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A Computational Study on the Conformational Behaviour of 1,1.2-Trihydroxyethane in Solution

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The conformational space of 1,1,2-trihydroxyethane were investigated with the PM3 method both in gas phase and in solution. Ab initio calculations at 6-31G level were also conformational equilibria in solution were studied and used to explain the behaviour of 2-hydroxycyclohexanone propylene and ethylene ketals.

Introduction

2-hydroxy cyclohexanone ethylene and propylene ketal systems are relevant to carbohydrate chemistry. In a previous study, we investigated the solvent effect on the conformational equilibria of 2-substituted cyclohexanone ethylene and propylene ketal derivatives using the SCRF approach and the PM3 method[1]. We now chose to investigate 1,1,2-trihydroxy ethane, as it is the simplest structure which incorporates the functional groups found in the large molecules of interest (Figure 1).

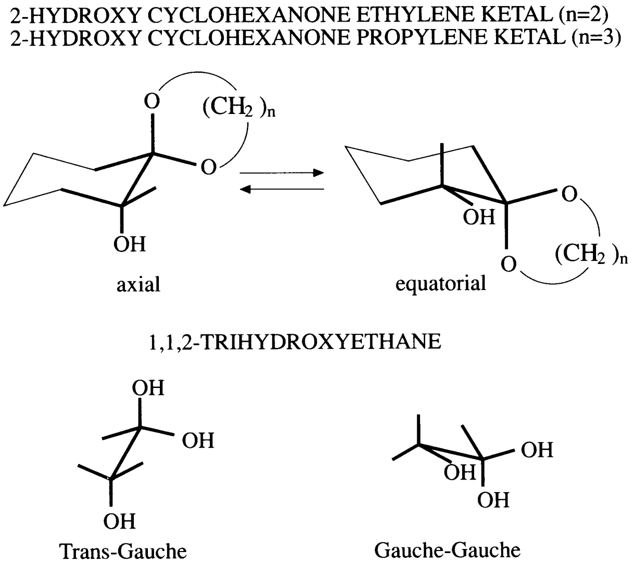


Figure 1. 1,1,2-Trihydroxyethane, a model molecule for 2-hydroxy cyclohexanone ketals.

Because of its small size, 1,1,2-trihydroxy ethane allowed us to perform ab initio calculations, which are extremely challenging to apply on large systems. Ab initio calculations at 6-31G level of sophistication provide information to ellucidate interactions that exist among these three functional groups. Our goal here is to highlight the abilities of the semiemprical PM3 method to produce the structural and energetic properties associated with many interactions in our model molecule and thus 2-hydroxy-cyclohexanone ketal systems.

Method

The semiemprical PM3 method was applied using MOPAC 6.0[2] in the gas phase and GEOMOS[3] in solution. Ab initio calculations were also performed both in gas phase and in solution using GAUSSIAN 92[4]. The effect of the solvent was taken into account with the cavity model[5,6,7,8], in which solvent is simplified as a dielectric continuum and the solute is subjected to SCF calculations. The shape of the cavity was chosen to be ellipsoidal. The electrostatic and induction energies are assumed to be responsible for the main variations of the solvation energies. Therefore, these are the only terms considered. The others, such as the dispersion term or the cavitation term, remain almost contant. The percentage of each conformation has been calculated from the computed energies using the Boltzman distribution law. In the conformational study of 1,1,2-trihydroxyethane, each stationary point has been fully optimized and checked by force calculations: all positive vibrational frequencies indicate a minimum.

Calculations

1,1,2-trihydroxyethane has four rotable bonds, as shown in Figure 2. Therefore, its conformations can be described with four individual dihedral englas, each of which corresponds to a rotation about a single bond represented below:

C2-C3 bond	O8-C2-C3-O6 dihedral angle
C2-O8 bond	C3-C2-O8-H9 dihedral angle
C3-O4 bond	C2-C3-O4-H5 dihedral angle
C3-O6 bond	C2-C3-O6-H7 dihedral angle

