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Systematic Evaluation of the Conformational Properties of Aliphatic ω-Hydroxy Acids

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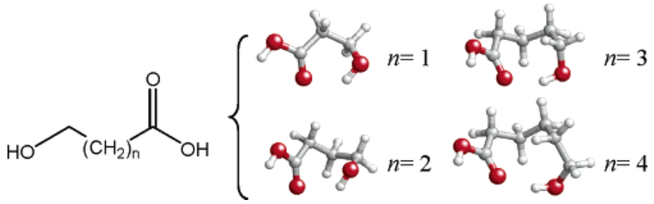

A systematic conformational study of ω-hydroxy acids, HO$-$(CH$_2$)$_n-$COOH with n ranging from 2 to 5, has been performed using quantum mechanical calculations at the MP2 level. To distinguish between intrinsic and environmentally induced conformational preferences, calculations have been carried out in both gas phase and chloroform solution, a polarizable continuum solvation model being used to represent the latter. Results indicate a consistent conformational behavior, as reflects the feature that the lowest energy minimum for $n = 2$, 3, 4, and 5 corresponds to the g^+g^-t, $g^+g^+g^-t$, $g^-g^+g^+g^-t$, and $g^+g^-g^-g^+g^+g^-t$ conformations, respectively. Furthermore, the stability of the extended and semiextended conformations increases systematically with the size of the central aliphatic segment. The relationship between the size of the aliphatic segment and the stability of folded conformations is analyzed and discussed.

Introduction

Conformational studies of simple organic and bioorganic molecules are particularly interesting because they provide information that can be relevant for the structural investigation of more complex and larger compounds. Furthermore, when studies of model molecules are performed in the absence of strong environmental forces, distinctive "*intrinsic*" conformational preferences are sometimes identified allowing rationalization of unexpected features found in condensed phases. Within this context, ab initio quantum mechanical methods have become useful and precise tools to study model molecules of small and medium size.

During the past decade, quantum mechanical calculations and experimental observations on difunctional model molecules including diamides,[1] diesters,[2] and diketones[3] showed an anomalous conformational feature, which has been referred to as "folding of methylene units". This is 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 $n < 5$. Moreover, recently published gas-phase calculations on succinic acid evidenced that diacids are also affected by the folding of methylene units, although in aqueous solution the intrinsic conformational preferences are altered by extensive hydrogen bonding with water.[4]

In the current study, we have used quantum mechanical calculations to explore the intrinsic conformational preferences of compounds containing small aliphatic segments flanked by acid and hydroxy groups. More specifically, we focused on 3-hydroxypropionic acid (**1**), 4-hydroxybutyric acid (**2**), 5-hydroxyvaleric acid (**3**) and

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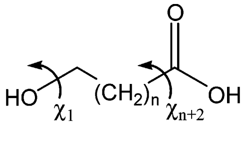

1: *n*= 1; **2:** *n*= 2; **3:** *n*= 3; **4**: *n*= 4

6-hydroxyhexanoic acid (**4**). The interest of aliphatic ω-hydroxy acids involves different fields of chemistry and biology: they are used to prepare important synthetic polyesters, they are contained in the ceramides located at the uppermost layer of the epidermis as well as in other important lipid phases, etc. An exhaustive conformational search through a systematic procedure has been performed for these compounds in the absence of external forces using Hartree−Fock (HF) and second-order Møller−Plesset (MP2) methods. Furthermore, solvation effects have been estimated by using a continuum model. The conformational preferences have been rationalized in terms of folding of methylene units and both O−H···O and C−H···O hydrogen bonds.

Methods

Gas-Phase Calculations. Molecular conformations were labeled according to their dihedral angles, which were listed in the following order: for **1** the dihedral angles $\{\chi_1, \chi_1, \chi_3\}$ correspond to the bond rotations $\{(H)O-CH_2, CH_2-CH_2, CH_2-C(OO)\}$, for **2** $\{\chi_1, \chi_1, \chi_3, \chi_4\}$ correspond to $\{(H)O-CH_2, CH_2-CH_2, CH_2-CH_2, CH_2-C(OO)\}$, and so on for **3** and **4**. The specific atomic sequences used to define the dihedral angles of the four compounds are provided in the next section. The rotamers were classified as follows: trans (t, for $150° \leq \chi_i < 210°$), skew$^-$ (s$^-$, for $210° \leq \chi_i < 270°$), gauche$^-$ (g$^-$, for $270° \leq \chi_i < 330°$), cis (c, for $330° \leq \chi_i < 30°$), gauche$^+$ (g$^+$, for $30° \leq \chi_i < 90°$) and skew$^+$ (s$^+$, for $90° \leq \chi_i < 150°$).

