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Systematic Evaluation of the Conformational Properties of Aliphatic ω-Methoxy Methyl Esters

Carlos Alemán,[*,†] Jordi Casanovas,[‡] and H. K. Hall, Jr.[*,§]

Departament d'Enginyeria Química, E.T.S. d'Enginyeria Industrial de Barcelona, Universitat Politècnica de Catalunya, Diagonal 647, Barcelona E-08028, Spain, Departament de Química, Escola Politècnica Superior, Universitat de Lleida, C/Jaume II 69, Lleida 25001, Spain, and Department of Chemistry, The University of Arizona, Tucson, Arizona 85721

carlos.aleman@upc.edu; hkh@u.arizona.edu

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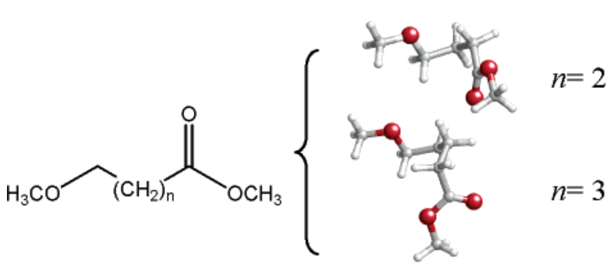

A systematic conformational study of ω-methoxy methyl esters, $CH_3O-(CH_2)_n-COO-CH_3$ with $n = 3$ and 4, has been performed using quantum mechanical calculations at the MP2 level. Calculations have been carried out in both gas phase and chloroform solution, a polarizable continuum solvation model being used to represent the latter. Results have been compared with those recently obtained for the analogues ω-hydroxy acids, $HO-(CH_2)_n-COOH$ with $n = 3$ and 4. The compounds with $n = 3$ clearly favor coiled conformations, the population expected for extended and semiextended conformations being very low. However, for compounds with $n = 4$ the minimum energy extended and semiextended structures become considerably more stable. The overall results indicate that the conformational preferences of the central aliphatic segment of ω-methoxy methyl esters and ω-hydroxy acids are not influenced by the formation of intramolecular O−H···O hydrogen bonds.

Introduction

In a very recent study, we systematically analyzed the conformational properties of simple aliphatic ω-hydroxy acids, $HO-(CH_2)_n-COOH$ with n ranging from 2 to 4, using quantum mechanical calculations.[1] This investigation was motivated by two different but equally important reasons. First, we were interested in the *intrinsic* conformational preferences of these simple molecules, which can be useful for the subsequent structural exploration of more complex and larger systems. Thus, although aliphatic ω-hydroxy acids are used to prepare important synthetic polyesters[2] and are contained in important lipid phases,[3] no study about their conformational properties was previously reported. Second, we examined if the *folding of methylene units* extends to this family of compounds. This anomalous conformational feature was defined as the tendency of the methylene units to adopt a gauche conformation in compounds with small aliphatic segments flanked by two carbonyl groups (i.e., $CO-(CH_2)_{n-CO}$ with $n < 5$).[4] The folding of methylene units was detected on difunctional molecules including diamides,[1,5] diesters,[6] and diketones.[7]

Results indicated a very consistent conformational behavior, as demonstrated by the fact that, for $n > 2$,

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[†] Universitat Politècnica de Catalunya.

[‡] Universitat de Lleida.

[§] University of Arizona.

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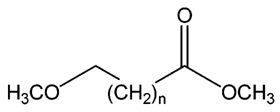
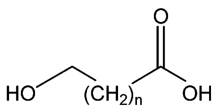
the lowest energy conformation of HO$-$(CH$_2$)$_n-$COOH is intimately related with the lowest energy conformation of HO$-$(CH$_2$)$_{n-1}-$COOH.[1] Furthermore, calculations in chloroform solution revealed that environmental forces can alter the intrinsic conformational preferences of ω-hydroxy acids. Thus, the potential energy surfaces of these compounds are flatter in solution than in the gas phase, the conformational flexibility being considerably higher in the former environment. A very noticeable feature predicted in both gas phase and solution is the systematic stabilization of the extended and semiextended conformations, which increases with the size of the central aliphatic segment.[1]