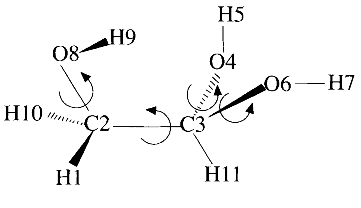


Figure 2. Four rotable bonds in 1,1,2-thirydroxyethane

In order to investigate all possible conformational minima, staggered configurations resulting from the rotation around C2-C3 and C2-O8 bonds were considered. For each staggered configuration around C2-C3 and C2-O8 bonds, C3-O4 and C3-O6 bonds were rotated together in a grid calculation. Rotations were done with 30° intervals of H7-O6-C3-C2 and H5-O4-C3-C2 torsional angles between 0° and 360°. C2-C3 and C2-O8 bonds were fixed while all the other parameters were fully optimized. The staggered positions of H9 give rise to two gauche-gauche (GG) and three trans-gauche (TG) arrangements. Thus five contour maps were obtained. The contour map for GG-1 (H9-O8-C2-C3=60 or -60) is given in Figure 3 as an example;

the others are available upon request. The structures of nine minima obtained from the five contour maps are given in Figure 4. The effect of the solvent was investigated for the nine optimized structures obtained in the gas phase. Acetonitrile was selected as a solvent since it was also used for cyclohexanone ethylene and propylene ketal derivatives. The results obtained are given in Table 1.

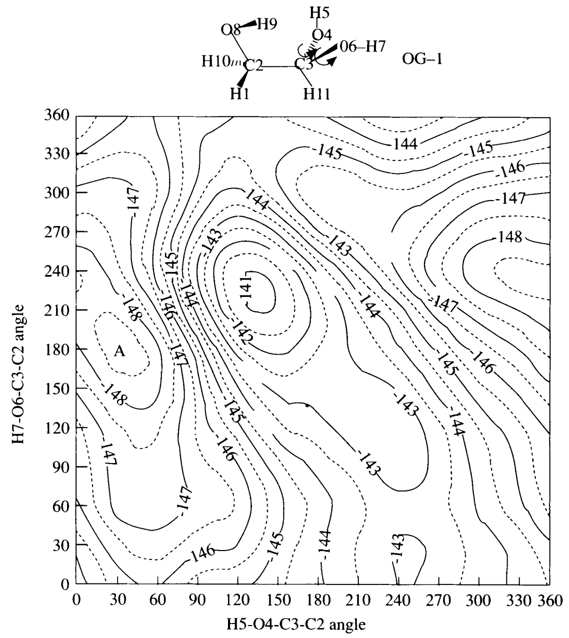


Figure 3. Contour map for GG-1

Tablo 1. The values of relative energies, E_{rel} (kcal/mol), dipole moments, μ(Debye for all conformers of 1,1,2-trihyrdoxyethane obtained from PM3 calculations in gas phase and in acetonitrile. E_{slov}= energy of solvated molecule-energy of isolated molecule

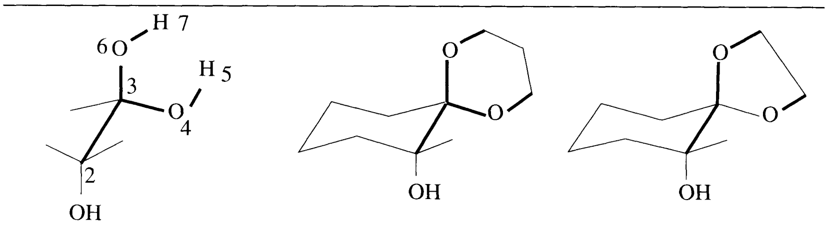
			in gas phase		in acetonitrile		
conformers		dihedral angles*	E_{rel}	μ	E_{solv}	E_{rel}	μ
GG-1	A	(63°,-65°,42° , 177)°)	0.00	1.17	-3.51	0.00	1.35
	B	(64°,-64°,-16°,-124°)	0.09	0.82	-3.55	0.05	0.97
GG-2	C	(63°,179°,51°,-51°)	2.28	3.22	-4.99	0.81	3.63
TG-1	D	(181°,69°,-45°,-111°)	0.17	1.23	-3.66	0.02	1.49
	E	(181°,52°,54°,61°,)	2.30	2.39	-5.56	0.25	2.76
TG-2	F	(190°,-58°,56°,165°)	0.74	1.06	-3.97	0.28	1.22
	G	(181°,-60°,108°,60°)	0.31	1.68	-3.54	0.28	1.97
	H	(191°,-63°,192°,-50°)	0.46	1.03	-3.84	0.13	1.21
TG-3	I	(181°,176°,-57°,-110°)	1.41	2.02	-3.25	1.67	2.27

*are the following in the order written O8-C2-C3-O6,H9-O8-C2-C3, H5-O4-C3-C2,H7-O6-C3-C2

