0.00	0.83	MP2/6-311+G(3df) //6-311+G(3df)	0.00	0.19
		semi empirical			
MNDO	0.02	0.00	PM3	0.00	0.36
MINDO/3	0.61	0.00	AM1	0.00	0.14

Table 2. Reported experimental and calculated relative energies (kcal/mol) of the *aaa* and *aga*† conformers of DME.

a) Experiment

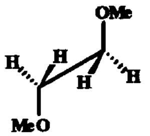
Phase	Method	Results	Ref.
Solid	NMR, IR, X-ray, Raman	*aga* sole conformer.	14-18
Glass	IR, Raman	*aaa*, *aga*, *agg* and perhaps others	14, 17
Argon matrix	IR	Order of stability: *aaa* > *aga* > *ag*$^+$*g*$^-$	29
Liquid	NMR	C-C bond: *g*=0.0; *a*=0.5-1.5 kcal/mol.	12, 19-21
		C-O bond: *a*=0.0; *g*=0.8-1.1 kcal/mol.	25-27
	Dipole Moment	C-C bond: *g*=0.0; *a*=0.4 kcal/mol.	13
		C-O bond: *a*=0.0; *g*=0.9 kcal/mol.	
	IR and Raman Spectroscopy	*aga* > *aaa* > *agg* > *aag*.	17
	Random distribution between *a*	and *g* around C-C and C-O bonds.	11
	IR	*aga*, *aaa* and additional conformers.	14
		aag and *gag* are the most stable.	22
		A mixture of *g* and *a* conformers	10
		agg, *aaa*, *aga*, *aag*.	23
Gas	NMR	C-C bond: *g*=0.0; *a*=0.3-0.4 kcal/mol.	20, 28
	IR	*aaa*, *aga*, *agg*, *aag*.	17
	ED	*agg* > *aga* > *aaa* > *gag* > *gaa* ≈ *ggg*	24

b) Calculations

Ab initio	*aaa*	*aga*	
3-21G//3-21G to 6-31G//6-31G	0.00	2.8 to 2.6	29, 31, 32
6-31G*//6-31G* to 6-311+G(dp)//6-31G*	0.00	1.4 to 1.2	31, 32
MP3/6-31G*//6-31G*	0.00	0.85	31, 32
to			
MP2/6-31+G(d)//6-31G*	0.00	0.40	32
and			
MP2/6-311+G(df)//6-31G*	0.00	0.21	32
Monte Carlo Simulations			30
Gas Phase	0.19	0.00	
Solution, solvent dipole size 0.0 (0.7)	0.00 (0.33)	0.93 (0.00)	

experimental and theoretical literature data. Most of the experimental data[10-29] (Table 2a) indicate the predominance of the *aga* and *aaa* conformers†, accompanied by small contributions of several higher energy ones, in particular the lower lying ag^+g^-, but also the *agg*, *aag*, *gag* and *ggg* forms. The *aga* form is the sole one observed in the crystal[14-17] and it prevails in the liquid and gas phases by 0.5-1.5 and 0.3-0.4 kcal/mol, respectively. A gas phase electron diffraction study[24] was concluded to show that the best fit to the experimental results is obtained for a conformer mixture composed of (in descending order of stability) *agg*, *aga*, *aaa*, *gag*, *gaa* and *ggg* (see footnote *a* in Table 2). However, a recent IR study of DME in an argon matrix[29] favors the *aaa* form and attributes the otherwise observed enhanced stability of the *aga* conformer in the liquid and crystalline states, to intermolecular interactions. In some studies, in particular using NMR, only the general *a* (**6a**) and *g* (**6g**) (in the C-C bond) cases could be concluded on.

As to theoretical (MO) calculations (Table 2b), (save one older CNDO/2 study[33]) they consistently assign the *aaa* form preference over the *aga* form, by up to 2.8 kcal/mol[29-32]. In general, most calculations do not reproduce the experimentally observed small preference of *aga* in the gas phase but predict rather large energy differences E*aga*-E*aaa*. However, as better descriptions of bonding regions are provided (by using polarization and diffuse functions) and correlation effects are taken into account, the *aaa-aga* energy gap is reduced, slightly favoring *aaa*. Entropy terms may then intervene to change the stability order altogether. It should be reiterated at this point, that our interest in DME stems from the fact that the C-O-C-C-O-C unit is one of the most important components of the TOD system. Hence, we are mainly interested in relative enthalpies and structural features of DME and how they affect the relative stabilities and geometries of the TOD stereoisomers.



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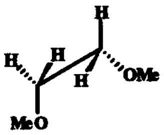


6g

On close scrutiny, several observations can be made:

1. Split valence basis sets (3-21G, 6-31G) yield the worst fit with the experimental findings. In particular, the 3-21G basis set, known to perform satisfactorily for O-C-O (anomeric) moieties, favors the *aaa* conformer by as much as 2.81 kcal/mol. Understandably now, this deficiency is carried over to the TOD system where this basis set erroneously favors the O-outside conformer (**3**) over the O-inside one (**2**), in contrast with experiment and more elaborate *ab initio* calculations. These basis sets should therefore be avoided in cases where the major conformational changes involve O-C-C-O moieties.

2. The inclusion of polarization and diffuse functions drastically improves the situation and ΔE values as low as 0.9 kcal/mol are attainable at HF level, which seems to mark the HF limit. Geometry optimization details are apparently less important than basis set effects as evident from a comparison of the series 6-31G*//6-31G* (1.40 kcal/mol), 6-31+G(d)//6-31G* (1.41 kcal/mol), 6-311+G(dp)//6-31G* (1.22 kcal/mol) and 6-311+G(3df)//6-31G* (0.89 kcal/mol) with 6-311+G(3df)//6-311+G(3df) (0.94 kcal/mol).

