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Determination of preferred conformations of benzenetricarboxylic acids by means of genetic algorithm MNC for multi-modal search

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ARTICLE INFO

Article type:

Research article

Article history:

Received August 2017

Accepted October 2017

October 2017 Issue

Keywords:

Genetic algorithm MNC

Hemimellitic acid

Trimellitic acid

Benzene tricarboxylic

PES

Ortho-position

Multi-modal

ABSTRACT

The structures of benzenetricarboxylic acids: hemimellitic, trimellitic and trimesic have been investigated using genetic algorithm MNC. Calculated structures and heats of formation, using semi-empirical method AM1, are reported for all the lower-energy conformers of each species. In effect, hemimellitic acid and trimellitic in which the carboxyl groups are linked to the benzene ring in adjacent (*ortho*) positions assume a non-planar geometry, while trimesic acid which having no carboxylic groups in the *ortho*-position adopted a planar structure in the two most stable conformations.

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Capsule Summary: The geometry and energy of benzenetricarboxylic acids were studied by means of genetic algorithm based on the Multi-Niche Crowding method and coupled to the semi-empirical method AM1. The hemimellitic acid and trimellitic in which the carboxyl groups are linked to the benzene ring in adjacent (*ortho*) positions assume a non-planar geometry, whereas trimesic acid showed a planar structure in the two most stable conformations which was due lack of carboxylic groups at the *ortho*-position.

Cite This Article As: R. Tijar, M. Bourjila, A. EL Guerdaoui, B. El Merbouh, R. Drissi El Bouzaidi and A. El Gridani. Determination of preferred conformations of benzene tricarboxylic acids by means of genetic algorithm MNC for multi-modal search. Chemistry International 3(4) (2017) 477-486.

INTRODUCTION

The benzene polycarboxylic acids represent a family of organic compounds of great importance, because of their abundance in nature and their vital role in organic synthesis. Along with their various ester derivatives are used as intermediates in the preparations of plasticizers, resins, alkaloidal solutions, dyes, inks, adhesives, pharmaceutical

(antifungal) aids and in the preservation of foods, fats, and fruit juices (Alexander et al., 2006; Oprea et al., 1992; Read and Purves, 1952).

These acids are also of interest in the environmental chemistry of natural waters due to the formation of toxic metal-benzene polycarboxylic ligands. However, as they are formed by the drastic oxidation of graphite, coals, wood lignin and similar materials, they have geochemical and ecological significance (Giammar and Dzombak, 1998).

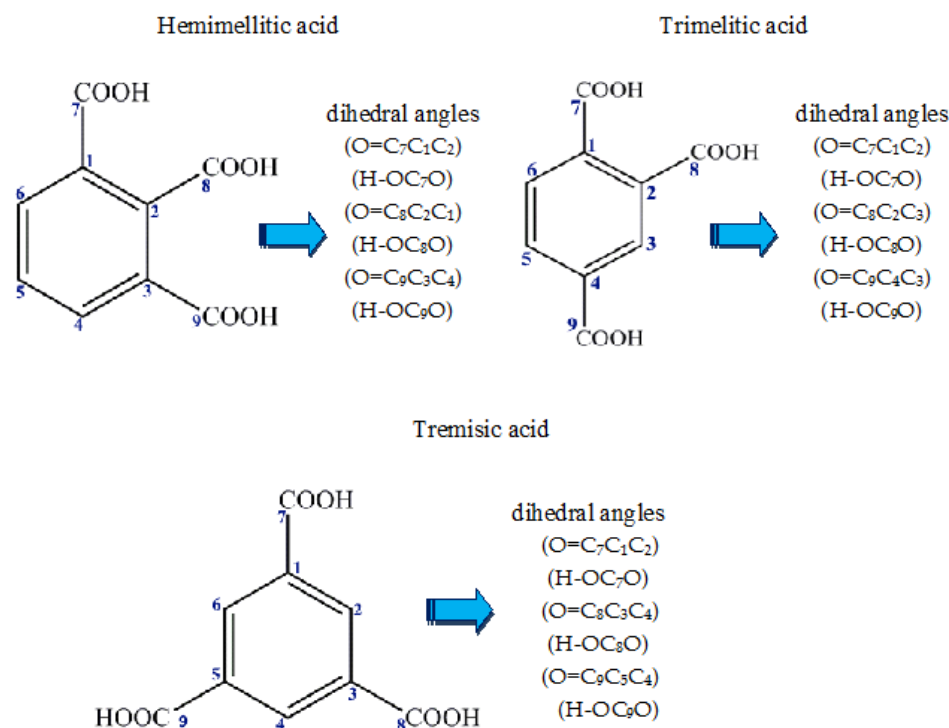


Fig. 1: Structural formulae and dihedre angles of hemimellitic acid, trimellitic acid, and trimesic acid

In this paper we became interested to study theoretically the geometry of isomeric benzenetricarboxylic acids: hemimellitic acid, trimellitic acid and trimesic acid (structural formulae are shown in Figure 1) which are chemically known as 1,2,3-benzenetricarboxylic; 1,2,4-benzenetricarboxylic and 1,3,5-benzenetricarboxylic, respectively. Several conformations of these molecular systems can be obtained by rotating the carboxyl groups and the hydroxyl groups around the C-C and O-C bonds, respectively. We are considering examining the most 10 stable conformations located on the potential energy surface of each species and discuss the influence of position of carboxylic groups on their structural rearrangements.

