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Conformational space analysis of neutral and deprotonated forms of benzoic acid, salicylic acid and phthalic acid using a genetic algorithm

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ABSTRACT

In this paper we present a detailed conformational study of three aromatic systems constituting the basic units of humic acids namely benzoic acid, salicylic acid and phthalic acid. The genetic algorithm, based on the multi-niche crowding (MNC) method, coupled with the semi-empirical AM1 method is used to analyze the potential energy surface (PES) of these systems. This algorithm, implemented in the MOPAC program and piloted by scripts, provides better detection of global and local minima in a reasonable time. The results obtained are comparable with those of previous studies. Three factors can be cited to justify the stability of conformations i.e. effects of conjugation, steric interactions and intramolecular hydrogen bonds.

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Capsule Summary: The genetic algorithm based on the MNC method is used with the semi-empirical method AM1 in order to scan the potential energy surfaces of benzoic acid, salicylic acid and phthalic acid. Three factors can be cited to justify the stability of conformations i.e., effects of conjugation, steric interactions and intramolecular hydrogen bonds.

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INTRODUCTION

Humic acids are the major components of the most common natural organic matter in the soil and in fresh water and water Sea (Witwicki and Jezierska, 2012). These naturally occurring acids play a major ecological and geochemical role. Their molecular structure is very complex and poorly defined which makes their full structural characterization extremely

difficult. Many efforts have been made and many available techniques and methods have been used to derive an average structure of these acids (Susan et al., 1996; Yu-hui and Ting, 1997; Mamadou et al., 2003).

Previously, they have been described as macromolecular polymers containing various functional groups such as carboxylic, phenolic, hydroxyl and carbonyl. Recently, based on experimental data, it has been suggested that such materials are likely rather supramolecular forming

into smaller molecular units interacting by non-covalent forces such as van der Waals forces and hydrogen bonds (Markus et al., 2004; Tossell, 2009). These molecular units are considered models of humic compounds, which are used to perform theoretical and experimental research in order to study the structure of these macromolecules, their physicochemical properties and their reactivity.

Irina et al. (1998) used model compounds of humic substances consisting of aliphatic chains and aromatic carboxylic acids and their hydroxylated derivatives in their experimental research (Irina et al., 1998). Tossell used

complex quinone-hydroquinone as model molecule of humic acids in order to study its structure, stability and UV-visible spectra (Tossell, 2009). From us and to provide a database for a deeper understanding of humic acid (HA) and its acid-base properties, a set of model compounds will be studied in our work by the semi-empirical method AM1. In this article, the choice fell on benzoic acid, phthalic acid and salicylic acid. They are the simplest benzene derivatives whose chemical structure is shown in Figure 1. Furthermore, the first acid (BA), industrially product from toluene, is used primarily as a preservative and as a food additive, and inhibits the growth

Table 1: Relative energies (in kcal /mol) and dihedral angles (in Å) of conformations of benzoic acid

Method	Bn-AC-n1		Relative energies	Bn-AC-n2	
	O ₈ -C ₇ -C ₁ -C ₂	H-O ₉ -C ₇ -O ₈		O ₈ -C ₇ -C ₁ -C ₂	H-O ₉ -C ₇ -O ₈
AM1	1.1	0.0	5.4	33.7	175.9
HF	0.01 ^a	-	8.08 ^a	24.94 ^a	-
	-	-	8.07 ^b	-	-
DFT	0.00 ^a	-	6.81 ^a	22.69 ^a	-
MP2	0.03 ^a	-	5.98 ^a	30.70 ^a	-
	0.0 ^b	0.0 ^b	5.97 ^b	30.00 ^b	-

^a(Alireza et al., 2011), ^b(Kirsten et al., 2006)

Table 2: Relative stability of conformations of salicylic acid (in kcal /mol)

Conformation	Relative stability						
	AM1	HF/6-31G** ^a	DFT/B3LYP/6-31G**// AM1 ^a	AM1 ^a		DFT/B3LYP/6-311G + (d, p) ^b	CNDO/2 ^c
				RHF	PECI = 8		
S-AC-n1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S-AC-n2	1.6	3.7	3.5	1.6	1.6	3.4	1.8
S-AC-n3	5.5	-	-	-	-	10.7	12.7
S-AC-n4	5.7	-	-	-	-	11.1	13.4
S-AC-n5	5.8	-	-	-	-	-	-
OS-AC-n6	7.0	-	-	-	-	9.7	14.0
S-AC-n7	8.1	-	-	-	-	-	-
S-AC-n8	10.5	-	-	-	-	-	-

^a(Suresh et al., 2014), ^b(Fiedler et al., 2006), ^c(Catalan and Fernandez-Alonso, 1973)

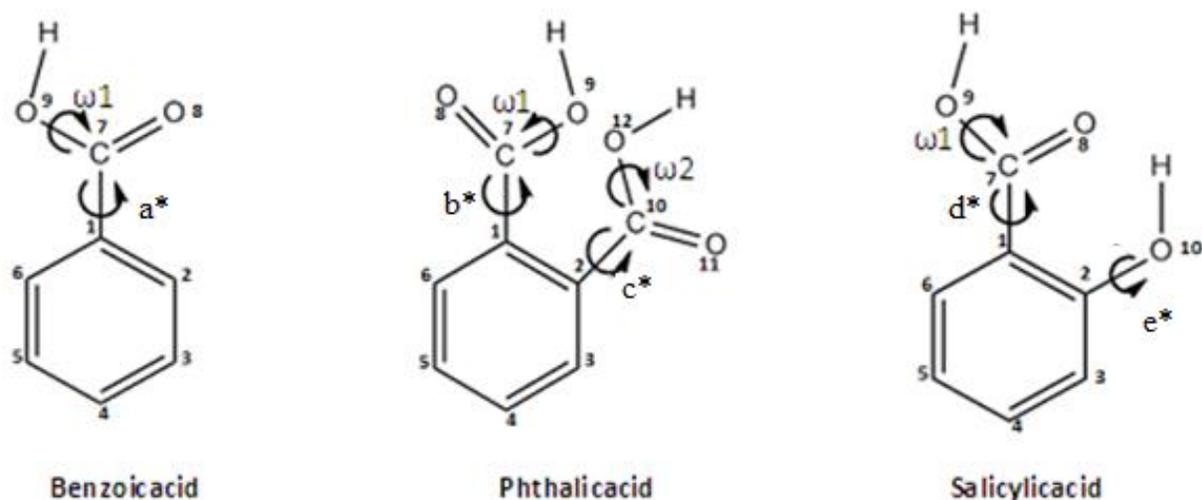


Fig. 1: The chemical structure and nomenclature of the three conformations of benzoic, phthalic and salicylic acids, where a^* , b^* , c^* , d^* and e^* are representing $\phi 1$, $\phi 1$, $\phi 2$, $\phi 1$ and $\phi 2$, respectively

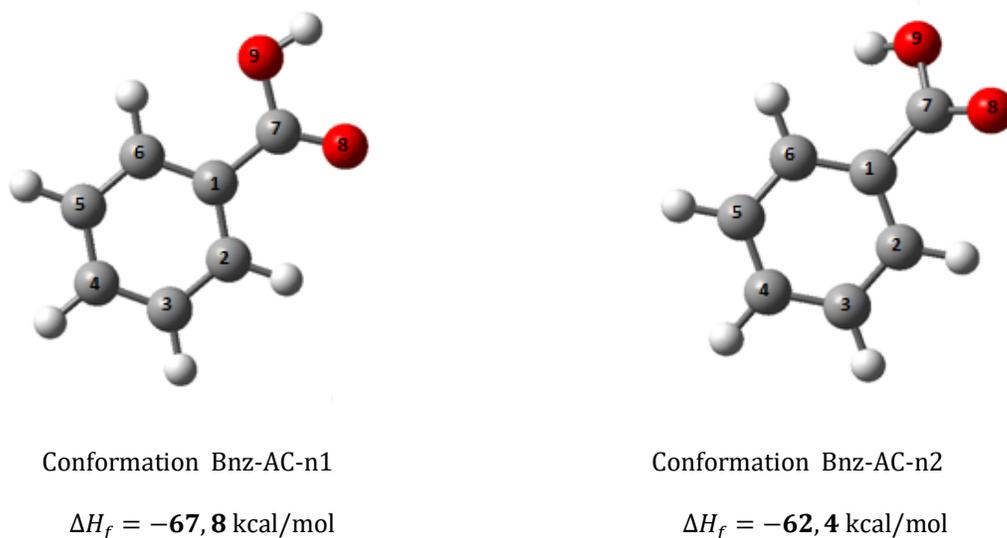


Fig. 2: Stable conformations of the PES of benzoic acid calculated using the method AM1

of yeast and certain bacteria. It is found naturally in certain plants and in particular, it is one of the main constituents of benzoin, aromatic resinous substance used in pharmacy. The second acid (PTA) is the basis of a very rich chemistry with multiple applications, from the feedstock to the textile fiber, from additives for polymers to the development of innovative materials. Its main application relates to the production of esters, amides and polymers. The third acid (SA) is widely used in organic synthesis and it functions as a plant hormone. It is known for its ability to relieve pain and reduce fever (Úlo et al., 1994; Suresh et al., 2014). Recently, salicylic acid was used primarily as an intermediate in the production of agrochemicals, dyes and dye products.

Our objective in this paper is to study theoretically the molecular structure and the stability of these three acids in neutral and deprotonated states. In addition, we will deduce the structural and energy changes produced during the substitution of the benzene hydrogen atom located ortho to the carboxyl group of the benzoic acid by another carboxyl group on one hand and by a hydroxyl group on the other hand. In addition, chemically, it should be noted that the hydrogen bond is a fundamental key to understanding the chemical structure, enzyme catalysis, physico-chemical properties, the assembly phenomenon and the function of the molecule (Alireza et al., 2011). For this reason, special attention was given to the intramolecular hydrogen bonds

