Computational analysis of dental material monomer Bisphenolglycidyldimethacrylate (BisGMA)

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Bisphenolglycidyldimethacrylate (BisGMA), a derivative useful for dental materials, is examined here examined with computational chemistry methods. Several levels of theory were employed: empirical (Sybyl and MMFF force fields), semiempirical (AM1, PM3), Hartree-Fock (STO-3G as well as 3-21G*) and DFT (BP86/6-31G**). There appears to be good agreement between the structures computed at various levels, with expected differences in the mobile ends of the molecules. This offers promise for employing the more time-efficient semiempirical and empirical methods for predicting molecular and supramolecular behavior of dental polymers obtained from monomers such as examined here. Preliminary results in this respect are shown, indicating the possibility of organized, non-random structures.

1. Introduction

Most of the commercial restorative composite materials contain BisGMA (bisphenolglycidyldimethacrylate, cf. Fig. 1) as main monomer, which was synthesized by Bowen in 1960 [1]. The reason for this dominance of BisGMA is that this bulky, difunctional monomer shows a relatively low polymerization shrinkage (approx. 6.0%), rapid hardening by free radical polymerization, and low volatility. Furthermore, it leads to cured materials with good mechanical properties.[2] However, one important deficiency of BisGMA is its high viscosity. A diluent, usually triethyleneglycol dimethacrylate TEGDMA, is usually necessary to reduce the viscosity of the resin; unfortunately, adding TEGDMA to BisGMA, the water uptake and polymerization shrinkage of the cured material increase. Water susceptibility and the relatively low degree of double bond conversion of BisGMA-based materials, represent other shortcomings of BisGMA monomer.

The preparation of novel low-viscosity base monomers which require addition of smaller/zero amounts of TEGDMA may be expected to improve the final properties of the materials. Modifications of the BISGMA hydroxyl groups and of the core structure (-CH$_3$-C-CH$_3$-) may be expected to affect hydrophilicity and viscosity in desirable ways, while retaining advantages such as low curing shrinkage and good mechanical properties. Fluorinated aromatic dimethacrylate monomers as structural analogues to BisGMA were synthesized by Sankarapandian et al.[3] and demonstrated significant lower viscosity and water uptake compared to BisGMA – based materials.[4] Use of the hydrophobic, low viscosity methyl-substituted version of BisGMA as a diluent in the conventional high viscosity BisGMA resin resulted in

significantly improved properties such as polymerization shrinkage, water sorption and extent of polymerization (decreased number of unreacted double bonds in cured resins).[5]

Although computational/molecular modeling methods have long been recognized as tools of predictive value in chemistry, a flourishing debate still exists on the meaning and usefulness of such data, and on the limits where high-accuracy meets overinterpretation.[6-13] Here, BisGMA is examined with computational chemistry methods - empirical, semiempirical, and *ab initio*, taking the first steps towards modeling the supramolecular structures in dental polymers, which may, among other things, help design more useful monomers following criteria described above – following upon our previous interest in dental materials.[14-17] Indeed, whereas viscosity and other macroscopic properties are not directly derivable from small-model quantum-mechanical or molecular-mechanical calculations, the knowledge gained on supramolecular-type interactions in such studies may be useful in subsequent attempts to understand the physical basis of the said macroscopic properties.

2. Methods

Geometries for all models (cf. Fig. 1) were optimized without any constraints, after exploring the conformational space at molecular-mechanics level for identification of the possible conformers and of the lowest-energy ones. The three common classes of molecular modeling methods were employed – molecular mechanics, semiempirical, and "ab initio" (using for this instance only, arguably very loosely, this latter term to describe Hartree-Fock as well as DFT data.) The Sybyl and MMFF force fields, AM1 and PM3 semiempirical methods, Hartree-Fock with the

3-21G* basis set (as the improvement brought by the larger 6-31G** is rather small[18, 19], and as the goal is to identify the most time-efficient way to obtain high-quality data on oligo- and polymers including the Bis-GMA moiety), HF/STO-3G, and BP86 density functional with the 6-31G** basis set were used with the default convergence criteria implemented in the Spartan software package.[20] The existence of minima was checked by computing vibrational spectra, so that no negative frequencies would be observed. The choice of functional (i.e., BP86 vs others, such as B3LYP) has been much debated in computational chemistry in general, with BP86 being shown to often (but not always) provide results of similar quality with the "competing" functionals,[8, 21-53] including some recent contributions on biopolymers by

ourselves;[12, 54] based on these data, it is expected that the BP86 would provide reasonable results here.