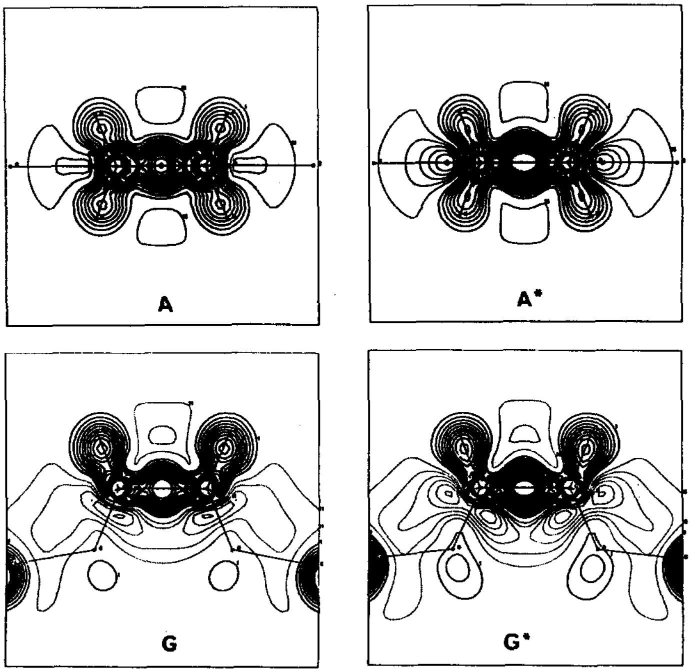
3. A second drastic decrease in ΔE values (by up to 1 kcal/mol) results from the inclusion of correlation energy. Within the Møller Plesset perturbation theory, the correlation effects seem to be moderately basis set dependent and to converge already at the MP2 level, while MP3 results are

identical with frozen-core CISD ones.

Thus, by employing a near HF limit basis set at MP2 level, we obtained what we consider to be the lowest (although, not necessarily the best) estimate for the enthalpy difference possible within this framework, namely, 0.19 kcal/mol in favor of *aaa*. This number is expected to decrease only slightly, if at all, at the limit of high basis set and complete treatment of electron correlation and is in excellent agreement with the most recent and elaborate study of Murcko and DiPaola[32] (see Table 2b), which has appeared after the conclusion of our own study and in which the *aaa-aga* energy difference had been reduced by increasing the sophistication of the method, down to 0.21 kcal/mol. Taking into account the entropy of mixing (Rln2) favoring the *aga* conformer of DME at room temperature by 0.41 kcal/mol we got a ΔG° value of 0.22 kcal/mol in favor of *aga*, in good agreement with the experimental results.

Following earlier findings[1] in the low temperature diffraction analyses of **2** and one of its derivatives, that the C-C bonds in the *cis*-TOD structure exhibit considerably enhanced electron density, it occured to us that a possible explanation for the large difference between 3-21G and 6-31G* results for DME could be found in the analysis of electron density maps (Figure 3). It turned out that, in our present DME study, in going from 3-21G to 6-31G*, the C-C bond electron density increases by 40% in *aga* and 25% in *aaa*. Thus, the 3-21G basis set puts too little negative charge in this region for *aga* or, alternatively, too much for *aaa (vide infra)*.

Figure 3. Electron density maps (molecular density minus spherically averaged atomic densities) for 1,2-dimethoxyethane (DME) presented in a plane containing the two carbon atoms and perpendicular to the molecular plane (*aaa*) or dissecting the O-C-C-O dihedral angles (*aga*). A = *aaa* (3-21G); A* = *aaa* (6-31G*); G = *aga* (3-21G); G* = *aga* (6-31G*). Contours are given in intervals of 0.005 e/au^3 and solid/dotted lines represent positive/negative electron densities, respectively. The largest contour values in the C-C bond region are: A = 0.06 e/au^3; A* = 0.075 e/au^3; G = 0.05 e/au^3; G* = 0.07 e/au^3.

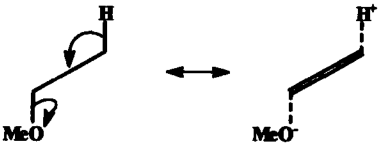


At this point and since contemporary, more powerful computational hardware has recently become available to us, we were able to perform MO *ab initio* calculations of large molecules with more sophisticated basis sets. Hence, all three 1,3,5,7-TOD diastereoisomers, **1**, **2** and **3** were also calculated at as high as the MP2/6-31G*//6-31G* level and, as expected after the DME study, the correct trend in relative stabilities was indeed restored (Figure 2 and Table 8 - *vide infra*).

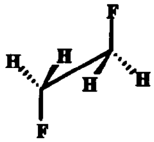
Although the importance of the *gauche effect* in the O-C-C-O moiety (and in X-C-C-Y moieties, X,Y electronegative atoms, in general) is manifested in the conformational behavior of many experimentally studied systems[6-33,44-46], its origin is still open to debate. Several possible mechanisms were suggested invoking *gauche* (with respect to the X-C-C-Y dihedral angle) stabilization or, alternatively, *anti* destabilization. Wolfe[9] had initially proposed a rationalization based on the dissection of the total energy in the system into attractive (Vne = nuclear-electron attraction) and repulsive (Vnn+Vee+T representing, respectively, nuclear-nuclear repulsion, electron-electron repulsion and kinetic energy of the electrons) components, arguing that for small electronegative substituents, in the *gauche* arrangement, $V_{attractive}$ is more important than $V_{repulsive}$.

Two additional proposals were put forward by Epiotis et al.[47]. Referring to the O-CH_2-CH_2-O moiety, one[47a] attributes *gauche* stabilization to σ - σ^* stabilizing interactions between the best σ-donor (a C-H bond) and the best σ-acceptor (a C-O bond) properly oriented (parallel) only in the *gauche* conformer (**7** ↔ **8**). The other mechanism[47b,c], invokes attractive non-bonded interactions between the oxygen atoms due to the stabilizing (charge withdrawing) interaction between $\sigma^*_{C\text{-}C}$ and the bonding and anti-bonding orbitals formed from the interaction between the oxygens' lone pairs.

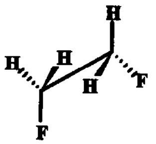
In contrast with these *gauche* stabilizing mechanisms, Wiberg et al.[48] explained the *gauche* preference in 1,2-difluoroethane (DFE, **9**) by an *anti* destabilization due to bond bending at the carbon nuclei, which leads to a decreased overlap between the C-C bond forming orbitals.



