# A DFT study of the G3-Factor and derivatives

Corinne Lacaze-Dufaure [a,*], Fadia Najjar [b], Christiane André-Barrès [b]

[a] *Centre Interuniversitaire de Recherche et d'Ingénierie des Matériaux, CNRS UMR 5085, ENSIACET, 118 route de Narbonne, 31077 Toulouse Cedex 4, France*
[b] *Laboratoire de Synthèse et Physicochimie de Molécules d'Intérêt Biologique, CNRS UMR 5068 Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse, France*

Abstract

We present theoretical studies of the G3-Factor and two derivatives, the methylated (G3Me) and the fluorinated (G3F) endoperoxides. These endoperoxides were previously tested as alternative drugs against the parasite causing malaria. They showed promising activity.

R = OH, OMe, F
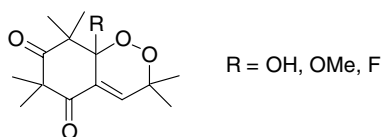
The geometry of each compound was optimized in its lowest singlet and triplet spin states at the B3LYP/6-311G* level of theory. It was followed by a NBO analysis. The ground state of the G-Factors is a singlet. The geometric parameters found by the DFT calculations are in agreement with available experimental results. The spin density distribution for the triplet state shows a biradical $[\dot{O}\ \dot{O}]$ molecule. The singlet–triplet splitting is of 36.60, 33.96 and 34.09 kcal/mol (B3LYP/6-311G*) and of 36.07, 33.51 and 33.60 kcal/mol (B3LYP/6-311++G**) for the G3-Factor and the G3Me and G3F derivatives, respectively.

Keywords: Density Functional Theory; Endoperoxides; G-Factors; Malaria; Singlet–triplet splitting

1. Introduction

Malaria affects millions of people in the world. The parasite causing this disease is getting resistant to traditional medicine, i.e. quinine, chloroquine and their derivatives. Many efforts are done to develop new antimalarial molecules to be used against chloroquine-resistant strains of *Plasmodium falciparum*, one of the agents causing malaria [1,2]. To this end, some alternative drugs are based on natural compounds, i.e. artemisinin. Artemisinin is an endoperoxide extracted from *Artemisia annua*, known from centuries in traditional Chinese medicine [3,4]. This molecule was widely studied experimentally and theoretically [5–18].

Recently, compounds called G1-, G2- and G3-Factor (see Fig. 1) and extracted from leaves of *Eucalyptus grandis* and other myrtaceae, were tested as alternative drugs against the parasite causing malaria. They showed promising activity [19,20]. Their therapeutic action is assumed to be related to the reductive cleavage of the O—O bond by heme or free Fe(II) ions present in the parasite. It is thus a dissociative electron transfer process according to a similar mechanism as artemisinin [5].

Chemical synthesis, antimalarial properties and redox behaviour of some derivatives of G-Factors were described previously [21,22], but no experimental structure is avail-
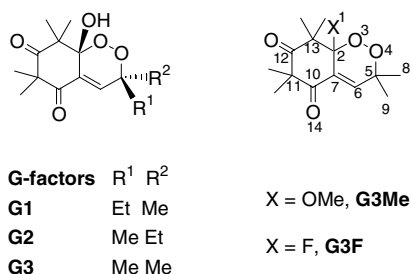
Fig. 1. G-Factors and derivatives.

able. We thus want to describe the geometry of these compounds. We are also interested in the estimation of the standard potential (E°) of the dissociative electron transfer process. The direct determination of this potential is not possible experimentally. To evaluate it, thermochemical data such as the singlet–triplet splitting of the compound is required [23].

We present here theoretical studies of the G3-Factor and of two derivatives, namely the methylated (G3Me) and fluorinated (G3F) endoperoxides. Our quantum studies focus on the determination of their stable conformation in their lowest singlet and triplet spin states.

2. Methods

The atom labelling is given in Fig. 1.

