

## A Calorimetric and Computational Study of Aminomethoxybenzoic Acids

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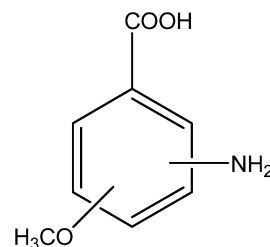
The standard ( $p^0 = 0.1$  MPa) molar enthalpies of formation, in the crystalline phase, of five aminomethoxybenzoic acids, at  $T = 298.15$  K, were derived from the standard molar energies of combustion in oxygen, measured by static-bomb combustion calorimetry. Combining these results with literature results of the standard molar enthalpies of sublimation, at  $T = 298.15$  K, the standard molar enthalpies of formation, in the gaseous phase, were derived. Additionally, the enthalpies of formation of the ten possible isomers of aminomethoxybenzoic acid were estimated using accurate Double Hybrid Density Functional Theory (DHDFT) computational methods. The good agreement between the experimental and estimated values of the enthalpies of formation of the five isomers studied experimentally allows us to be confident on the estimated values for the other five isomers. A quantitative evaluation and analysis of the aromatic character of all the studied isomers based on the calculation of Nucleus Independent Chemical Shifts (NICS) was also conducted.

## 1. Introduction

Our research group has been studying thermodynamic and thermochemical properties of several benzoic acid derivatives for more than a decade,<sup>1</sup> to understand the effect of different substituents on the energetics and aromaticity of these compounds.<sup>2,3</sup> One of these studies<sup>3</sup> deals with aminomethylbenzoic acid isomers. To evaluate the influence of the methoxy substituent in aminobenzoic acids, it was decided to perform an experimental and theoretical thermochemical study of five aminomethoxybenzoic acid isomers.

Aminobenzoic acids and their derivatives are useful intermediates for producing pharmaceuticals,<sup>4</sup> aromatic compounds absorbing UVB and/or UVA,<sup>5</sup> dyes,<sup>6</sup> and flavours and fragrances.<sup>7</sup> Conducting polymers,<sup>8</sup> nanocrystalline particles,<sup>9</sup> materials with luminescent characteristics,<sup>10</sup> peptides and peptidomimetics,<sup>11</sup> and other molecules with biological properties<sup>12–15</sup> are also built from these aromatic amino acids. Aminomethoxybenzoic acids are trisubstituted benzene compounds with the general structure shown in Figure 1 and will generally be referred to as XA–Y–MOBA, where X represents the position of the amino group A; Y represents the position of the methoxy group MO; and BA is the acronym for benzoic acid.

The standard molar enthalpies of sublimation of five aminomethoxybenzoic acid isomers have been recently<sup>16</sup> derived from vapor pressure measurements at different temperatures using the Knudsen effusion method.<sup>17</sup> In the present work, the standard ( $p^0 = 0.1$  MPa) molar enthalpies of formation, in the crystalline phase, at  $T = 298.15$  K, of those isomers were derived from the standard molar energies of combustion measured by static-bomb combustion calorimetry. From experimental values, the standard molar enthalpies of formation, in the gaseous state, of the compounds were derived and



**Figure 1.** General structural formula for the isomers of aminomethoxybenzoic acid.

compared with the corresponding values estimated from computational chemistry.

## 2. Experimental Section

**2.1. Materials and Purity Control.** All the compounds studied in this work are commercial products from Aldrich Chemical Co. with purity certificates of 0.999 for 2A-3-MOBA (CAS n. 3177-80-8), 0.968 for 2A-5-MOBA (CAS n. 6705-03-9), 0.980 for 3A-4-MOBA (CAS n. 2840-26-8), 0.974 for 3A-5-MOBA (CAS n. 74165-74-5), and 0.989 for 4A-3-MOBA (CAS n. 2486-69-3). Samples of the compounds were purified by repeated sublimation under reduced pressure ( $p = 1$  Pa) previous to the experimental study. The final purity of each sample was checked by gas–liquid chromatography and confirmed during the combustion experiments by closeness to unity of the carbon dioxide recovery ratios. The average ratios of the mass of carbon dioxide recovered after combustion to that calculated from the mass of samples used in each experiment were:  $(1.00045 \pm 0.00027)$  for 2A-3-MOBA,  $(1.00042 \pm 0.00020)$  for 2A-5-MOBA,  $(0.99985 \pm 0.00018)$  for 3A-4-MOBA,  $(1.00028 \pm 0.00036)$  for 3A-5-MOBA, and  $(1.00038 \pm 0.00032)$  for 4A-3-MOBA, where the uncertainties are twice the standard deviations of the mean. The specific densities used to calculate the true mass from the apparent mass in air were determined from the ratio mass/volume of a pellet of the