In the current work, we have extended our previous conformational study to methyl 4-methoxybutyrate (**1**) and methyl 5-methoxyvalerate (**2**), which are closely related to 4-hydroxybutyric acid (**3**) and 5-hydroxyvaleric acid (**4**), respectively. Despite their simplicity and notable interest as model molecules of chain segments of important synthetic polyesters, the intrinsic conformational preferences of **1** and **2** have not been explored yet. Moreover, **1**$-$**4** provide a complete range of substrates to investigate the influence of O$-$H$\cdots$O hydrogen bonds in the conformational preferences of the central aliphatic segment in compounds RO$-$(CH$_2$)$_n-$COOR.



1: *n=2*

2: *n*=3



3: *n*= 2

4: *n*= 3.

Methods

Gas Phase Calculations. Molecular conformations were labeled according to their dihedral angles, which were listed in the following order: for **1** and **3** the dihedral angles $\{\chi_1, \chi_1, \chi_3, \chi_4\}$ correspond to the consecutive bond rotations {O$-$CH$_2$, CH$_2-$CH$_2$, CH$_2-$CH$_2$, CH$_2-$C(OO)}, and for **2** and **4** $\{\chi_1, \chi_1, \chi_3, \chi_4, \chi_5\}$ correspond to {O$-$CH$_2$, CH$_2-$CH$_2$, CH$_2-$CH$_2$, CH$_2-$CH$_2$, CH$_2-$C(OO)}. The rotamers were classified as follows: trans (t, for $150^\circ \leq \chi_{\rm i} < 210^\circ$), skew$^-$ (s$^-$, for $210^\circ \leq \chi_{\rm i} < 270^\circ$), gauche$^-$ (g$^-$, for $270^\circ \leq \chi_{\rm i} < 330^\circ$), cis (c, for $330^\circ \leq \chi_{\rm i} < 30^\circ$), gauche$^+$ (g$^+$, for $30^\circ \leq \chi_{\rm i} < 90^\circ$), and skew$^+$ (s$^+$, for $90^\circ \leq \chi_{\rm i} < 150^\circ$).

The minimum energy conformations of **1** and **2** were characterized using a systematic conformational search procedure. Because each flexible dihedral angle is expected to have three minima, the number of minima that may be anticipated for the potential energy hypersurfaces (PEHs) of **1** and **2** is $3^4 = 81$ and $3^5 = 243$, respectively. However, due to the absence of stereochemistry, the number of theoretical minima can be reduced to 41 and 122, respectively, since $\{\chi_{\rm i}\} = \{-\chi_{\rm i}\}$, where $\chi_{\rm i}$ refers to the dihedral angles used to define the conformation. All these structures were taken as starting points for HF geometry optimizations using the 6-31G(d) basis set.[8] To account for electron correlation effects, all the structures resulting from HF/6-31G(d) optimizations were fully reoptimized at the MP2/6-31G(d) level.[9] Frequency analyses were carried out to verify the nature of the minimum state of all the stationary points located during MP2 geometry optimizations. Subsequently, single-point energy calculations were performed for all the minima of each compound at the MP2/6-311G(d,p) level[10] on the MP2/6-31G(d) optimized geometries. The computed frequencies were used to obtain the zero-point vibrational energies (ZPVE) and both thermal and entropic corrections. To provide the conformational Gibbs free energies in the gas phase ($\Delta G_{\rm gp}$), such statistical terms were added to the gas phase energies computed at the MP2/6-311G(d,p) level. The same procedure was applied in our previous study to explore the conformational preferences of **3** and **4**.[1]