The aim of this work was to locate the global and local minima on the potential energy surface for hemimellitic, trimellitic and trimesic acids by using genetic algorithm MNC coupled to the semi-empirical method AM1 (GA-MNC/AM1). This technique, originally created and developed in our own laboratories (El Merbouh et al., 2014), has proven in the past to be quite productive in structural studies of a wide variety of organic compounds of low volatility including aminoacids (Bourjila et al., 2016; 2017; EL Guerdaoui et al., 2016) and carboxylic acids (Tijar et al., 2016).

Computational procedure

For exploring and exploiting the potential energy surface of an isolated molecular system, we are considering using the stochastic techniques that based on the simulation of a biological system, such as genetic algorithms (Holland, 1975).

These are based on the mechanisms of natural selection and genetic recombination. They work on a population point candidates, called chromosomes or individuals, in order to optimize an objective function or fitness. Each chromosome is composed of a set of elements called characteristics or genes. In the study of the conformational space problem of a given molecule, individuals correspond to conformations, the genes to dihedral angles and the fitness function to the heat of formation of the system.

The location of local minima in addition to the global minimum can be of great interest. To do this, we used the method known as Multi Niche Crowding (MNC) (Cedeño and al., 1994; Cedeño, 1995) that using the filler concept (Crowding) not only during the insertion of children in the population, but also when selecting individuals who will breed 'Crowding selection'. For each individual li of the population, a 'partner' lj is selected from a group of individuals of size Cs (Crowding size selection) taken randomly from the population.

The partner thus chosen should be as similar to li . During the replacement, the algorithm uses a technique called Worst Among Most Similar (WAMS) (Cedeño and Vemuri, 1999). It is first to choose randomly Cf groups of each individuals s . These groups are called 'Crowding Factor groups'. Subsequently an individual of each group is identified so that it is most similar to the child. Among these individuals Cf candidates for replacement, whichever is the less suitable is replaced by the child. The assessment criterion is the calculated heat of formation for the conformation generated by the AM1 method both during

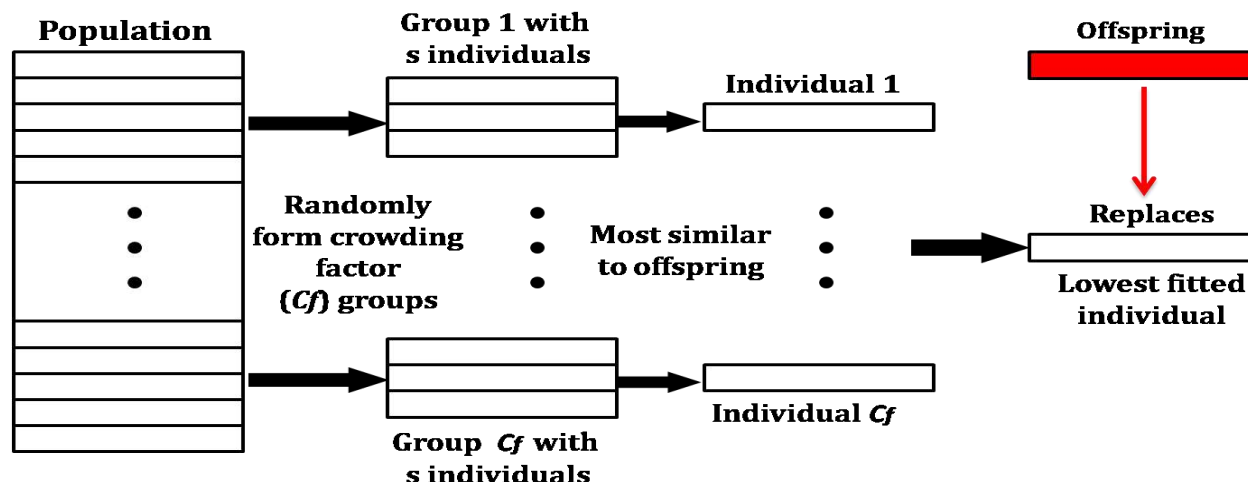


Fig. 2: Schematic illustration of worst among most similar

construction of the initial population and after application of crossover operators and possibly mutation. Once the algorithm converges after the maximum number of generation sets (500 generation), unconstrained optimization allows releasing the structure so that individuals of the same niche converge towards the corresponding minimum.

