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ROTATIONAL ISOMERS, NMR AND REACTIVITY ANALYSES OF TERT-PENTYL-1-BENZYL-4-METHYL-2,6-GLUTARIMIDE-3-CARBOXYLATE (PBMG)

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Abstract
The stable isomers of *tert*-pentyl-1-benzyl-4-methyl-glutarimide-3-carboxylate (PBMG) are determined. Optimized geometrical parameters of the stable isomers of PBMG are predicted by DFT/B3LYP/6-311++G(d,p). The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) chemical shifts of the molecules were calculated using the GIAO method and conform to the experimental values. To assess chemical reactivity of the molecule, the molecular electrostatic potential (MEP) surface map is plotted over the optimized geometry of the molecule.

Introduction
Glutarimide derivatives are recognized as anticonvulsants [1], sedatives [2] and antitumor agents [3]. Substituted imide rings are also found in some of the pharmacologically active natural products, such as cycloheximide [4], sesbanimide [5], izomigrastatine and migrastatine [6]. Numerous compounds containing six-memebered imide ring are synthesized and express different farmacological activities such as anxiolytic (buspirone, tandospirone) [2], immunosuppressive (thalidomide and analogues) [2], and others.
In our previously reported research PBMG has been synthesized by a novel tandem process [7].

The understanding of molecular geometry and reactive electrophilic and nucleophilic sites of the compound are of particular importance in the synthesis of a drug. Hence, in the present study, the energies and stability of different possible rotational isomers of PBMG are determined, as well as ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra for the title molecule are analyzed. Moreover, molecular electrostatic potential (MEP) surface is plotted over the optimized geometry to elucidate the reactivity of PBMG molecule.

Experimental
The chemical structure and purity of the synthesized compound was confirmed by its melting point, ^{1}H and ^{13}C NMR and FT-IR spectra. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a Varian Gemini 200 spectrometer at 200 MHz and 50 MHz, respectively.

Computational details

All the calculations were performed using Gaussian 03 program package. Geometry of PBMG was fully optimized with DFT/B3LYP/6-311++G(d,p) method. ^{1}H and ^{13}C NMR chemical shifts are calculated with GIAO approach by applying B3LYP/6-311++G(d,p) method. To investigate the reactive sites of the title compound, the molecular electrostatic potentials for the 0.002 a.u. isosurfaces of electron density was evaluated using the B3LYP/6-311++G(d,p) method.

Results and Discussions

Molecular geometry

The molecule of PBMG could exist as *trans* and *cis* diastereomers. To find most stable isomer geometry, the DFT energy calculation is performed on the eight possible isomers of PBMG. The possible isomer geometry is found by locating -CH_2Ph group of the title molecule in two different orientations, above and below the plane of the glutarimide ring. The positioning of *tert*-pentyl group in two different orientations gives rise to eight isomers. The DFT energy calculation and the statistical Boltzmann distribution (shown in Table 1) reveal that, the isomers **1d** and **1h** acquire dominant stability among others *trans* (**1a-1d**) and *cis* (**1e-1h**) isomers, respectively. The optimized molecular structure of the most stable isomer **1d** of the title molecule is shown in Fig. 1.

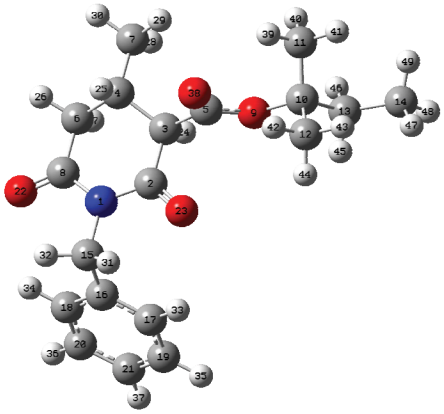

Figure 1. Geometry optimized structure of **1d** isomer of PBMG.

Table 1. The energies and the statistical Boltzmann distribution weighted values of the most stable PBMG isomers.

Isomer	Energy / a.u.	%
1a	-1095.0792247	11.22
1b	-1095.0801943	31.15
1c	-1095.0793179	12.38
1d	-1095.0804938	42.69
1e	-1095.0750486	0.14
1f	-1095.0769821	1.06
1g	-1095.0750302	0.14
1h	-1095.0771161	1.22

NMR spectra

From experimental data the ratio between *trans*/*cis* diastereomers (5:1) is determined by ratio of the two signals at 3.08 and 3.45 ppm (two doublets from atom H(24) on C(3)). The same signal ratios are found at 1.26 (1.34) ppm from two singlets of methyl groups at C(11) and C(12) in *trans*/*cis* isomers, as well as for signals at 0.94 (0.98) ppm from methyl groups on C(7) and at 0.68 (0.77) ppm from methyl groups on C(14). Doublets at 2.62 (2.70) ppm mark methylene of

glutarimide ring, while quartets at 2.20 (2.45) and 1.66 (1.68) ppm mark atom H(25) on C(4) and methylene hydrogens on C(13), respectively. Singlet at 4.82 (4.84) ppm mark methylene hydrogens on C(15). Peaks at 7.05-7.26 ppm indicate the presence of aromatic hydrogen atoms. In ^{13}C NMR spectra signals for carbonyl groups are at 170.54 (171.29), 168.54 (168.79) and 167.03 (165.83) ppm in *trans*/*cis* isomers. The peaks appearing in the range 138.62–127.09 ppm are assigned to the carbon atoms of phenyl group. The signals at 84.76 (85.43) is assigned to C(10) carbon. The aliphatic CH_2 (C(6), C(13), and C(15)) carbons are observed at 42.55, 38.24 (36.62) and 57.55 (55.04) ppm, respectively. The carbon atoms of the CH groups belonging to the glutarimide ring are observed at 33.09 and 26.27 (27.4) ppm, for C(3), and C(4), respectively. Methyl groups are at 24.87 (24.95), 18.69 (17.03) and 7.74 ppm, for C(11, 12), C(7), and C(14), respectively. The theoretical ^{1}H and ^{13}C chemical shift results for PBMG are generally close to the experimental ^{1}H and ^{13}C shift data.

MEP

The MEP map shows that the negative potential sites are on electronegative O atoms of the carbonyl groups and the positive potential sites are around the carbon C(4) of the glutarimide ring. These sites give information about the region from where the compound can make intermolecular interactions. Thus, it would be predicted that the carbonyl groups fragment of PBMG will be the most reactive site for electrophilic, and C(4) atom for nucleophilic attack.

Acknowledgments

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References

[1] S. A. Dandekar, S. N. Greenwood, T. D. Greenwood, S. Mabic, J. S. Merola, J. M. Tanko, , J. F. Wolfe, J. Org. Chem., 1999, 64, 1543-1553.
[2] The Merck Index, 13th Ed; Merck & Co., Inc., NJ, 2001.
[3] D. K. K. Ha, W. H. Lau, Cancer Lett., 1988, 41, 217-224.
[4] C. Christner, R. Wyrwa, S. Marsch, G. Küllertz, R.Thiericke, S. Grabley, D. Schumann, G. Fischer, J. Med. Chem., 1999, 42, 3615-3622.
[5] F. Matsuda, S. Terashima, Tetrahedron, 1988, 44, 4721-4736.
[6] J. Ju, S. R. Rajski, S.-K. Lim, J.-W. Seo, N. R. Peters, F. M. Hoffmann, B. Shen, Bioorg. Med. Chem. Lett., 2008, 18, 5951-5954.
[7] J. B. Popović-Đorđević, M. D. Ivanović, V. D. Kiricojević, Tetrahedron Lett., 2005, 46, 2611–2614.