7 **8**



9*a*



9*g*

Each of the above mechanisms should be manifest in distinct structural and electron density differences between the *aaa* and *aga* conformers of DME and thus may possibly be confirmed or excluded by comparing appropriate parameters. A $\sigma_{C\text{-}H}$- $\sigma^*_{C\text{-}O}$ interaction should elongate the C-H and C-O bonds, shorten the C-C bond and transfer electron density from the hydrogen to the oxygen, as in **7**/**8**. Attractive non-bonded interaction, on the other hand, should elongate the C-C bond, shorten the C-O bond, reduce the oxygen's negative charge and render the overlap population between the oxygen atoms, positive. Finally, bond bending should elongate the C-C bond in *aaa* relative to *aga* due to a poorer overlap between the bond forming orbitals.

In Table 3 we present the results of our calculations of energies, electronic overlap population, atomic charges and structural parameters for the *aaa* vs. *aga* conformers of DME (**6**) and the *a* vs. *g* conformers of DFE (**9**), performed using the highest, 6-311+G(3df) basis set in this study, with full geometry optimization. As evident from there and from the comparison in Table 4, save bond bending (*vide infra*), none of the above possible mechanisms including steric/electrostatic interactions can

Table 3. A comparison of relative energies (Erel; kcal/mol), overlap populations (OP), atomic charges and selected bond lengths (R; Å) for the *aaa* and *aga* conformers of 1,2-dimethoxyethane (DME) and the *a* and *g* conformers of 1,2-difluoroethane (DFE) as calculated with 6-311+G(3df).

$X\text{-}CH_2\text{-}CH_2\text{-}X$:	DME		DFE	
	aaa	*aga*	*a*	*g*
Erel	0.00	0.94	0.36	0.00
OP(C-X)	0.038	0.103	0.046	0.070
R(C-X)	1.389	1.387	1.359	1.357
OP(C2-Ha)	0.478	0.487	0.456	0.465
R(C2-Ha)	1.089	1.091	1.082	1.084
OP(C-C)	-0.669	-0.611	-0.677	-0.723
R(C-C)	1.512	1.509	1.512	1.503
Ha - positive charge	0.280	0.269	0.303	0.307
X - negative charge	-0.574	-0.587	-0.475	-0.488
OP between X's	0.024	0.014	0.006	0.015

Table 4. A comparison of charges, overlap populations (OP), bond lengths and relative stabilities as calculated *ab initio* (6-311+G(3df)) for the *aaa* and *aga* conformers of DME and the *a* and *g* conformers of DFE and predicted by various explanations to the origin of the *gauche effect*.

	$\sigma_{C\text{-}H}\text{-}\sigma^*_{C\text{-}X}$	Attractive non-bonded interactions	steric/ electrostatic	bent bonds	*ab initio* X=O	X=F
Erel	*g*>*a*	*g*>*a*	*a*>*g*	*g*>*a*	*a*>*g*	*g*>*a*
OP(C-X)[a]	*a*>*g*	*g*>*a*	*a*>*g*		*g*>*a*	*g*>*a*
R(C-X)	*g*>*a*	*a*>*g*	*g*>*a*		*a*≥*g*	*a*≥*g*
OP(C2-Ha)	*a*>*g*				*g*>*a*	*g*>*a*
R(C2-Ha)	*g*>*a*				*g*≥*a*	*g*≥*a*
OP(C-C)	*g*>*a*	*a*>*g*	*a*>*g*	*g*>*a*	*g*>*a*	*a*>*g*
R(C-C)	*a*>*g*	*g*>*a*	*g*>*a*	*a*>*g*	*a*≥*g*	*a*>*g*
Ha - positive charge	*g*>*a*				*a*>*g*	*g*≥*a*
X - negative charge	*g*>*a*	*a*>*g*	*a*>*g*		*g*>*a*	*g*>*a*
OP between X's		positive in *g*			*a*: 0.024 *g*: 0.014	*a*: 0.006 *g*: 0.015

[a] X = O or F.

fully account for the *ab initio* results in what concerns the predicted differences in atomic charges, overlap populations and bond lengths between the different conformers.

Replacing the formalism for Mulliken atomic charges and overlap population/bond length by force constants (using GAMESS[37]) did not add much to the clarity of the picture. Indeed, the small magnitude of the effect, together with the inevitable interference of other steric and stereoelectronic effects (e.g., $lp_O\text{-}\sigma^*_{C\text{-}H}$ interactions, known to occur in dimethoxyethane, lead to C-O bond shortening, C-H bond elongation and O to H charge transfer) are bound to prevent a clear distinction between the origins of trends in structural and atomic charges, even when using high level *ab initio* calculations and attempting highly accurate analysis.

In previous studies it had been shown that trends in structural parameters, in particular bond lengths, are reliable probes for the *anomeric effect*[2-5] and related stereoelectronic effects[7], in various X-C-Y systems. We wish to extend this approach to the *gauche effect*, noting the trends in conformational stability *vs.* C-C bond lengths in both 1,2-difluoroethane (DFE) and 1,2-dimethoxyethane (DME) *viz.*, DFE: $E_a\text{-}E_g$ = 0.4-1.8 kcal/mol (*cf.* references 47 & 48 and Table 3 in our own study) and

$R(C\text{-}C)_a - R(C\text{-}C)_g = 0.01$ Å; DME: $E_{aga} - E_{aaa} = 0.2\text{-}0.9$ kcal/mol (*cf.* Tables 1, 2 & 3), $R(C\text{-}C)_{aaa} - R(C\text{-}C)_{aga} = 0.003$ Å and taking in consideration that bond length is the hardest of structural parameters and the least affected by other factors. This has been paid little or no attention in published studies on the *gauche effect*.

Hence, we searched the Cambridge Structural Database (CSD; January 1991 edition[50]) for X-C-C-X fragments with X=F, Cl, OCH_3, recalling that, with proper qualifications, the relative abundance of isomeric structures in the CSD file bears testimony to their relative stabilities[3,7]. We came up with the following observations:

1. *X=F:* Although 25 entries were retrieved, only five have *gauche* (i.e., ±30-90°) F-C-C-F dihedral angles and none, *anti* (i.e., ±160-180°) ones. Thus, no meaningful analysis could be performed.

2. *X=OCH_3:* 2327 entries were found, 2236 of them belonging to the *gauche* group while only 91, to the *anti* group. Average C-C bond lengths are 1.49 Å in *gauche* arrangements and 1.52 Å in *anti* ones. Thus, the larger population of the *gauche* group is in accord with the experimental findings on DME in condensed phase, namely, *aga* being by far the preferred conformation, and the decrease in the average C-C bond length on going from *anti* to *gauche* parallel the *aaa* to *aga* trend in DME *(vide supra)*.