In addition to the various geometry optimizations, full conformational searches were performed as well using the MMFF method, as implemented in the Spartan software package with default values, which implies that only the distinct conformers within 10 kcal/mol of the global minimum are reported.[20] Molecular dynamic (MD) simulations were performed using the extended Lagrangian approach with the ADMP (Atom Centered Density Matrix Propagation) model, with the BP86 functional and the 6-31G** basis set, using steps of 1 femtoseconds for a total of 10000 femtoseconds with fully converged SCF results at each point..[55]
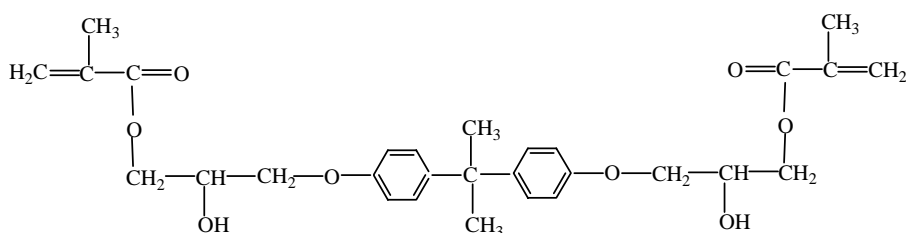

Fig. 1. Structure of BisGMA.

3. Results and Discussion

The following systems were examined: the adduct of BisGMA with trifluoracetic acid, cyclohexanoxy-BisGMA, dicyclohexyl diol ester, diglyhcidyl ester, 6F BisGMA (H), 6F BisGMA (CH3), 3F Bis GMA (CH3), phosphin-oxide dimetacrylate and Bis GMA (CH3). Scheme 1 structures for these models computed at various levels of theory: empirical (Sybyl and MMFF force fields), semiempirical (AM1, PM3), Hartree-Fock (STO-3G as well as 3-21G*) and DFT (BP86/6-31G**). There appears to be good agreement between the structures computed at various levels, with expected differences in the mobile ends of the molecules.

Table 1 shows numerical data for the comparison shown in Scheme 1. As ageneral rule, methods generally

accepted to yield reliable results (DFT/6-31G**, HF/3-21G*) and empirical methods (Sybyl and MMFF) appear to yield similar geometrical parameters. On the other hand HF/STO-3G fails to properly describe the bond P=O (a difference of ~0.1 Å compared to other methods, including those of higher level), while AM1 cannot describe accurately the P-C bond (differences of 0.1-0.2 Å compared to HF and DFT). For the rest of the chemical bonds inventoried in Table 1, there are differences of up to 0.03 Å between the various computational methods, suggesting reasonable accuracies for the lower-level methods in these respects, which should be useful in attempting to describe supramolecular-type structures based on systems related to those examined here, with potential applications in ab initio predictions of macromolecular properties.
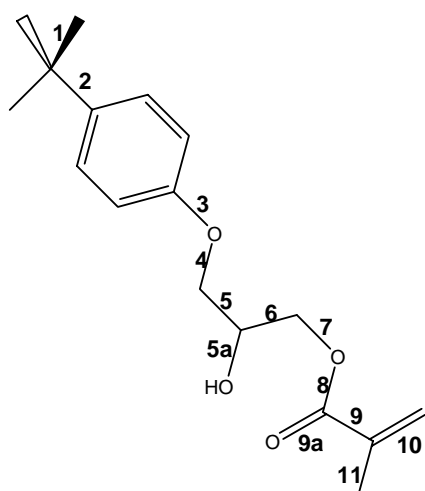
Table 1. Relevant bond lengths computed for the models employed in the present study at several levels of theory. Bonds are labeled as in Fig. 2.

Method\bond	Sybyl	MMFF	AM1	PM3	HF/STO-3G	HF/3-21G*	BP86/6-31G**
1	1.56	1.56	1.53	1.53	1.55	1.55	1.55
2	1.56	1.55	1.51	1.52	1.55	1.54	1.54
3	1.40	1.37	1.38	1.38	1.41	1.39	1.38
4	1.44	1.43	1.43	1.42	1.44	1.45	1.44
5	1.55	1.53	1.53	1.55	1.56	1.52	1.53
5A	1.43	1.44	1.42	1.41	1.43	1.43	1.43
6	1.55	1.53	1.53	1.54	1.55	1.51	1.53
7	1.44	1.44	1.44	1.43	1.44	1.45	1.45
8	1.34	1.36	1.37	1.36	1.39	1.35	1.38
9	1.48	1.49	1.48	1.49	1.52	1.48	1.49
9A	1.22	1.22	1.23	1.21	1.22	1.21	1.22
10	1.34	1.34	1.34	1.33	1.31	1.32	1.35
11	1.51	1.50	1.48	1.48	1.52	1.51	1.50

Fig. 2. Bond labeling in BisGMA for the purpose of the present study. Only one half of the molecule is illustrates, as the other half is a mirror image of what is shown here.