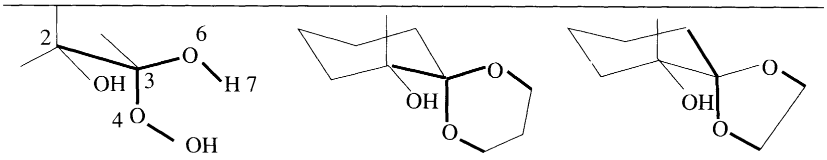
Conformational equilibria of 2-hydroxy cyclohexanone propylene and ethylene ketals were investigated previously[1] considering the conformations in Figure 5, where a and b represent the axial and equatorial -OH groups, respectively. In syn conformations (IIa, IIb) the heterocyclic rings extend toward the substituent, and in anti conformations (Ia and Ib), the heterocyclic rings extend away from the substituent.

The next step was to test if 1,1,2-trihydroxyethane can mimic 2-OH cyclohexanone ketal derivatives. The GG maps correspond to the equatorial -OH, whereas TG maps correspond to axial -OH on the cyclohexanone ketals. H5-O4-C3-C2 and H7-O6-C3-C2 torsional angles of 1,1,2-trihydroxyethane were fixed at the corresponding angles of propylene and ethylene ketals, and all the other parameters were optimized. These dihedral angles are shown in Table 2. Both PM3 and 6-31G calculations were performed on the model. The energies and the percentages obtained from PM3 and ab initio calculations in gas phase and in acetonitrile are given in Table 3 and 4.

Table 2. C-O-C-C dihedral angles of 2-hydroxy cyclohexanone propylene and ethylene ketals corresponding to H7-O6-C3-C2 and H5-O4-C3-C2 dihedral angles of thirydroxyethane.



trihydroxyethane	propylene ketal		ethylene ketal	
	Ia	IIa	Ia	IIa
H7-O6-C3-C2	189.3	-65.8	-135.2	-96.2
H5-O4-C3-C2	169.9	64.3	133.8	97.8



trihydroxyethane	propylene ketal		ethylene ketal	
	Ib	IIb	Ib	IIb
H7-O6-C3-C2	189.8	-78.5	132.1	-108.8
H5-O4-C3-C2	171.0	78.5	132.4	110.2

Results and Discussion

Five contour maps obtained from PM3 calcutions of 1,1,2-trihydroxy ethane give rise to nine minima (Figure 4) and five transition states. The transition states in general fall in the region where the dihedral angles H7-O6-C3-C2 and H5-O4-C3-C2 are approximately 240° and 120°, respectively. The first transition state, which falls in between the two minima A and B, can be seen in Figure 3 as an example. The energy gaps between the minima and the transition states vary from 6 kcal/mol to 9 kcal/mol. For our purpose, we focused our attention on the stable conformations rather than the transition states. Relative energies and the dipole moments of nine stable conformations are given in Table 1. Among the nine minima, structures A, B, and C have two gauche interactions (GG) between O8-O6, whereas the other minima have one gauche and one trans (TG) interaction with the same oxygens. The intramolecular H-bonding may play an important role among many factors affecting the stabilities of these conformations. For this reason, the interatomic O-H distances are given in Table 5. In the literature, the examples of H-bonding distances calculated with PM3 method are in the order of 1.8 Å[9,10]. The interactions between H7-O4 in structures A, B, D and I or between H5-O6 in structures E and G may be intramolecular H-bonding of varying strength.