3. *X=Cl:* 131 entries were retrieved, 111 belonging to the *gauche* group with average C-C bond length, 1.537 Å and 20 to the *anti* group with average C-C bond length, 1.487 Å. All theoretical and experimental studied on 1,2-dichloroethane[48e-h] are consistent with the predominance of the *anti* conformer, in fact, to a larger extent than observed in butane[42] (i.e., no *gauche effect*). Accordingly, the average C-C bond in the *gauche* conformer is larger than in the *anti* one, as expected from steric considerations. Furthermore, a cursory examination revealed that most Cl-C-C-Cl fragments are part of a 1,2-disubstituted ring systems, in particular, six-membered ones. The larger population of the *gauche* group may be due to the two substituents occupying the energetically more favored diequatorial or axial/equatorial positions.

The bond bending mechanism, already discussed in the past in connection with DFE[47], is in fact a viable explanation to the apparent correlation between C-C bond shortening and the *gauche effect*. Using Bader's method[41], we analyzed the 3-21G, $6\text{-}31G^*$ and 6-311+G(3df) wavefunctions in order to measure C-C, C-O and C-H bond paths and O-C-C path angles (Table 5). The difference between the latter and the geometric bond angle, together with the values of α and β (see Figure 4), uniquely define the direction in which the C-C and C-O bond paths deviate from their corresponding axes. Focussing our attention on the 6-311+G(3df) results (Table 5 and Figure 4), we note that the large α value (3.05°) observed in the

Figure 4. Schematic representations of C-O and C-C bond paths and O-C-C path angles for the *aaa* and *aga* conformers of 1,2-dimethoxyethane (DME) as derived from 3-21G, $6\text{-}31G^*$ and 6-311+G(3df) wavefunctions. The values of α and β and the difference between path angles and geometry angles (Table 5), uniquely define the direction in which C-O and C-C bond paths deviate from their corresponding axes.

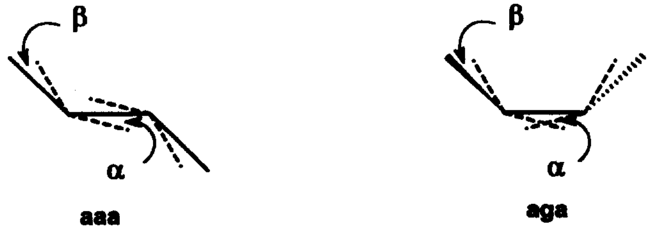


Table 5. Relevant bond paths (Å) and path angles (degrees) as derived by the AIMPAC set of programs from *ab initio* 3-21G, 6-31G* and 6-311+G(3df) calculations.

		3-21G		6-31G*		6-311+G(3df)	
		aaa	*aga*	*aaa*	*aga*	*aaa*	*aga*
bond paths:							
C-C	bond length	1.5162	1.5157	1.5142	1.5107	1.5124	1.5086
	bond path	1.5163	1.5158	1.5143	1.5109	1.5129	1.5096
	difference	0.0001	0.0001	0.0001	0.0002	0.0005	0.0010
C-O	bond length	1.4336	1.4336	1.3944	1.3925	1.3889	1.3874
	bond path	1.4345	1.4344	1.3953	1.3933	1.3913	1.3879
	difference	0.0009	0.0008	0.0009	0.0008	0.0024	0.0005
C-H	bond length	1.0837	1.0863	1.0881	1.0908	1.0890	1.0913
	bond path	1.0839	1.0865	1.0883	1.0910	1.0891	1.0915
	difference	0.0002	0.0002	0.0002	0.0002	0.0001	0.0002
bond angles[a]:							
	α	1.76	1.82	2.04	2.01	3.05	1.06
	β	2.29	2.42	1.44	2.06	2.32	3.67
O-C-C	bond angle	105.94	107.33	107.73	109.32	108.13	109.93
	path angle	105.41	106.75	108.33	109.31	109.28	107.23
	difference	0.53	0.58	0.60	0.01	1.15	2.60

[a] see Figure 4 for the definition of α and β.

C$_{2h}$ (*aaa*) conformer indicates the withdrawal of charge density away, and in opposite directions, from the C-C bond axes leading to its elongation due to a poor overlap between the bond forming orbitals and to a general destabilization of this conformer. A much smaller α value (1.06°) is observed for the C$_2$ (*aga*) conformer where deviations in the same direction are forced by symmetry. At the same time, however, the large β value (3.67°) observed for this conformer indicates an inwards (i.e., one towards the other) deviation of the C-O bond paths and, together with the smaller O-C-C-O dihedral angle (3-21G = 78.2°; 6-31G* = 71.8°; 6-311+G(3df) = 72.5°) and the resulting shorter O...O distance (3-21G = 2.932Å, 6-31G* = 2.879Å; 6-311+G(3df) = 2.899Å), may be taken as a stabilizing attractive non-bonded interactions[49b,c] between the two oxygens.

We proceeded now to apply semiempirical methods to our problem. Of calculations within the the MOPAC 6.0 package, AM1 and PM3 provided what we now consider acceptable relative energies for the *aaa* and *aga* forms of DME (Tables 1 and 6) and PM3 also for the *a* and *g* forms of DFE (**9**). Thus, using the PM3 method for DFE, we got (Table 6): *g* = 0.00, *a* = 1.39 kcal/mol again consistent with the experimental results (*g* = 0.00, *a* = 0.8 - 1.76 kcal/mol)[47,48].

Table 6. Relative energy components (kcal/mol) for the *a* and *g* forms of 1,2-difluroethane (DFE) and for *aaa* and *aga* in DME, as obtained from PM3 calculations.