The genetic algorithm based on the MNC technique is implemented in a package of program interfaced with MOPAC in order to evaluate the quality of the individual to insert into the population in each iteration (El Merbouh et al., 2014). The criteria of evaluation are the energy of the molecule (the heat of formation in our case). The semi-empirical method AM1 is used to accomplish this task. The data file has been conceived so that a constraint is imposed to the values of the dihedral angles defining the degrees of freedom of the conformation generated beforehand randomly. This constraint permits indeed to calculate exactly the energy of the conformation generated during the construction of the initial population and after the application of crossover and eventually the mutation operators as well. Once the algorithm converges after the fixed maximum number of generation, an optimization without constraint is performed in order to release the

structure so that the individuals of the same niche converge to the corresponding minimum.

It has been discussed elsewhere that real encoding is ideally suited to handle problems in a continuous search space (Deb, 2001). The encoding scheme is so that the genome of each individual (conformation) is composed of n dihedral angles ($\phi_1, \phi_2, \dots, \phi_n$), in the case of a molecule of n degrees of freedom, whose values represent a location on the PES. The crossover operator used is called interval crossover (Cedeño, et al., 1994). In interval crossover, only one offspring is generated. For each pair of parent genes ϕ_1 and ϕ_2 , the offspring's gene is selected at random from the interval $[\phi_1 - \varepsilon/2, \phi_2 + \varepsilon/2]$ assuming without loss of generality that $\phi_1 < \phi_2$, if we use a real encoding as in our case. The parameter ε will be called in the following the parameter of interval crossover. The crossover operation is thus performed so that it generates an offspring close to the parents. The mutation is applied to the offspring, generated by the crossover operation, with a probability P_m , while permuting a couple of genes of the offspring selected at random. Table 1 regroups the different control parameters of the algorithm used in this study.

RESULTATS AND DISCUSSION

Conformational analysis of neutral hemimellitic acid

The calculations carried out using the genetic algorithm MNC coupled to the AM1 method on the neutral hemimellitic acid have revealed the existence of several possible conformations.

Figure 3 shows the 10 lowest energy structures localised and characterized as minima on the PES of neutral hemimellitic acid. Table 2 summarize the heats of formation and dihedr angles calculated by means of AM1 method, also shown in the energy difference of the different conformers as compared with the most stable one.

Table 1: Control parameters of the MNC genetic algorithm

Population size	500
Crowding selection size (C_s)	25
Crowding Factor size (C_f)	3
Crowding size (s)	25
Interval crossover parameter (ε)	10
Crossover Probability (P_c)	1.0
Mutation probability (P_m)	0.06