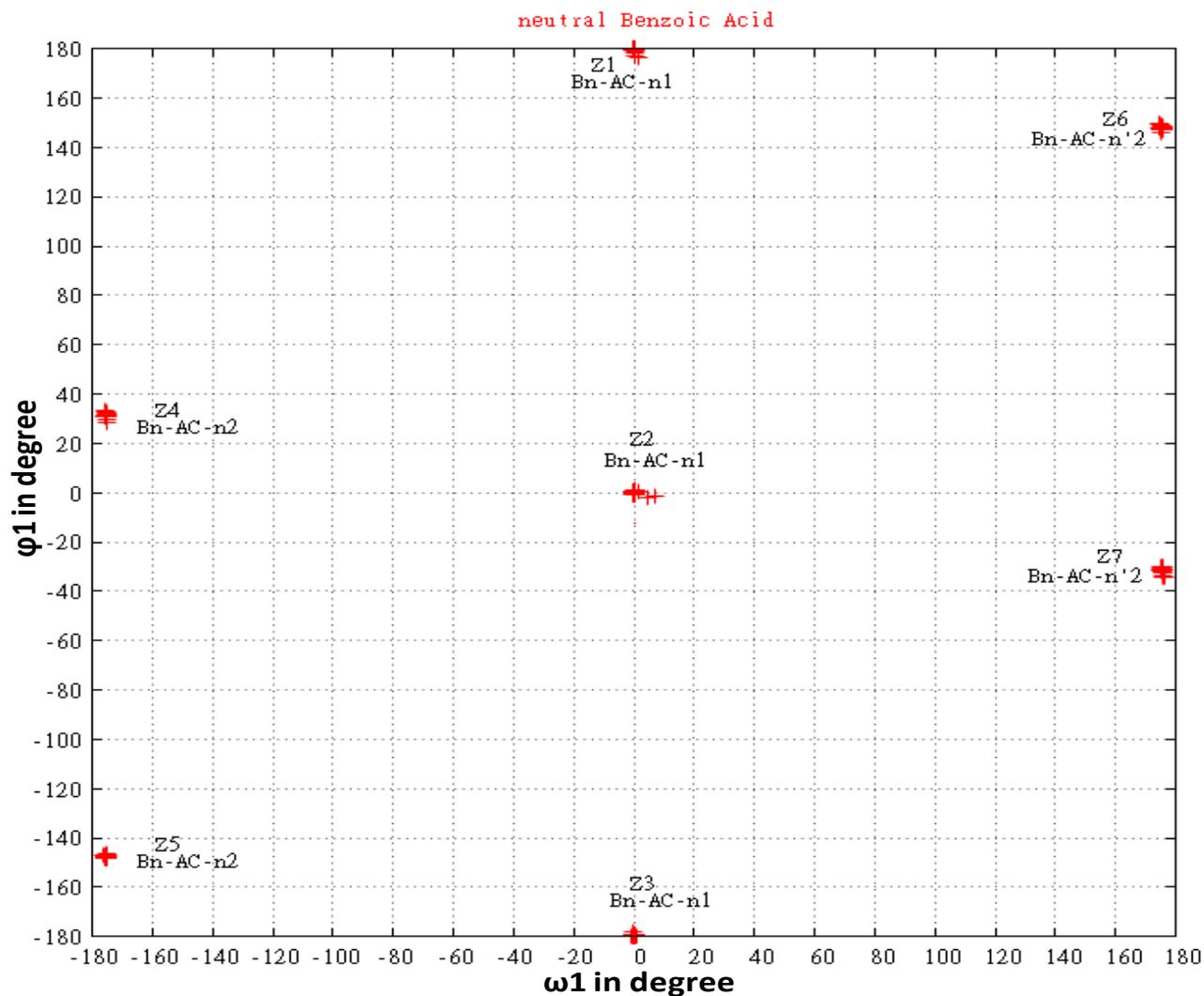


Fig. 3: Distribution of all conformations detected on the PES of neutral benzoic acid depending to ω_1 and ϕ_1

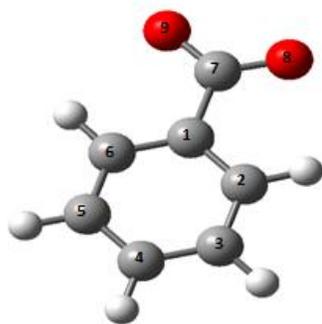


Fig. 4: The only conformation detected on the PES of the anion benzoate

and their effect on the stability of the molecule in the gas phase.

For this purpose and to explore the PES of these systems at low cost and to consider all possible conformations, we used the stochastic algorithm encoded by B. El Merbouh et al. which takes into consideration the different intramolecular effects (El Merbouh et al. , 2014). This algorithm has been used in a previous study to analyze the potential energy surface of some polypeptides containing cysteine (Bourjila et al., 2016).

COMPUTATIONAL PROCEDURE

The approach adopted in this work, published recently by B. El Merbouh et al. (2014), for exploring the potential energy surface of an isolated molecular system is to use stochastic techniques based on the simulation of a biological system, such as genetic algorithms (Holland, 1975). These are based

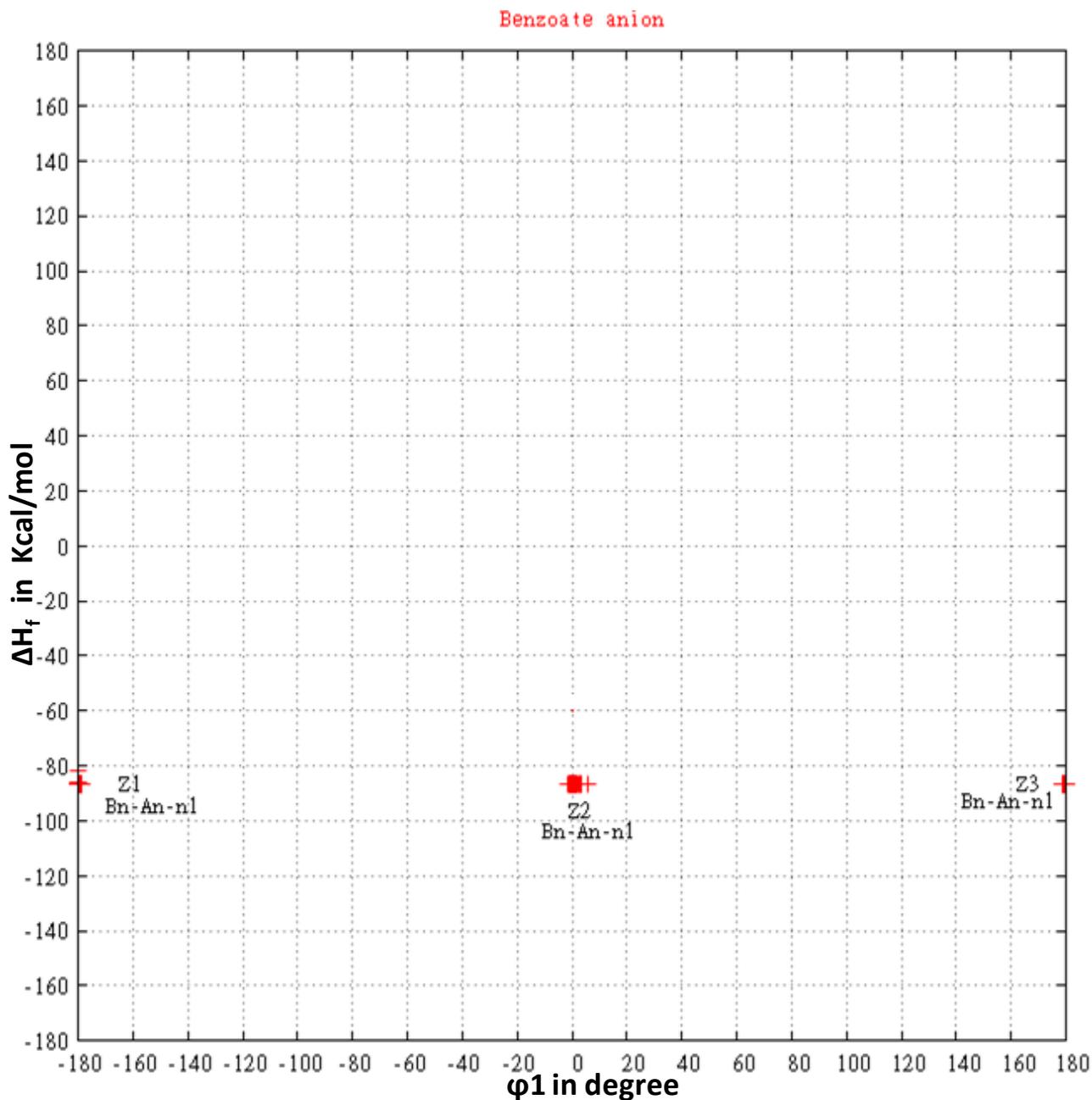


Fig. 5: Distribution of all conformations detected on the PES of the benzoate anion depending on ϕ_1 and ΔH_f

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) proposed by Cedeño et al. (Cedeño and al., 1994; Cedeño, 1995) 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 I_i of the population, a 'partner' I_j is selected from a group of individuals of size C_s (Crowding size selection) taken randomly from the population. The partner thus chosen should be as similar to I_i . During the replacement, the algorithm uses a technique called Worst Among Most Similar (WAMS) (Cedeño and Vemuri, 1999).

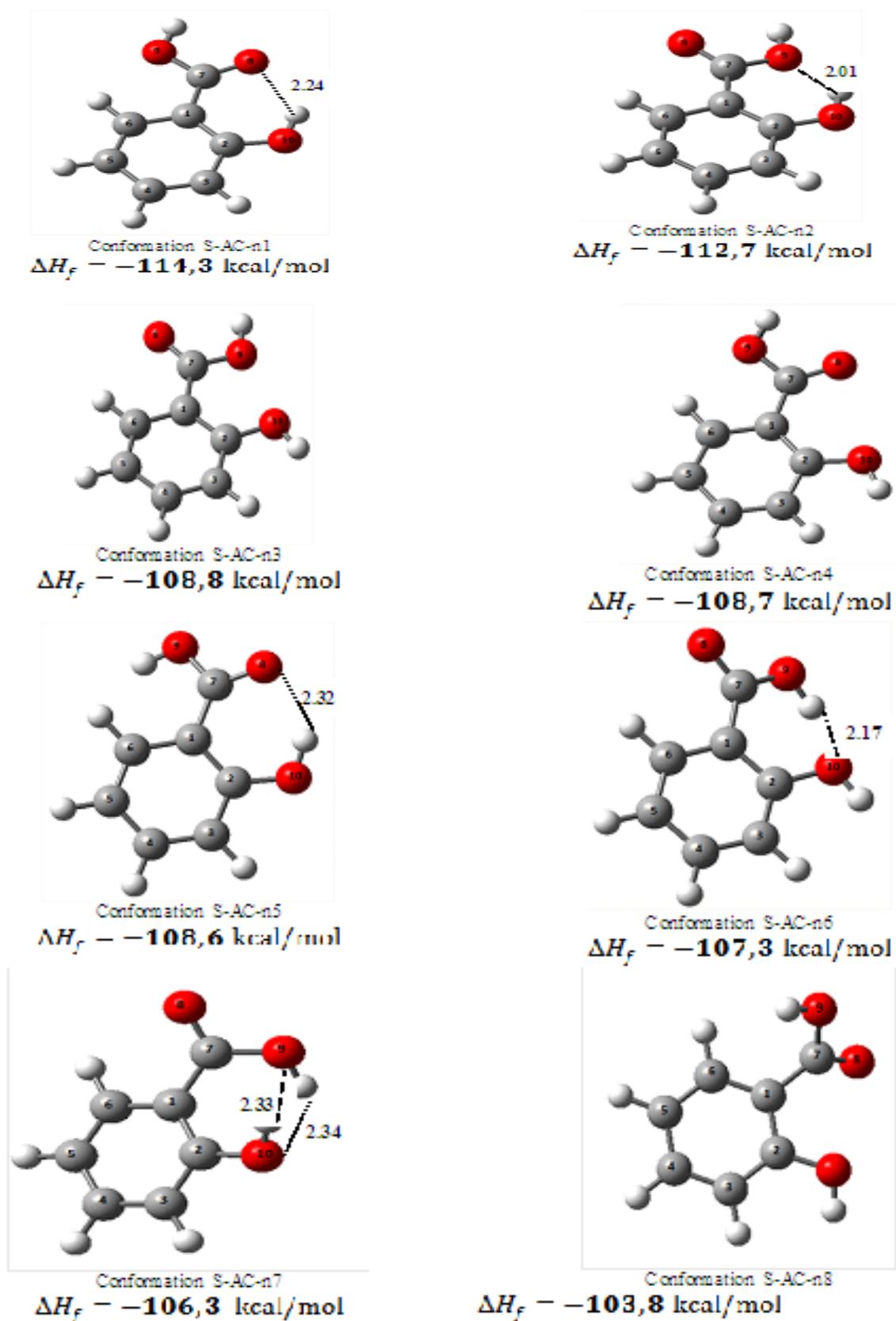


Fig. 6: The structures and heats of formation of the eight conformations obtained on the PES of salicylic acid