Solution Calculations. To estimate the solvation effects, single-point calculations were also conducted on the MP2/6-31G(d) energy minima using a self-consistent reaction field (SCRF) model. The SCRF methods treat the solute at the quantum mechanical level, while the solvent is represented as a dielectric continuum. Specifically, we chose the polarizable continuum model (PCM) developed by Tomasi and co-workers to describe the bulk solvent.[11-13] The PCM method involves the generation of a solvent cavity from spheres centered at each atom in the molecule and the calculation of virtual point charges on the cavity surface representing the polarization of the solvent. The magnitude of these charges is proportional to the derivative of the solute electrostatic potential at each point calculated from the molecular wave function. The point charges may, then, be included in the one-electron Hamiltonian, thus inducing polarization of the solute. An iterative calculation was carried out until the wave function and the surface charges were self-consistent. PCM calculations were performed in the framework of the ab initio HF/6-311G(d,p) level using the standard protocol and considering the dielectric constant of chloroform ($\epsilon = 4$). The conformational free energies in chloroform solution ($\Delta G_{\rm chl}$) were computed using the classical thermodynamics scheme: the free energies of solvation ($\Delta G_{\rm sol}$) provided by the PCM model were added to the $\Delta G_{\rm gp}$, $\Delta G_{\rm chl} = \Delta G_{\rm sol} + \Delta G_{\rm gp}$.

Gas phase and PCM calculations were performed using the Gaussian 98 computer program.[14]

Results and Discussion

Methyl 4-Methoxybutyrate (1). A total of 22 stationary points were characterized as minimum energy conformations, 21 being 2-fold degenerated. However, many of these minima are not significant since their population in the gas phase and chloroform solution is expected to be negligible (i.e., $\Delta G_{\rm gp}$ and $\Delta G_{\rm chl}$ relative to the global minimum are higher than 1.5 kcal/mol). Table 1 lists the dihedral angles $\{\chi_1, \chi_2, \chi_3, \chi_4\}$ and the gas phase relative energies for such significant minima, while Table 2 shows the values of $\Delta G_{\rm gp}$, $\Delta G_{\rm sol}$, and $\Delta G_{\rm chl}$. A complete description of all the minimum energy structures characterized at the MP2/6-31G(d) level is provided in the Supporting Information.

Relative energies (Table 1) indicate that the effects produced by the enlargement of the basis set are negligible. Accordingly, MP2/6-31G(d) and MP2/6-311G(d,p) relative energies are in excellent agreement, the largest

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TABLE 1. Dihedral Angles[a] (deg) and Relative Energies (kcal/mol) of Methyl 4-Methoxybutyrate (1) Minimum Energy Conformations[b]

label	χ_1	χ_2	χ_3	χ_4	MP2/6-31G(d)	MP2/6-311G(d,p)
$\mathrm{tg^{+}g^{+}t}$	−178.2	59.1	69.1	−170.4	0.0	0.0
$\mathrm{tg^{+}g^{-}g^{-}}$	−158.9	74.0	−53.1	−72.7	0.1	0.1
$\mathrm{g^{+}g^{+}g^{-}s^{+}}$	79.3	56.6	−69.9	131.3	0.1	0.1
$\mathrm{tg^{-}g^{+}s^{-}}$	173.9	−58.6	73.7	−127.3	0.8	0.7
$\mathrm{tg^{+}g^{+}g^{+}}$	−174.9	59.3	58.4	52.6	1.0	0.8
$\mathrm{tg^{-}tt}$	179.3	−59.6	−178.5	179.4	0.8	0.9
$\mathrm{g^{+}g^{+}g^{+}t}$	72.8	53.0	69.2	−170.4	1.2	1.2
$\mathrm{g^{+}g^{+}g^{-}g^{-}}$	79.6	61.6	−62.6	−53.8	1.2	1.2
$\mathrm{tg^{-}tg^{-}}$	178.5	−60.0	−177.2	−59.6	1.4	1.4
$\mathrm{ttg^{+}t}$	177.6	175.2	68.6	−170.0	1.7	1.7
$\mathrm{g^{+}g^{+}tt}$	73.0	55.4	−174.5	−167.6	1.9	1.9
$\mathrm{ttg^{+}g^{+}}$	179.5	176.8	59.2	70.3	2.0	2.0
tttt	180.0	180.0	180.0	180.0	2.3	2.3
$\mathrm{g^{+}g^{+}tg^{+}}$	70.2	54.2	−177.1	65.3	2.4	2.4
$\mathrm{tttg^{-}}$	−179.7	−179.7	−178.0	−65.8	2.7	2.7