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compounds (made in vacuum, with an applied pressure of  $10^5$  kg/cm<sup>2</sup>). The values of specific densities used for the studied compounds were:  $\rho = 1.26$  g/cm<sup>3</sup> for 2A-3-MOBA;  $\rho = 1.22$  g/cm<sup>3</sup> for 2A-5-MOBA;  $\rho = 1.37$  g/cm<sup>3</sup> for 3A-4-MOBA;  $\rho = 1.30$  g/cm<sup>3</sup> for 3A-5-MOBA; and  $\rho = 1.19$  g/cm<sup>3</sup> for 4A-3-MOBA.

**2.2. Combustion Calorimetry.** The standard molar enthalpies of the five compounds, in the condensed phase, were obtained from combustion calorimetry with an isoperibol static bomb calorimeter, equipped with a Parr 1108 model twin valve bomb, made of stainless steel and with an internal volume of 0.342 dm<sup>3</sup>.<sup>18,19</sup> Benzoic acid (NIST Thermochemical Standard 39j) with a certified massic energy of combustion, under bomb conditions of  $-(26\,434 \pm 3)$  J/g,<sup>20</sup> was used for calibration of the bomb. The procedure described by Coops et al. was followed.<sup>21</sup> From six independent calibration experiments, the value of the energy equivalent of the calorimeter was determined as  $\epsilon_{\text{cal}} = (15\,995.3 \pm 1.1)$  J/K, for an average mass of water added to the calorimeter of 3119.6 g; the quoted uncertainty is the standard deviation of the mean.

The samples of the crystalline compounds were burnt in pellet form, and 1.00 cm<sup>3</sup> of deionized water was introduced into the bomb, which was purged twice with oxygen to remove air, before being filled with 3.04 MPa of oxygen.

The calorimeter temperatures were measured to  $\pm 1 \times 10^{-4}$  K, at intervals of 10 s, with a quartz crystal thermometer (Hewlett-Packard HP 2804 A), interfaced to a PC. The ignition of the samples was made at  $T = 298.15$  K, at least 100 readings after the start of the experiment, by the discharge of a 1400  $\mu$ F capacitor through a platinum ignition wire of diameter 0.05 mm. After ignition, another 100 readings were taken for each the main and the after periods. Data acquisition, control of the calorimeter temperature, and the calculation of the adiabatic temperature change were performed using the program LAB-TERMO.<sup>22</sup>

For the cotton-thread used as a fuse in all the experiments, the empirical formula and the massic energy of combustion are, respectively, CH<sub>1.686</sub>O<sub>0.843</sub> and  $-16\,240$  J/g.<sup>23</sup> This value has been previously confirmed in our laboratory. The corrections for nitric acid formation  $\Delta U$  (HNO<sub>3</sub>) were based on  $-59.7$  kJ/mol for the molar energy of formation of 0.1 mol/dm<sup>3</sup> HNO<sub>3</sub>(aq) from N<sub>2</sub>(g), O<sub>2</sub>(g), and H<sub>2</sub>O(l).<sup>24</sup> The amount of compound,  $m(\text{compound})$ , used in each experiment and on which the energy of combustion was based was determined from the total mass of carbon dioxide produced taking into account that formed from the combustion of the cotton thread fuse and from the combustion auxiliary *n*-hexadecane (Aldrich Gold Label, mass fraction >0.999, stored under nitrogen,  $\Delta_c u^0 = -(47\,132.7 \pm 2.6)$  J/g used for combustion experiments of 4A-3-MOBA. For all the studied isomers, an estimated pressure coefficient of specific energy,  $(\partial u/\partial p)_T = -0.2$  J/g/MPa at  $T = 298.15$  K, a typical value for most solid organic compounds, was assumed.<sup>25</sup> For each compound, the corrections to the standard state to derive the standard massic energy of combustion,  $\Delta_c u^0$ , were made by the procedure given by Hubbard et al.<sup>26</sup> The atomic weights of the elements were those recommended by the IUPAC commission in 2005.<sup>27</sup>