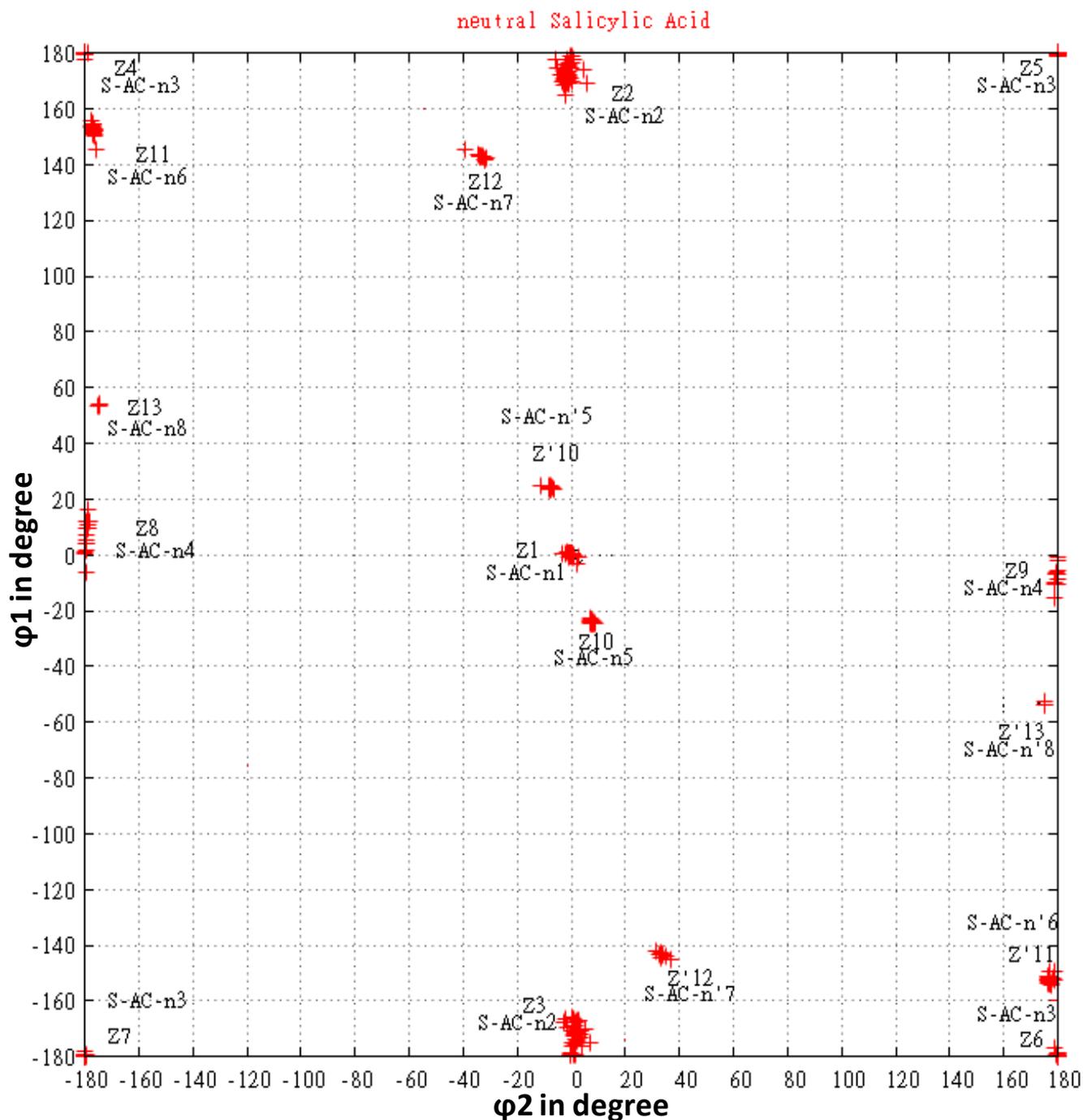


Fig. 7: Distribution of all detected conformations on the PES of the salicylic acid as a function of ϕ_1 and ϕ_2

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 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.