The energy minima of **1**, **2**, and **3** were characterized by 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**, **2**, and **3** is $3^3 = 27$, $3^4 = 81$, and $3^5 = 243$, respectively. However, due to the absence of stereochemistry, the number of theoretical minima can be reduced to 14, 41, and 122, respectively, since $\{\chi_i\} = \{-\chi_i\}$, where χ_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.[5] To account for electron correlation effects, all the structures resulting from HF/6-31G(d) optimizations were fully re-optimized at the MP2/6-31G(d) level. Frequency analyses were carried out to verify the force constants 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[6] 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 (ΔG_{gp}), such statistical terms were added to the gas-phase energies computed at the MP2/6-311G(d,p) level.

On the other hand, the number of anticipated minima that should be considered as starting geometries for **4**, 365, is too large. Accordingly, calculations on this compound were performed on selected conformations to confirm the evolution of some conformational tendencies observed in the three smaller compounds. The methods used for geometry optimizations and energy evaluations were exactly the same as those described for **1**, **2**, and **3**.

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.[7,8] 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 is carried out until the wave function and the surface charges are 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 (ΔG_{chl}) were computed by using the classical thermodynamics scheme: the free energies of solvation (ΔG_{sol}) provided by the PCM model were added to the ΔG_{gp}, $\Delta G_{chl} = \Delta G_{sol} + \Delta G_{gp}$.

Gas phase and PCM calculations were performed with the Gaussian 98 computer program.[9]

Results and Discussion

3-Hydroxypropionic Acid (1). A total of 11 stationary points were characterized as minimum energy conformations at the MP2/6-31G(d) level. From these, one is the all-trans (ttt) and the other 10 correspond to 2-fold degenerated minima, i.e. the structures with $\{\chi_1, \chi_1, \chi_3\}$ and $\{-\chi_1, -\chi_1, -\chi_3\}$ are equivalent and isoenergetic. Table 1 lists the dihedral angles $\{\chi_1, \chi_1, \chi_3\}$ and the gas-

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TABLE 1. Dihedral Angles^a (deg) and Relative Energies (kcal/mol) of 3-Hydroxypropionic Acid (1) Minimum Energy Conformations

label	χ_1	χ_2	χ_3	MP2/ 6-31G(d)	MP2/ 6-311G(d,p)
g^+g^-t	66.0	−63.2	−169.4	0.0^b	0.0^c
$g^+g^-g^+$	60.1	−75.0	45.8	2.2	2.0
tg^+s^-	−162.2	66.9	−145.2	3.4	3.0
$g^+g^+g^+$	59.3	50.1	65.1	3.4	3.0
ttt	180.0	180.0	180.0	3.7	2.3
$g^+g^+s^-$	60.9	55.1	−111.4	3.7	3.2
tg^+g^+	−171.0	58.2	52.3	3.8	3.5
g^+tt	69.6	−176.2	177.9	4.1	3.6
g^+tg^-	68.6	−179.3	−57.7	4.7	4.1
ttg^+	−178.9	−177.3	49.3	4.9	4.3
g^+tg^+	70.1	−176.2	61.7	4.9	4.3

^{a} From MP2/6-31G(d) geometry optimizations. The dihedral angles are defined by the following sequences of bonds: H−O−CH$_2$−CH$_2$ (χ_1), O−CH$_2$−CH$_2$−C(=O) (χ_2), and CH$_2$−CH$_2$−C(=O)−O (χ_3). ^{b} $E = -342.612599$ au. ^{c} $E = -342.822696$ au.

TABLE 2. Hydrogen Bonding Parameters (Distances and Angles in Å and deg), Relative Free Energies in the Gas Phase (ΔG_{gp} in kcal/mol) and Chloroform Solution (ΔG_{chl} in kcal/mol), and Free Energy of Solvation (ΔG_{sol} in kcal/mol) of 3-Hydroxypropionic Acid (1) Minimum Energy Conformations

label	intramolecular interactions^a	ΔG_{gp}	ΔG_{sol}	ΔG_{chl}
g^+g^-t	O−H···O (2.127 Å, 129.6°)	0.0^b	−4.0	0.0
$g^+g^-g^+$	O−H···O (2.074 Å, 130.3°)	1.7	−4.4	1.3
tg^+s^-	C−H···O (2.550 Å, 93.0°)	2.0	−4.7	1.2
$g^+g^+g^+$		2.5	−4.8	1.6
ttt		2.3	−4.5	1.7
$g^+g^+s^-$		2.4	−4.8	1.6
tg^+g^+	C−H···O (2.539 Å, 93.5°)	2.9	−5.3	1.6
g^+tt		2.5	−4.8	1.7
g^+tg^-		3.1	−4.8	2.3
ttg^+		3.1	−4.7	2.4
g^+tg^+		3.2	−4.8	2.4

^{a} H···O distance and ∠X−H···O angle (with X = O or C) in Å and deg, respectively. ^{b} $G = -342.754719$ au.

phase relative energies for such structures, while Table 2 shows the values of ΔG_{gp}, ΔG_{sol}, and ΔG_{chl} for each conformation. Furthermore, geometric parameters for the O−H···O and C−H···O hydrogen bonds detected in some conformers are also displayed in Table 2. It should be noted that in the past decade, a multitude of close contacts between the C−H group and the electronegative oxygen atom have been identified as hydrogen bonds, this interaction being found in an enormous variety of chemical systems.[10] According to the literature, the thresholds chosen for the O···H distance in O−H···O and C−H···O stabilizing interactions were 2.25 and 2.55 Å, respectively.

