Article

A Chirality Chain in Phenylglycine, Phenylpropionic Acid, and Ibuprofen

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† Dedication: Dedicated to Prof. Dr. Peter Göllitz, who navigated Angewandte Chemie, the flagship of the German chemistry journals, as Captain through the waves of time for 35 years.

Abstract: Our strategy to analyze the structures of natural amino acids with respect to the interaction of three different elements of chirality within the molecules was applied to the non-natural amino acid (S)- α -phenylglycine, its analogue (S)- α -phenylpropionic acid, and the drug (S)-ibuprofen. The three chirality elements are the configuration at C $_{\alpha}$, the conformation at the C $_{\alpha}$ -C' bond, and the distortion of the planar carboxylic group to a flat asymmetric tetrahedron. In all three compounds, a given (S) configuration at C $_{\alpha}$ predominantly induces (M) conformation at the C $_{\alpha}$ -C' bond, which in turn preferentially distorts the carboxylic group to a tetrahedron with (R) configuration. Both steps of this chirality chain display high selectivities. Due to varying co-crystallization partners, in all the structures the molecules are in different environments with respect to packing and hydrogen bonding. Nevertheless, the structural pattern and the diastereoselectivities of the chirality chain persist. For phenylglycine, DFT (Density Functional Theory) calculations confirm the structural results.

Keywords: amino acids; α -phenylpropionic acid; ibuprofen; chirality; diastereoselectivity; analysis of CSD structures; X-ray structure determination

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1. Introduction

In amino acids there is chirality and selectivity beyond the configuration at the α -carbon atom. Previously, we established an unprecedented chirality chain in the amino acids alanine [1] and valine [2]. Then, we showed that 1179 natural amino acids H₃NC $_{\alpha}$ HRC'(O_{cis})O_{trans}X [3] and 420 glycine derivatives H₃NC $_{\alpha}$ H₂C'(O_{cis})O_{trans}X [4] follow the chirality chain. X indicates that the carboxylic group may be protonated, esterified or coordinated. The chirality chain consists of three different elements of chirality: (1) the C $_{\alpha}$ configuration, which in natural amino acids is L, (2) the conformation concerning rotation around the central C'-C $_{\alpha}$ bond, and (3) the distortion of the planar carboxylic group C $_{\alpha}$ C'O_{cis}O_{trans} to a flat asymmetric tetrahedron with four different corners. The chirality chain involves two induction steps. The L configuration at C $_{\alpha}$ induces preferably (M $_{\psi}$) conformation at the C'-C $_{\alpha}$ bond with small negative rotation angles $\psi = \text{O}_{\text{cis}}\text{C}'\text{C}_{\alpha}\text{N}$ and the (M $_{\psi}$) conformation distorts the planar carboxylic group preferentially to a flat tetrahedron O_{cis}O_{trans}C'C $_{\alpha}$ with (R $_{\theta}$) configuration. Both steps show high diastereoselectivities. The arrows in Figure 1 point to the three different elements of chirality.

Worldwide, international companies collect data to establish profiles for commercial use. Data compiled in the Cambridge Structural Database (CSD) have been used to find chemical relationships for a long time. Seminal contributions identified energy minima and even reaction pathways using single crystal X-ray data [5–7]. Stimulated by the progress in X-ray crystallography, today, a wealth of CSD structures is available for exploitation.

We used this information for an analysis of phenylglycine, α -phenylpropionic acid, and ibuprofen with respect to chiral selectivities within the molecules.

Figure 1. Formulas of (S)-phenylglycine, (S)- α -phenylpropionic acid, and (S)-ibuprofen and chirality chain of the amino acid (S)-phenylglycine: for a given (S) configuration at C_α , chiral induction favors (M_ψ) conformation of the $C'-C_\alpha$ bond and (S_θ) configuration of the flat tetrahedron $O_{cis}O_{trans}C'C_\alpha$.

2. Results and Discussion

2.1. Analysis of (S)-Phenylglycine Structures

After having analyzed the natural amino acids [1–4], we turned to the non-natural amino acid phenylglycine $H_3N-CHPh-C'(O)O$ and its derivatives $H_3N-CHPh-COO(H/R/M)$ protonated, esterified or coordinated at the carboxylic group. A search in the Cambridge Structural Database and seven new structure determinations, added from our side, gave 25 hits. Eight structures contain independent molecules, differentiated by numbers in parentheses after the CSD symbol. Thus, 33 different structures are available for analysis, summarized in Table S1 (Supplementary Materials). (R)-Phenylglycine configurations were inverted to (S) by inverting the rotation and pyramidalization angles, and in the following discussion, we only use (S)-phenylglycine configurations.

In the present paper we truncated Table S1 to Table 1 with eight entries, which show the relevant trends. Ordering is done according to decreasing negative rotation angles ψ . Table 1 includes the first and the last entry of Table S1 and all the multiples of 5. As structures, determined several times, should have the same weight as structures determined only once, we average rotation angles ψ and pyramidalization angles θ for multiple structure determinations, indicating the number of independent structure determinations in the footnotes of the Tables.

Table 1. Phenylglycine (S)-NH₃CH(Ph)COO and its derivatives (S)-NH₃CH(Ph)COO(H/R/M) protonated, esterified, and coordinated at the carboxylic group.