RESULTS AND DISCUSSION

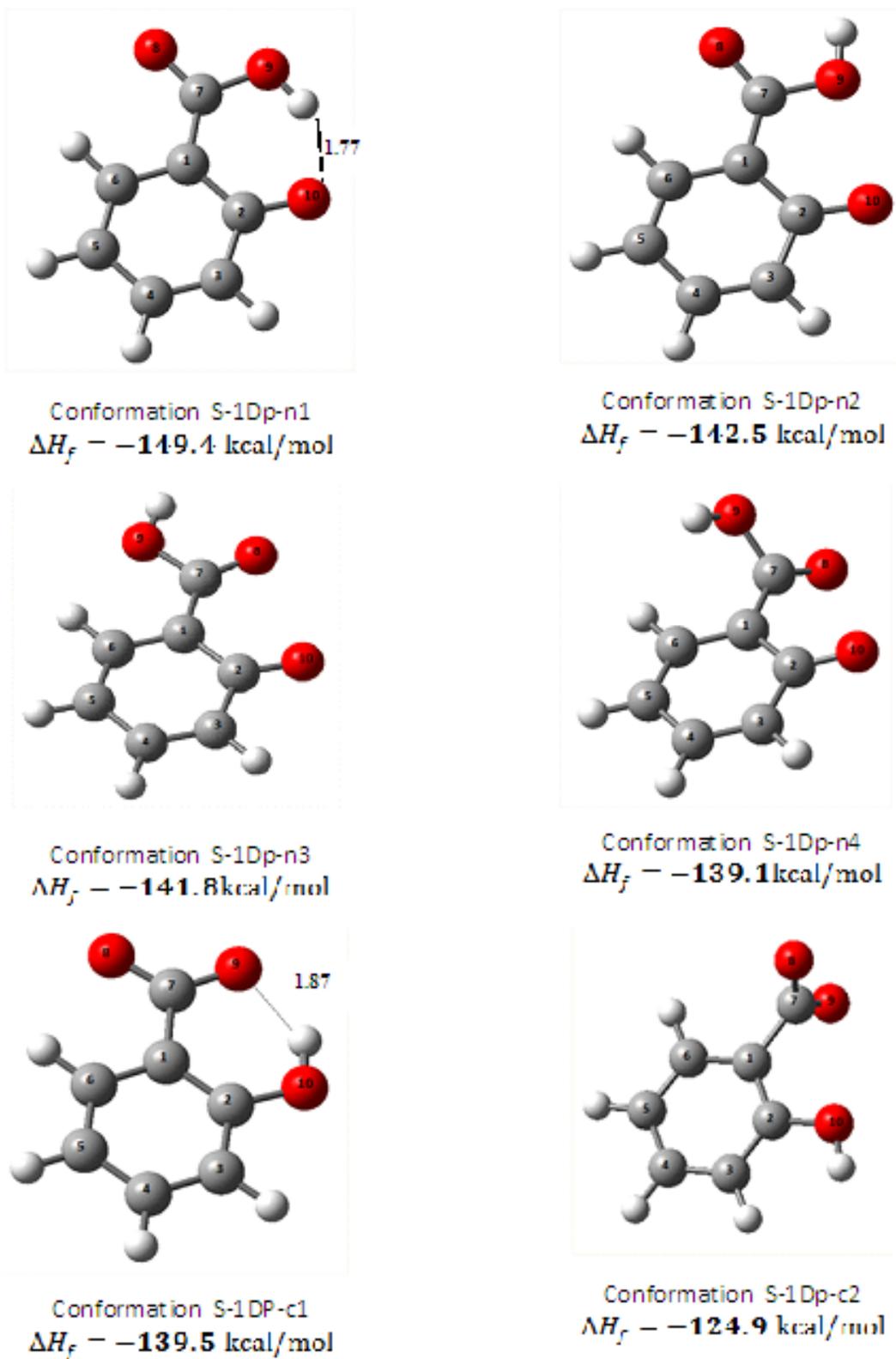


Fig. 8: The six minima of salicylic acid anion localized by the AM1 method

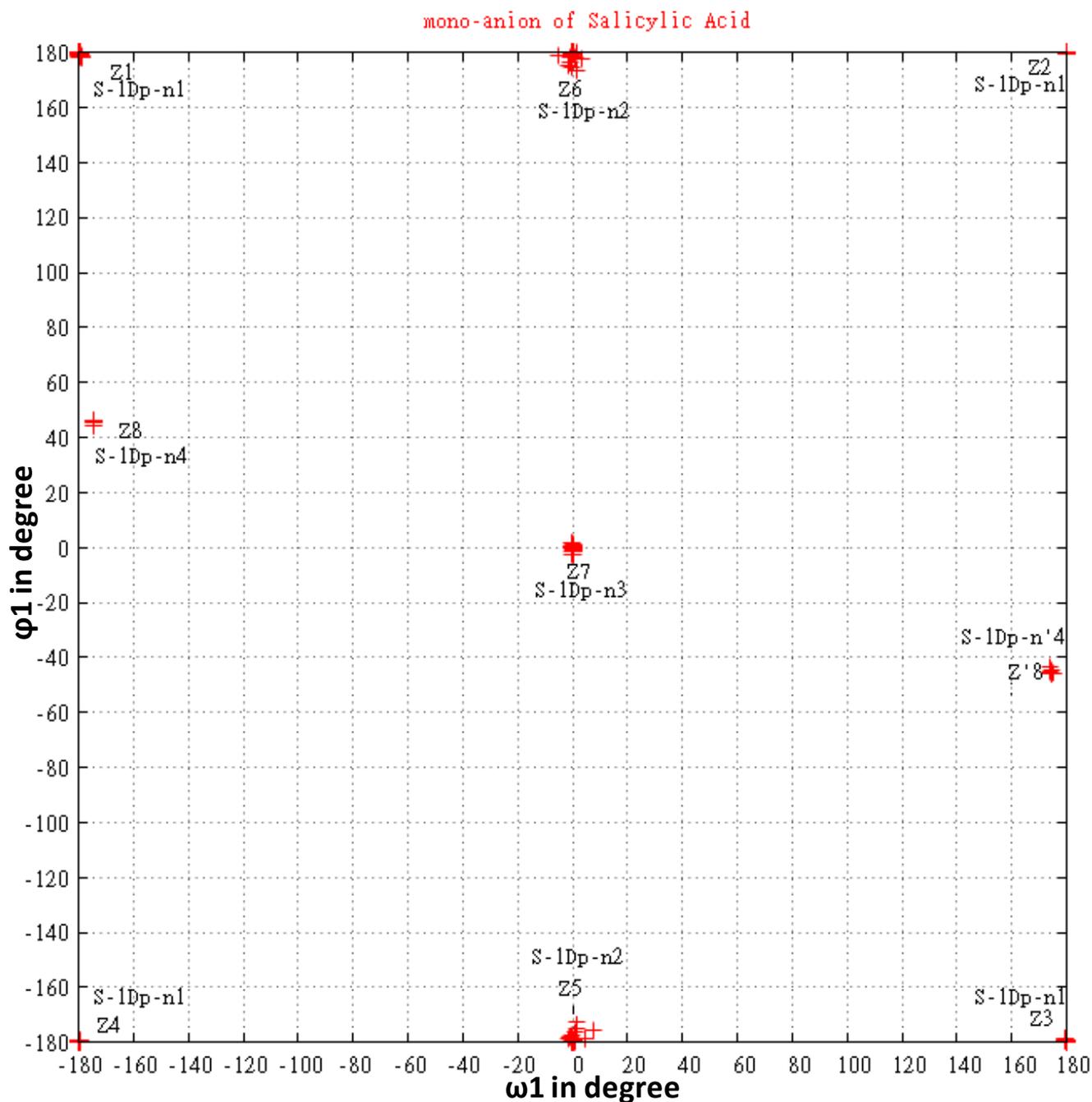


Fig. 9: Distribution of all detected conformations on the PES of the mono-anion of the salicylic acid as a function of ω_1 and ϕ_1

Isolated benzoic acid in the neutral state

Analysis of the potential energy surface of benzoic acid in the neutral state, using the genetic algorithm, identifies two stable conformations which are geometrically different. These two configurations are illustrated in Figure 2 where the conformation denoted Bn-AC-n1 represents the global minima, thus the most stable of the potential energy surface with a heat of formation equals -67.8 kcal/mol. This value is

similar to that found by Tomoko et al. (Tomoko et al., 1989) (-67.9 kcal/mol) using the AM1 method. Furthermore, the second conformation denoted Bn-AC-n2 represents the local minima with a heat of formation of about -62.4 kcal/mol. In order to arrange all conformations detected on the PES and to ensure the existence of these two configurations only, we drew on Ramachandran diagrams (Ramachandran and Sasisekharan, 1968) by representing the variation of the angle ϕ_1 according to ω_1 (Figure 3).

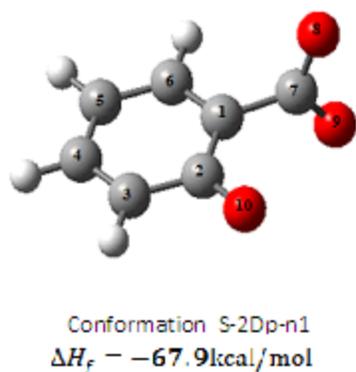


Fig. 10: The structure of the global minimum located on the PES of dianion of the salicylic acid.

From this figure, we notice the presence of seven regions which are denoted Z_i with $i = 1-7$. Bn-AC-n1 structure is located in the regions Z1, Z2 and Z3 where ω_1 is almost 0° in the three regions, while ϕ_1 values are almost equal to 180° , 0° and -180° respectively. The presence of this structure in the three regions is due to the fact that the structure does not change at the cited values of ω_1 and ϕ_1 . Bn-AC-n2 structure is shown in the two Z4 and Z5 regions where ω_1 varies between 175° and 180° , while ϕ_1 equal to $30^\circ \pm 2^\circ$ in Z4 and $-148^\circ \pm 2^\circ$ in Z5. Its image is located in the Z6 and Z7 regions where angles ω_1 and ϕ_1 take values opposite to those found in the regions Z4 and Z5.

In table 1, we have recorded the relative energies and the structural parameters of these two conformations obtained according to our calculations and those of the previous work.

Referring to the geometrical parameters, we find that Bn-AC-n1 conformation is characterized by the flatness of the carboxyl group with the benzene ring with a carbonyl dihedral angle of about 1.10° and a cis form of the COOH group, that has promoted the development of a hydrogen bond $C = O \cdots OH$ relatively large (2.23 \AA) and therefore the stability of the conformation. This cis form of the carboxyl group was also observed in formic acid treated by ab initio method with the STO-3G minimal basis set (Radom et al., 1971). This allowed us to deduce that benzene and hydrogen atom bonded to the carboxyl group in benzoic acid and formic acid respectively have the same effect on the shape of this group. The same result regarding the most stable conformation of benzoic acid was found in the crystal structure acid (Sim et al., 1955).

The conformation Bn-AC-n2 adopts a non-planar geometry with trans form of the carboxyl group in which carbonyl is deviated from the benzene ring of a dihedral angle equal 29.77° . In this regard, we can say that the low stability of the conformation Bn-AC-n2 relative to the reference conformation Bn-AC-n1 is due to the loss of conjugation between the carbonyl group and the COOH of the benzene ring. In addition, the calculated energy barrier to

move from the cis form to the trans one of the carboxyl group in the benzoic acid is somewhat low in the order of 5.5 kcal/mol . This is due to the presence of σ - π interaction, which contributes to the stabilization of the molecule.

According to our results, Alireza et al. (Alireza et al., 2011) have examined theoretically the molecular properties of benzoic acid and its derivatives using three quantum methods: HF, DFT and MP2 with the basis set 6-311 ++ G (d, p). It comes out of their results that the PES of benzoic acid contains two types of conformations cis (Bn-AC-n1) and trans (Bn-AC-n2). The relative energies corresponding to these two configurations are shown in Table 1. According to these authors, the planar conformation cis is considered more stable than the trans one of 8.08 , 6.81 and 5.98 kcal/mol at HF, DFT and MP2 levels respectively. These relative energy values found by the three theoretical methods are superior to our value with a relatively small gap (2.7 kcal/mol maximum). As regards the geometry of the conformation Bn-AC-n2, Alireza et al. found that the carbonyl group is deflected from the benzene ring plane of an angle equal to 25° at HF level and 22.7° and 30.8° at the DFT and MP2 levels respectively. The differences between the other geometrical parameters (atomic distances, dihedral angles ...) of conformation Bn-AC-n1 and those of AC-Bn-n2 calculated by the three theoretical methods were found insignificant. All these results are also in very good agreement with those of Kirsten et al. (Kirsten et al., 2006) obtained using quantum methods HF and MP2 with electron diffraction gas phase using the same basis set 6-311 + G (d, p).

Isolated benzoic acid in deprotonated state

The benzoate anion is the conjugate base of benzoic acid deprotonated at the carboxyl function. The resulting negative charge is delocalized between the two oxygen atoms of the carboxylate group. The complete scan of the potential energy surface of this anion, using the genetic algorithm, shows the existence of a single conformation which is characterized by the flatness of the molecule, in which its stability can be explained by resonance effect established between the charge distributed in the benzene ring and the negative charge of the carboxylate group (Figure 4). To ensure the existence of this single conformation in the PES, we have represented the variation of ΔH_f according to the angle ϕ_1 whose diagram is given in Figure 5. From this diagram, we deduce that the only conformation obtained for the benzoate ion (Bn-An-n1) is located in the three present regions, due to the same obtained value of ΔH_f ($\Delta H_f = -67.9 \text{ kcal/mol}$) and the values -180° , 0° and 180° of ϕ_1 corresponding to these three regions, respectively.

Study of the PES of salicylic acid in the neutral state

Analysis of the potential energy surface of salicylic acid shows that it adopts eight conformations shown in Figure 6. The first two conformations called S-AC-n1 and S-AC-n2 are the most stable of the PES of isolated salicylic acid.

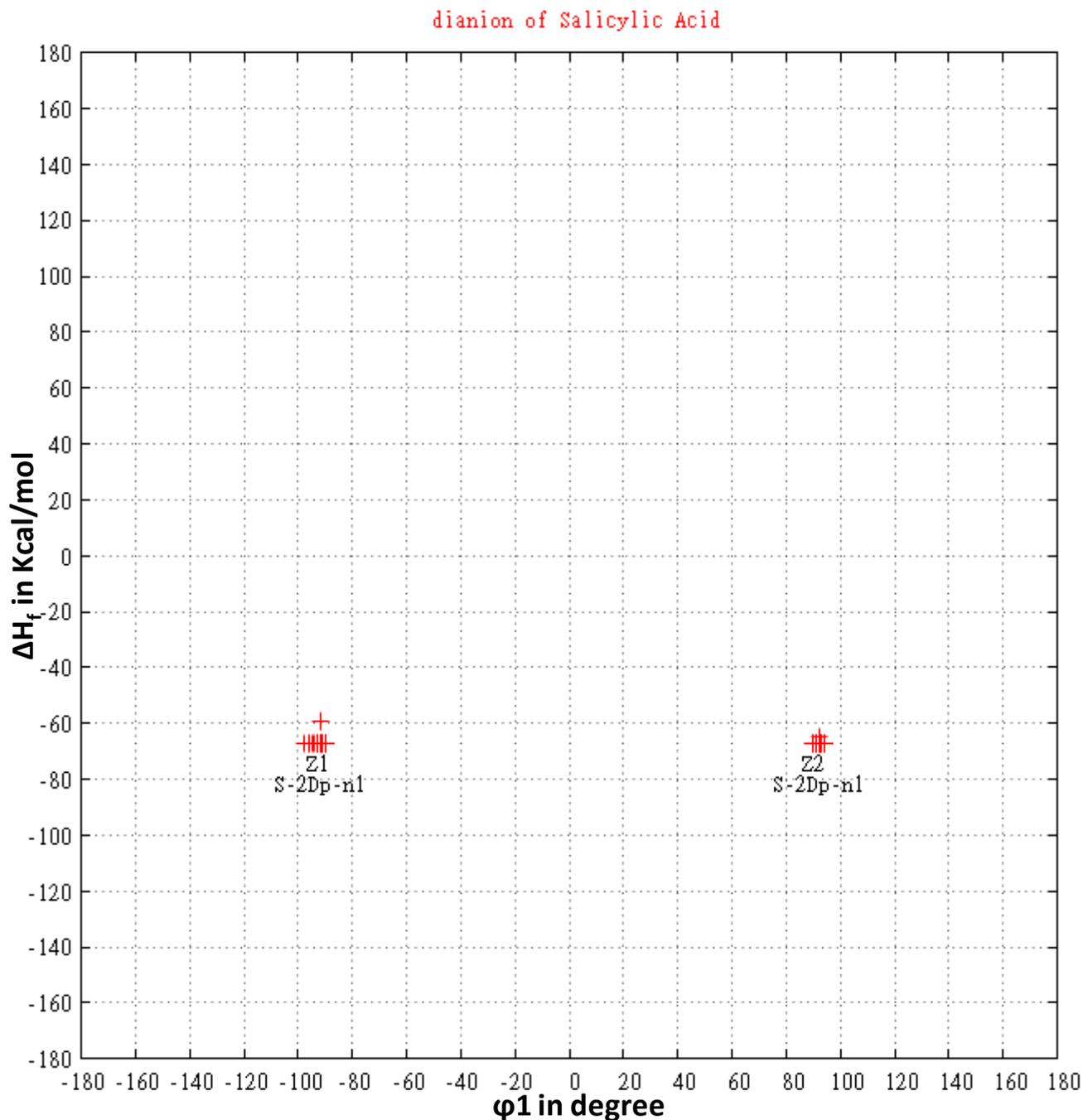


Fig. 11: Distribution of all detected conformations on the PES of dianion of salicylic acid as a function of ϕ_1 and ΔH_f