Comparison between the relative energies computed at the MP2/6-31G(d) and MP2/6-311G(d,p) levels (Table 1) indicates that the increase of the basis set produces a general stabilization of about 0.6 kcal/mol. This stabilization is notably larger (~1.4 kcal/mol) for the extended ttt conformation. Thus, the MP2 relative energy of this structure decreases from 3.7 to 2.3 kcal/mol when the 6-31G(d) basis set is changed by the 6-311G(d,p) one. On the other hand, comparison between the MP2/6-311G(d,p) relative energies and the values of ΔG_{gp} listed in Table 2 reveals that, in general, the role of the ZPVE, thermal, and entropic corrections is not negligible, producing an average stabilization of about 0.7 kcal/mol. Inspection of the ΔG_{chl} indicates that the solvent tends to provide an additional stabilization of about 0.7 kcal/mol reducing the range of variation of the free energy by 0.9 kcal/mol with respect to that obtained in the gas phase.

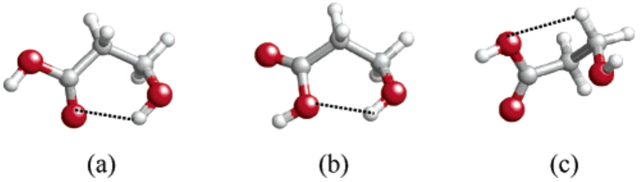

FIGURE 1. Selected conformations of 3-hydroxypropionic acid: (a) g^+g^-t, (b) $g^+g^-g^+$, and (c) tg^+s^-. Dashed lines indicate the formation of O−H···O and C−H···O hydrogen bonds.

The g^+g^-t conformation (Figure 1a), which is the lowest energy minimum in both gas phase and chloroform solution, is stabilized by a strong O−H···O hydrogen bond between the hydroxyl and the carbonyl groups. Similarly, the completely folded conformation $g^+g^-g^+$ (Figure 1b) also contains a stabilizing O−H···O intramolecular interaction, this structure being 1.7 and 1.3 kcal/mol less stable than the global minimum in the gas phase and solution, respectively (Table 2). The tg^+s^- structure, which presents a C−H···O interaction (Figure 1c), is 0.3 kcal/mol less stable than the $g^+g^-g^+$ in the gas phase and 0.1 more stable than the latter in solution. In addition to the latter minimum, the tg^+g^+ is the only structure with a C−H···O hydrogen bond, although it is 2.9 and 1.6 kcal/mol less stable than the global minimum in the gas phase and chloroform solution, respectively.

Interestingly, the fully extended conformation, ttt, is 2.3 and 1.7 kcal/mol less stable in the gas phase and chloroform solution, respectively, than the g^+g^-t global minimum. Moreover, semiextended structures, which are characterized by at least two dihedral angles in trans, are among the least stable. These results evidence that the central methylene groups of **1** tend to adopt a folded conformation rather than an extended one. This is not an unexpected result since, although the central aliphatic segment of **1** is not flanked by two carbonyl groups as in the "folding of methylene units",[1−3] the carbonyl and hydroxyl electronegative groups should induce the typical *gauche effect*. This is defined by IUPAC[11] as "the stabilization of the gauche conformation in a two-carbon unit (X−CH$_2$−CH$_2$−Y) bonded vicinally to electronegative elements (X and Y)". Indeed, the dihedral angle χ_2, which is defined by the O−CH$_2$−CH$_2$−C(=O) sequence, shows a gauche conformation in the four more stable structures of **1**.

4-Hydroxybutyric Acid (2). Calculations at the MP2/6-31G(d) level allowed characterization of 28 minima, 27 being 2-fold degenerated structures. Tables 3 and 4 provide the structural and energetic information for the

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TABLE 3. Dihedral Angles[a] (deg) and Relative Energies (kcal/mol) of 4-Hydroxybutyric Acid (2) Minimum Energy Conformations[b]