### 3. Computational Details

The optimum geometries of all aminomethoxybenzoic acid isomeric molecules have been determined using density functional theory (DFT) with the Becke three-parameter hybrid exchange<sup>28</sup> and the Lee–Yang–Parr<sup>29</sup> correlation functionals (B3LYP) together with the 6-31G(d)<sup>30,31</sup> basis set. The optimum

structures so obtained have further been confirmed as true minima by constructing and diagonalizing the corresponding Hessian matrices, a procedure that also provides reliable estimates of the harmonic vibrational frequencies which, after being properly scaled by the accepted factor of 0.9614,<sup>32</sup> allows the estimations of the molecular thermal corrections needed to obtain molecular energies and enthalpies at any temperature. These structures also served as the reference structures to more accurate single-point energy calculations we further carried out, namely, at the DFT/B3LYP level with the 6-311+G(2df,2p).<sup>33</sup>

We have also conducted energy calculations based on the doubly hybrid density functional theory (DHDFT),<sup>34</sup> namely, the multicoefficient three-parameter Becke88-Becke95 (MC3BB) method and the multicoefficient three-parameter modified Perdew–Yang (MC3MPW) method. These last methods involve combinations of correlated wave function methods, at the MP2 level, with hybrid density functional methods. The coefficients in those combinations have been properly optimized against atomization energies and chemical reaction barrier heights.<sup>34</sup>

The aromatic behavior of a molecule can be assessed on the basis of the analysis of their magnetic properties, namely, the observable effects of the circular ring current induced by applied external magnetic fields. For aromatic systems, these currents produce an induced magnetic field opposing the external one, a phenomenon which can be experimentally probed by the nuclear magnetic resonance (NMR) chemical shifts measured at each nucleus. This concept has been generalized and converted into a useful aromaticity index by Schleyer et al.<sup>35</sup> who developed a methodology involving the calculation of the chemical shifts not just at every nucleus but at any point in the space in the vicinity of molecules, leading to what is now described as Nucleus Independent Chemical Shifts (NICS); these are just the negative of the isotropic component (the trace) of the chemical shielding tensor evaluated at the specific points. So, aromaticity has been very often assessed by calculating the NICS at the geometric center of the rings and also, to specifically avoid the shielding effects of the framework of  $\sigma$  electrons, at some point somewhat (generally 1.0 Å) above the geometric center of the ring.<sup>36,37</sup> Significantly negative (shielded) NICS values inside rings are due to induced diatropic ring currents and denote aromaticity, whereas positive (deshielded) values denote paratropic ring currents associated with antiaromatic behavior. Additionally, it has also been recognized that, since ring currents resulting from cyclic  $\pi$ -electron delocalization are induced primarily by the external magnetic field applied perpendicularly to the ring (conventionally the ZZ direction), the out-of-plane (ZZ) component of the magnetic shielding tensor should contain the most relevant information for the aromaticity evaluation.<sup>38</sup> We thus have chosen to calculate both the isotropic and the out-of-plane components of the chemical shielding tensor, denoted, respectively, as  $\sigma_{\text{iso}}$  and  $\sigma_{\text{ZZ}}$ , evaluated at the ring centers and 1.0 Å above, using the B3LP/6-311G\*\* wave functions and the GIAO<sup>39–42</sup> method, as a convenient way of characterizing aromaticity.

### 4. Results and Discussion

Table 1 lists the combustion results for one experiment of each studied compound in which  $\Delta m(\text{H}_2\text{O})$  is the deviation of the mass of water added to the calorimeter from 3119.6 g, the mass assigned for  $\epsilon_{\text{cal}}$ ;  $\Delta U_{\Sigma}$  is the correction to the standard state; and the remaining quantities are as previously described.<sup>26,43</sup> For the static bomb measurements, as samples were ignited at  $T = 298.15$  K, the internal energy for the isothermal bomb process,  $\Delta U(\text{IPB})$ , was calculated through eq 1

$$\Delta U(\text{IBP}) = -\{\varepsilon_{\text{cal}} + \Delta m(\text{H}_2\text{O}) \cdot C_p(\text{H}_2\text{O}, \text{l}) + \varepsilon_f\} \Delta T_{\text{ad}} + \Delta U_{\text{ign}} \quad (1)$$

where  $\Delta T_{\text{ad}}$  is the calorimeter temperature change corrected for the heat exchange and the work of stirring. The individual values of  $-\Delta_c u^0$ , together with the mean value,  $\langle -\Delta_c u^0 \rangle$ , and its standard deviation are given in Table 2. The values of  $\Delta_c u^0$  refer to the combustion reaction, represented by