Referring to their heats of formation, it can be said that the conformation S-AC-n1 represents the global minimum of the PES with a heat of formation in order of -114.3 kcal/mol. This result is in good agreement with previous work (Catalan and Fernandez-Alonso, 1973; Fiedler et al., 2006; Suresh et al., 2014)

Relative stabilities of the conformations of salicylic acid according to our calculations and according to those of previous work are shown in Table 2. To ensure the existence

of these eight conformations only, we arranged in Figure 7 all conformations detected on the PES representing the variation of the angle ϕ_1 according to the angle ϕ_2 .

The analysis of this figure shows that the eight structures of the neutral salicylic acid are located in eight areas with different angles ϕ_1 and ϕ_2 . The structure S-AC-n1 is located in only one region Z1 where ϕ_1 and ϕ_2 take the value $0^\circ \pm 2^\circ$.

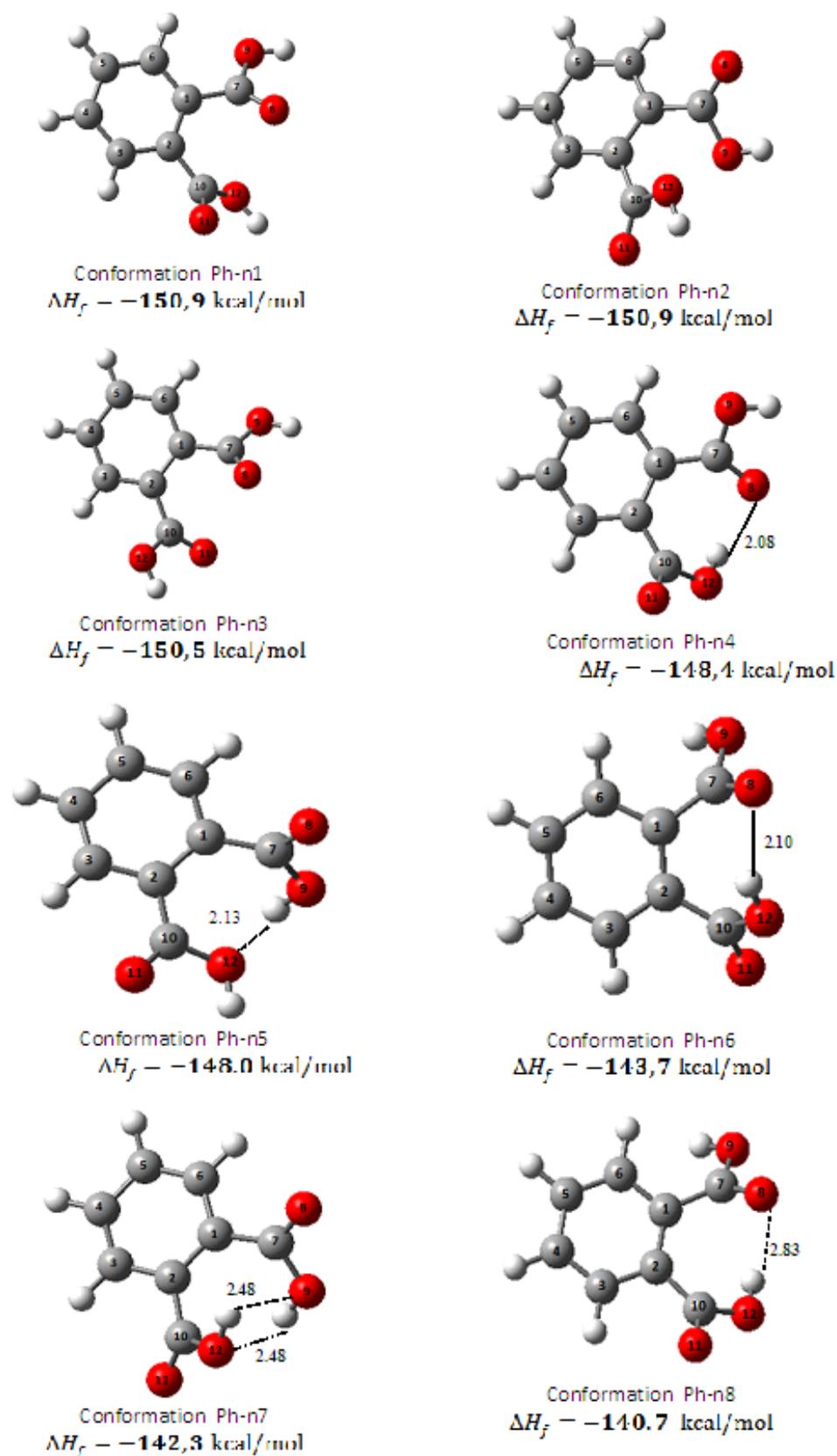


Fig. 12: The eight stable conformations found on the PES of phthalic acid in the neutral state

Table 3: Heats of formation (in kcal/mol) and dihedral angles (in degrees) of possible conformations of the mono-deprotonated salicylic acid

Conformation	ΔH_f	O ₈ -C ₇ -C ₁ -C ₂	H-O ₉ -C ₇ -O ₈	H-O ₁₀ -C ₂ -C ₁
S-1Dp-c1	-139.6	-179	-	0.0
S-1Dp-c2	-124.9	-92.1	-	-178.4
S-1Dp-n1	-149.4	-179.89	179.95	-
S-1Dp-n2	-142.5	-179.3	0.0	-
S-1Dp-n3	-141.8	-0.13	0.01	-
S-1Dp-n4	-139.1	45.64	-174.65	-
S-1Dp-n'4	-139.10	-45.36	174.70	-

Table 4: Relative stability of conformations of salicylic acid (in kcal /mol)

Conformation	Relative Energies		H...O/A°	
	AM1	DFT ²²	AM1	DFT ²²
S-1Dp-n1	0.0	0.0	1.76	1.48
S-1Dp-n2	6.9	18.5	-	-
S-1Dp-n3	7.5	19.9	-	-
S-1Dp-n4	10.2	-	-	-
S-1Dp-c1	9.8	0.6	1.87	1.45
S-1Dp-c2	24.4	25.7	-	-

The structure S-AC-n2 is positioned in two areas Z2 and Z3 where φ_2 equal almost 0°, while φ_1 takes either $180^\circ \pm 4^\circ$ or $180^\circ \pm 4^\circ$. The structure S-AC-n3 is shown in four regions Z4, Z5, Z6 and Z7 in which φ_1 and φ_2 take one of two values: 180° and -180° , that of S-AC-n4 is in two different parts Z8 and Z9 where (φ_1, φ_2) are equal to ($3^\circ \pm 4^\circ, -179^\circ \pm 1^\circ$) and ($-6^\circ \pm 6^\circ, 179^\circ \pm 1^\circ$), respectively. Conformations S-AC-n5, 6, 7 and 8 are centered in four different regions with angles (φ_1, φ_2) respectively equal ($-24^\circ \pm 1^\circ, 8^\circ \pm 1^\circ$) ($152^\circ \pm 2^\circ; -177^\circ \pm 1^\circ$), ($-143^\circ \pm 1^\circ, 33^\circ \pm 2^\circ$) and ($53^\circ \pm 1^\circ, -174^\circ \pm 1^\circ$). Moreover, their images structures S-AC-n'5, S-AC-n'6, S-AC-n'7 and S-AC-n'8 are located in regions with opposite angles ($-\varphi_1; -\varphi_2$) to those of their images.

Structurally, S-AC-n1 and S-AC-n2 are characterized by the coplanarity of the benzene ring with two adjacent groups (COOH and OH) indicating that steric hindrance between these two groups is negligible. In addition, both conformations are stabilized by the establishment of a strong intramolecular hydrogen bond. Indeed, in the conformation

S-AC-n1, this bond is established between the hydrogen atom H-O10 and the carbonyl C7=O8 with bond length equal 2.03 Å, whereas in S-AC-n2, it is established between the hydrogen atom H-O10 and the oxygen atom O9 with a length equal 1.98 Å.

The conformations denoted S-AC-n3, S-AC-n4, S-AC-n5 and S-AC-n6 are less stable by 5.5 to 7 kcal/mol with respect to the conformation reference S-AC-n1. Their heats of formation are -108.8, -108.6, -108.5 and -107.3 kcal/mol respectively. The low stability of the two conformations S-AC-n3 and S-AC-n4 is explained by the loss of hydrogen bonding due to the rotation of the hydroxyl group of an angle of approximately 180 degrees. In addition, it is noted that the geometries of S-AC-n3 and S-AC-n4 are plane where the two adjacent groups are located in the plane of the benzene ring. This flatness is absent in the last four Minimum S-AC-ni (i = 5, 6, 7 and 8), where the value of the angles (φ_1, φ_2) are ($-24.15^\circ, 7.20^\circ$) ($152.22^\circ, -176.94^\circ$) ($-142.9^\circ, 33.25^\circ$) and ($53.27^\circ, -174.95^\circ$), respectively.