All structures were fully optimized using conjugate gradient methods with the GAUSSIAN03 software package [24]. We chose the B3LYP hybrid functional [25,26]. First computations were done with the B3LYP/6-31G* scheme and the stationary points were characterized as minima by a vibrational analysis. Starting from these structures, a new geometry optimization was done using the 6-311G* basis set. The optimization step was followed by a NBO analysis and a Mulliken population analysis in order to have the charge and spin density on the atoms. Moreover, to see the influence of the basis set on the energy, we also performed single point computations on the optimized 6-311G* minima by using the larger 6-311++G** basis set. Throughout all unrestricted calculations for the triplet states, spin contamination was low with a deviation of $\langle S^2 \rangle$ from the theoretical value of 2 of at most 0.02.

3. Results and discussion

3.1. The G3-Factor

We performed preliminary calculations at the HF/6-31G* level of theory on the lowest singlet and triplet state of the G3-Factor. Due to the size of the molecules, higher level correlated methods were too computationally expensive. We calculated an optimized O—O bond length of 1.392 Å for the singlet state of the G3-Factor. We wanted to compare this value with experimental data. But the only experimental structure available is for the G1-Factor

(Fig. 1). This compound has two different alkyl functions (Me and Et) on C5 whereas the G3-Factor has two Me functions on C5. We assumed that the O—O bond length should have close values in the two molecules. The calculated value of 1.392 Å for the singlet state of the G3-Factor thus does not compare well with the experimental counterpart of 1.479 Å for the G1-Factor [27].

Surprisingly, the most stable conformation for the triplet state is more stable by 3.5 kcal/mol than the most stable conformation for the S_0 singlet state. This is unexpected, as the ground state of organic compounds (C, O, H atoms) is commonly a singlet. We conclude that the HF/6-31G* method is not adapted to our studies.

We further performed geometry optimizations at the B3LYP/6-311G* level of theory. This method is an interesting alternative. It gives good results with moderate computational expenses. The SCF absolute energies calculated for the G3-Factor (singlet and triplet state) are given in Table 1. The ground state of the G3-Factor is then a singlet. Some optimized bond lengths and angles are given in Table 2. For the singlet state, the cyclohexanone ring has a boat geometry slightly distorted. No chair geometry was found. It can be explained by strong steric effects between the CH_3 functions branched on the ring. The C5, C6, C7, C10 and O14 atoms are coplanar (C5—C6—C7—C10 and C6—C7—C10—O14 angles at a value of −179.7° of and 1.7°, respectively). The O3—O4 bond length is of 1.451 Å. This compares well with the experimental data of 1.479 Å for the similar G1 molecule [27]. The C6—C7 bond length, with a value of 1.332 Å, is characteristic of a double bond.

The net charges for some selected atoms are given in Table 3. It is well known that the Mulliken charges strongly depend of the used basis set. We thus performed a NBO analysis. The charge is of −0.32 e on O3 and O4. The global charge distribution shows a polarized molecule. It is confirmed by the calculated value of 3.69 D for the dipole moment.

Table 1
SCF absolute energies (in u.a.) and relative energies (in kcal/mol) for the G3-Factor and the G3Me and G3F derivatives (singlet and triplet states)

Level of theory	Compound	Multiplicity	Energy in a.u.	Relative energy in kcal/mol
B3LYP/6-311G*	G3	1	−921.839294	0
	G3	3	−921.780884	36.65
	G3Me	1	−961.146992	0
	G3Me	3	−961.092876	33.96
	G3F	1	−945.868118	0
	G3F	3	−945.813794	34.09
B3LYP/6-311++G**	G3	1	−921.883876	0
	G3	3	−921.826392	36.07
	G3Me	1	−961.191325	0
	G3Me	3	−961.137928	33.51
	G3F	1	−945.909611	0
	G3F	3	−945.856064	33.60

Optimized geometries for the B3LYP/6-311G* calculations and B3LYP/6-311++G** single point calculations on B3LYP/6-311G* optimized geometries.