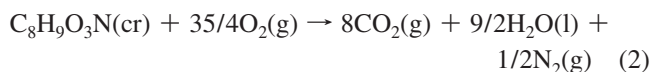


Table 3 shows the derived standard molar energies and enthalpies of combustion,  $\Delta_c U_{\text{m}}^0(\text{cr})$  and  $\Delta_c H_{\text{m}}^0(\text{cr})$ , and the standard molar enthalpies of formation in the crystalline phase,  $\Delta_f H_{\text{m}}^0(\text{cr})$ , at  $T = 298.15$  K. In accordance with customary thermochemical practice,<sup>44</sup> the uncertainty assigned to the standard molar enthalpies of combustion is twice the overall standard deviation of the mean and includes the uncertainties in calibration and in the values of auxiliary quantities used. To derive  $\Delta_f H_{\text{m}}^0(\text{cr})$  from  $\Delta_c H_{\text{m}}^0(\text{cr})$ , the standard molar enthalpies of formation of  $\text{H}_2\text{O}(\text{l})$  and  $\text{CO}_2(\text{g})$ , at  $T = 298.15$  K,  $-(285.830 \pm 0.042)$  kJ/mol, and  $-(393.51 \pm 0.13)$  kJ/mol, respectively, were used.<sup>45</sup> From the values for the standard molar enthalpies of formation and of sublimation<sup>16</sup> of the crystalline compounds, the values of the standard molar enthalpies in the gaseous phase were derived. These results are summarized in Table 4.

**TABLE 3: Derived Standard ( $p^0 = 0.1$  MPa) Molar Values at  $T = 298.15$  K**

compound	$-\Delta_c U_{\text{m}}^0$	$-\Delta_c H_{\text{m}}^0$	$-\Delta_f H_{\text{m}}^0(\text{cr})$
	kJ/mol	kJ/mol	kJ/mol
2A-3-MOBA	$3857.5 \pm 1.7$	$3858.1 \pm 1.7$	$576.2 \pm 2.0$
2A-5-MOBA	$3863.7 \pm 1.7$	$3864.3 \pm 1.7$	$570.0 \pm 2.0$
3A-4-MOBA	$3865.2 \pm 1.6$	$3865.8 \pm 1.6$	$568.5 \pm 1.9$
3A-5-MOBA	$3872.2 \pm 1.3$	$3872.8 \pm 1.3$	$561.5 \pm 1.7$
4A-3-MOBA	$3845.7 \pm 1.5$	$3846.3 \pm 1.5$	$588.0 \pm 1.8$

The optimum B3LYP/6-31G(d) geometries indicate that the aminomethoxybenzoic acid isomers tend preferentially to adopt planar conformations, with all substituents oriented so that the relevant atomic species occupy the same plane as the benzenic ring. This finding is in agreement with a similar behavior found for the monosubstituted molecules, aniline, methoxybenzene, and benzoic acid, and reflects the possibility of stabilization by  $\pi$ -electron donation from the amino and methoxyl groups through the aromatic ring to the strong  $\pi$ -electron-withdrawing acid group. The only exception occurs for 3-amino-2-methoxybenzoic acid for which the close proximity of the bulky substituents originates large steric repulsions thus forcing such substituents to become mutually oriented in such a way that the repulsions are largely minimized: thus, we observe that the dihedral angle  $\text{C}_b\text{--C}_b\text{--O--C}(\text{H}_3)$ , which measures the deviation of the  $\text{O--CH}_3$  bond from coplanarity with the benzenic ring, assumes a value of  $89.7^\circ$  and also a slight deviation of  $19.4^\circ$  of the carboxyl substituent from the coplanarity with the same ring.