label	χ_1	χ_2	χ_3	χ_4	MP2/ 6-31G(d)	MP2/ 6-311G(d,p)
$g^-g^+g^+s^+$	−81.6	47.7	51.5	97.7	0.0[c]	0.0[d]
$g^+g^+g^-t$	50.9	47.9	−77.8	166.3	0.0	0.2
$g^-g^+g^+s^-$	−80.8	52.2	55.5	−91.3	1.1	0.9
$g^+s^-g^+t$	54.3	−91.0	54.3	163.8	1.2	1.2
$g^-g^+g^-g^-$	−78.8	69.2	−65.5	−81.8	0.9	1.3
$g^+g^+g^+t$	67.6	57.1	71.6	−174.9	1.7	1.4
tg^+g^+t	−174.7	59.4	70.1	−174.6	1.5	1.3
$g^+g^+g^-g^-$	53.6	53.2	−66.6	−39.9	1.7	1.6
g^+g^+tt	66.6	58.5	−173.4	−171.4	2.3	2.0
tg^+tt	−178.9	59.7	179.3	−179.4	2.4	2.2
g^+tg^+t	69.0	177.9	70.9	−171.2	2.8	2.5
$tg^+g^+g^+$	−170.7	60.3	60.0	53.3	2.9	2.5
$g^+g^+tg^+$	66.1	57.9	−177.3	61.7	3.0	2.7
$g^+g^+g^+g^+$	66.8	56.2	62.0	40.0	3.3	2.8
$tg^-g^+s^-$	171.2	−55.9	78.3	−136.5	3.0	2.8
tg^+tg^+	−177.3	60.1	177.6	58.4	3.2	3.0
g^-tg^+t	−63.8	178.8	69.3	−172.1	3.4	3.0
g^+g^-tt	79.3	−60.9	176.1	−177.0	3.4	3.2
g^+ttt	61.9	176.6	176.9	174.8	3.6	3.2
$g^+tg^-g^-$	65.7	179.3	−59.3	−64.1	4.0	3.5
tttt	180.0	180.0	179.9	180.0	4.0	3.7
$g^+g^-tg^-$	79.9	−60.8	−175.4	−64.2	4.0	3.7
g^+ttg^-	64.8	177.5	−179.1	−64.4	4.3	3.8

[a] From MP2/6-31G(d) geometry optimizations. The dihedral angles are defined by the following sequences of bonds: H−O−CH_2−CH_2 (χ_1), O−CH_2−CH_2−C(=O) (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). [c] $E = -381.778138$ au. [d] $E = -382.014838$ au.

TABLE 4. Hydrogen Bonding Parameters (Distances and Angles in Å and deg), Relative Free Energies in the Gas Phase (ΔG_{gp} in kcal/mol) and Chloroform Solution (ΔG_{chl} in kcal/mol), and Free Energy of Solvation (ΔG_{sol} in kcal/mol) of 4-Hydroxybutyric Acid (2) Minimum Energy Conformations

label	intramolecular interactions[a]	ΔG_{gp}	ΔG_{sol}	ΔG_{chl}
$g^-g^+g^+s^+$	O−H···O (2.135 Å, 140.7°)	0.4	−1.5	1.2
$g^+g^+g^-t$	O−H···O (2.234 Å, 123.5°) C−H···O (2.546 Å, 95.6°)	0.0[b]	−1.8	0.5
$g^-g^+g^+s^-$	O−H···O (2.175 Å, 140.3°)	1.0	−1.8	1.5
$g^+s^-g^+t$	O−H···O (1.915 Å, 153.7°)	0.7	−2.5	0.5
$g^-g^+g^-g^-$	O−H···O (2.128 Å, 139.3°)	1.1	−2.8	0.6
$g^+g^+g^+t$	C−H···O (2.545 Å, 100.4°)	0.5	−2.4	0.4
tg^+g^+t	C−H···O (2.489 Å, 99.2°)	0.4	−1.8	0.9
$g^+g^+g^-g^-$		1.5	−2.4	1.4
g^+g^+tt		0.5	−2.8	0.0
tg^+tt	C−H···O (2.525 Å, 96.3°)	0.7	−2.5	0.5
g^+tg^+t		1.4	−2.6	1.1
$tg^+g^+g^+$		1.1	−2.3	1.1
$g^+g^+tg^+$		1.5	−2.9	0.9
$g^+g^+g^+g^+$		1.8	−2.9	1.2
$tg^-g^+s^-$		2.0	−3.0	1.3
tg^+tg^+	C−H···O (2.523 Å, 96.6°)	1.6	−2.8	1.1
g^-tg^+t		1.9	−2.9	1.3
g^+g^-tt		1.6	−3.0	0.9
g^+ttt		1.5	−3.2	0.6
$g^+tg^-g^-$		1.9	−2.9	1.3
tttt		1.9	−3.0	1.2
$g^+g^-tg^-$		2.3	−3.2	1.2
g^+ttg^-		2.3	−3.2	1.4

[a] H···O distance and ∠X−H···O angle (with X = O or C) in Å and deg, respectively. [b] $G = -381.922169$ au.

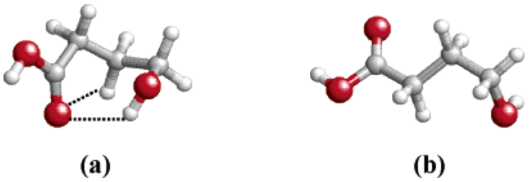

FIGURE 2. Selected conformations of 4-hydroxybutyric acid: (a) $g^+g^+g^-t$ and (b) g^+g^+tt. Dashed lines indicate the formation of O−H···O and C−H···O hydrogen bonds.

more significant minima, which are those with ΔG_{gp} and/or ΔG_{chl} smaller than 1.5 kcal/mol, i.e. those that are expected to present significant population in the gas phase and/or chloroform solution. However, a complete description of all the minimum energy structures characterized at the MP2/6-31G(d) level is reported in the Supporting Information section.