Table 2
Optimized structural parameters for the singlet and triplet states of the G3-Factor and its derivatives, G3Me and G3F, at the B3LYP/6-311G* level of theory

Bond lengths in Å, angles in °	G3 singlet	G3 triplet	G3Me singlet	G3Me triplet	G3F singlet	G3F triplet
X1[a]—C2	1.409	1.431	1.409	1.441	1.401	1.439
C2—O3	1.421	1.294	1.418	1.301	1.388	1.281
O3—O4	1.451	2.547	1.455	2.583	1.453	2.605
O4—C5	1.442	1.375	1.436	1.372	1.437	1.371
C5—C6	1.500	1.521	1.499	1.522	1.500	1.526
C6—C7	1.332	1.334	1.331	1.333	1.331	1.333
C2—C7	1.513	1.527	1.510	1.540	1.505	1.526
C2—C13	1.546	1.664	1.558	1.615	1.544	1.609
C7—C10	1.492	1.497	1.492	1.500	1.490	1.499
C10—O14	1.211	1.209	1.212	1.208	1.211	1.208
X1—C2—O3	110.9	114.7	113.6	115.4	109.1	111.9
O3—C2—C7	109.1	117.4	110.3	114.0	111.7	116.7
O3—C2—C7—C6	18.8	1.7	11.6	−3.1	14.6	−3.0
C13—C2—C7—C6	136.6	119.6	128.0	118.6	135.8	122.3
O4—C5—C6—C7	13.8	−47.4	16.1	−42.8	14.6	−47.0
C5—C6—C7—C10	−179.7	174.5	179.3	173.6	179.4	174.5
C6—C7—C10—O14	1.7	24.0	11.7	28.9	2.0	21.7

Bond lengths in Å and angles in °.
[a] X1 = O for G3 and G3Me; X1 = F for G3F.

Table 3
Selected atomic net charges (q in e) for the G3, G3Me and G3F endoperoxides in their lowest singlet state and charge variation going from the singlet to the triplet state (Δq in e); B3LYP/6-311G* calculations and NBO analysis

Compound	X1[a]	C2	O3	O4	C5
Atomic net charges q in e					
Singlet G3	−0.75	+0.59	−0.32	−0.33	+0.26
Singlet G3Me	−0.61	+0.59	−0.32	−0.32	+0.26
Singlet G3F	−0.41	+0.69	−0.31	−0.30	+0.25
Δq[b] (singlet to triplet state) in e					
G3	−0.02	0.00	−0.12	−0.01	−0.04
G3Me	−0.01	−0.03	−0.08	−0.02	−0.04
G3F	−0.03	−0.04	−0.06	−0.03	−0.03

[a] X1 = O for G3 and G3Me; X1 = F for G3F.
[b] $\Delta q = q_{atom}$ (triplet state) − q_{atom} (singlet state).

The most stable conformation for the triplet state is higher in energy ($\Delta E = 36.65$ kcal/mol – see Table 1). The optimized geometry for the triplet state is different to the optimized geometry of the singlet state (Table 2). The O—O bond is of 2.547 Å and so is broken. The distances in the cyclohexanone ring remain unchanged except for the C2—C7 and C2—C13 bonds that are elongated (+0.014 and +0.118 Å, respectively). The C—O bonds in the endoperoxide ring are shortened (C2—O3: −0.127 Å and O4—C5: −0.067 Å). The C6—C7 double bond is preserved. Changes in the torsion angles show the reorganization of the molecule due to the rupture of the O—O bond in the triplet state. There is a rotation of the molecule around the C5—C6 bond (O4—C5—C6—C7 = 13.8° in the singlet state and −47.4° in the triplet state) and C6—C7 bond (C5—C6—C7—C10 = −179.7° in the singlet state and 174.5° in the triplet state).

The atomic net charges are given in Table 3. The O3 atom is slightly more negative than in the ground state ($\Delta q_{O3} = −0.12$ e). The spin densities for the triplet state given in Table 4 show a radical on O3 (+0.689 e) and O4 (+0.903 e).

We also found a less stable conformation associated with the triplet state. It is 26.66 kcal/mol higher in energy than the absolute minimum for the triplet state. The radical is here delocalized on the C6, C7, C10 and O14 atoms. The C7—C10 bond is reduced and the C6—C7 and C10—O14 bonds are elongated. The O—O bond is of 1.449 Å as in the ground state.