Fig. 3 illustrates an overlay of the geometries computed for BisGMA with several methods as indicated in Table 1. It may be seen that although these structures overlay well at the center of the molecule, the large number of degrees of freedom accessible at both ends of the chain leads to different spatial arrangements, depending on the method employed. We have therefore identified points where conformational heterogeneity may be achieved in BisGMA, and verified, as illustrated in Figure 4, the relative energies of conformers produced by rotation around these bonds.

Fig. 3. Overlay of optimized geometries, obtained at levels of theory indicated in Table 1, for BisGMA.

Fig. 4 illustrates the two conformers possible around the central quaternary carbon atom in BisGMA. Perhaps counter intuitively, the conformer featuring the two phenyl rings perpendicular to each other appears more stable one with all methods for the smaller model (used cf. Fig. 4 to specifically probe the conformational mobility of this particular structural unit), although BP86 predicts a reversed trend in the full BisGMA molecule. Nevertheless, the energy difference between the two conformers is very low, suggesting that both of them are likely to be present at room temperature.

	ΔE (kcal/mol)	
MMFF	0	-3.30
BP86	0	-2.96
HF/STO-3G	0	-3.32
HF/6-311+G**	0	-3.08

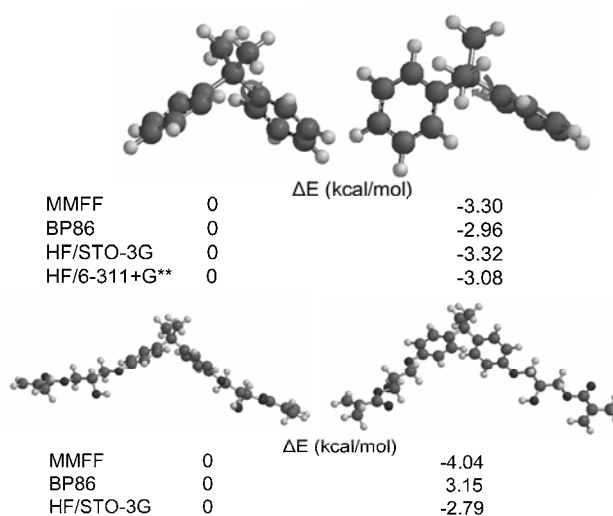|	ΔE (kcal/mol)	
MMFF	0	-4.04
BP86	0	3.15
HF/STO-3G	0	-2.79

Fig. 4. Relative energies of BisGMA conformers differing by rotation around bond labeled 2 in Fig. 2, at various levels of theory. Top panel – smaller model, with arrows indicating the bond around which rotation can be achieved in order two generate the two conformers.

Fig. 5 illustrates two other pairs of conformers in BisGMA, resulted from rotation around bonds 2 and 7 cf. notation in Fig. 2. Once again the energy differences are very small, with HF and DFT methods predicting opposite conformers as more stable.

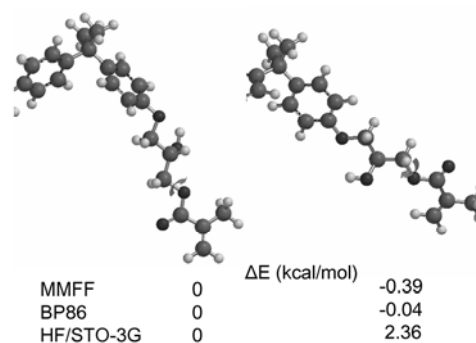|	ΔE (kcal/mol)	
MMFF	0	-0.39
BP86	0	-0.04
HF/STO-3G	0	2.36

Fig. 5. Relative energies at various levels of theory for BisGMA conformers differing by rotation around bonds labeled 7 and 3, respectively, in Fig. 2. Arrows indicate the bond around which rotation can be achieved in order two generate the two conformers.

The main use of BisGMA is for polymerization reactions, which lead to three-dimensional structures characterized by useful properties for dental material preparation. In order to help understand these structures, and building on knowledge illustrated in Figs. 1-5, we have therefore set to examine possible conformations of BisGMA oligomers. Fig. 6 illustrates two possible conformations of a BisGMA dimer. The top structure conserves within each BISGMA unit the conformers found more stable in the detailed studies shown in Figs. 2-5; we chall refer to this structural motif as 'boat-shaped'.