In general, the stabilizing effect produced by the enlargement of the basis set is, on average, 0.4 kcal/mol smaller than that detected for **1**. Accordingly, MP2/6-31G(d) and MP2/6-311G(d,p) relative energies are, in this case, in excellent agreement from a quantitative point of view. On the other hand, comparison between the relative energies and the values of ΔG_{gp} indicates that the ZPVE, thermal, and entropic corrections have a stabilizing effect, which is on average 0.9 kcal/mol, i.e. slightly larger than that observed for **1**. Furthermore, a detailed analysis of the results shows that the stabilizing role of the thermodynamical corrections is larger for the less favored minimum energy conformations, this feature being also found in **1**. For instance, the relative energy of the fully extended conformation tttt is 3.7 kcal/mol at the MP2/6-311G(d,p) level, while the ΔG_{gp} is 1.9 kcal/mol, i.e. the thermodynamical corrections to the Gibbs free energy amount to 1.8 kcal/mol.

Another point that deserves special consideration is that only 12 of the structures listed in Tables 3 and 4 can be considered as significant structures in the gas phase. The remaining 16 minimum energy conformations show $\Delta G_{gp} \geq 1.5$ kcal/mol, their expected population in the gas phase being negligible. Inclusion of solvent effects considerably enhances the flexibility of **2**. Accordingly, the Boltzmann distribution used to describe the conformational preferences of this compound in chloroform solution shows that the 23 structures listed in Tables 3 and 4 are significantly populated, i.e. $\Delta G_{chl} \geq 1.5$ kcal/mol for only 5 minima. Furthermore, the solvent not only reduces the conformational free energy differences but also alters the relative energy order between the different conformers as is reflected in Table 4.

Inspection of Table 4 indicates that six minimum energy conformations of **2** are stabilized by O−H···O hydrogen bonds with parameters ranging from 1.915 to 2.234 Å for the H···O distance and from 123.5° to 153.7° for the ∠O−H···O angle. On the other hand, five minima are stabilized by interactions of the C−H···O type. The structure of lowest ΔG_{gp}, which corresponds to the $g^+g^+g^-t$ (Figure 2a), is stabilized by both O−H···O and C−H···O interactions, the acceptor oxygen atom being the same in the two hydrogen bonds. Interestingly, this conformation is 0.5 kcal/mol less stable than the g^+g^+tt (Figure 2b) in chloroform solution. The latter conformer, which is the most stable in solution, does not form intramolecular hydrogen bonds indicating that the conformational preferences in this environment are greatly determined by the strength of the solute−solvent interactions.

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

label	χ_1	χ_2	χ_3	χ_4	χ_5	MP2/ 6-31G(d)	MP2/ 6-311G(d,p)
$g^-g^+g^+g^-t$	−79.1	60.0	64.8	−84.2	171.5	0.0[c]	0.0[d]
$g^-g^-g^+g^+s^+$	−42.2	−59.8	64.0	54.1	94.0	0.2	0.3
$g^+g^+g^+g^+g^+$	64.7	50.0	54.5	54.5	73.1	2.9	2.4
$g^-g^+g^-s^+s^+$	−86.7	64.4	−72.2	108.4	139.6	2.2	2.5
$g^+g^+g^+g^+t$	62.0	50.1	53.7	62.4	−165.6	3.1	2.5
$tg^+g^+g^+t$	178.5	52.7	51.2	60.7	−159.3	3.2	2.7
$g^+g^+g^+tt$	61.8	49.4	56.4	173.0	180.0	3.6	3.1
g^+tg^-tt	62.1	−179.1	−64.5	−173.6	−177.9	4.8	3.2
$g^+g^+tg^+g^+$	63.2	57.3	178.8	58.0	58.9	3.6	3.2
$tg^+tg^-g^-$	−178.1	61.7	−176.5	−58.1	−61.6	3.6	3.3
g^+g^+ttt	65.3	59.3	−177.5	−178.6	−177.2	3.8	3.5
g^+tttt	64.9	177.1	−179.9	−179.9	−179.5	4.2	3.5
tg^+ttt	−175.5	63.1	−178.0	−178.0	−176.1	3.7	3.5
tg^-g^+tt	−179.8	−68.4	72.2	176.6	−176.8	3.8	3.6
ttttt	180.0	180.0	180.0	180.0	180.0	4.2	4.1

[a] From MP2/6-31G(d) geometry optimizations. The dihedral angles are defined by the following sequences of bonds: H−O−CH_2−CH_2 (χ_1), O−CH_2−CH_2−C(=O) (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). [c] $E = -420.945165$ au. [d] $E =$ au.