X-CH$_2$-CH$_2$-X :	DFE		DME	
	a	*g*	*aaa*	*aga*
Total energy	1.39	0.00	0.00	0.36
Total one center energy	0.06	0.00	0.29	0.00
Total two center energy	1.32	0.00	0.00	0.65
Resonance energy	2.72	0.00	1.74	0.00
Exchange energy	0.40	0.00	0.00	0.00
Electrostatic energy[a]	0.00	1.79	0.00	2.41

a) electrostatic energy = nuclear-nuclear repulsion + electron-electron repulsion + nuclear-electron attraction

Some additional insight into the origins of the *gauche effect* may, perhaps be gained from the analysis of the PM3 results on DME[33] and on DFE. Dissecting the total energy of the two conformers into their relevant components (Table 6 and footnote a there), it appears that the electrostatic term favours the *a* (in DFE) and *aaa* (in DME). In doing so it works **against** the strong *gauche* preference (calculated and found) in DFE and for the small preference of *aaa* in DME. On the other hand, both resonance terms favor *g* in DFE and *aga* in DME.

MM3 PARAMETRIZATION: MM3-GE

The declared *raison d'être* of this study was to find a good computational tool for the 1,3,5,7-tetraoxadecalin (TOD) system. The MM3 force field failed to provide reliable results for both relative energy and structural parameters in the TOD series and neither could it faithfully reproduce these in 1,2-dimethoxyethane (DME), a major component of TOD.

To find a suitable remedy, we had to match our reasoning against the facts (Figure 2 and ref. 1) that, much like the high level *ab initio* methods, MM3 calculates *cis*-O-outside TOD (3) to be the highest energy form, but unlike them (and the experimental inferences[1]), MM3 prefers the *cis*-O-inside isomer over the *trans* (1) one. In addition, the *cis*-O-inside conformer is calculated to have longer C-C bond lengths than observed in the X-ray structure or calculated *ab initio*. In the DME system this is paralleled by too low an energy of the *aga* conformer relatively to the *aaa* form, as well as the too long C-C bonds.

In light of the findings in our above described study of DME, we reasoned that allowing for more C-C bond shortening (as actually demanded by the electronegative C-O bond flanking[51]) and making this conformation dependent (*i.e.*, shorter C-C in *aga*), would implicitly cause also the desired increase in the relative energy E*aga*-E*aaa*. All other conformations of DME (Figure 1) should follow suit, based on the above dependence of the energy on the central C-C bond, accompanied by the methylethylether *a*/*g* relationship for the flanking C-O bonds, *viz.*, E*a* - E*g* = 1.5 kcal/mol[52,53] and other smaller contributions to the total energy (CH---O bonds, non-bonded interactions).

Hence, we reparameterized the MM3 force field for the *gauche effect* by decreasing l_0 for C-C bond lengths incorporated in O-C-C-O moieties from 1.5247 Å to 1.515 Å for *g* and 1.520 for *a* . However, the turnabout in energy was eventually achieved only after modifying the O-C-C-O torsional potential, by changing the V2 term from -2.0 to -1.5. As aimed, this torsionally dependent modification corrected the energies in the DME conformational manifold and was carried over to the TOD system and for that matter, to any other -O-C-C-O- containing system. A clarification and qualification are in order: both the effects and the corrections are small and can be "seen" best when they are additively amplified, as in the case of the TOD systems; the approach we have taken is really very pragmatic, we think that it could be refined to attain higher accuracy and we expect this to be done by the MM3 founders[8].

The modified force field, applied first to the *aaa* and *aga* conformers of DME (Table 7) and subsequently to the three conformers of 1,3,5,7-tetraoxadecalin (Table 8), showed a considerably improved agreement with both experimental and *ab initio* results. Thus, the TOD relative energies are in the order *trans* < *cis*-O-inside < *cis*-O-outside, in good agreement with experiment and high level *ab initio* calculations, as are also the structural details.

Table 7. **Relative energies (Erel, kcal/mol) and structural parameters of interest (bond lengths L in Å, bond angles A and dihedral angles T in degrees) of 1,2-dimethoxyethane (DME), as calculated *ab initio* (6-31G*//6-31G* and MP2/6-31G*//6-31G*) for the *aaa* and *aga* conformers and by force field (MM3 and MM3-GE, see text and Figure 1) calculations for all its conformers.**

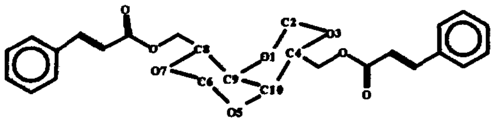
	aaa				*aga*			
	6-31G*// 6-31G*	MP2/^{a} 6-31G*// 6-31G*	MM3	MM3 -GE	6-31G*// 6-31G*	MP2/ 6-31G*// 6-31G*	MM3	MM3 -GE
L								
C1-O2	1.392	1.416	1.418	1.418	1.391	1.415	1.418	1.418
O2-C3	1.394	1.417	1.421	1.421	1.392	1.414	1.421	1.421
C3-C4	1.514	1.512	1.525	1.520	1.511	1.507	1.527	1.517
A								
C1-O2-C3	114.3	111.4	112.1	112.1	114.2	111.3	112.1	112.1
O2-C3-C4	107.7	107.0	108.4	108.5	109.3	108.5	109.0	109.1
T								
C1-O2-C3-C4	180.0	180.0	180.0	180.0	-175.5	-176.3	-179.3	-179.3
O2-C3-C4-O5	180.0	180.0	179.8	179.9	71.8	71.7	73.3	72.2
				E_{rel}				
	aaa				*aga*			
	0.00	0.00	0.00	0.00	1.40	0.56	0.05	0.56
			$ag^{+}g^{-}$				aag	
			1.21	1.78			1.72	1.74
			agg				gag	
			1.97	2.48			3.23	3.36
			$g^{+}g^{-}g^{-}$				$g^{+}ag^{-}$	
			3,06	3.65			3.47	3.49
			ggg				$g^{-}g^{+}g^{-}$	
			3.71	4.18			converged to $g^{-}ag^{-}$	

a Optimization at MP2 involved structural parameters of heavy atoms only.

Furthermore, using the modified MM3 for the computation of literature examples of O-C-C-O containing compounds, excellent agreement of geometrical parameters was obtained with those of the published[54] structures of TOD derivatives **10**, **11**, **12** and **13** (Table 9), as well as with other O-C-C-O containing systems, such as PEG and crown ethers.

Table 8. Relative energies (Erel, kcal/mol) and structural parameters of interest (bond lengths L in Å, bond angles A and dihedral angles T in degrees) for the three diastereoisomers of 1,3,5,7-tetraoxadecalin (TOD) as obtained from *ab initio* (3-21G//3-21G and MP2/6-31G*//6-31G*) and the modified MM3 force field calculations and compared with the X-ray data of **2**.