However, the lower-panel structure in Figure 6 illustrates another conformer, 3 kcal/mol more stable than the boat-shaped one, where although several bonds are rotated to values corresponding to less stable conformers, the overall stability is ensured by formation of a hydrogen bond between hydroxyl groups belonging to the two monomers. This type of intramolecular hydrogen bonding may be important under conditions of low water concentration, when hydroxyl groups would be attracted to each other as long as there would not be enough water molecules to hydrogen bond to each hydroxyl.
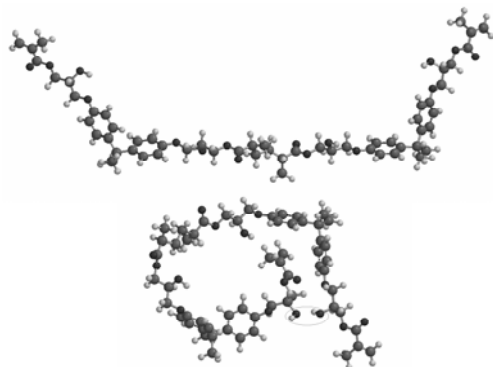

Fig. 6. Two conformers of the BisGMA dimer; geometries optimized with the MMFF force field. The two hydroxyl groups engaging in a hydrogen bond are circled; the computed O---H distance is 1.84 Å.

Fig. 7 illustrates how starting from the boat-shaped conformer of the BisGMA dimer, the structure may be extended to reach, at the hexamer stage, an helicoidal-type arrangement.
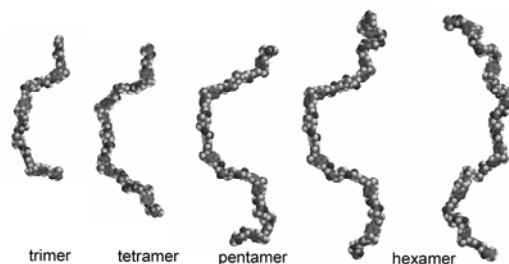

Fig. 7. BisGMA oligomers – structures computed using the MMFF force field. For the hexamer, two different views of the same molecule are shown.

Fig. 8 illustrates three possibilities for optimum interaction between two BisGMA molecules. It may be seen that the two molecules are able to align in several ways; the three structures are isoenergetic despite the fact that only one of them contains hydrogen bonds, and all three are 10 kcal/mol more stable than a structure where the two bisGMA molecules are separated at 10-12 Å from each other.

An important note may be taken on the conformational diversity available to the models employed in the present study. Fig. 9 shows results from a full MMFF conformational study on BisGMA. The top ~100 conformers fall within ~ 8 kcal/mol of each other, with four conformers within less than 1 kcal/mol of each other and a further 20 within 2 kcal/mol of the lowest-energy conformer (Table 1 discusses the lowest-energy conformer). As already seen especially in Figure 4, the relative energies of the conformers in this class of compounds can show a method dependence going as high as 7-8 kcal/mol, i.e., encompassing most of the top 100 conformers resulted from the search illustrated in Fig. 9.
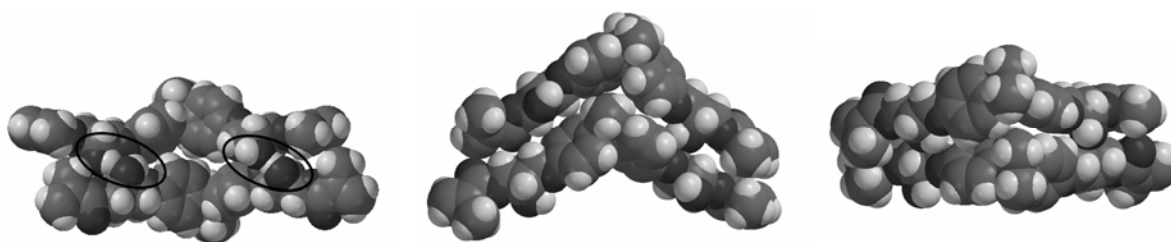

Fig. 8. Three possibilities for intermolecular association of two BisGMA monomers. The first structure features two hydrogen bonds between hydroxyl groups, highlighted with ovals.

Therefore, any conclusion about the identity of the lowest-energy conformers ought to be taken conservatively. Fig. 10 shows that the overall volume of the molecule, an important parameter in establishing supramolecular arrangements, is at 600 Å^3, varying by essentially +/- 2 Å^3 within the set of lowest-energy 100 conformers examined here; less than 10% of the conformers are in the 598-596 Å^3 range. More detailed conformational searches, including not only semiempirical but preferably ab initio methods, would be needed for establishing a complete picture of the conformational mobility within the models examined here[56, 57].