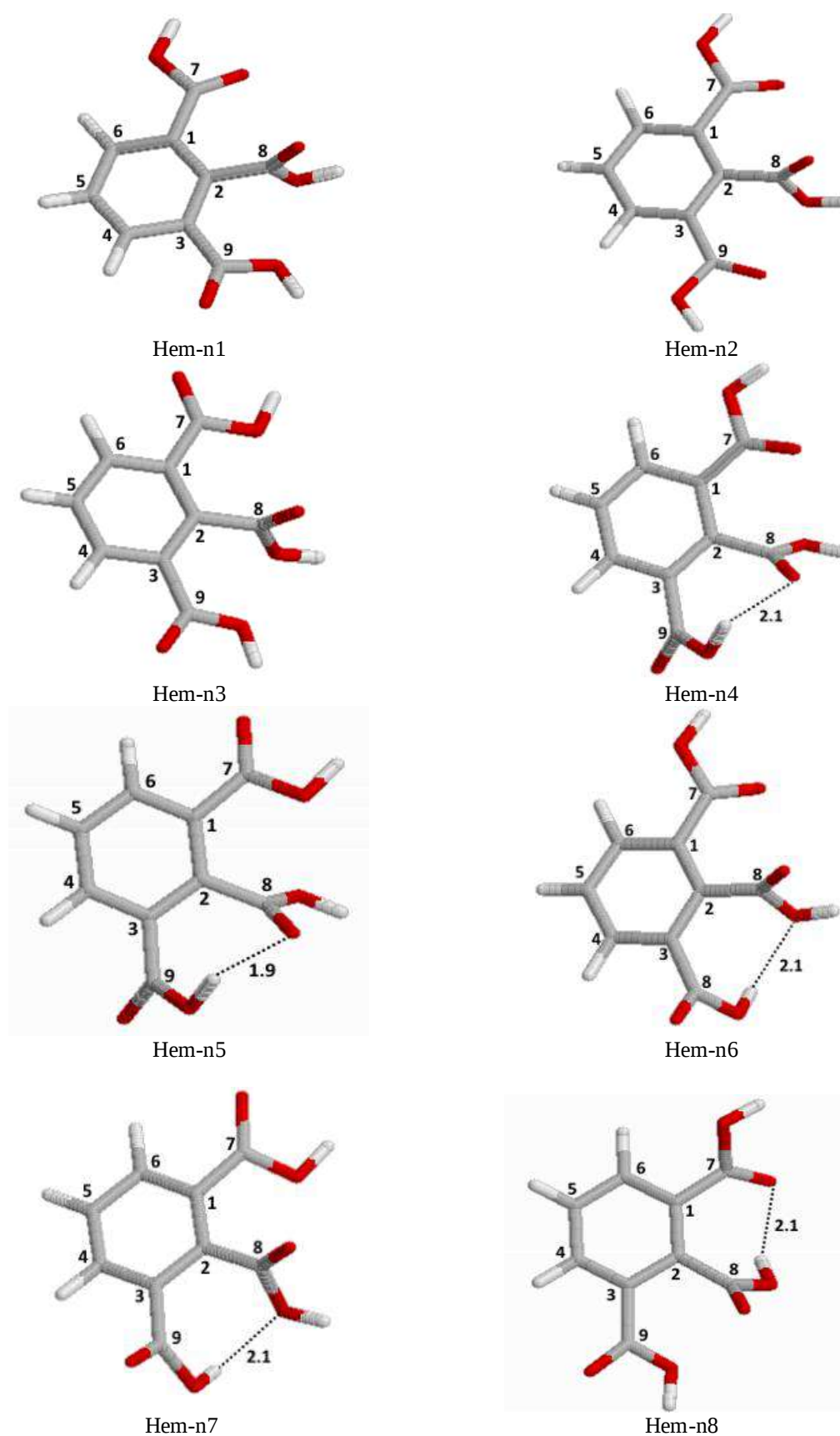


Fig. 3: The 10 lowest energy structures located on the PES of neutral hemimellitic acid by GA-MNC/AM1

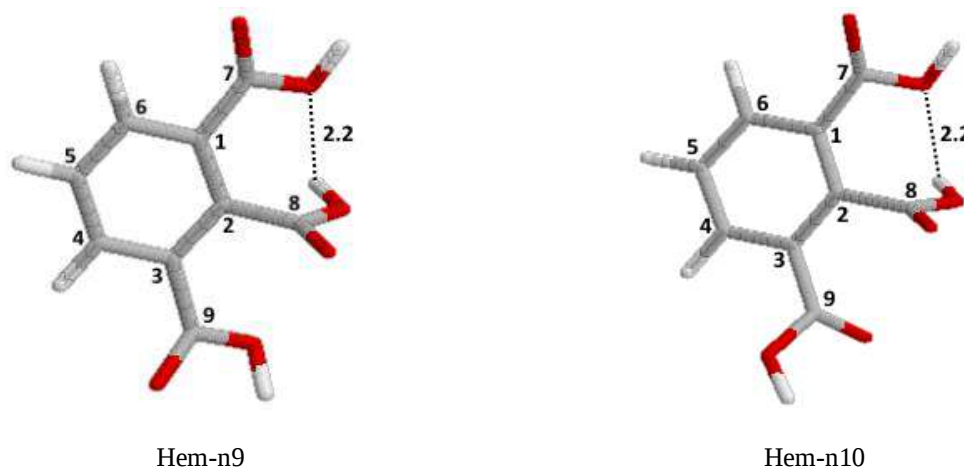


Fig. 3: Continue...

Regarding hemimellitic acid, the calculations showed that rotation around the C–C bond is not favorable in this isomer. Rotation around the C–C bond is sterically hindered by the neighboring carboxyl groups. The steric repulsion between three carboxyl groups gives rise to a high rotation barrier. By inspecting the geometries of the all stable conformers of hemimellitic acid, it can be concluded that none is planar.

As seen from table 2, the conformers denoted Hem-n1, Hem-n2 and Hem-n3 have less energy values, making them energetically more favorable and hence structurally more stables. Indeed, their heats of formation are respectively -234.9, -234.8 and -234.7 kcal/mol. Indeed, these conformations have practically equal energies where their ΔH_f are -234.9, -234.8 et -234.7 Kcal/mol, respectively. In these three stables conformations, AM1 Calculations show that the carboxyl group bonded to C₂ lies perpendicular to the benzene ring (the corresponding dihedral angle is close to 90°) whereas the two other carboxyl groups C₁-COOH and C₃-COOH lie in the plane of the benzene ring. This can be explained by the fact that the three close-lying voluminous carboxyl groups cannot all be positioned in the same plane. Thus, at least one of them has to assume an off-planar orientation. In order to have an as-large-as-possible resonance stabilization, the non-planarity is not equally shared among the three carboxyl groups, but two of them (at the extremities) remain in plane, thus maximizing their resonance effect, whereas one (the middle one) is then bent 90° (thus minimizing steric repulsion). In addition, the rotation of this group around the corresponding C–C bond is sterically hindered.

The other conformers Hem-ni/ i = 4,5,.....,10 are corresponding to the local minima on the PES of neutral hemimellitic acid. Their heats of formation are varied from -231.9 kcal/mol to -230.9 kcal/mol and they are less stable from 3 to 4 kcal/mol compared to the reference structure Hem-n1. AM1 calculations show that the three carboxyl groups are lie out of the plane of the benzene ring, where a hydrogen bond is established between the proton of trans-

COOH group and the oxygen atom of the group adjacent. In fact, this bond is formed between the proton of C₃-COOH group and the oxygen atom of C₂-COOH group in Hem-n4, Hem-n5, Hem-n6 and Hem-n7, while it is formed between the proton of C₂-COOH group and the oxygen atom of C₁-COOH group in the conformations Hem-n8, Hem-n9 and Hem-n10.