**TABLE 1: Typical Combustion Results, at  $T = 298.15$  K ( $p^0 = 0.1$  MPa), for the Studied Isomers<sup>a</sup>**

	2A-3-MOBA	2A-5-MOBA	3A-4-MOBA	3A-5-MOBA	4A-3-MOBA
$m(\text{CO}_2, \text{total})/\text{g}$	1.45864	1.49027	1.66301	1.07468	1.31104
$m(\text{cpd})/\text{g}$	0.68988	0.70526	0.78737	0.50769	0.40418
$m(\text{fuse})/\text{g}$	0.00348	0.00301	0.00288	0.00334	0.00313
$m(n\text{-hexadecane})/\text{g}$	--	--	--	--	0.14582
$\Delta T_{\text{ad}}/\text{K}$	1.00047	1.02385	1.14276	0.73954	1.01660
$\varepsilon_f(\text{J/K})$	15.68	15.99	16.15	14.96	16.07
$\Delta m(\text{H}_2\text{O})/\text{g}$	0.0	0.0	0.0	0.1	0.0
$-\Delta U(\text{IBP})/\text{J}$	16017.44	16392.05	18296.46	11839.70	16276.07
$\Delta U(\text{fuse})/\text{J}$	56.52	48.88	46.77	54.24	50.83
$\Delta U(\text{HNO}_3)/\text{J}$	30.01	25.36	30.39	18.40	23.24
$\Delta U(n\text{-hexadecane})/\text{J}$	--	--	--	--	6897.46
$\Delta U(\text{ign})/\text{J}$	1.07	1.11	0.78	0.84	1.09
$\Delta U_{\Sigma}/\text{J}$	12.24	12.54	14.16	8.35	8.76
$-\Delta_c u^0(\text{J/g})$	23074.55	23119.52	23121.45	23161.20	23007.27

<sup>a</sup>  $m(\text{CO}_2, \text{total})$  is the total mass of  $\text{CO}_2$  formed in the experiment;  $m(\text{compound})$  is the mass of compound burnt in the experiment;  $m(\text{fuse})$  is the mass of fuse (cotton); and  $m(n\text{-hexadecane})$  is the mass of Melinex used in the experiment;  $\Delta T_{\text{ad}}$  is the corrected temperature rise;  $\varepsilon_f$  is the energy equivalent of contents in the final state;  $\Delta m(\text{H}_2\text{O})$  is the deviation of the mass of water added to the calorimeter from 3119.6 g;  $\Delta U(\text{IBP})$  is the energy change for the isothermal combustion reaction under actual bomb conditions;  $\Delta U(\text{IBP})$  includes the ignition energy,  $\Delta U(\text{ignition})$ ;  $\Delta U(\text{fuse})$  is the energy of combustion of the fuse (cotton);  $\Delta U(n\text{-hexadecane})$  is the energy of combustion of  $n$ -hexadecane;  $\Delta U(\text{HNO}_3)$  is the energy correction for the nitric acid formation;  $\Delta U_{\Sigma}$  is the energy correction to the standard state; and  $\Delta_c u^0$  is the standard massic energy of combustion.

**TABLE 2: Individual Values of Standard ( $p^0 = 0.1$  MPa) and Massic Energies of Combustion, of the Studied Compounds, at  $T = 298.15$  K**

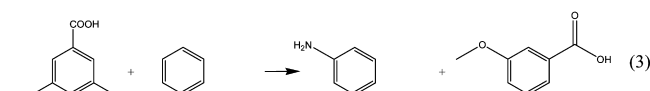
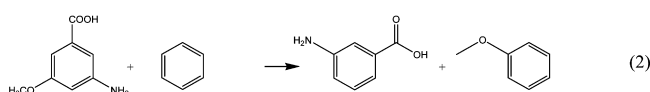
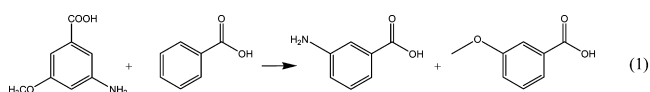
2A-3-MOBA	2A-5-MOBA	3A-4-MOBA	3A-5-MOBA	4A-3-MOBA
$-\Delta_c u^0(\text{J/g})$				
23077.79	23098.85	23118.49	23168.83	23016.30
23075.34	23102.84	23135.08	23156.19	22999.04
23074.55	23121.11	23116.46	23167.07	23007.18
23060.90	23117.81	23132.62	23161.20	22996.47
23093.23	23120.45	23121.45	23171.95	23007.56
23076.33	23119.52	23112.02	23159.39	23007.27
$\langle -\Delta_c u^0 \rangle(\text{J/g})$				
$23076.4 \pm 4.2$	$23113.4 \pm 4.0$	$23122.7 \pm 3.8$	$23164.1 \pm 2.5$	$23005.6 \pm 2.9$