On the other hand, ab initio dynamics based on DFT protocols, illustrated in Fig. 11, reveal yet another facet of BisGMA's mobility: whereas over the course of the 10000 fs of the simulations individual conformationally-flexible functional groups oscillate within expected limits of a very fast time scale, there is an overall flexibility of the molecule with a much slower movement – as illustrated by the evolution of the distance between the two quaternary carbon atoms found at the two extremes of the molecule (Figure 11). Indeed, the amplitude of the movement here is ~4 Å, with an average value of 20 Å. This very slow movement is expected to impact the plasticity and other physical properties of the BisGMA-derived materials, and deserves more extended consideration.
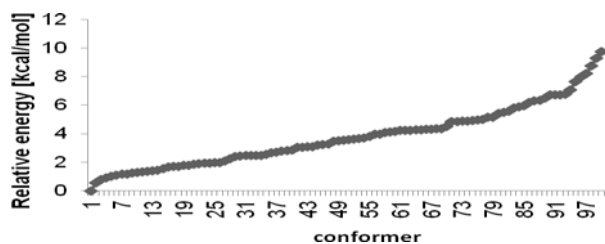
Fig. 9. Relative energies of the lowest-energy 100 conformers obtained from a full conformational search on BisGMA using MMFF.
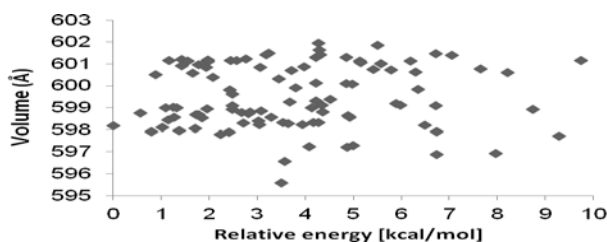

Fig. 10. Molecular volume (CPK option [12]) for the conformers illustrated in Fig. 9, as a function of the conformer energy.

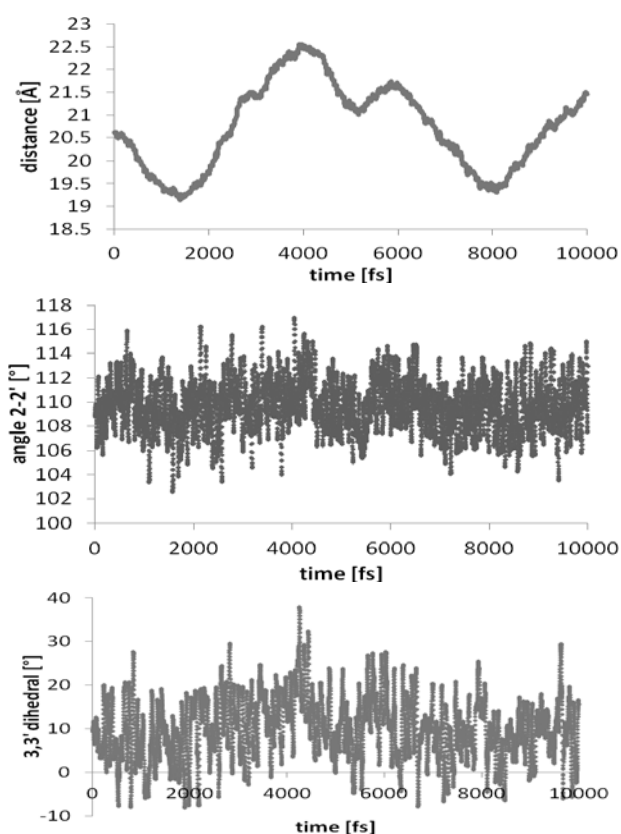*Fig. 11. Illustrative plots for ab initio dynamics on BisGMA, run over 10000 fs: the distance between the two quaternary carbon atoms, the angle formed by bonds 2 and 2' at the central carbon atom, and the dihedral defined by bonds 3 and 3'.*

To conclude, a computational examination of the BisGMA monomer has been reported here for the first time. Preliminary data is also shown indicating that the interaction of two BisGMA molecules may be as high as 10 kcal/mol in the optimal orientations for interaction, and that the forces dictating these interactions need not include hydrogen bonds. Oligomers of BisGMA (n=2-6) are also examined, and the trends seen in these structures indicate the possibility of a helicoidal structure in BisGMA polymers, although hydrogen bonding within the polymer may in principle induce irregularities.

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