1,3,5,7-TOD	*trans* (1)			*cis*-O-inside (2)				*cis*-O-outside (3)		
	3-21G	MP2/ 6-31G*// 6-31G*	MM3 -GE	X-ray	3-21G	MP2/ 6-31G*// 6-31G*	MM3 -GE	3-21G	MP2/ 6-31G*// 6-31G*	MM3 -GE
Erel	0.00	0.00	0.00		4.74	0.59	0.55	3.53	4.70	4.97
L										
O1-C2	1.430	1.392	1.419	1.411	1.422	1.385	1.414	1.425	1.389	1.417
O1-C9	1.434	1.398	1.436	1.436	1.436	1.400	1.438	1.439	1.406	1.439
C2-O3	1.422	1.386	1.418	1.413	1.417	1.381	1.414	1.418	1.382	1.414
O3-C4	1.447	1.407	1.437	1.434	1.437	1.398	1.435	1.443	1.403	1.434
C4-C10	1.519	1.516	1.517	1.510	1.523	1.519	1.518	1.528	1.526	1.522
C9-C10	1.526	1.521	1.519	1.529	1.535	1.532	1.521	1.541	1.535	1.525
A										
C2-O1-C9	111.9	111.3	108.8	110.8	114.3	113.7	110.4	116.7	116.6	113.5
C2-O3-C4	114.3	114.2	110.5	109.8	113.5	112.9	110.1	112.6	112.3	109.5
O1-C2-O3	112.1	112.6	112.5	112.1	112.2	112.4	111.4	112.2	112.5	112.2
O3-C4-C10	106.9	107.4	107.2	111.3	111.1	111.2	110.0	107.8	108.5	107.8
O1-C9-C8	110.3	112.2	110.3	108.6	106.6	108.3	108.1	111.5	112.7	110.8
O1-C9-C10	108.4	109.1	106.6	110.2	110.6	110.4	109.1	110.7	111.0	108.5
C4-C10-C9	109.1	108.4	109.6	110.1	110.8	109.9	112.0	111.2	111.0	113.0
T										
C2-O1-C9-C8	177.8	-176.6	179.5	176.4	173.0	173.9	178.5	78.9	80.2	74.2
C2-O1-C9-C10	-58.4	-58.4	-61.5	55.8	52.4	53.5	56.5	-45.5	-45.0	-50.4
O3-C2-O1-C9	-56.3	58.4	63.9	-63.3	-56.5	-59.7	-65.4	51.2	53.7	60.3
C2-O3-C4-C10	56.4	56.4	57.4	-56.5	-53.9	-54.5	-55.8	61.0	60.5	60.0
O1-C2-O3-C4	-56.2	-58.5	-62.0	63.0	56.8	59.7	64.7	-59.1	-61.6	-64.7
O3-C4-C10-O5	176.5	-175.6	-175.4	-69.8	-71.3	-72.5	-70.5	-178.8	-176.5	-176.1
O3-C4-C10-C9	-57.5	-55.0	-58.2	50.8	49.2	48.1	49.7	-54.7	-51.3	-54.1
O1-C9-C10-O5	180.0	180.0	180.0	69.6	69.8	72.1	69.9	171.7	169.8	171.9
O1-C9-C10-C4	59.8	57.5	60.6	-50.0	-48.3	-47.3	-49.8	47.2	43.6	48.5
C4-C10-C9-C8	180.0	180.0	-179.9	-169.7	-166.3	-166.7	-169.4	-77.3	-82.6	-74.8



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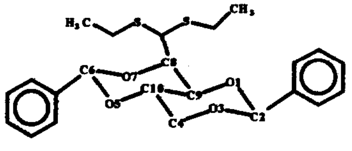

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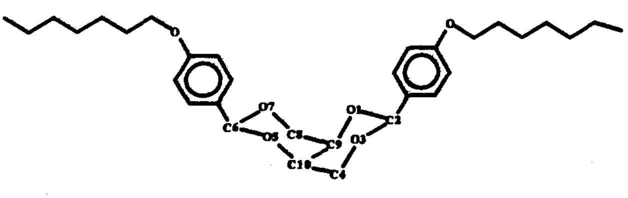

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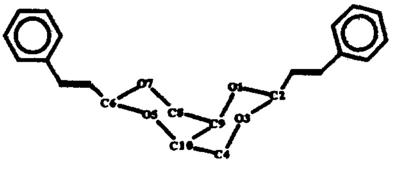

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Table 9. Structural parameters of interest (bond lengths, L in Å, bond angles, A and torsion angles, T in degrees) for four 1,3,5,7-TOD derivative molecules **10**[33a], **11**[33b], **12**[33c] and **13**[1], as calculated by the modified MM3-GE force field and compared with literature X-ray data.

Compound:	**10**[a]		**11**[a]		**12**[a]		**13**	
Method:	MM3-GE	X-ray[b]	MM3-GE	X-ray[b]	MM3-GE	X-ray[b]	MM3-GE[a]	X-ray[b,c]
L								
O1-C2	1.417	1.406	1.418	1.414	1.415	1.423	1.414	1.414 (1.419)
C2-O3	1.414	1.410	1.417	1.422	1.415	1.399	1.414	1.421 (1.416)
O1-C9	1.439	1.428	1.433	1.437	1.437	1.438	1.437	1.438 (1.437)
O3-C4	1.438	1.433	1.437	1.42	1.434	1.433	1.434	1.435 (1.442)
C4-C10	1.528	1.526	1.516	1.51	1.517	1.513	1.515	1.519 (1.514)
C9-C10	1.526	1.526	1.516	1.494	1.518	1.512	1.516	1.528
A								
C2-O1-C9	113.6	113.4	110.0	108.4	111.1	110.0	111.7	111.4 (111.4)
C2-O3-C4	110.1	111.0	111.0	111.4	110.6	110.4	111.2	110.6 (110.5)
O1-C2-O3	112.3	112.5	108.4	111.1	105.8	110.5	108.5	111.3 (111.1)
O3-C4-C10	106.8	107.6	107.0	108.3	109.8	110.8	109.1	111.5 (111.1)
O1-C9-C8	112.9	110.8	112.0	110.4	108.0	108.4	107.9	108.1 (107.7)
O1-C9-C10	108.0	110.2	106.9	108.8	108.8	111.3	108.5	110.3 (110.8)
C4-C10-C9	112.9	111.3	109.4	107.3	111.9	111.5	111.1	110.7 (110.5)
T								
C2-O1-C9-C8	73.1	74.6	-175.5	-174	-179.4	177.4	179.3	176.6 (176.2)
C2-O1-C9-C10	-51.1	-50.8	62.6	63	59.1	54.7	58.4	55.7 (55.0)
O3-C2-O1-C9	59.9	58.1	-66.4	-62	-70.3	-65.1	-65.7	-63.4 (-62.9)
C2-O3-C4-C10	60.2	59.7	-60.4	-58	-58.4	-56.4	-58.3	-55.5 (-56.6)
O1-C2-O3-C4	-64.2	-63.0	65.5	61	69.4	66.1	65.3	62.7 (63.3)
O3-C4-C10-O5	-176.9	-179.0	173.0	177	-72.9	-74.1	-69.2	-72.4 (-71.4)
O3-C4-C10-C9	-55.3	-53.7	56.6	58	46.6	46.9	51.2	48.9 (49.4)
O1-C9-C10-C4	50.2	49.4	-57.9	-61	-46.5	-46.5	-50.9	-48.4 (-48.5)
O1-C9-C10-O5	173.3	175.5	176.9	180	73.2	72.5	69.0	71.0
C4-C10-C9-C8	-72.8	-77.8	179.6	177	-165.7	-167.5	-168.0	-167.9