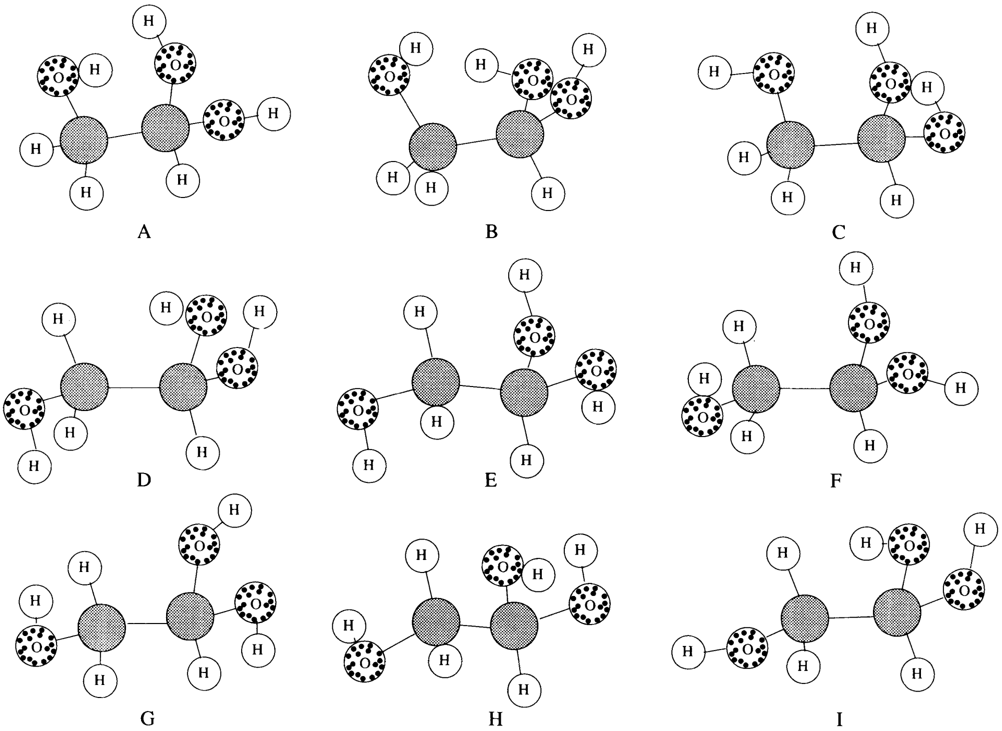


Figure 4. Structures of nine conformers for 1,1,2-trihydroxyethane.

Table 3. **P M 3** energies in kcal/mol and percentages for the conformations of 1,1,2-trihydroxyethane corresponding to 2-OH cyclohexanone ketals

				propylene ketal				
		in gas phase				in acetonitrile		
axial	E(la)	%(la)	E(lla)	%(lla)	E(la)	%(la)	E(lla)	%(lla)
TG-1	-	-	-27936.36	10.93	-	-	-27942.01	25.96
TG-2	-27934.21	0.29	-27936.94	29.29	-27938.79	0.11	-27942.16	33.95
TG-3	-27931.62	0.00	-27934.09	0.24	-27936.91	0.00	-27940.54	2.19
% aixal		0.29		40.46		0.11		62.10
eq	E(lb)	%(lb)	E(llb)	%(llb)	E(lb)	%(lb)	E(llb)	%(llb)
GG-1	-27932.755	0.05	-27937.188	44.61	-27938.20	0.04	-27942.07	28.75
GG-2	-27928.287	0.00	-27936.527	14.60	-27934.92	0.00	-27941.37	8.83
% eq		0.05		59.20		0.04		37.74
				ethylene ketal				
		in gas phase				in acetonitrile		
axial	E(la)	%(la)	E(lla)	%(lla)	E(la)	%(la)	E(lla)	%(lla)
TG-1	-27930.20	0.41	-27931.77	5.88	-27935.12	0.50	-27937.09	13.84
TG-2	-27931.37	2.98	-27932.93	41.54	-27935.34	0.71	-27937.48	27.60
TG-3	-27928.56	0.03	-27929.95	0.27	-27933.50	0.03	-27935.63	1.16
%axial		3.42		47.69		1.24		41.70
eq	E(lb)	%(lb)	E(llb)	%(llb)	E(lb)	%(lb)	E(llb)	%(llb)
GG-1	-27930.65	0.88	-27932.98	45.05	-27935.84	1.65	-27937.87	50.97
GG-2	-27927.63	0.01	-27931.37	2.98	-27933.20	0.01	-27936.42	4.41
% eq		0.89		48.66		1.67		55.38

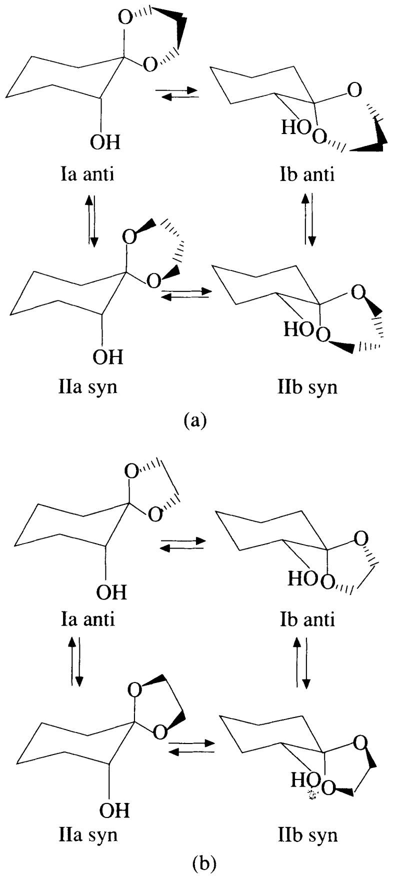


Figure 5. Conformational equilibria of (a) 2-hydroxycyclohexanone propylene ketal (b) 2-hydroxycyclohexanone ethylene ketal.