[a] From MP2/6-31G(d) geometry optimizations. The dihedral angles are defined by the following sequences of bonds: $CH_3-O-CH_2-CH_2$ (χ_1), $O-CH_2-CH_2-CH_2$ (χ_2), $CH_2-CH_2-CH_2-C(=O)$ (χ_3), and $CH_2-CH_2-C(=O)-O$ (χ_4). [b] Information is provided only for the more relevant structures (see text).

TABLE 2. Geometric Parameters for the C−H···O Interactions, Relative Free Energies in the Gas Phase (ΔG_{gp}; kcal/mol) and Chloroform Solution (ΔG_{chl}; kcal/mol), and Free Energy of Solvation (ΔG_{sol}; kcal/mol) of Methyl 4-Methoxybutyrate (1) Minimum Energy Conformations

label	C−H···O interactions[a]	ΔG_{gp}	ΔG_{sol}	ΔG_{chl}
$\mathrm{tg^{+}g^{+}t}$	2.503 Å, 98.6°	0.0	−5.0	0.5
$\mathrm{tg^{+}g^{-}g^{-}}$	–	0.8	−5.5	0.8
$\mathrm{g^{+}g^{+}g^{-}s^{+}}$	2.430 Å, 118.0°	1.2	−5.5	1.1
$\mathrm{tg^{-}g^{+}s^{-}}$	–	0.7	−6.2	0.0
$\mathrm{tg^{+}g^{+}g^{+}}$	–	0.8	−5.8	0.1
$\mathrm{tg^{-}tt}$	2.542 Å, 95.8°	0.8	−6.1	0.0
$\mathrm{g^{+}g^{+}g^{+}t}$	2.541 Å, 99.2°	1.3	−5.6	1.1
$\mathrm{g^{+}g^{+}g^{-}g^{-}}$	–	2.3	−6.5	1.2
$\mathrm{tg^{-}tg^{-}}$	2.538 Å, 96.3°	1.1	−5.9	0.6
$\mathrm{ttg^{+}t}$	–	1.4	−5.6	1.2
$\mathrm{g^{+}g^{+}tt}$	–	1.3	−6.0	0.7
$\mathrm{ttg^{+}g^{+}}$	–	1.5	−5.7	1.2
tttt	–	1.6	−6.2	0.9
$\mathrm{g^{+}g^{+}tg^{+}}$	2.549 Å, 98.8°	2.1	−6.2	1.3
$\mathrm{tttg^{-}}$	–	2.1	−6.1	1.4

[a] H···O distance and ∠C−H···O angle in Å and degrees, respectively.

difference being 0.2 kcal/mol. On the other hand, comparison between the relative energies and the values of ΔG_{gp} indicates that the ZPVE and thermal and entropic corrections have a destabilizing effect for the more favored conformations, while the less favored conformations are stabilized by these thermodynamical corrections. For instance, the corrections applied to the second conformation $\mathrm{tg^{+}g^{-}g^{-}}$ produce a relative destabilization of +0.7 kcal/mol, while the fully extended conformation tttt stabilizes the same amount when the energy is transformed into Gibbs free energy.

The $\mathrm{tg^{+}g^{+}t}$ (Figure 1a) is the lowest energy conformation in the gas phase, this structure being stabilized by an intramolecular interaction of the C−H···O type. For consistency with our previous study,[1] the interaction between a C−H group and a neighbor electronegative oxygen was identified as hydrogen bond when the H···O distance was lower than 2.55 Å.[15−17] The $\mathrm{g^{+}g^{+}g^{-}t}$ was characterized as the lowest energy conformation in the gas phase for **3**, being stabilized not only by a C−H···O interaction but also by a conventional O−H···O hydrogen bond between the carboxylic acid and the hydroxyl moieties. The absence of the latter interaction in **1** explains the unfavorable ΔG_{gp} value of the $\mathrm{g^{+}g^{+}g^{-}s^{+}}$ conformation (1.2 kcal/mol in Table 2), which is the closest structure to the global minimum of **3**. The Supporting Information shows that seven minimum energy conformations of **1** are stabilized by C−H···O hydrogen bonds, six of them being listed in Table 2.