a) A crystallographic C2 axis through C(9)-C(10) makes atoms 05, 07, C6, C8 & C10 equivalent to 01, 03, C2, C4 & C9, respectively.

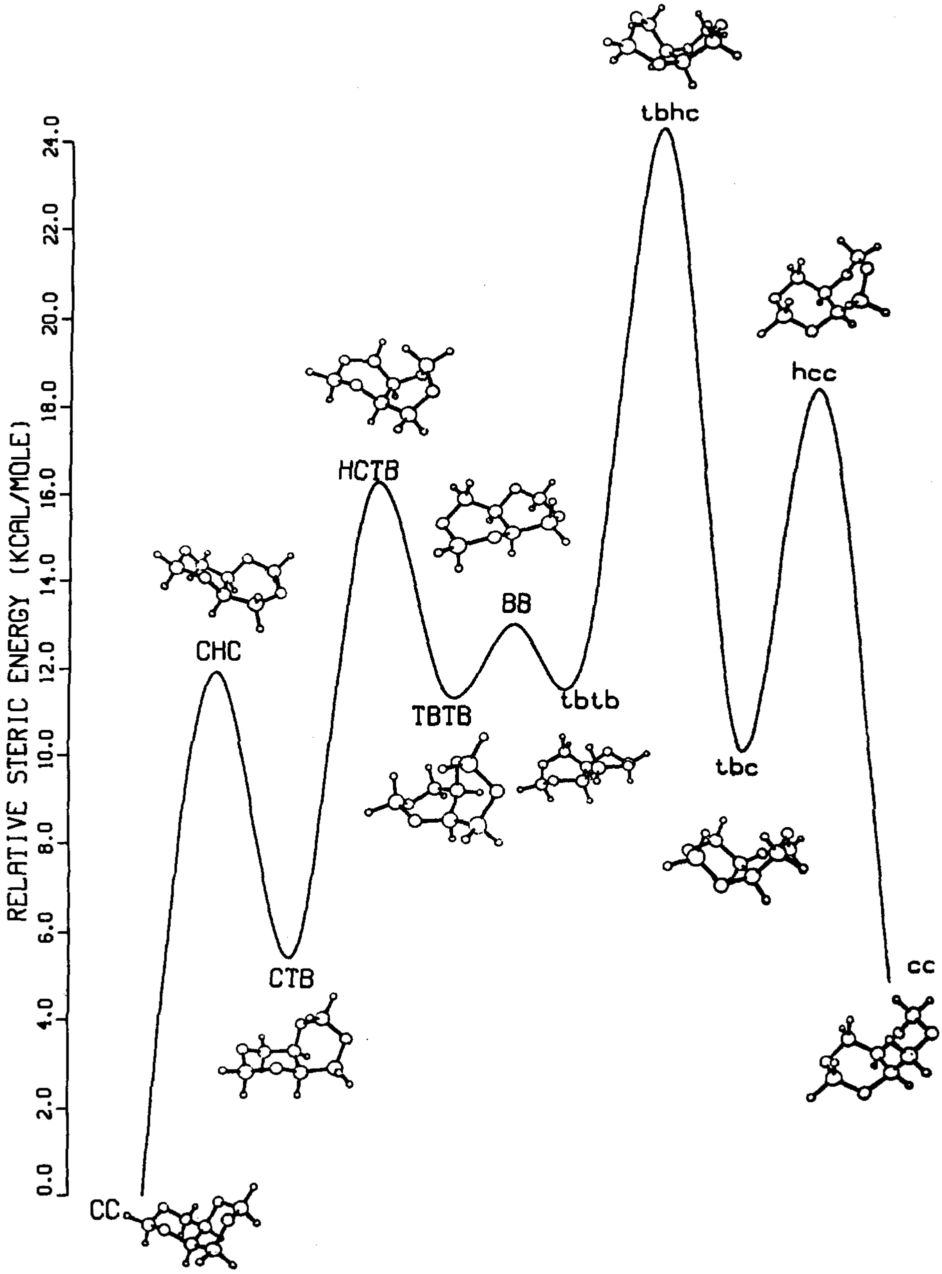
b) X-ray data from the quoted references are given without standard deviations and rounded off for comparison with calculated data.

c) The parenthetical values for **13**, are of parameters involving atoms 05, 07, C6, C8 and C10.

Finally, another subject of considerable interest was the dynamic behavior of *cis*-1,3,5,7- TOD, a C_2 system occuring as two rapidly interconverting double-chair diastereoconformers **2** and **3** (Figure 1). The kinetics of the ring-inversion (**2** ⇄ **3** interconversion) process of the system could not be followed in the adjacently reported variable temperature NMR spectroscopic study[1]. It was, therefore, simulated in a computational study using the above reparametrized MM3-GE, including an analysis of the conformational stations (ground and transition states) encountered on the ring inversion itinerary **2** ⇄ **3**. The MM3 driver option was used to sleuth after energy minima and, in particular, the transition states (where full matrix energy minimization gave one negative eigenvalue and an imaginary vibrational frequency).