All the TG structures are less favored than GG structures (Table 1), although they also exhibit intramolecular O-H interactions. The stability of GG A and GG B is in agreement with the well-known “gauche effect” in the literature[11-19], which states that when electron pairs or polar bonds are placed on adjacent pyramidal atoms, the maximum number of gauche interaction is favored.

Examples are 2-fluoroethanol, 2-chloroethanol, and ethylene glycol[18,19]. However, there are other examples of gauche preference in which no H-bonding is possible[14-18] and the cause of the unusual gauche preference is less clear. GG, C has a high dipole moment and is less stable than GG A and GG B.

The results of the calculations in a polar environment are given in Table 1. The dipole moments of the conformers change drastically because the direction of oxygen lone pairs are different in each conformer. As a result, it is expected that a polar solvent will affect the relative stability of the conformers. It is known that compounds with large dipole moments are stabilized more in polar solvents due to the dipole-dipole interactions between the solvent and the solute. Parallel to this, the relative energies of the most polar conformers, C and E decrease in comparison to their gas phase values. Furthermore, their solvations energies have larger negative values. As a result, they are stabilized in a moderately polar solvent, acetonitrile.

Contour maps indicate that syn structures (IIa and IIb in Figure 5) fall in lower energy levels and are therefore favored with respect to anti structures (Ia and Ib). This is in agreement with our previous results[1], with the exception that 2-OH propylene ketal prefers Ib over IIb, which is the anti configuration in the equatorial position. The reason is that 1,1,2-trihydroxyethane does not represent the steric repulsions in IIb conformation of 2-hydroxy cyclohexanone propylene ketal (the axial hydrogens of the dioxane fragment are very close to the -OH substituent in IIb conformation of 2-hydroxy cyclohexanone propylene ketal).

Table 4. 6-3 1 G energies in kcal/mol and percentages for the conformations of 1,1,2-trihydroxyethane corresponding to 2-OH cyclohexanone ketals

propylene ketal								
	in gas phase				in acetonitrile			
axial	E(Ia)	%(Ia)	E(IIa)	%(IIa)	E(Ia)	%(Ia)	E(IIa)	%(IIa)
TG-1	-	-	-	-	-	-	-	-
TG-2	-190550.62	9.82	-190546.93	0.02	-190556.10	6.24	-190553.59	0.09
TG-3	-	-	-190543.65	0.00	-	-	-190547.85	0.00
% axial		9.82		0.02		6.24		0.09
eq	E(Ib)	%(Ib)	E(IIb)	%(IIb)	E(Ib)	%(Ib)	E(IIb)	%(IIb)
GG-1	-190547.24	0.03	-	-	-190554.45	0.38	-	-
GG-2	-190540.57	0.00	-190551.93	90.13	-190548.81	0.00	-190557.71	93.29
% eq		0.03		90.13		0.38		93.29

ethylene ketal								
	in gas phase				in acetonitrile			
axial	E(Ia)	%(Ia)	E(IIa)	%(IIa)	E(Ia)	%(Ia)	E(IIa)	%(IIa)
TG-1	-190540.11	0.01	-190540.38	0.02	-190546.67	0.00	-190547.34	0.00
TG-2	-190545.16	57.71	-190544.75	27.46	-190550.05	0.00	-190550.58	0.00
TG-3	-	-	-190540.61	0.03	-	-	-190551.87	0.02
% axial		57.71		27.51		0.00		0.02
eq	E(Ib)	%(Ib)	E(IIb)	%(IIb)	E(Ib)	%(Ib)	E(IIb)	%(IIb)
GG-1	-190543.05	1.55	-190544.06	8.54	-190549.53	0.00	-190550.01	0.00
GG-2	-190539.27	0.00	-190543.99	7.68	-190545.84	0.00	-190556.92	99.98
% eq		1.55		16.22		0.00		99.98

Table 5. Interatomic H-O distances(in Angstroms) in 9 conformations of 1,1,2-trihydroxy ethane obtained from PM3 calculations.