Interestingly, the solvent alters the relative energy order between the different conformers and reduces the conformational free energy difference between them, as is reflected in Table 2. Thus, the $\mathrm{tg^{-}g^{+}s^{-}}$ (Figure 1b) and the semiextended $\mathrm{tg^{-}tt}$ (Figure 1c) are isoenergetic and the more stable conformations in chloroform solution. The latter is stabilized by a C−H···O interaction, while no intramolecular hydrogen bond was found for the former. The ΔG_{gp} of the $\mathrm{tg^{-}g^{+}s^{-}}$ and $\mathrm{tg^{-}tt}$ structures are unfavored with respect to the global minimum by 0.7 and 0.8 kcal/mol, respectively, indicating that the strength of the solute−solvent interactions greatly determines the conformational preferences in solution. In opposition, the solvent destabilizes the $\mathrm{tg^{+}g^{+}t}$ conformation by 0.5 kcal/mol.

The number of significant minima in the gas phase and chloroform solution is 11 and 15, respectively, the population expected for the remaining minima being negligible. Comparison with the results reported for **3** indicates that the conformation flexibility decreases, especially in solution, when the hydroxyl and carboxylic acid functional groups are transformed into ether and ester groups, respectively, replacing the polar hydrogen atoms by CH_3. Thus, 28 minima were characterized for **3** at the same computational level, the number of representative minima in gas phase and chloroform solution being 12 and 23, respectively.[1] This is a surprising result since, a priori, some conformational restrictions would be expected in the latter compound due to the formation of O−H···O interactions.

Finally, it should be noted that in the gas phase the fully extended conformation tttt is 1.6 kcal/mol unfavored with respect to the global minimum. Solvent effects

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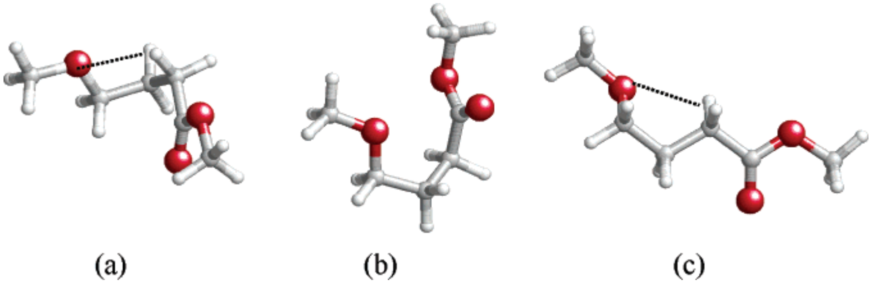

FIGURE 1. Selected conformations of methyl 4-methoxybutyrate: (a) $tg^{+}g^{+}t$, (b) $tg^{-}g^{+}s^{-}$, and (c) $tg^{-}tt$. Dashed lines indicate the formation of C−H···O interactions.

TABLE 3. Dihedral Angles[a] (deg) and Relative Energies (kcal/mol) of Methyl 5-Methoxyvalerate (2) Minimum Energy Conformations[b]