**TABLE 4: Derived Standard ( $p^0 = 0.1$  MPa) Molar Enthalpies of Formation at  $T = 298.15$  K**

compound	$-\Delta_f H_m^0(\text{cr})$ kJ/mol	$\Delta_{\text{cr}}^g H_m^0$ kJ/mol	$-\Delta_f H_m^0(\text{g})$ kJ/mol
2A-3-MOBA	576.2 $\pm$ 2.0	115.5 $\pm$ 0.8	460.7 $\pm$ 2.2
2A-5-MOBA	570.0 $\pm$ 2.0	119.3 $\pm$ 0.8	450.7 $\pm$ 2.2
3A-4-MOBA	568.5 $\pm$ 1.9	130.7 $\pm$ 0.8	437.8 $\pm$ 2.1
3A-5-MOBA	561.5 $\pm$ 1.7	136.1 $\pm$ 1.0	425.4 $\pm$ 2.0
4A-3-MOBA	588.0 $\pm$ 1.8	132.0 $\pm$ 1.2	456.0 $\pm$ 2.2

<sup>a</sup> Ref 16.

We used the following homodesmotic reactions to get reliable estimates of the enthalpies of formation of the aminomethoxybenzoic acid isomers



The energies of all isomers including all auxiliary molecules used in the selected homodesmotic reactions (1–3), at each theoretical level adopted, as well as the scaled thermal corrections are shown, under the appropriated headings, in Table 5.

These reactions were chosen on the basis of available experimental data for all the auxiliary molecules involved in the reactions. The experimental values for the standard molar enthalpies of formation of the auxiliary molecules in gaseous state, at  $T = 298.15$  K, were taken from Pedley compendium (all values in kJ/mol):<sup>46</sup> benzene, (82.6  $\pm$  0.7); benzoic acid, (–294.0  $\pm$  2.2); aniline, (87.03  $\pm$  0.88); methoxybenzene, (67.9

$\pm$  0.8); 2-aminobenzoic acid (2-ABA), (–296.0  $\pm$  1.3); 3-ABA, (–283.6  $\pm$  3.8); 4-ABA, (–296.7  $\pm$  3.8); 2-methoxybenzoic acid (2-MOBA), (–433.8  $\pm$  0.7); 3-MOBA, (–446.1  $\pm$  0.7); 4-MOBA, (–451.9  $\pm$  1.0). The computationally calculated enthalpies of reaction were combined with the experimental standard molar enthalpies of formation of all the intervening molecules, to obtain the standard molar enthalpy of formation of each isomer in the gaseous phase, at  $T = 298.15$  K, whose values are presented in Table 6 along with the experimental values.

As can be observed from the results in Table 6, our computational estimates agree closely with the experimentally available data. The results obtained from the DHDFT calculations are seen to be the most reliable, providing in most cases energetic estimates falling within the “chemical accuracy” standard, i.e., 4 kJ/mol. These observations can thus be invoked to support the reliability of our energetic estimates for the cases where, due to the lack of experimental measurements, they assume the status of predictions.

Analyzing the electronic energies for the ten isomers calculated by DHDFT (Table 5), the thermochemical stability seems to be greater for the isomers where the stabilizing interactions involving one of the hydrogen atoms of the amino group and the terminal oxygen of the carboxylic group or the oxygen atom of the methoxyl group are present. In the isomers 2A-3-MOBA, 2A-4-MOBA, and 2A-5-MOBA, the intramolecular hydrogen interaction between the  $\text{NH}_2$  and  $\text{COOH}$  groups and eventually the additional hydrogen interaction between  $\text{NH}_2$  and the oxygen of the vicinal  $\text{OCH}_3$  substituent in the isomer 2A-3-MOBA may explain their high stabilities. In the isomers 3A-4-MOBA and 4A-3-MOBA, a stabilizing hydrogen interaction between  $\text{NH}_2$  and the oxygen of the vicinal  $\text{OCH}_3$  may explain their higher stabilities relative to 3A-5-MOBA. In the isomers 2A-6-MOBA and 3A-2-MOBA, the steric interactions may be responsible for their lower stability. The least stable are the isomers 4A-2-MOBA and 3A-6-MOBA due to the repulsive  $\text{O}\cdots\text{O}$  interaction resulting from the proximity between the  $\text{COOH}$  and  $\text{OCH}_3$  groups.