Finally, it should be noted that the fully extended conformation is 1.9 kcal/mol unfavored with respect to the global minimum in the gas phase. Solvent effects reduce the free energy gap to 1.2 kcal/mol. However, although solute−solvent interactions tend to stabilize the tttt conformation, the population expected for this conformation in chloroform solution is very small (1.1%). Moreover, the populations expected for semiextended conformations, i.e. structures with three dihedral angles in trans, in both gas phase and chloroform solution are also relatively small (3.7% and 7.0%, respectively). These results clearly indicate that **2** tends to adopt a folded conformation as **1**, even although in the former the central aliphatic segment contains an additional methylene unit.

5-Hydroxyvaleric Acid (3). MP2/6-31G(d) geometry optimizations on **3** provided a total of 71 minimum energy conformations. However, analysis of the free energies indicates that only 11 and 39 structures are expected to present significant populations in the gas phase and chloroform solution, respectively. The structural and energetic information of such representative conformations have been summarized in Tables 5 and 6 (due to the large number of minima, only the structures with $\Delta G_{gp} \leq 1.5$ and the ttttt conformation are listed), while a complete description of the whole set of minimum energy conformations is available in the Supporting Information section.

As can be seen, the stabilizing effect of the 6-311G(d,p) basis set with respect to the 6-31G(d) one is consistent with the results found for **1** and **2**. Similarly, the statistical terms tend to reduce the energy gap between the most and the least stable structures, the stabilizing effect produced by the ZPVE, thermal, and entropic corrections being on average 1.6 kcal/mol. This effect is even larger than that predicted for **2**, being more pronounced in the structures with a high relative energy. Thus, the relative energy of the least stable structure ($g^+g^-s^+g^+g^+$) with respect to the global minimum ($g^-g^+g^+g^-t$) is 5.7 kcal/mol while the largest value of ΔG_{gp}, which is referred to the same two structures, is 3.3 kcal/mol. Thus, in this case statistical terms produce a stabilization of 2.4 kcal/mol.

TABLE 6. Hydrogen Bonding Parameters (Distances and Angles in Å and deg), Relative Free Energies in the Gas Phase (ΔG_{gp} in kcal/mol) and Chloroform Solution (ΔG_{chl} in kcal/mol), and Free Energy of Solvation (ΔG_{sol} in kcal/mol) of 5-Hydroxyvaleric Acid (3) Minimum Energy Conformations

label	intramolecular interactions[a]	ΔG_{gp}	ΔG_{sol}	ΔG_{chl}
$g^-g^+g^+g^-t$	O−H···O (1.982 Å, 151.3°)	0.0[b]	−6.5	0.0
$g^-g^-g^+g^+s^+$	O−H···O (2.051 Å, 147.6°)	0.8	−5.8	1.5
$g^+g^+g^+g^+g^+$		1.5	−6.8	1.2
$g^-g^+g^-s^+s^+$	O−H···O (1.941 Å, 157.1°)	1.4	−6.1	1.8
$g^+g^+g^+g^+t$		1.0	−6.4	1.1
$tg^+g^+g^+t$		1.1	−6.5	1.1
$g^+g^+g^+tt$		1.5	−7.3	0.7
g^+tg^-tt		1.1	−6.6	1.0
$g^+g^+tg^+g^+$		1.4	−7.2	0.7
$tg^+tg^-g^-$	C−H···O (2.525 Å, 118.5°)	1.4	−6.9	1.0
g^+g^+ttt		1.4	−7.8	0.1
g^+tttt		1.3	−7.7	0.1
tg^+ttt		1.4	−7.4	0.5
tg^-g^+tt	C−H···O (2.348 Å, 115.8°)	1.5	−6.6	1.4
ttttt		1.8	−7.4	0.9

[a] H···O distance and ∠X−H···O angle (with X = O or C) in Å and deg, respectively. [b] $G = -421.086701$ au.

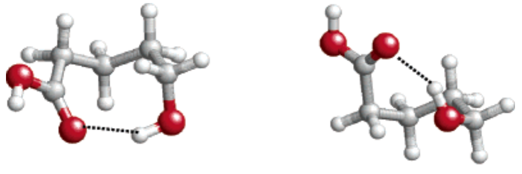
(a) (b)

FIGURE 3. Selected conformations of 5-hydroxyvaleric acid: (a) $g^-g^+g^+g^-t$ and (b) $g^-g^-g^+g^+t$. Dashed lines indicate the formation of O−H···O hydrogen bonds.