label	χ_1	χ_2	χ_3	χ_4	χ_5	MP2/6-31G(d)	MP2/6-311G(d,p)
$tg^{+}g^{+}g^{+}g^{+}$	−179.7	52.4	53.5	54.2	70.9	0.0	0.0
$tg^{+}g^{-}g^{-}t$	−174.1	75.5	−49.5	−56.7	157.8	0.1	0.1
$tg^{+}g^{+}g^{+}s^{-}$	−179.9	53.1	51.8	57.3	−131.9	0.4	0.1
$tg^{+}tg^{-}g^{-}$	−178.9	61.5	−177.2	−57.9	−63.1	0.9	1.1
$tg^{+}tg^{+}g^{+}$	−179.0	61.1	177.1	59.0	68.6	1.0	1.2
$tg^{+}tg^{+}t$	−179.6	59.9	173.9	67.0	−163.8	1.2	1.4
$tg^{+}g^{+}tt$	179.2	52.4	55.4	172.5	174.4	1.4	1.5
$tg^{-}ttt$	177.7	−62.6	178.7	178.1	174.4	1.2	1.6
$tg^{+}g^{-}g^{-}t$	−174.1	75.5	−49.5	−56.7	157.8	1.2	1.7
$tg^{-}g^{+}tt$	−179.5	−69.5	70.8	176.6	−176.0	1.3	1.7
$tttg^{+}t$	−179.1	−178.7	−179.8	68.5	−162.1	1.5	1.8
$tg^{+}g^{+}tg^{+}$	179.0	53.2	56.0	171.1	65.2	1.7	1.8
$ttg^{+}g^{+}s^{-}$	178.1	172.8	59.1	57.0	−113.3	1.9	1.8
$tg^{+}ttg^{+}$	−178.7	61.3	179.7	178.2	65.8	1.6	1.9
$tttg^{+}g^{+}$	−179.9	178.9	177.5	57.5	56.1	1.9	2.2
$tg^{+}g^{-}tg^{-}$	179.6	70.2	−70.6	−175.1	−63.3	2.0	2.2
ttttt	180.0	−179.9	180.0	180.0	180.0	1.9	2.3
$tg^{-}g^{+}tg^{-}$	179.5	−72.6	67.1	177.7	−31.6	2.0	2.3

[a] From MP2/6-31G(d) geometry optimizations. The dihedral angles are defined by the following sequences of bonds: CH_3−O−CH_2−CH_2 (χ_1), O−CH_2−CH_2−CH_2 (χ_2), CH_2−CH_2−CH_2−CH_2 (χ_3), CH_2−CH_2−CH_2−C(=O) (χ_4), and CH_2−CH_2−C(=O)−O (χ_5). [b] Information is provided only for the more relevant structures (see text).

reduce the free energy gap to 0.9 kcal/mol with respect to the new global minima. These values are 0.3 kcal/mol smaller than those predicted for **3** (i.e., 1.9 and 1.2 kcal/mol in the gas phase and chloroform solution, respectively).[1] However, although the population of the tttt conformation calculated for **1** (2.3 and 4.1% in the gas phase and solution, respectively) is higher than that calculated for **3** (0.0 and 1.1% in the gas phase and solution, respectively), it is still very small. Moreover, the populations expected for semiextended conformations, that is, structures with three or four dihedral angles in trans, in gas phase and chloroform solution are also relatively small for both **1** (15.4 and 27.1%, respectively) and **3** (3.7 and 7.0%, respectively). These results clearly indicate that **1** tends to adopt coiled conformations as **3**, even although the suppression of conventional O−H···O hydrogen bonds increases the population of semiextended conformations in the former with respect to the latter.

Methyl 5-Methoxyvalerate (2). MP2/6-31G(d) geometry optimizations on **2** provided a total of 57 minimum energy conformations, indicating a reduction of 14 minima with respect to **4**. Analysis of the free energies reveals that only 18 structures are expected to present significant populations in the gas phase. However, in chloroform solution the number of populated conformations increases to 29. The structural and energetic information of the more representative conformations has been summarized in Tables 3 and 4 (due to the large number of significant minima, only the conformations with relative $\Delta G_{gp} \leq 1.5$ kcal/mol are listed). A complete