The results obtained through Zoran et al. (Zoran et al, 2004) show that neutral hemimellitic acid has four distinct stable structures named 4a, 4b, 4c et 4d, where the C₂-COOH group is perpendicular to the benzene plane, whereas the two other carboxyl groups are in the same plane of the benzene ring. These structures have similar values of energy, varying in the narrow interval between -982.8 KJ/mol and -983.5 kJ/mol. Indeed, the structures 4a, 4b and 4d correspond successively to the structures Hem-n1, Hem-n2 and Hem-n3 obtained by GA-MNC/AM1.

Conformational analysis of neutral trimellitic acid

The conformational analysis of neutral trimellitic acid shows the presence of several minima on its PES of which the 10 structures considering the most stable are grouped in Figure 4. The corresponding heats of formation as well as the relative energies and the dihedral angles optimized using the AM1 method is recorded (Table 3).

The results of calculations obtained by the GA-MNC/AM1 method, reveals that trimellitic acid has non-planar structures. Generally, the both ortho carboxyl groups C₁-COOH and C₂-COOH are out the plane of the benzene ring, whereas the other carboxyl group C₄-COOH lie in the plane of the benzene ring.

From the results indicated in the Table 3, it is deduced that the most stable structures for neutral trimellitic acid are Trim-n1, Trim-n2, Trim-n3, Trim-n4, Trim-n5, Trim-n6, Trim-n7 and Trim-n8. These structures are energetically close, where their heats of formation are -238.7, -238.6, -238.5, -238.4, -238.4, -238.4, -238.3 and -238.2 kcal/mol, respectively.

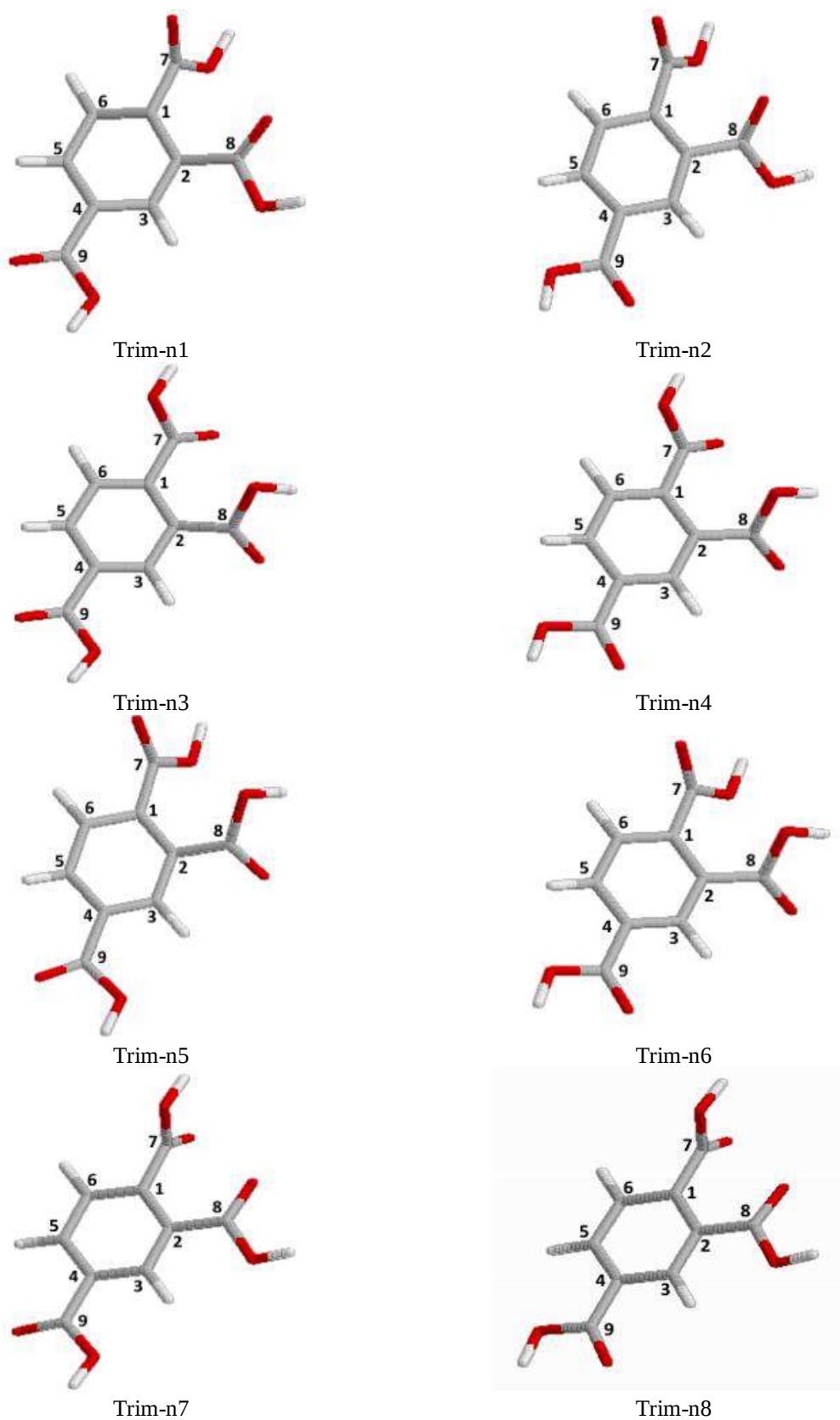


Fig. 4: The 10 lowest energy structures located on the PES of neutral trimellitic acid by GA-MNC/AM1