Interestingly, only 6 of the 71 minimum energy conformations present O−H···O hydrogen bonds, while the number of structures with C−H···O interactions is 15. The most stable conformation in both the gas phase and chloroform solution corresponds to $g^-g^+g^+g^-t$ (Figure 3a), which is stabilized by an O−H···O hydrogen bond. This result is fully consistent with those reported in Tables 1−4 for the smaller compounds, as demonstrated by the fact that the g^+g^-t and $g^+g^+g^-t$ conformations correspond

TABLE 7. Dihedral Angles[a] (deg) and Relative Energies (kcal/mol) of 6-Hydroxyhexanoic Acid (4) Minimum Energy Conformations[b]

label	χ_1	χ_2	χ_3	χ_4	χ_5	χ_6	MP2/ 6-31G(d)	MP2/ 6-311G(d,p)
$g^-g^-g^+g^+g^-t$	−50.7	−54.9	77.1	66.6	−85.7	173.1	0.0[c]	0.0[d]
$g^-g^-g^+g^+g^+t$	−71.2	−73.5	60.0	57.5	60.3	−153.7	2.9	2.3[d]
$g^-g^+g^+g^+g^+t$	−69.6	58.6	57.5	57.9	64.1	−161.0	3.4	2.7
tttttt	180.0	180.0	180.0	180.0	180.0	180.0	3.3	3.2
$g^-g^+g^-tg^+t$	−76.6	58.3	−89.9	174.9	67.6	−166.6	4.0	3.7
$g^+g^+g^-g^+g^+t$	61.7	71.8	−65.3	90.0	67.7	−173.5	4.2	3.7
$g^+g^-g^+tg^-t$	68.2	−81.6	57.7	169.1	−79.6	−169.1	4.3	3.7

[a] From MP2/6-31G(d) geometry optimizations. The dihedral angles are defined by the following sequences of bonds: H−O−CH$_2$−CH$_2$ (χ_1), O−CH$_2$−CH$_2$−C(=O) (χ_2), CH$_2$−CH$_2$−CH$_2$−CH$_2$ (χ_3), CH$_2$−CH$_2$−CH$_2$−CH$_2$ (χ_4), CH$_2$−CH$_2$−CH$_2$−C(=O) (χ_5), and CH$_2$−CH$_2$−C(=O)−O (χ_6). [b] Information is provided for all the calculated structures (see text). [c] $E = -460.109182$ au. [d] $E = -460.408069$au.

to the gas-lowest energy minima predicted for **1** and **2**, respectively. The next minimum in the gas phase is $g^-g^-g^+g^+s^+$ (Figure 3b). This folded conformation, which is also stabilized by a conventional O−H···O interaction, is 0.8 less favored than the global minimum. According to a Boltzmann distribution, the population predicted in the gas phase for the two conformations of lower energy amounts to 54%, while the individual contribution of the remaining 9 conformations with $\Delta G_{gp} < 1.5$ kcal/mol is relatively small (around 4−8%). In opposition, the conformational distribution in chloroform solution is influenced by a notable number of structures denoting a large conformational flexibility. For instance, the g^+g^+ttt and g^+tttt conformations are unfavored with respect to the global minimum by only 0.1 kcal/mol in solution. However, the global minimum and the latter two conformations contribute by only 30% to the whole description of the molecule in solution since the number of structures with $\Delta G_{chl} < 1.5$ kcal/mol is very large. Thus, there are 36 conformations with individual populations ranging from 0.1% to 5%.

On the other hand, the ΔG_{gp} and ΔG_{chl} of the fully extended conformation is 1.8 and 0.9 kcal/mol, respectively, these values being smaller than those computed for **2** (1.8 and 1.2 kcal/mol, respectively) and **1** (2.3 and 1.7 kcal/mol, respectively). Thus, both the relative intrinsic stability and the favorable energy effects induced by the solvent of the fully extended conformation clearly increase with the size of the aliphatic segment. Furthermore, the stability of the semiextended conformations g^+-ttt and tg^+ttt is notably high in the gas phase ($\Delta G_{gp} =$ 1.3 and 1.4 kcal/mol, respectively) and, especially, in solution ($\Delta G_{chl} = 0.1$ and 0.5 kcal/mol, respectively). As a consequence, the populations expected for semiextended conformations (8.7% and 15.9% in the gas phase and chloroform solution, respectively) are twice as high as those reported for **2**. These results clearly indicate that both the intrinsic and solvent-induced stability of the trans rotamers increase with the size of the central aliphatic segment for the hydroxy acids studied in this work.

TABLE 8. Hydrogen Bonding Parameters (Distances and Angles in Å and deg), Relative Free Energies in the Gas Phase (ΔG_{gp} in kcal/mol) and Chloroform Solution (ΔG_{chl} in kcal/mol), and Free Energy of Solvation (ΔG_{sol} in kcal/mol) of 5-Hydroxyhexanoic Acid (4) Minimum Energy Conformations

label	intramolecular interactions[a]	ΔG_{gp}	ΔG_{sol}	ΔG_{chl}
$g^-g^-g^+g^+g^-t$	O−H···O (1.981 Å, 159.9°) C−H···O (2.398 Å, 121.2°)	0.0[b]	−3.6	0.7
$g^-g^-g^+g^+g^+t$		0.2	−3.5	1.0
$g^-g^+g^+g^+g^+t$		1.0	−4.2	1.1
tttttt		0.5	−4.8	0.0
$g^-g^+g^-tg^+t$		1.9	−4.1	2.1
$g^+g^+g^-g^+g^+t$	C−H···O (2.273 Å, 130.0°)	2.1	−4.0	2.4
$g^+g^-g^+tg^-t$		1.8	−3.6	2.5

[a] H···O distance and ∠X−H···O angle (with X = O or C) in Å and deg, respectively. [b] $G = -460.256664$ au.