3.2. The G3Me and G3F compounds

We therefore studied the G3Me and the G3F derivatives (Fig. 1) at the B3LYP/6-311G* level of theory.

For the G3Me and G3F derivatives, the ground state is also a singlet (Table 1). Some structural parameters are given in Table 2. For the ground state, the O—O bond length is of 1.455 and 1.453 Å for the G3Me and G3F molecules, respectively. It is in agreement with the experimental value of 1.479 Å for the G1-Factor. Most of the geometrical parameters have the same value for the G3, G3Me and G3F compounds. When the OH function on C2 is substituted by a fluorine atom, there are small changes in the X1—C2 (−0.008 Å), C2—O3 (−0.033 Å) and C2—C7 (−0.008 Å) bonds.

The atomic net charges (Table 3) show a small change on the C2 atom related to the function on C2. We see the electro-withdrawing effect of the F atom. The calculated value of the dipole moment is of 3.69 D, 3.43 D and 3.23 D for the G3, G3Me and G3F compounds, respectively.

Table 4
Atomic spin densities (in e) for the G3, G3Me and G3F Factors (triplet state) at the B3LYP/6-311G* level of theory

Compound	Multiplicity	Atomic spin densities in e											
		X1[a]	C2	O3	O4	C5	C6	C7	C8	C9	C10	C13	O14
G3	Triplet	+0.024	−0.101	+0.689	+0.903	−0.092	−0.002	+0.090	+0.026	+0.100	−0.003	+0.255	+0.017
G3Me	Triplet	+0.016	−0.139	+0.757	+0.904	−0.092	−0.007	+0.133	+0.029	+0.103	−0.002	+0.184	+0.029
G3F	Triplet	+0.006	−0.123	+0.754	+0.910	−0.091	−0.014	+0.118	+0.034	+0.104	−0.003	+0.182	+0.028

[a] X1 = O for G3 and G3Me; X1 = F for G3F.

The most stable conformation for the triplet state is higher in energy ($\Delta E = 33.96$ and 34.09 kcal/mol – see Table 1) for the G3Me and G3F derivatives. Going from singlet to triplet, the O—O bond is stretched of 1.096 Å for the G3-Factor. For the G3Me and G3F derivatives, the O—O bond is more elongated with a change of +1.128 Å and +1.152 Å. There is also a rotation around the C6—C7 bond.

The atomic net charges (Table 3) show a very small influence of the function on the C2 carbon atom. The most stable conformations for the triplet state of the G3Me and G3F compounds correspond to [O O] molecules (see Table 4) as in the case of the G3-Factor.

We also wanted to evaluate the influence of the basis set on the singlet–triplet splitting. We calculate a value of 36.65, 33.96 and 34.09 kcal/mol at the B3LYP/6-311G* level and of 36.07, 33.51 and 33.60 kcal/mol at the B3LYP/6-311++G** level for the G3-Factor and the G3Me and G3F derivatives, respectively (Table 1). The small difference (2.5 kcal/mol) between the splitting of the G3-Factor and the splitting of its derivatives is in the same range than the method errors. It applies for a small influence of the nature of the function on C2, as we already notice from the comparison of the geometric parameters and charge distribution.

4. Conclusions

We present theoretical studies of the G3-Factor and two derivatives, the methylated G3 (G3Me) and the fluorinated G3 (G3F) endoperoxides. Our calculations show that:

(1) for the G3 endoperoxide, and its G3Me and G3F derivatives, the DFT computations for the ground state give bond lengths that compare well with available experimental results,
(2) the most stable conformations for the triplet state show a biradical [O O] electronic structure with an homolytic rupture of the O—O bond,
(3) substitution of the OH function by the OMe function or the F atom gives few variations of the geometrical parameters, charge distribution and spin density in the molecules.

These contributions give us new insights on the geometry of the G3-Factor and two derivatives, the G3Me and G3F endoperoxides.

Moreover, the singlet–triplet splitting is calculated for the three compounds. It will allow us to estimate the standard potential (E°) of the dissociative electron transfer process which is the first step in the action mechanism of antimalarial endoperoxides [23].