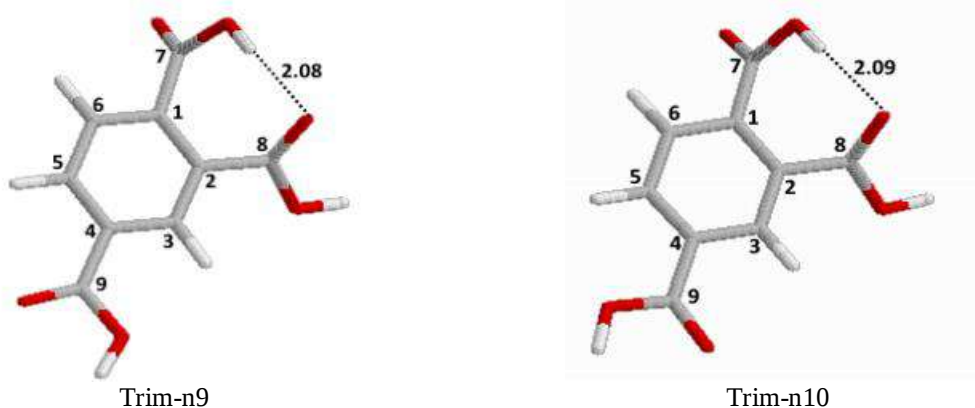


Fig. 4: Continue....

This allows us to say that one of these conformations can be the global minimum on the PES of the neutral trimellitic acid.

Referring to the geometrical parameters, we see that in the conformations Trim-n1, Trim-n2, Trim-n3 and Trim-n4, the two carbonyls of C₁-COOH and C₂-COOH lie in the same sides of the plane of the benzene ring. In fact, this carbonyls are below the benzene ring by about -121° and -162°, respectively, in the conformations Trim-n1 and Trim-n2, while they are above the benzene ring by about 37.4° and 37°, respectively, in the conformations Trim-n3 and Trim-n4 (Table 3). We also noted that the difference between Trim-n1 and Trim-n2 and between Trim-n3 and Trim-n4 is located only in the position of the C₄-COOH group.

Concerning the conformations Trim-n5 and Trim-n6, the two C=O groups of C₁-COOH and C₂-COOH lie on opposite sides of the plane of the benzene ring, where their angles of deviation are -136.24° and 28.10°, respectively, in the conformation Trim-n5 and -138.11° and 30.55°, respectively, in the conformation Trim-n6. For the conformations Trim-n7 et Trim-n8, our calculations show that the carboxylic group C₁-COOH is almost perpendicular to the plane of the benzene ring, whereas the carboxyl group C₂-COOH is in the same plane as the benzene ring. Otherwise, AM1 calculations show that the two conformations Trim-n9 and Trim-n10 have the same energy -235.9 kcal/mol, and they are less stable by 2.8 kcal/mol compared to reference structure Trim-n1. These two structures differ only in the position of the carboxyl group C₅-COOH, and they are characterized by the presence of an intramolecular hydrogen bond (about 2.09 Å) which occurs between the proton of C₁-COOH and the carbonyl of C₂-COOH.

Conformational analysis of neutral trimesic acid

Table 4 summarize the structural and energetic parameters calculated for the 10 lowest energy minima located on the potential energy surfaces of the neutral trimesic acid by GA-MNC/AM1. The geometries corresponding to these minima are given in Figure 5.

In the AM1 calculation, the first two minima called Tris-n1 and Tris-n2 are the lowest energy structures located on the PES of the neutral trimesic acid, so one of them can probably be the global minimum. Indeed, the energy difference between Tris-n1 and Tris-n2 is slightly lower (0.1 kcal/mol), where their heats of formation are -244.7 kcal/mol and -244.6 kcal/mol, respectively. The others conformations Tris-n3,4,.....10 represent local minima and they are less stable from 6 kcal/mol to 13.1 kcal/mol relative to the reference structure Tris-n1.

At the structural level, we note that the conformers Tris-n1 and Tris-n2 are the only planar structures detectable on the PES of the neutral trimesic acid. This implies that the steric hindrance is of little importance and that planarity is caused by the tendency to maximize the resonance effect.