The results, namely, the full potential curve with ORTEP drawings of the species in the ground and transition states are depicted in Figure 5 and the relative energies, as well as the dihedral angles of these molecular species are given in Table 10.

Figure 5. ORTEP drawings and the calculated (MM3) energy differences of ground and transition state conformations of *cis*-1,3,5,7-tetraoxadecalin, shown on its ring inversion itinerary.



The global minimum is, of course, the double-chair (CC) form *cis*-O-inside (**2**), which starts the inversion process by going to the next minimum, the chair twist-boat (CTB), through the first, chair half-chair (CHC) transition state. The third minimum is a double-twist-boat (TBTB) and is attained through the second transition state, the half-chair twist-boat (HCTB). This concludes the O-inside manifold, for which the last and lowest barrier is, as expected, the double-boat (BB). The latter leads the system, by inversion (around the C9-C10 bond) of the decalin system's helicity, into the O-outside manifold, in which both the ground and transition states are higher in energy than their O-inside counterparts.

Table 10. Calculated (MM3) steric energies (E_{rel}, kcal/mol) and dihedral angles (T, deg) of the ground and transition state forms of *cis*-1,3,5,7-tetraoxadecalin (2 $\rightleftarrows$ 3) on its inversion itinerary.

	9,10-*M*									9,10-*P*	
Conformation[a]	CC	CHC	CTB	HCTB	TBTB	BB	tbtb	hctb	ctb	chc	cc
T											
O1-C2-O3-C4	64.6	11.4	-74.4	-38.9	-73.0	0.3	32.0	72.9	74.5	-7.3	-64.4
C2-O3-C4-C10	-55.8	16.4	39.3	-20.2	41.5	54.9	31.0	-31.1	-32.3	-10.7	60.1
O3-C4-C10-C9	49.8	1.3	19.7	49.3	19.5	-53.2	-57.6	-28.4	-24.5	-10.8	-54.3
O1-C9-C10-C4	-49.8	-43.9	-51.3	-16.5	-56.7	-2.8	18.2	52.8	45.8	47.3	48.7
C2-O1-C9-C10	56.4	73.3	20.8	-41.4	29.6	59.1	43.4	-14.7	-7.8	-67.5	-50.3
O3-C2-O1-C9	-65.3	-58.1	40.1	75.2	32.8	-60.9	-74.6	-46.2	-51.0	49.3	60.1
O7-C6-O5-C10	-65.3	-66.9	-65.3	-73.9	32.8	-60.9	-74.6	36.4	60.2	61.3	60.1
O5-C6-O7-C8	64.6	65.8	64.1	32.3	-73.0	0.3	32.0	3.2	-64.1	-65.9	-64.4
C6-O7-C8-C9	-55.8	-54.9	-56.2	14.1	41.5	54.9	31.0	-9.1	60.7	60.4	60.1
O7-C8-C9-C10	49.8	46 9	51.7	-21.7	19.5	-53.2	-57.6	-21.9	-55.4	-54.0	-54.3
O7-C10-C9-C8	-49.8	-45.8	-52.1	-16.0	-56.7	-2.8	18.2	56.7	49.7	47.9	48.7
C6-O5-C10-C9	56.4	54.9	57.7	61.6	29.6	59.1	43.4	-64.9	-51.2	-50.2	-50.3
H-C10-C9-H	-51.0	-47.6	-52.9	-19.2	-57.8	-4.3	16.5	51.1	45.6	43.9	46.4
E_{rel}	0.0	11.9	5.6	16.0	11.7	12.1	11.1	23.4	9.4	17.4	4.5

a. Capitals stand for conformations in the left manifold and lower case for the ones in the right conformational manifold: C, c = chair; B, b = boat; HC, hc = half-boat; TB, tb = twist-boat. Only the two dissymetric chair-chair ground state systems have C_2 symmetry.

CONCLUSIONS

The failure of split valence *ab initio* methods as well as of the MM3 force field to reproduce relative stabilities and certain structural parameters in the 1,3,5,7-tetraoxadecalin (TOD) series is due to their basic inadequacy to deal with the stereoelectronics in -O-C-C-O- systems. Specifically, the "gauche effect" is largely overestimated in the force fields parametrization and is much underestimated in the low level "ab initio" calculations. We corrected this in a study of

1,2-dimethoxyethane (DME): the very large energy difference between the *aaa* and *aga* conformers observed in *ab initio* calculations of 1,2-dimethoxyethane (DME) using split valence basis sets (3-21G, 6-31G) was found to decrease considerably (down to 0.2 kcal/mol) when polarized, diffuse basis sets were used and, furthermore, when electron correlation was included. The latter is not needed for 1,2-difluoroethane (DFE), which indicates the existence of additional, specific steric and stereoelectronic effects with particular demands in DME, *viz.*, the conformational behavior of the C-O-C-C (methylethylether) unit, 1,5-nonbonded interactions and C-H--O bonds. The experimentally observed small preference of *gauche* over *anti* conformations in 1,2-dimethoxyethane (DME) in the gas phase is, hence, attributed to entropy contributions, while in condensed phases *gauche* forms prevail, due also to medium effects and intermolecular interactions. Satisfactory results could also be obtained with two of the semiempirical methods available in this work, in particular PM3. Thus, correlation effects which are introduced into the calculation either explicitly (*ab initio*) or via (semiempirical) parameters, play a role in assigning the correct *aga*/*aaa* order. The central C-C bond length was shown to be a sensitive probe for the *gauche effect*. The conformation dependent C-C bond shortening (shorter C-C in *gauche* than in *anti*) can be seen as a result of bond bending, $\sigma_{C\text{-}H}$-$\sigma^*_{C\text{-}O}$ interaction and attractive forces between the two oxygens in the *gauche* form. These findings led to a reparametrization of MM3 by (conformationally dependent) shortening the C-C bond l_0 and slightly changing the torsional potential, providing a reliable tool (MM3-GE) for computation of O-C-C-O (*gauche effect*) containing systems, as shown in Tables 8 and 9 and by the analysis of the ring inversion potential of *cis*-1,3,5,7-tetraoxadecalin.

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