The electronic effects of substituents on the benzene ring may be correlated with aromaticity. However, in monosubstituted

**TABLE 5: Calculated Energies (Hartree) and Thermal Corrections  $E_{\text{th}}$  (kJ/mol) for the Studied Isomers and Auxiliary Molecules**

molecule	B3LYP			DHDFT	
	6-31G(d)	6-311+G(2df,2p)	$E_{\text{th}}^a$	MC3BB	MC3MPW
2A-3-MOBA	–590.701806	–590.924112	447.448	–590.440410	–590.539674
2A-4-MOBA	–590.707431	–590.926756	447.552	–590.441542	–590.540393
2A-5-MOBA	–590.702181	–590.921072	447.427	–590.436414	–590.536410
2A-6-MOBA	–590.696858	–590.915401	447.284	–590.430438	–590.529977
3A-2-MOBA	–590.690288	–590.908343	447.229	–590.426005	–590.524711
3A-4-MOBA	–590.700132	–590.920244	447.991	–590.436562	–590.535699
3A-5-MOBA	–590.698661	–590.918541	447.246	–590.434394	–590.533520
3A-6-MOBA	–590.688704	–590.907663	447.383	–590.423737	–590.523538
4A-2-MOBA	–590.694087	–590.913930	447.251	–590.429184	–590.528013
4A-3-MOBA	–590.702322	–590.922449	447.889	–590.438442	–590.537493
2-MOBA	–535.466007	–476.360580	399.087	–535.087276	–535.172799
3-MOBA	–535.476775	–476.354518	400.043	–535.098341	–535.184443
4-MOBA	–535.478299	–476.360580	400.169	–535.099515	–535.185469
2ABA	–476.300404	–476.360580	356.845	–475.967927	–476.047663
3ABA	–476.294000	–476.354518	356.877	–475.962585	–476.042136
4ABA	–476.297293	–476.357939	356.852	–475.965159	–476.044447
2A-MO-Benzene	–402.124060	–402.270539	402.108	–401.919426	–401.990785
3A-MO-Benzene	–402.124386	–402.270513	401.720	–401.918621	–401.989834
4A-MO-Benzene	–402.121416	–402.267231	401.555	–401.915531	–401.987295

<sup>a</sup>  $E_{\text{th}}(T = 298.15 \text{ K}) = E_{\text{trans}} + E_{\text{rot}} + E_{\text{ZP}} + \Delta_{0\text{K}}^{298.15\text{K}} E_{\text{vib}}$ .



**TABLE 6: Estimates of the Standard Molar Enthalpies of Formation of All the Isomers of Aminomethoxybenzoic Acid, in the Gas Phase, at  $T = 298.15$  K**

molecule	reaction	$-\Delta_f H_m^0(\text{g})/\text{kJ/mol}$			
		B3LYP/6-311+G (2df,2p)	MC3BB	MC3MPW	experimental
2A-3-MOBA	1	442.95	444.90	447.56	$460.7 \pm 2.2$
	2	441.46	442.90	447.53	
	3	452.33	451.85	457.56	
2A-4-MOBA	1	451.42	450.93	452.90	---
	2	448.62	446.09	449.63	
	3	460.80	457.89	462.90	
2A-5-MOBA	1	435.31	434.75	439.34	$450.7 \pm 2.2$
	2	433.82	432.76	439.30	
	3	444.69	441.71	449.34	
2A-6-MOBA	1	437.84	435.00	439.91	---
	2	419.08	417.21	422.55	
	3	446.86	441.95	449.90	
3A-2-MOBA	1	422.56	425.07	428.28	---
	2	404.15	407.28	410.93	
	3	428.39	430.37	436.13	
3A-4-MOBA	1	437.43	439.08	442.28	$437.8 \pm 2.1$
	2	434.63	434.24	439.01	
	3	443.26	444.37	450.14	
3A-5-MOBA	1	432.40	431.29	434.07	$425.4 \pm 2.0$
	2	430.91	429.29	434.04	
	3	438.23	436.58	441.93	
3A-6-MOBA	1	420.62	418.97	425.05	---
	2	402.21	401.17	407.69	
	3	426.45	424.26	432.90	
4A-2-MOBA	1	442.30	440.72	444.94	---
	2	423.89	422.92	427.58	
	3	443.03	438.69	444.78	
4A-3-MOBA	1	442.75	449.23	452.51	$456.0 \pm 2.2$
	2	445.62	446.59	451.83	
	3	447.85	446.57	451.72	

benzenes, the presence of a single substituent appears not to affect significantly the aromaticity of the ring.<sup>47,48</sup> In the present work, we have studied the simultaneous effect of the three substituents, COOH, NH<sub>2</sub>, and OCH<sub>3</sub>, on the energetics of benzene.