Table 5: Heats of formation (in kcal/mol) and geometric parameters of the eight minima of phthalic acid and their images, calculated by the AM1 method

Conformation	ΔH_f	O ₈ -C ₇ C ₁ C ₆	O ₁₁ -C ₁₀ C ₂ C ₃	H-O ₉ C ₇ O ₈	H-O ₁₂ C ₁₀ O ₁₁
Ph-n1 (Z1, Z10)	-150.9	149.60	-44.39	1.72	-7.73
Ph -n'1 (Z'1, Z'10)	-150.9	42.99	-148.33	7.72	-1.76
Ph-n2(Z4)	-150.9	38.1	36.3	4.90	4.80
Ph -n'2 (Z'4)	-150.9	-35.45	-36.12	-4.55	-4.64
Ph-n3 (Z5)	-150.5	139.56	131.56	2.89	3.58
Ph-n'3 (Z'5)	-150.5	-137.99	-133.09	-3.02	-3.43
Ph-n4 (Z2, Z7)	-148.4	142.25	51.94	1.76	172.43
Ph-n'4 (Z'2, Z'7)	-148.4	-51.63	-142.04	-172.69	-1.81
Ph-n5 (Z3)	-148.0	62.02	-27.93	173.21	-4.08
Ph-n'5 (Z'3)	-148.0	26.73	-60.67	4.07	-173.67
Ph-n6 (Z6, Z8)	-143.7	127.01	50.27	176.75	175.34
Ph-n'6 (Z'6, Z'8)	-143.7	-50.19	-126.55	-174.97	-176.87
Ph-n7(Z4)	-142.3	38.49	39.72	-176.17	-176.53
Ph-n'7 (Z'4)	-142.3	-37.15	-37.15	176.30	176.74
Ph-n8 (Z1, Z10)	-140.7	140.45	-33.94	177.12	-171.19
Ph-n'8 (Z'1, Z'10)	-140.7	34.13	-140.52	171.22	-177.19

O₈-C₇C₁C₆ and O₁₁-C₁₀C₂C₃ correspond to ϕ_1 et ϕ_2

H-O₉C₇O₈ and H-O₁₂C₁₀O₁₁ correspond to w_1 et w_2

Table 6: Heats of formation (in Kcal/mol) and dihedral angles (in degrees) of the three conformations and their images calculated by AM1 for the mono-deprotonated of phthalic acid

Conformation	ΔH_f	O ₈ -C ₇ C ₁ C ₆	O ₁₁ -C ₁₀ C ₂ C ₃	H-O ₁₂ C ₁₀ O ₁₁
Ph-1Dp-n1 (Z1, Z4)	-182.4	55.33	-36.72	-173.43
Ph-1Dp-n'1 (Z'1, Z'4)	-182.4	120.38	36.96	173.15
Ph-1Dp-n2 (Z2, Z5)	-180.9	24.02	29.26	161.87
Ph-1Dp-n'2 (Z'2, Z'5)	-180.9	143.58	-19.65	-165.51
Ph-1Dp-n3 (Z3, Z6)	-177.3	2.26	70.33	37.17
Ph-1Dp-n'3 (Z'3, Z'6)	-177.3	-177.06	-69.60	-39.00

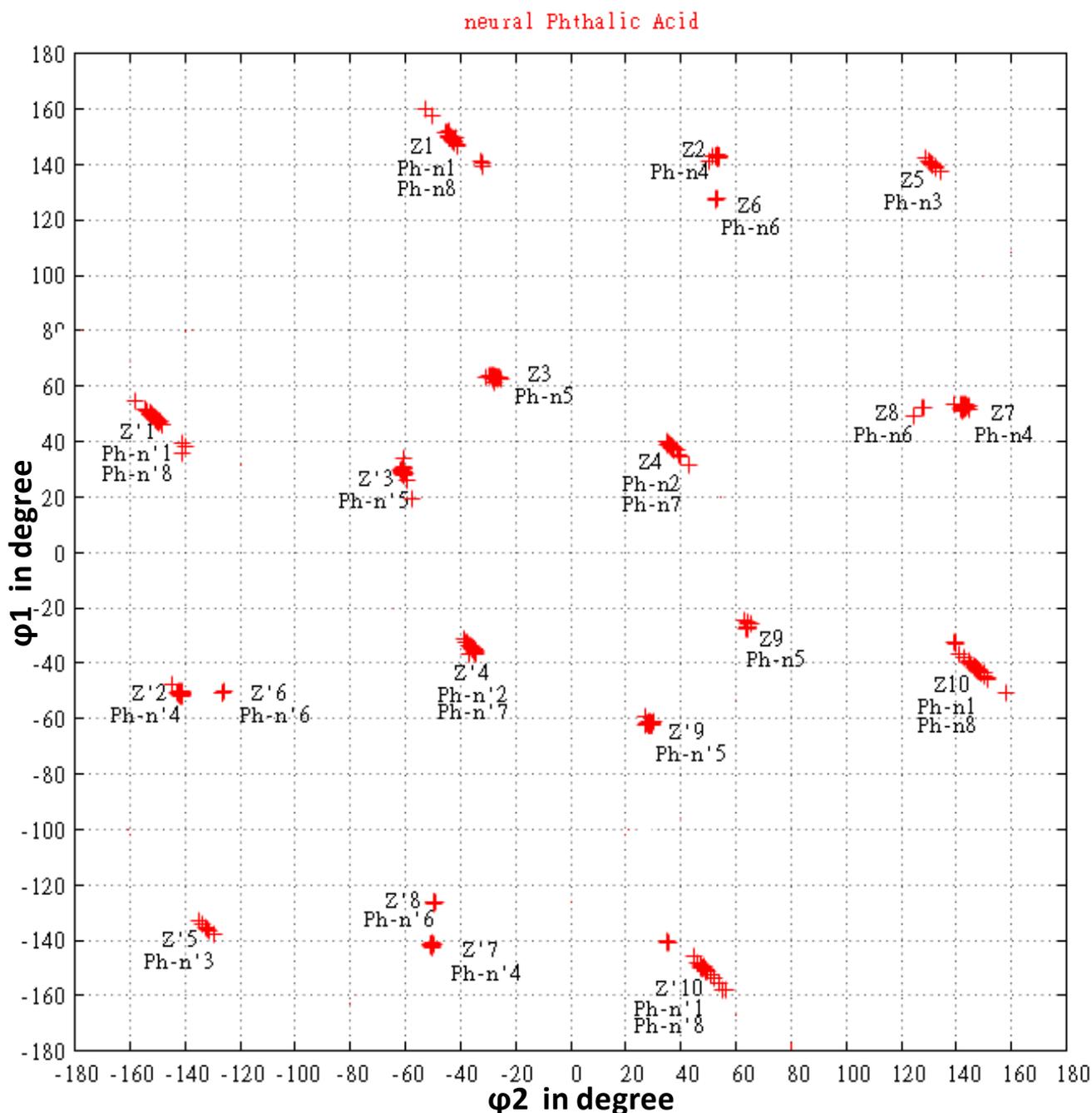


Fig. 13: Distribution of all detected conformations on the PES of phthalic acid according to ϕ_1 and ϕ_2

In addition, a hydrogen bond $O_{10}-H\cdots O_8$ with a length of 2.05 Å has been noted in S-AC-n5, whereas in S-AC-n6 a bond $O_9-H\cdots O_{10}$ of 2.07 Å. The same for the conformation of S-AC-n7, where two hydrogen bonds $O_{10}-H\cdots O_9$ and $O_9-H\cdots O_{10}$ stabilized this molecule were present. For the structure of the conformation S-AC-n8, we note that the carbonyl is deviated from benzene plane by an angle equal -53.54° with a trans form of the COOH group, which thus promotes a σ - π interaction between the H-O bond and π electrons of benzene.

Experimental studies by Murray and Sundaran (Murray and Sundaram, 1961) using infrared spectra indicate that the conformations S-AC-n1 and S-AC-n6 are the only possible conformations of the salicylic acid in low concentrations of benzene. However, theoretical calculations of salicylic acid using HF and MP2 / 6-311 + G (d, p) methods (Kirsten et al., 2006) generally lead to seven conformations. The two stable conformations are identical to S-AC-n1 and S-AC-n2, with an energy barrier in the order of 3.27 kcal/mol at HF and 2.79 kcal/mol at MP2 level.

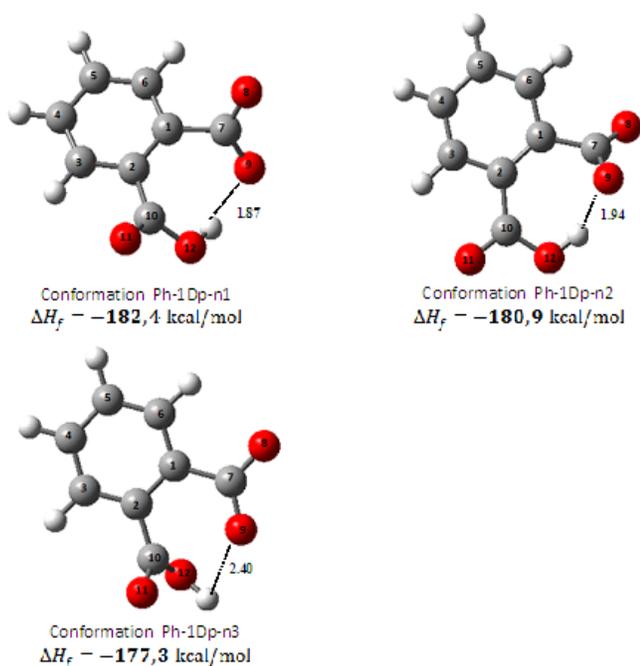


Fig. 14: The three minima detected on the PES of the phthalate mono-anion

Anandan et al. (Anandan et al., 2005), have studied the molecular structure of the conformations of salicylic acid using Ab initio and DFT methods. The geometrical and energy parameters of conformations are obtained at MP2/6-311G (2d, 2p) and B3LYP/6-311G (2d, 2p) levels. According to this study, salicylic acid adopts six planar conformations named SAL1, SAL2, SAL3, SAL4, SAL5 and SAL6 where conformer SAL2, obtained from the conformer SAL1 optimized by the migration of the hydrogen atom H-O of COOH group to the oxygen atom of the carbonyl group, became the tautomeric form of SAL1. The remaining four conformations are geometric isomers of salicylic acid. Intramolecular hydrogen bonds were noted in the conformers SAL1, SAL2, SAL5 and SAL6 and their bond lengths are in the order of 1,759, 1,803, 1,706, 1,768 Å at MP2/6-311G (2d, 2p) and 1,740, 1,804, 1,686, 1,787 Å at B3LYP/6-311G (2d, 2p) respectively. In addition, the six obtained conformations have different energies with an order of stability in the gas phase as follows: SAL1 > SAL2 > SAL5 > SAL6 > SAL3 > SAL4. This order is changed by passing to aqueous phase in which there is a considerable reduction of energy, which leads consequently to an increase in the stability of the six molecular systems and therefore a new order: SAL1 > SAL2 > SAL3 > SAL6 > SAL4 > SAL5. Comparing these results with those of our study, we can say that the conformations SAL1, SAL2, SAL3 and SAL4 correspond to S-AC-n1, S-AC-n2, S-AC-n3 and S-AC-n4, while the two conformations SAL5 and SAL6 are found non-planar by the AM1 method. In addition, the hydrogen bond length

established in SAL1 and SAL2 has been found higher than that established in S-AC-n1 and S-AC-n2.

According to Fiedler et al. (Fiedler et al., 2006), the salicylic acid can adopt five planar conformations 1a, 1b, 1c, 1d and 1e, their relative energies are given in the sixth column of Table 2. The results of these authors show that 1a corresponding to S-AC-n1 is the only preferred conformation of salicylic acid wherein a strong hydrogen bond was noticed with a length equal 1.76 Å. Concerning 1b, 1d and 1e which correspond to S-AC-n2, S-AC-n3 and S-AC-n4, Fiedler et al. note that these minima can be neglected since the energy difference between them and 1a is great. In addition, the two conformations 1d and 1e were found unstable from 1 to 1.4 kcal/mol relative to 1c whose structure was found plane.