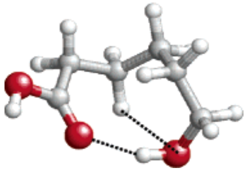

FIGURE 4. Lowest energy conformation of 6-hydroxyhexanoic acid in the gas phase: $g^-g^-g^+g^+g^-t$. Dashed lines indicate the formation of O−H···O and C−H···O hydrogen bonds.

6-Hydroxycaproic Acid (4). The fact that the g^+g^-t, $g^+g^+g^-t$, and $g^-g^-g^+g^-t$ are the lowest energy minima in the gas phase of **1**, **2**, and **3**, respectively, indicates that these compounds clearly follow a systematic conformational behavior. Assuming that **4** retains this conformational pattern, we considered the $g^+g^-g^-g^+g^-t$ and $g^-g^-g^+g^+g^-t$ conformations for geometry optimizations. Additionally, the tttttt as well as four selected folded conformations, which were chosen using the information provided in Tables 2, 4, and 6, were also considered for this compound. The results derived for such 7 conformations are listed in Tables 7 and 8.

The lowest energy minimum in the gas phase corresponds to $g^-g^-g^+g^+g^-t$, which is stabilized by both O−H···O and C−H···O hydrogen bonds (Figure 4), while in chloroform solution the tttttt is the most stable conformer. Although the conformational preferences of **4** have been scarcely studied, results displayed in Tables 7 and 8 are fully consistent with those obtained for compounds containing a smaller aliphatic segment. Interestingly, the ΔG_{gp} and ΔG_{chl} values predicted for the tttttt conformation are 0.5 and 0.0 kcal/mol, respectively, indicating that the gradual stabilization of the fully extended conformation detected for the other compounds follows in **4**. Thus, analysis of the results obtained for all the compounds investigated in this work reveals that the stability of the extended conformation increases about 0.5 and 0.4 kcal/mol in gas phase and chloroform solution, respectively, per methylene unit added to the central aliphatic segment.

Conclusions

The conformational preferences of ω-hydroxy acids, HO−$(CH_2)_n$−COOH with n ranging from 2 to 5, have been investigated by using ab initio calculations. The intrinsic conformational preferences of these compounds are systematic, as demonstrated by the fact that for $n >$ 2 the lowest energy conformation of HO−$(CH_2)_n$−COOH is intimately related to the lowest energy conformation of HO−$(CH_2)_{n-1}$−COOH. Thus, the lowest energy conformation in the gas phase of **1**, **2**, **3**, and **4** corresponds to g^+g^-t, $g^+g^+g^-t$, $g^-g^+g^+g^-t$, and $g^-g^-g^+g^+g^-t$, respectively. Environmental forces can alter these intrinsic conformational preferences as was shown in chloroform, where the solution−solvent interactions play a crucial role. Indeed, comparison between results obtained in the gas phase and chloroform solution suggests that the potential energy surfaces of the investigated compounds become flatter with the polarity of the environment, i.e. the energy differences decrease when the polarity increases. Similar findings were reported in previous studies devoted to compare the conformational preferences of bioorganic compounds in chloroform and aqueous solutions.[12]

Conventional O−H···O hydrogen bonds but also those of the C−H···O type have been detected in many of the lower energy conformations of the ω-hydroxy acids. However, in general, the influence of the latter interactions in the stability of the conformers is smaller for **3** and **4** than for **1** and **2**. Presumably, this is because in the latter compounds the terminal electron-drawing groups are closer than in the former ones, enhancing the positive character of the aliphatic hydrogens and, therefore, the strength of C−H···O interactions. On the other hand, the conformational flexibility, which is measured by the number of conformations with significant populations considering a Boltzmann distribution, is larger in chloroform solution than in the gas phase for all the investigated compounds. This is because the solvent tends to reduce the conformational free energy increasing drastically the number of structures significantly populated. Furthermore, environmental forces also alter the relative energy order obtained in the gas phase. Thus, solvent modifies, in general, the intrinsic conformational preferences of ω-hydroxy acids.

A structural feature detected in both gas phase and chloroform solution is the stabilization of the extended and semiextended conformations, which increases with the size of the central aliphatic segment. Thus, the populations of these conformations in the gas phase and solution are negligible for **1** (<1%), relatively small for **2** (4−7%), and appreciable for **3** (9−16%). Calculations on selected conformations of **4** suggest a consistent behavior. This result is in concordance with our previous studies on diamides, diesters, and diketones.[1−3]

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Supporting Information Available: Optimized geometries and energies for all the minimum energy conformations of compounds **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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