TABLE 4. Geometric Parameters for the C−H···O Interactions, Relative Free Energies in the Gas Phase (ΔG_{gp}; kcal/mol) and Chloroform Solution (ΔG_{chl}, kcal/mol), and Free Energy of Solvation (ΔG_{sol}, kcal/mol) of Methyl 5-Methoxyvalerate (2) Minimum Energy Conformations

label	intramolecular interactions[a]	ΔG_{gp}	ΔG_{sol}	ΔG_{chl}
$tg^{+}g^{+}g^{+}g^{+}$	–	0.3	−5.1	0.8
$tg^{+}g^{-}g^{-}t$	–	0.5	−5.4	0.7
$tg^{+}g^{+}g^{+}s^{-}$	-	0.0	−5.5	0.1
$tg^{+}tg^{-}g^{-}$	2.531 Å, 98.6°	0.3	−5.9	0.0
$tg^{+}tg^{+}g^{+}$	–	0.5	−6.0	0.1
$tg^{+}tg^{+}t$	–	0.8	−5.0	0.6
$tg^{+}g^{+}tt$	–	0.7	−5.8	0.5
$tg^{-}ttt$	–	0.3	−6.0	0.0
$tg^{+}g^{-}g^{-}t$	2.511 Å, 98.2°	0.5	−4.9	0.7
$tg^{-}g^{+}tt$	2.364 Å, 115.4°	0.6	−4.8	0.8
$tttg^{+}t$	–	0.7	−6.0	0.7
$tg^{+}g^{+}tg^{+}$	–	1.2	−6.1	0.7
$ttg^{+}g^{+}s^{-}$	-	1.5	−6.0	1.1
$tg^{+}ttg^{+}$	–	1.0	−6.1	0.5
$tttg^{+}g^{+}$	–	1.5	−6.4	0.7
$tg^{+}g^{-}tg^{-}$	2.381 Å, 114.6°	1.3	−5.8	1.1
ttttt	–	1.0	−6.2	0.5
$tg^{-}g^{+}tg^{-}$	2.407 Å, 112.7°	1.2	−5.9	0.9

[a] H···O distance and ∠C−H···O angle in Å and degrees, respectively.

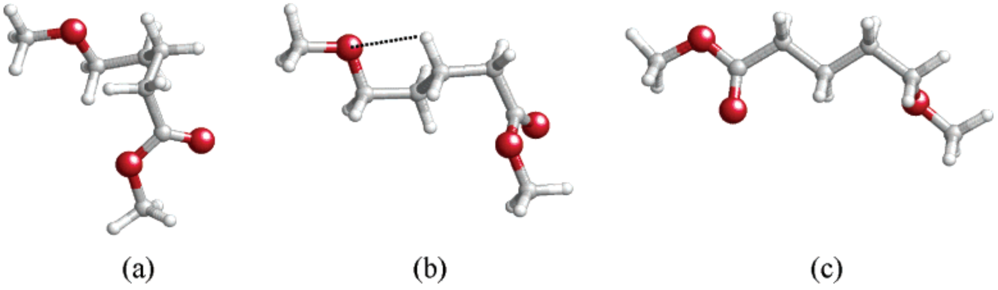

FIGURE 2. Selected conformations of methyl 5-methoxyvalerate: (a) $tg^+g^+g^+s^-$, (b) $tg^+tg^-g^-$, and (c) tg^-ttt. Dashed lines indicate the formation of C−H···O interactions.

description of the whole set of minimum energy conformations is available in the Supporting Information.

Again the energies provided by the 6-31G(d) and 6-311G(d,p) basis sets are fully consistent. The statistical terms tend to reduce the energy gap between the significant structures, with the stabilizing effect produced by the ZPVE, thermal, and entropic corrections being on average 0.8 kcal/mol. However, in general (i.e., considering all the minimum energy conformations), the energy gap between the least and most stable conformations is not influenced by the statistical corrections, even though the relative order between the conformations is severely altered.

Interestingly, 14 of the 57 minimum energy conformations present C−H···O interactions, although only five are significant conformations. The conformation with the lowest ΔG_{gp} value is the $tg^+g^+g^+s^-$ (Figure 2a), which is 0.1 kcal/mol unfavored in chloroform solution. The most stable conformation in the latter environment is the $tg^+tg^-g^-$ (Figure 2b), although the tg^-ttt (Figure 2c) is almost isoenergetic (i.e., the difference in ΔG_{chl} is smaller than 0.02 kcal/mol). The latter is analogous to one of the more stable conformations of **1** in chloroform solution (tg^-tt). The ΔG_{gp} values of both the $tg^+tg^-g^-$ and tg^-ttt conformations are 0.3 kcal/mol.