Catalan and Fernandez-Alonso (Catalan and Fernandez-Alonso, 1973) had examined all possible conformations of ortho-hydroxybenzoic acid and di-ortho-hydroxybenzoic acid using the semi-empirical method CNDO/2. They also studied the strength of intramolecular hydrogen bonds formed in these acids and their anions. The relative stabilities of the envisaged five different conformations of salicylic acid have been shown in the last column of Table 2. These five conformations denoted, III, IV, V, VI and VII depending on the order of their stability correspond to the structures S-AC-n1, 2, 3, 4 and 6 with a slight difference (maximum 7 kcal/mol) at the values of relative stability. Furthermore, CNDO/2 calculations show that the difference in energy between III and IV of about 1.8 kcal/mol is due to the great strength of the intramolecular hydrogen bond of value 13.4 kcal/mol in the conformation III, and 10.9 kcal/mol in the conformation IV. The energy difference between the other possible conformations and the reference conformation III is varied in a range of 12.7 to 14 kcal/mol.

Peter et al. (1993), through theoretical studies on the 2- and 4-hydroxybenzoic acid using the HF method and using the bases STO-3G and 6-31G, found that salicylic acid can adopt seven planar conformations denoted 1, 2, 5, 6, 7, 8 and 11. These seven conformations have also been found in studies by Giuliano and Caterina (Giuliano and Caterina, 1994), but with a different stability order in which they are denoted (0,0), (0,180), (180,180), (180,0), (t0,0), (t0,180) and (t180,180). Comparing these seven conformations with those found in our study, we note that the conformations S-AC-n1, S-AC-n2, S-AC-n3 and S-AC-n4 correspond to the structures of the four minima 1, 2, 8 and 7 localized by the HF method (Peter et al., 1993), and to structures of conformations (0,0) (180,0) (180,180) and (0,180) found by Giuliano and Caterina (Giuliano and Caterina, 1994).

In summary, we can say that the structure of conformations S-AC-ni (i = 5, 6, and 8) is not planar according to AM1 method while it is planar whichever Ab initio method or DFT method used. In addition, the existence of the conformation S-AC-n7 on the PES of neutral salicylic acid shows the great ability of the genetic algorithm to explore and exploit the totality of the studied surface.

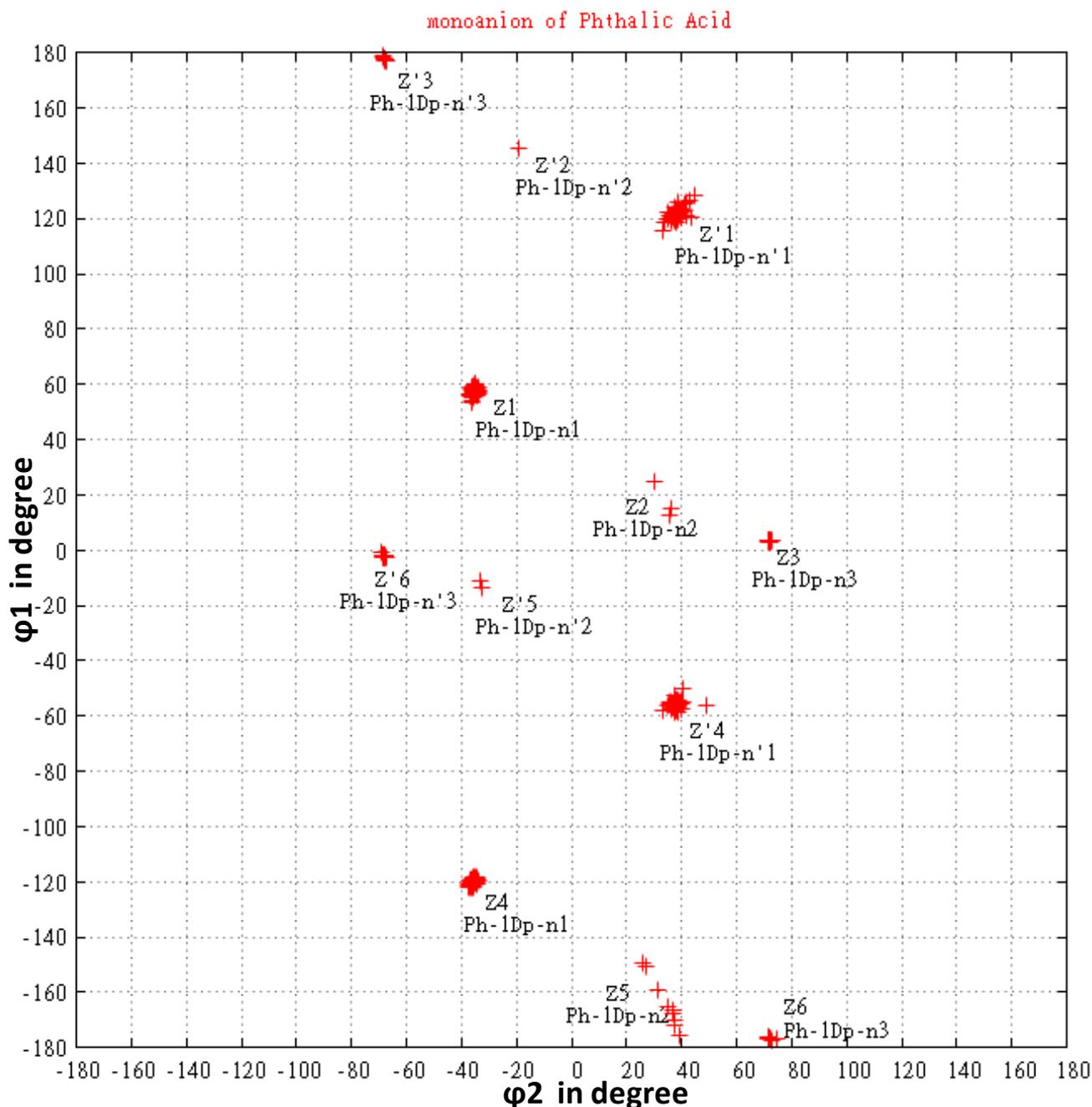


Fig. 15: Distribution of all conformations detected on the PES of mono-anion of phthalic acid according to ϕ_1 and ϕ_2

Study of the PES of the mono-deprotonated salicylic acid

In principle, salicylic acid has two acid groups namely carboxyl and hydroxyl. For its first deprotonation study, we tested the two acid sites. Figure 8 shows the structures resulting from deprotonation at the levels of the hydroxyl group and carboxyl group, obtained by scanning the PES.

In Figure 9 we have illustrated the variation of the angle ϕ_1 according to the angle ω_1 . The experimental results obtained by Fiedler et al. (Fiedler et al., 2006) showed that

the anion structure of salicylic acid is characterized by the existence of a strong hydrogen bond. Two structures, which differ by the position of the hydrogen atom involved in the bond, were found. Using the DFT method, Fiedler et al. predict that the deprotonation of salicylic acid may be on the carboxyl group as on the hydroxyl group with a substantially low energy difference of 0.7 kcal/mol between corresponding structures. However, Catalan and Fernandez-Alonso (Catalan and Fernandez-Alonso, 1973), found that the anion of the salicylic acid is induced by deprotonation of the

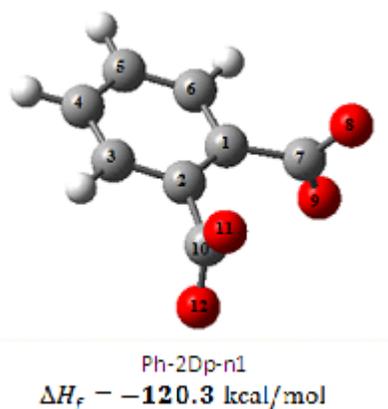


Fig. 16: Structure of the alone conformation of the di-deprotonated of phthalic acid

carboxyl group. Two conformations were predicted; the first is stabilized by hydrogen bond between the phenolic group and the carboxylate group and the second is less stable by 20.9 kcal/mol with 180° rotation of the hydroxyl group.

According to our calculations, six minima were located on the PES of the mono-deprotonated salicylic acid, of which two are minima of the deprotonation at the COOH group and four at the OH group. These conformations illustrated in Figure 8 are respectively denoted S-1Dp-ci ($i = 1, 2$) for deprotonated COOH and S-1Dp-ni ($i = 1, 2, 3, 4$) for deprotonated OH. Their obtained energy and structural parameters are resembled in both Tables 3 and 4.

The two minima S-1Dp-c1 and S-1Dp-c2, resulting from abstraction of the COOH proton correspond to conformations 2b and 2e localized by the DFT method (Fiedler et al., 2006) and to conformations XIV and XV found by the CNDO / 2 method (Catalan and Fernandez-Alonso, 1973). Structurally, our calculations show that S-1Dp-c1 conformation is stabilized by the formation of a hydrogen bond between the COO⁻ group and the OH group, while this bond is absent in S-1Dp-c2 due to the rotation of the OH group of an angle equal 179.9°, which causes instability of 14.6 kcal/mol for S-1Dp-c2. The length of the hydrogen bond formed in S-1Dp-c1 is about 1.87 Å with a deviation of 0.42 Å relative to its value obtained by DFT (1.45 Å) (Fiedler et al., 2006).

For the four minima resulting from deprotonation of the OH group, we find that the conformation S-1Dp-n1 has the lowest energy (-149.3 kcal/mol) compared with other conformations, which allowed us to say that S-1Dp-n1 represents the global minimum, while the three other conformations represent local minima. At the structural level, we note that the S-1Dp-n1 structure is planar and a strong intramolecular hydrogen bond was noted with a bond length of about 1.76 Å below 0.11 Å with respect to the bond established in the conformation S-1Dp-c1. Furthermore, this bond is absent in the other three conformations, which explains their instability, of 6.8 to 10.2 kcal/mol, with respect

to the reference conformation S-1Dp-n1. In addition, the structures of S-1Dp-n2 and S-1Dp-n3 are planar and the hydrogen atom of the carboxyl group is cis with respect to the carbonyl. The only difference between these two configurations resides in the position of the carbonyl group where the dihedral angle value ϕ_1 is almost 180° in the S-1Dp-n2 conformation, while it is almost 0.0° in the conformation S-1Dp-n3. These first three conformations of OH deprotonation obtained by our calculations are similar to those found previously (Fiedler et al., 2006) wherein S-1Dp-n1 corresponds to the conformation 2a and S-1Dp-n2 and S-1Dp-n3 correspond to conformations 2c and 2d, respectively. According to AM1 and DFT (Fiedler et al., 2006) methods, the energy barrier to pass from S-1Dp-n1 to the S-1Dp-n2 is equal to 6.9 and 18.5 kcal/mol, respectively. These values increase of 7.5 and 19.96 kcal/mol respectively passing to conformation S-1Dp-n3.