References

[1] S.R. Meshnick, T.E. Taylor, S. Kamchonwongpaisan, Microbiol. Rev. 60 (1996) 301.
[2] D.L. Klayman, Science 228 (1985) 1049.
[3] X.D. Luo, C.C. Shen, Med. Res. Rev. 7 (1987) 29.
[4] S.R. Meshnick, C.W. Jefford, G.H. Posner, M.A. Avery, W. Peters, Parasitol. Today 12 (1996) 79.
[5] O. Provot, B. Camuzat-Dedenis, M. Hamzaoui, H. Moskowitz, J. Mayrargue, A. Robert, J. Cazelles, B. Meunier, F. Zouhiri, D. Desmaële, J. d'Angelo, J. Mahuteau, F. Gay, L. Cicéron, Eur. J. Org. Chem. 8 (1999) 1935.
[6] G. Bernardinelli, C.W. Jefford, D. Maric, C. Thomson, J. Weber, Int. J. Quant. Chem, Quant. Biol. Symp. 21 (1994) 117.
[7] R.L. Donkers, M.S. Workentin, J. Phys. Chem. B 102 (1998) 4061.
[8] S. Tonmunphean, S. Irle, S. Kokpol, V. Parasuk, P. Wolschann, J. Molec. Struct. (Theochem.) 454 (1998) 87.
[9] A.K. Bhattacharjee, J.M. Karle, Molec. Eng. 8 (1999) 391.
[10] J. Gu, K. Chen, H. Jiang, H. Ji, J. Ruyun, J. Molec. Struct. (Theochem.) 459 (1999) 103.
[11] J. Gu, K. Chen, H. Jiang, J. Leszczynski, J. Molec. Struct. (Theochem.) 491 (1999) 57.
[12] S. Tonmunphean, V. Parasuk, S. Kokpol, J. Mol. Model. 7 (2001) 26.
[13] A.G. Taranto, J.W.M. de Carneiro, F.G. Oliveira, J. Molec. Struct. (Theochem.) 539 (2001) 267.
[14] A.G. Taranto, J.W.M. de Carneiro, F.G. Oliveira, M.T. de Araujo, C.R. Correa, J. Molec. Struct. (Theochem.) 580 (2002) 207.
[15] M.G.B. Drew, J. Metcalfe, F.M.D. Ismail, J. Molec. Struct. (Theochem.) 711 (2004) 95.
[16] R. Guha, P.C. Jurs, J. Chem. Inf. Comput. Sci. 44 (2004) 1440.
[17] C. Arantes, M.T. de Araujo, A.G. Taranto, J.W.M. de Carneiro, Int. J. Quant. Chem. 103 (2005) 749.
[18] M.G.B. Drew, J. Metcalfe, F.M.D. Ismail, J. Molec. Struct. (Theochem.) 756 (2005) 87.
[19] F. Najjar, M. Baltas, L. Gorrichon, Y. Moreno, T. Tzedakis, H. Vial, C. André-Barrès, Eur. J. Org. Chem. 17 (2003) 3335.
[20] F. Najjar, L. Gorrichon, M. Baltas, H. Vial, T. Tzedakis, C. André-Barrès, Bioorg. Med. Chem. Lett. 14 (2004) 1433.

[21] M. Gavrilan, C. André-Barrès, M. Baltas, T. Tzedakis, L. Gorrichon, Tetrahedron Lett. 42 (2001) 2465.

[22] F. Najjar, F. Fréville, F. Desmoulin, L. Gorrichon, M. Baltas, V. Vial, T. Tzedakis, C. André-Barrès, Tetrahedron Lett. 45 (2004) 6919.

[23] C. André-Barrès, et al., Chem. A Europ. J. (2006) doi:10.1002/chem.2006.00.445.

[24] Gaussian 03, Revision B.05, M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery, Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, and J.A. Pople, Gaussian, Inc., Pittsburgh, PA, 2003.

[25] A.D. Becke, J. Chem. Phys. 98 (1993) 5648.

[26] C. Lee, W. Yang, R.G. Parr, Phys. Rev. B 37 (1988) 785.

[27] M. Sterns, J. Cryst. Mol. Struct. 1 (1971) 373.