The single NICS values we obtained are collected in Table 7. Significantly negative NICS values inside rings denote aromaticity. Either NICS component,  $\sigma_{\text{iso}}$  or  $\sigma_{\text{ZZ}}$ , but especially those measured 1.0 Å above the ring centers, unequivocally indicates that the benzene ring shows always lower aromaticity in the isomers of aminomethoxybenzoic acids than in the parent benzene molecule.

In monosubstituted systems, just a slight loss of aromaticity is observed, being however more evident in aniline (amino substitution). NH<sub>2</sub> and OCH<sub>3</sub> are two mesomeric electron-donor groups ( $\pi$ -donors), while COOH is a mesomeric electron acceptor. Apparently, all three groups disturb aromaticity of the ring. NH<sub>2</sub> has the stronger donor effect and seems also to be the most disturbing. In disubstituted benzenes, where one of the substituents is always COOH, the lowering of aromaticity is more evident in *ortho* and *para* aminobenzoic acids than in the corresponding *ortho* and *para* methoxybenzoic acids, indicating again a stronger effect of the amino group relative to the methoxy group on the aromaticity of the benzene ring.

For the trisubstituted benzenes studied in this work, we can observe from the out-of-plane component of the chemical shielding tensor measured 1.0 Å above the ring centers,  $\sigma_{\text{ZZ}}$ , that the disturbing effect over aromaticity is larger when either of the additional substituents, NH<sub>2</sub> or OCH<sub>3</sub>, is located at positions favoring their cooperative electronic interaction with the electron-acceptor group, COOH. Thus, all isomers with NH<sub>2</sub>

**TABLE 7: Isotropic ( $\sigma_{\text{iso}}$ ) and Out-of-Plane ( $\sigma_{\text{ZZ}}$ ) NICS Components (in ppm), Calculated at the Center of the Benzenoid Ring and 1.0 Å Above This Point, for the Aminomethoxybenzoic Acid Isomers and for Other Related Systems**

	NICS(0)		NICS(+1)	
	$\sigma_{\text{iso}}$	$\sigma_{\text{ZZ}}$	$\sigma_{\text{iso}}$	$\sigma_{\text{ZZ}}$
benzene	-8.91	-14.51	-11.12	-29.24
benzoic acid (BA)	-8.69	-12.26	-10.95	-27.77
aniline	-8.75	-10.11	-9.88	-24.99
methoxybenzene	-9.72	-12.89	-10.81	-27.23
2ABA	-7.39	-4.27	-8.81	-20.47
3ABA	-8.69	-8.22	-10.08	-24.17
4ABA	-8.04	-6.26	-9.36	-22.26
2-MOBA	-9.57	-12.26	-10.74	-26.32
3-MOBA	-9.57	-10.77	-10.71	-25.83
4-MOBA	-9.10	-9.40	-10.36	-24.77
2A-3-MOBA	-8.73	-5.27	-9.29	-20.63
2A-4-MOBA	-7.94	-2.01	-8.36	-17.62
2A-5-MOBA	-8.75	-4.69	-9.17	-20.20
2A-6-MOBA	-7.42	-1.01	-7.93	-16.77
3A-2-MOBA	-9.69	-8.58	-10.07	-23.10
3A-4-MOBA	-9.71	-7.33	-10.18	-22.97
3A-5-MOBA	-9.38	-6.32	-9.72	-21.84
3A-6-MOBA	-9.56	-7.28	-10.00	-22.64
4A-2-MOBA	-8.56	-4.17	-8.71	-19.16
4A-3-MOBA	-9.45	-6.45	-9.72	-21.89

or OCH<sub>3</sub> at the *meta* position evidence the higher aromaticity within the group.

There is no evidence of a correlation between the relative thermochemical stabilities of the ten isomers studied and the relative values of calculated NICS for the benzene ring, which are a measure of aromaticity.

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