	A	B	C	D	E	F	G	H	I
H9-O6	2.579	2.650	3.776	3.907	3.862	3.875	3.883	3.941	4.316
H9-O4	3.237	3.149	3.756	3.445	3.241	2.723	2.691	2.655	3.820
H7-O8	3.765	3.300	2.544	4.117	3.907	4.313	3.926	3.912	4.065
H7-O4	2.385	1.886	2.548	1.879	2.983	2.492	2.961	2.454	1.877
H5-O8	2.529	2.651	2.523	2.687	3.291	3.357	3.785	3.736	2.655
H5-O6	2.532	2.859	2.551	2.946	2.342	2.410	1.878	2.463	2.960

According to the experimental results[20], for both 2-OH cyclohexanone propylene and 2-OH cyclohexanone ethylene ketals, preference for axial orientation decreases as solvent polarity increases. The results of 6-31G calculations for the model structures (Table 4) are in agreement with these experimental findings. Total axial percentage of the model structures representing both ketal systems shown a decrease going from gas phase to acetonitrile. Thus, one can say that 1,1,2-trihydroxy ethane mimics 2-OH cyclohexanone ketal systems with regard to solute-solvent interactions. The shift produced in going from gas phase to solvated medium is mainly due to the electrostatic interactions between the solute and the solvent. PM3 calculations predicted the equatorial shift for both syn and anti ethylene ketal (Table 3). For the propylene ketal, axial shift is produced for the syn and equatorial shift is produced for the anti corresponding structures.

One needs to differentiate between the syn and anti corresponding structures due to the fact that they are of crucial importance in the 6-membered ketal fragment. Steric interactions between the -OH substituent and the axial hydrogens of the dioxane fragment is not present in 1,1,2-trihydroxyethane. Therefore, 1,1,2-trihydroxyethane does not mimic structures in which steric interactions predominate.

Table 4 shows that, in the models of 2-OH cyclohexanone propylene ketal, the main contributions to the total energy in gas phase come from Ia and IIb, whereas in the model structures of 2-OH cyclohexanone ethylene ketal, Ia and IIa structures contribute to the total energy more than Ib and IIb in the gas phase.

When the solvation energies are compared (Table 6), it is seen that for propylene ketal, Ia is stabilized slightly less than IIb in acetonitrile, which is the reason for the decrease in axial percentage. However, for the models of ethylene ketal, GG (IIb) exhibits an extremely large solvation energy in comparison to the other structures, in spite of its small dipole moment. As a result, a sharp drop of the total axial percentage is observed in acetonitrile. This is because the solvation energies are dependent on higher moments as well as dipole moments. Multipole contributions to solvation energy play an important role. In GG (IIb), the first five terms all contribute to the solvation energy to a considerable extent, whereas in the other structures the higher terms are not as influential.

Table 6. Solvation energies E_s lov (kcal/mol) in acetonetrile from 6-3 1 G calculations and gas phase dipole moments, μ(Debye) of 1,1,2-trihydroxyethane for the models corresponding the conformers of 2-OH cyclohexanone ketals

	propylene ketal				ethylene ketal			
	E solv(la)	μ(la)	*E solv*(lla)	μ(lla)	*E solv*(la)	μ(la)	*E solv*(lla)	μ(lla)
TG-1	-	-	-	-	-6.557	3.236	-6.962	2.238
TG-2	-5.483	4.129	-6.661	3.434	-4.897	4.165	-5.883	3.976
TG-3	-	-	-8.224	4.933	-	-	-7.237	3.896
	E solv(lb)	μ(lb)	*E solv*(llb)	μ(llb)	*E solv*(lb)	μ(lb)	*E solv*(llb)	μ(llb)
GG-1	-7.207	5.228	-	-	-6.487	3.355	-5.952	1.733
GG-2	-8.239	3.448	-5.772	4.214	-6.574	0.748	-12.930	1.695

In conclusion, the semiemprical PM3 method gave satisfactory results is gas phase and in solution. The role of the multipole moments proved to be important, and the ellipsoidal cavity and the SCRF approach appropriately described the behavior of the conformational equilibria in solution. Ab initio calculations on 1,1,2-trihydroxyethane provided a suitable model for 2-hyroxycyclohexanone ketal derivatives to study the electrostatics and the effect of the solvent on the balance of electrostatic interactions, although it does not mimic the steric interactions present in the ketals due to ring hydrogens.

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