Furthermore, our calculations show that the energy barrier between S-1Dp-n1 and S-1Dp-n4 is relatively greater than 10.2 kcal/mol. In addition, the S-1Dp-n4 structure is not planar and the carbonyl group is deflected from the benzene ring plane of an angle equal 46.4° with a trans form of COOH, which enables a σ - π interaction between H-O and π electrons of benzene. From an energy point of view, the S-1Dp-c1 structure is less stable by 9.8 kcal/mol relative to the S-1Dp-n1 structure; this value is relatively significant enabling us to say that according to the AM1 method the phenolic proton is more acidic than the carboxylic acid proton in the gas phase. However, the study by Humbert et al. (Humbert et al., 1998) showed that in the aqueous phase the proton of the carboxyl group is the most acid.

At the structural level, we note that other conformation is detected on the PES of deprotonated salicylic acid at the hydroxyl group. It denoted S-1Dp-n'4, it presents the image conformation of S-1Dp-n4 and it has the angles values ($-\phi$, $-\omega$).

Study of the PES of di-deprotonated salicylic acid

The di-anion of salicylic acid is induced by abstraction of the proton of COOH and OH groups. The resulting structure depends on the variation of a single dihedral angle ϕ_1 . The analysis of PES using the genetic algorithm shows that the di-anion can adopt one conformation denoted S-2Dp-n1 (Figure 10). This conformation has the global minimum of PES of salicylic acid in di-deprotonated state with a heat of formation equal -67.9 kcal/mol. From a structural point of view, the S-2Dp-n1 geometry is not planar, and the COO⁻ group is perpendicular to the plane of the benzene, indicating that steric hindrance between these two deprotonated groups is very important.

Figure 11, which represent the variation of the heat of formation ΔH_f as a function of angle ϕ_1 , shows the presence of two regions Z1 and Z2. Referring to our results, we find that these two regions are identical as they locate the same structure of the di-anion. The heat of formation is in the range of -67.9 kcal/mol in the two regions and the angle ϕ_1

takes two opposite values $-94^\circ \pm 4^\circ$ in the region Z1 and $92^\circ \pm 2^\circ$ in the region Z2.

Isolated phthalic acid in the neutral state

The conformational analysis of the PES of phthalic acid, using the genetic algorithm, shows the existence of eight conformations denoted Ph-ni ($i = 1, 2, \dots, 8$) (Figure 12). These eight conformations with their images are also only found on the PES of phthalic acid and are shown in the above diagram according to the angle φ_1 and φ_2 angle (Figure 13).

In Table 5, we have recorded their energy and structural parameters as well as those of their images conformations (Ph-n'i ($i = 1, 2, \dots, 8$)). We note that the first three conformations called Ph-n1, Ph-n2 and Ph-n3 have lower almost equal heats of formation, so one of them can probably be the global minimum of the PES of phthalic acid. On their geometry, we note that in Ph-n1 both carbonyls are located outside the plane of the benzene ring, and positioned on the same side of this plane. Dihedral angles φ_1 and φ_2 associated with these two carbonyls are 149.60° and -44.39° respectively. In the conformation Ph-n2, the two carbonyls are on two opposite sides relative to the plane of benzene with φ_1 and φ_2 dihedral angles equal to 38.10° and 36.30° , respectively. For conformation Ph-n3, we note that its heat of formation is less than 0.4 kcal/mol relative to the reference conformation Ph-n1. We also note that these two carbonyls are located in different sides with torsion angles, φ_1 and φ_2 , in the order of 139.56° and 131.56° , respectively. In addition, in the first three conformations, the H-O bond in the two-carboxyl groups adopts a cis form with respect to the carbonyl of the same group.

The conformations called Ph-n4 and Ph-n5 are local minima on the PES of phthalic acid with heats of formation equal to -148.4 and -148.0 kcal/mol respectively. They are stabilized by the presence of an intramolecular hydrogen bond, but the presence of steric hindrance which is important between the two adjacent COOH groups makes these two conformations unstable of 2.5 to 2.9 kcal/mol relative to the Ph-n1 conformation. In addition, in the conformation Ph-n4, the hydrogen bond is established between the hydrogen of the COOH group carried by C2 and the carbonyl of the other group positioned ortho with a length of about 2.08 Å, while in the conformation Ph-n5, it is an intramolecular bond between the hydrogen atom of the COOH group carried by C1 and OH of COOH group carried by the C2 with a length equal to 2.12 Å. In addition, as shown in Table 5, both carbonyls are positioned outside the benzene plane with dihedral angles φ_1 and φ_2 equal to 142.25° and 51.94° in the conformation Ph-n4 and 62.02° and -27.93° in the conformation Ph-n5.

The conformations Ph-n6, Ph-n7 and Ph-n8 are unstable of 7.2, 8.6 and 10.6 kcal/mol, respectively relative to reference conformation Ph-n1. Their heats of formation are in the range of -143.6, -142.2 and -140.2 kcal/mol, respectively. From a structural point of view, the conformations Ph-n6 and Ph-n8 are characterized by the establishment of an intramolecular hydrogen bond O12-

H...O8 where H and O8 atoms, which form this bond, are located in the same side of benzene in Ph-n6, while they are situated in two different sides in Ph-n8. Furthermore, these two conformations are also characterized by the existence of σ - π interaction established between the O9-H bond and π electrons benzene. For Ph-n7, we note that this conformation is stabilized by the establishment of two hydrogen bonds O12-H...O9 and O9-H...O12 in which their lengths is about 2.48 Å.

Using the NMR spectra, Daniel and Mordecai (Daniel and Mordecai, 1977), confirmed that the structure of phthalic acid cannot be planar and may adopt three conformations, which differ from each other by the position of the two carbonyls. The NMR data show that the most stable conformation of phthalic acid is one in which the two carbonyl groups are similar and in the same side. The non-flatness of the molecule of the phthalic acid has also been demonstrated by Marković et al. (Marković et al., 2004). These authors, using the AM1 method show that the phthalic acid may adopt only three minima nonplanar rated according to their study, 1a, 1b and 1c. More explicitly, the conformation 1a is characterized by an almost orthogonal form of one of two carboxyl groups on the benzene ring plane (about 84°), while the other group located in ortho is almost coplanar with the plane of the benzene ring (about 10°). For conformation 1b, the two-carboxyl groups are outside of the benzene ring plane with the dihedral angles equal to 26° and 47° . However, the angles corresponding to the two-carboxyl groups in the 1c conformation are about 36° and 38° , which is in agreement with the values obtained for the conformation Ph-n2. It should be noted that the angles mentioned in the study by Marković et al (Marković et al., 2004), refer to the angle between the benzene ring plane and the C=O group, noting that the two carbonyls are in two opposite sides of the benzene ring plane. The heats of formation associated with the three rotamers 1a, 1b and 1c, are very close, and are successively -150.62, -150.95 and -150.93 kcal/mol.

Fiedler et al (2006) also studied the structure of phthalic acid using DFT (at B3LYP / 6-311 + G (d, p) level) integrated into the GAUSSIAN 03 program. The results point in the same direction as those obtained by Marković et al. (2004) in non-coplanarity of the two carboxyl groups with the benzene ring plane. Indeed, the calculations performed by Fiedler et al (Fiedler et al., 2006) predict the existence of four stable conformations with very similar energies. These structures differ in the rotation angles of the two COOH groups relative to the benzene plane, with a strong hydrogen bond in the order of 1.62 Å established in the third conformation.

Study of the PES of the mono-deprotonated phthalic acid

The full scan of PES of the phthalate anion identifies three minima shown in Figure 14 and confirmed by the representation of the angle φ_1 according to φ_2 (Figure 15).

In Table 6, we recorded the energy and structural parameters of these three conformations with those of their images. The three minima obtained correspond to three different conformations with a more or less strong hydrogen bond. They are denoted Ph-1Dp-n1, Ph-1Dp-n2 and Ph-1Dp-n3. The conformation Ph-1Dp-n1 is the most stable with a heat of formation equal to -182.4 kcal/mol, thus representing the global minimum of the PES of phthalate ion. Its structure is not planar; the two functional groups are diverted from the benzene plane of angles φ_1 and φ_2 equal to 55.33° and -36.72° respectively. Moreover, Ph-1Dp-n1 is stabilized by strong intramolecular hydrogen bond O12-H...O9, with a length of about 1.87 Å. However, according to Fiedler et al. (Fiedler et al., 2006), the geometry of the stable form of the phthalate anion is planar. Dihedral angles associated to the COO⁻ and COOH groups are 1.3° and 181.6° respectively, with the establishment of a strong intramolecular hydrogen bond of length 1.19 Å. They also located another non-planar conformation of the phthalate anion, but it is not considered in their studies, due to its rotation barrier which is relatively high (17.39 kcal/mol).

Moreover, Ph-1Dp-n2 was found unstable of 1.4 kcal/mol relative to the reference conformation Ph-1Dp-n1. The geometry is characterized by the rotation of COO⁻ groups and COOH outside the plane of the benzene with angles φ_1 , φ_2 equal to 24.02° and 29.26°, respectively. This conformation is stabilized by the formation of hydrogen bond O12-H...O9, which has a length of about 1.94 Å. The difference between the conformations Ph-1Dp-n1 and Ph-1Dp-n2 lies in the fact that in the first, the two H and O9 atoms forming hydrogen bond are positioned in the same side of benzene, while in the second, these atoms are positioned in two different sides.

Between Ph-1Dp-n1 and Ph-1Dp-n3, the energy difference is only 5.1 kcal/mol. The COO⁻ group in the conformation Ph-1Dp-n3 is almost in the benzene plane, while the carbonyl of the COOH group is out of the plan of an angle equal -67.88°. The length of hydrogen bond in this conformation is considerably low 2.45 Å, and H-OOC is deviated from his plan of an angle ω_1 of 37.17°.

Study of the PES of the di-deprotonated phthalic acid

The doubly deprotonated form of phthalic acid is obtained by abstraction of hydrogen atoms of the two COOH groups. To determine its structure, two angles φ_1 and φ_2 are varied around the C7-C1 and C10 -C2 bonds, respectively. The analysis of its PES detected a single conformation with a heat of formation equal -120.2 kcal/mol (Figure 16). This conformation, denoted Ph-2Dp-n1, is characterized by a non-planarity of the molecule, due to significant steric hindrance between the two carboxylate groups which are deflected to 81.73° and -91.83°. Results revealed the variation of the φ_1 according to the angle φ_2 shows four regions locating the dianion structure of phthalic acid. The allowed values for the angle φ_1 are varied in the range [120°.80°] and [-60°, -100°],

while for the angle φ_2 , are varied in the range [60°, 100°] and [-60°, -100°].

CONCLUSIONS

In this study, we did a full scan of PES of benzoic acid, salicylic acid and phthalic acid in a neutral and deprotonated state using genetic algorithm MNC coupled with semi-empirical method AM1. The possible minimum of these three systems and their images are determined. The results obtained are in agreement with those of previous studies.

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