Regarding conformers Tris-n3, Tris-n4, Tris-n5 and Tris-n6, our calculations showed that they have similar values of energy, varying in the narrow interval between -238.7 and -238.4 kcal/mol. Their geometry are non-plane, where the two carboxyl groups C₃-COOH and C₅-COOH remain in plane (thus maximizing their resonance effect) whereas the carboxyl group C₁-COOH which adopts a trans form assumes an off-planar orientation. The less stability of these conformers may be explained by van der Waals interaction between hydrogen of the C₁-COOH group and hydrogen of phenyl ring in the ortho position. Otherwise, the conformers Tris-n7, Tris-n8, Tris-n9 and Tris-n10 differ insignificantly in energy (by only 1.2 kcal/mol), and they are more unstable than Tris-n1 in the range of 11.9-13.1 kcal/mol. Structurally, these conformations are also adopted a non-planar structure, where the carboxyl group C₃-COOH is coplanar with the phenyl ring, while both carboxyl groups C₁-COOH and C₅-COOH which have adopted a trans forms lie out of the plane of the benzene ring. In fact, the less stability of these conformations can be explained by van der Waals interaction between hydrogen of the C₁-COOH and C₅-COOH groups and hydrogen atoms of phenyl ring in the ortho positions.

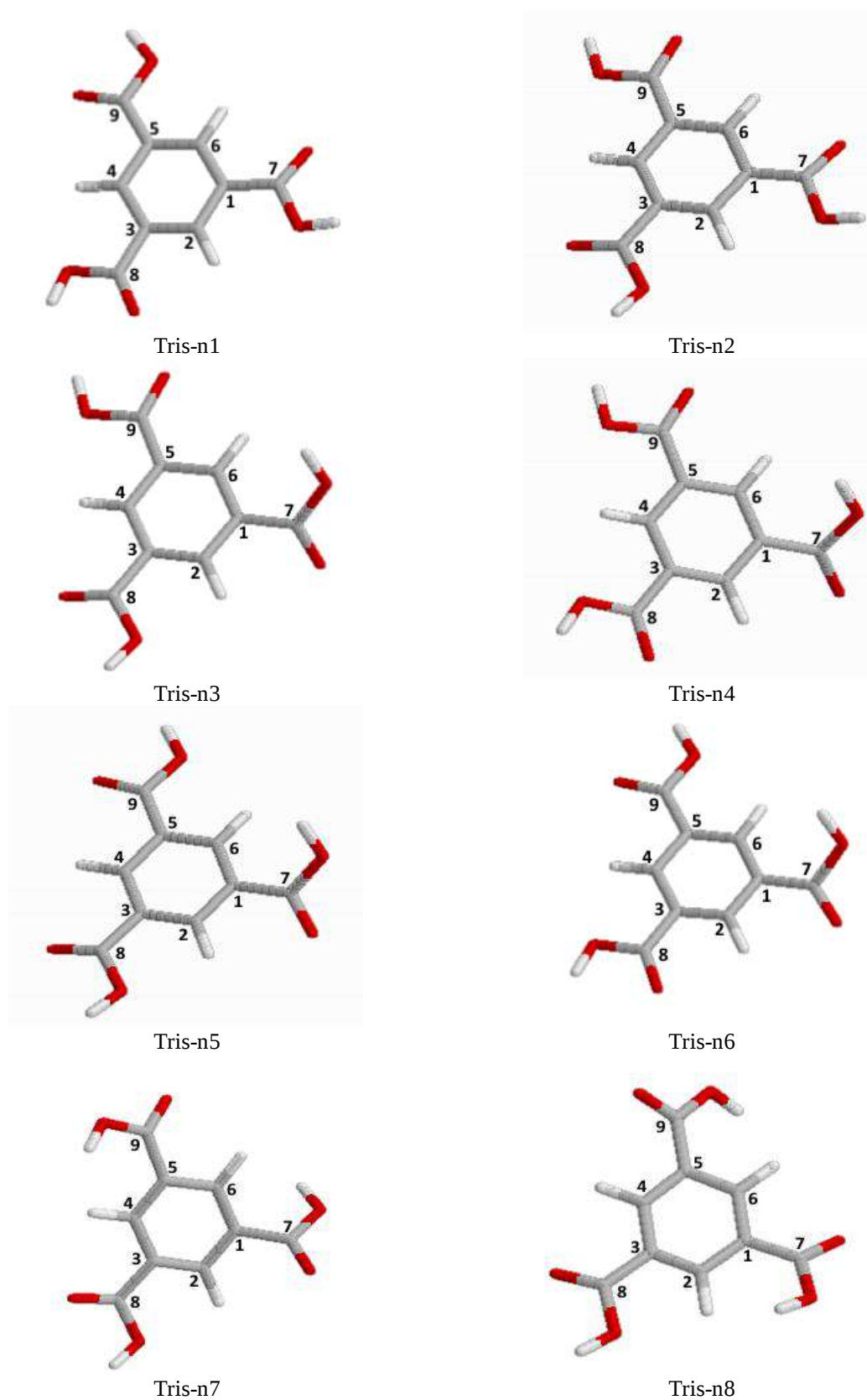


Fig. 5: The 10 lowest energy structures located on the PES of neutral trimesic acid by GA-MNC/AM1



Fig. 5: continue...