Results listed in Tables 3 and 4 show an important difference with respect to the conformational preferences of **1**. This is the tendency to stabilize the extended and semiextended conformations in the gas phase and, mainly, in chloroform solution. Thus, inspecting Tables 3 and 4 reveals that there are three significant minimum energy conformations with four or five dihedral angles in trans: tg^-ttt, $tttg^+t$, and ttttt. According to a Boltzmann distribution, the population predicted in the gas phase for these conformations amounts to 18%, although this frequency increases to 34% in chloroform solution. The change in conformational distribution is especially remarkable for the tg^-ttt, which contributes by 10 and 19% in the gas phase and chloroform solution, respectively. Moreover, it should be noted that six of the 18 significant minima in the gas phase present three dihedral angles in trans, which is in agreement with a reduction in the tendency to adopt folded conformations with respect to **1**. The population predicted in the gas phase and chloroform solution for the conformations with three or more dihedral angles in trans amounts to 37 and 58%, respectively.

It should be emphasized that similar findings were found for **3** and **4**. Thus, the populations computed for semiextended conformations of the latter in both the gas phase and chloroform solution are twice as high as those predicted for **3**. Table 5 compares the frequencies calculated for the semiextended conformations of **1**−**4**. As can be seen, the results clearly indicate that the stability of the trans rotamers increases, especially in solution, with the size of the aliphatic segment for both pairs of compounds. The overall results allow us to conclude that, in general, the conformational preferences of the aliphatic segments of ω-methoxy methyl esters and ω-hydroxy acids are not altered by the formation of intramolecular O−H···O hydrogen bonds

TABLE 5. Frequencies Calculated for the Semiextended[a] Conformations of Methyl 4-Methoxybutyrate (1), Methyl 5-Methoxyvalerate (2), 4-Hydroxybutyric Acid (3), and 5-Hydroxyvaleric Acid (4) in Both Gas Phase and Chloroform Solution

	1	2	3	4
gas phase	0.15	0.18	0.04	0.09
chloroform solution	0.27	0.34	0.07	0.16

[a] For **1** and **3**, semiextended conformations refer to structures with three or four dihedral angles in trans. For **2** and **4**, semiextended conformations refer to structures with four or five dihedral angles in trans.

Conclusions

The conformational preferences of ω-methoxy methyl esters, $CH_3O-(CH_2)_n-COOCH_3$ with $n = 3$ and 4, have been investigated using ab initio calculations at the MP2 level. Results have been compared with those reported for the corresponding ω-hydroxy acids, which were studied using the same computational methods.

The lowest energy conformation in the gas phase of the compound with $n = 3$ is the tg^+g^+t, while both the $tg^-g^+s^-$ and tg^-tt are the most favored conformations in chloroform solution. Comparison with our previous results for **3** indicates that the lack of O−H···O hydrogen bonding interactions in **1** produces a reduction in the number of conformational energy minima and a stabilization of the extended and semiextended conformations with respect to the coiled ones. However, the latter are clearly the more favored conformations for both **1** and **3**. Regarding the compound with $n = 4$, the most favored conformation in the gas phase is the $tg^+g^+g^+s^-$, while in chloroform solution the most stable is the $tg^+tg^-g^-$. In this case, comparison between **2** and **4** also reveals important conformational differences, which should be attributed to the absence of polar hydrogen atoms able to form hydrogen bonds in the former compound.

A global analysis of the results obtained for the pairs of compounds **1**−**3** and **2**−**4** reveals a common trend. This is the stabilization of the semiextended conformations in compounds with $n = 4$ with respect to the corresponding analogues with $n = 3$. This result is in concordance with our previous studies on diamides, diesters, and diketones.[4–7]

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Supporting Information Available: Dihedral angles, energies, and coordinates for the minimum energy conformations of the compounds under study. This material is available free of charge via the Internet at http://pubs.acs.org.

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