Table 2: Heats of formation ΔH_f (in kcal/mol), relative energy $\Delta(\Delta H_f)$ (in kcal/mol) and dihedral angles (in degree) of the 10 lowest energy minima obtained for hemimellitic acid by GA-MNC/AM1

	ΔH_f	$\Delta(\Delta H_f)$	O=C ₇ C ₁ C ₂	H-OC ₇ O	O=C ₈ C ₂ C ₁	H-OC ₈ O	O=C ₉ C ₃ C ₄	H-OC ₉ O
Hem-n1	-234.9	0.0	-1.95	-0.05	96.35	-3.37	-7.98	-3.10
Hem-n2	-234.8	0.1	4.68	-0.44	89.11	0.08	174.54	0.45
Hem-n3	-234.7	0.2	179.70	0.84	94.18	-0.25	-6.59	-2.49
Hem-n4	-231.9	3	-17.3	1.00	117.20	-7.50	49.50	177.39
Hem-n5	-231.6	3.3	162.44	-2.13	117.76	-4.09	50.37	177.19
Hem-n6	-231.4	3.5	18.19	-1.30	75.86	-4.49	-49.74	178.88
Hem-n7	-231.4	3.5	-160.01	4.50	68.56	-1.48	-53.39	179.51
Hem-n8	-231.4	3.5	37.61	-2.18	114.78	-170.73	-28.68	-6.54
Hem-n9	-231.3	3.6	-145.12	5.79	106.02	173.94	-26.97	-4.80
Hem-n10	-230.9	4	-148.42	-2.95	104.49	173.87	147.84	-2.82

Table 3: Heats of formation ΔH_f (in kcal/mol), relative energy $\Delta(\Delta H_f)$ (in kcal/mol) and dihedral angles (in degree) of the 10 lowest energy minima obtained for trimellitic acid by GA-MNC/AM1

	ΔH_f	$\Delta(\Delta H_f)$	O=C ₇ C ₁ C ₂	H-OC ₇ O	O=C ₈ C ₂ C ₃	H-OC ₈ O	O=C ₉ C ₄ C ₃	H-OC ₉ O
Trim-n1	-238.7	0.0	-121.56	7.8	-162.11	-1.0	-178.62	0.1
Trim-n2	-238.6	0.1	-121.35	8.1	-162.61	-0.7	0.88	0.0
Trim-n3	-238.5	0.2	37.41	-2.3	36.97	6.6	-178.52	0.4
Trim-n4	-238.4	0.3	37.31	-2.4	37.60	6.4	2.35	-0.14
Trim-n5	-238.4	0.3	-136.24	4.9	28.10	3.8	-178.48	0.3
Trim-n6	-238.4	0.3	-138.11	4.9	30.55	3.5	1.98	0.0
Trim-n7	-238.3	0.4	86.49	-6.4	-170.53	-0.6	-179.36	0.3
Trim-n8	-238.2	0.5	94.47	-7.17	-174.85	-0.4	0.40	-0.1
Trim-n9	-235.9	2.8	123.48	-171.6	-143.51	-1.6	-179.34	-0.2
Trim-n10	-235.9	2.8	123.74	-172.0	-143.05	-1.3	1.61	-0.3

Table 4: Heats of formation ΔH_f (in kcal/mol), relative energies $\Delta(\Delta H_f)$ (in kcal/mol) and dihedral angles (in degree) of the 10 lowest energy minima obtained for trimesic acid by GA-MNC/AM1

	ΔH_f	$\Delta(\Delta H_f)$	O=C ₇ C ₁ C ₂	H-OC ₇ O	O=C ₈ C ₃ C ₄	H-OC ₈ O	O=C ₉ C ₅ C ₄	H-OC ₉ O
Tris-n1	-244.7	0.0	179.14	0.04	179.34	0.01	0.90	0.01
Tris-n2	-244.6	0.1	-179.94	-0.05	-0.08	0.02	179.97	-0.04
Tris-n3	-238.7	6	29.44	-175.54	0.68	0.43	178.14	0.23
Tris-n4	-238.6	6.1	30.35	-175.06	-178.08	-0.28	178.66	0.28
Tris-n5	-238.5	6.2	30.25	-174.48	0.67	0.44	-1.09	-0.54
Tris-n6	-238.4	6.3	31.41	-174.69	-178.30	-0.26	-1.08	-0.57
Tris-n7	-232.8	11.9	-34.01	174.76	-3.92	-0.23	-149.25	-175.40
Tris-n8	-232.5	12.2	148.07	174.91	3.51	0.22	32.62	-174.15
Tris-n9	-232.4	12.3	-145.81	-174.60	-3.79	-0.24	-147.09	-175.17
Tris-n10	-231.6	13.1	-37.56	174.16	-3.33	-0.18	-36.77	173.19

CONCLUSIONS

The main conclusion of this research is that the presence of two carboxyl groups ortho to one another is sufficient to make the molecule non-planar in all of its structures. This is appears clearly in the case of the hemimellitic acid and trimellitic acid. Whereas, trimesic acid that has no carboxylic groups in the ortho-position (carboxyl groups are mutually in meta positions), and thus sufficiently removed from each other, are planar in their most stable conformations.

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