Entry	CSD Symbol ¹	Chirality Chain			Space Group	Comments Acid, Ester or Metal Co-Crystallization Partners
		Config. at C _α ²	O _{cis} -C'-C _α -N Rotation Angle $\psi/^\circ$	O _{trans} -C'-C _α -O _{cis} Pyramidal Angle $\theta/^\circ$		
1	FAPMOZ(1)	(S)	−34.17	−177.16	P2 ₁	18-crown-6-ether(CO ₂ H) ₄ , H ₂ O
5	CCDC1981269(1) ³	(S)	−27.05	−178.70	P2 ₁	-
10	FAPMIT	(S)	−22.19	−178.61	P3 ₁	18-crown-6-ether(CO ₂ H) ₄ , H ₂ O
15	GACVIP(1)	(S)	−18.77	−173.15	P2 ₁	HClO ₄ , AcOH, crown ether
20	DOXWAO	(S)	−16.02	−181.59	P2 ₁	Me ester, HPF ₆ , benzo-18-crown-6-ether
25	CCDC1981272 ⁴	(S)	−11.65	−179.42	P2 ₁ /c	Me ester, HCl
30	FITPUT(2)	(S)	−8.10	−181.79	P2 ₁ 2 ₁ 2 ₁	Me ester, HClO ₄ , H ₂ O, binaphthyl-crown-6-ether
33	XALCUI	(S)	−3.95	−177.26	C2	D-campher-SO ₃ H
	Average 1-33		−17.88	−178.70		

¹ Parentheses indicate independent molecules in the unit cell. ² Rotation and pyramidalization angles of (R)-compounds inverted.

³ Average of (R)/(S)-, (R)-, and (S)-α-phenylglycine: CCDC1981269, 1981270, 1981271. ⁴ (R)/(S)-methyl phenylglycinate hydrochloride: CCDC1981272.

The rotation angle is defined as the torsion angle $\psi = \text{O}_{\text{cis}}\text{-C}'\text{-C}_\alpha\text{-N}$ (Figure 1, top middle). We differentiate the oxygen atoms of the carboxylic group as O_{cis} and O_{trans} according to their orientation with regard to the nitrogen atom. Four-atom-systems, such as O_{cis}C'C_αN, are chiral, unless the torsion angle ψ is 0° or 180°. According to the helicity rule of the CIP system [8,9], positive rotation angles ψ result in (P_ψ) conformation and negative in (M_ψ) conformation (Figure 1, top middle).

The carboxylic group C_αC'O_{cis}O_{trans} with its sp²-hybridized C' atom should be planar and achiral. Deviation from planarity results in a flat asymmetric tetrahedron with four different corners: C_α, C', O_{cis}, and O_{trans}. The pyramidalization angle $\theta = \text{O}_{\text{trans}}\text{-C}'\text{-C}_\alpha\text{-O}_{\text{cis}}$ measure the deviation of O_{cis} from the plane O_{trans}C'C_α (Figure 1, top right). The configuration of the flat tetrahedron is specified by the (R)/(S) symbols of the CIP system [8,9], following the priority sequence O_{cis} > O_{trans} > C' > C_α (Figure 1, top right). Pyramidalization angles θ below −180° define (R_θ) configuration and pyramidalization angles θ above −180° indicate (S_θ) configuration at the flat tetrahedron.

The rotation angles ψ in Table 1 and Table S1 extend between −34.2° and −4.0°. C_α-C' bond conformations ψ in the range −40° to −90° are absent. Small negative rotation angles ψ had been typical for all the natural amino acids, favoring (S_{Cα},M_ψ) compared to a (S_{Cα},P_ψ) configuration [1–4]. For a given (S_{Cα}) configuration in phenylglycine, there are no positive rotation angles. Thus, the diastereoselectivity (S_{Cα}→M_ψ):(S_{Cα}→P_ψ) = 33:0 in the first step of the chirality chain from the (S_{Cα}) configuration to the (M_ψ) conformation is 100%. The predominance of small negative rotation angles for a given (S) configuration is also expressed in the average $\psi_{\text{av}} = -17.9^\circ$ of the 33 structures in Table S1. Figure 2 shows a plot of the rotation angles ψ on the abscissa versus the frequency of occurrence of the rotation angles ψ in percent on the ordinate. In each of the 33 entries of Table S1, the (S)-phenylglycine molecule is in completely different environments with respect to lattice effects and hydrogen bond networks. This is demonstrated in the Comments of Table 1 and Table S1, in which its co-crystallization partners are listed. The appearance of a common structural motif, irrespective of the changing environment, indicates an energy minimum, represented by the envelope in Figure 2, which covers the columns representing the frequency of occurrence. Obviously, such a robust pattern is competitive with packing forces and intermolecular hydrogen bonding.

Figure 2. Upper part: frequency of occurrence of (S)-phenylglycine structures in percent as a function of the rotation angle ψ . Each of the columns represents a 5° interval of ψ such as 0° to −5°, −5° to −10°, etc. Lower part: rotation angles ψ versus pyramidalization angles θ of the 33 structures of (S)-phenylglycine of Table S1 and the best-fit line.

Table S1 and Figure 3 show that the pyramidalization angles θ concentrate below -180° , in particular for small negative rotation angles ψ . The preference of pyramidalization angles θ below -180° also shows up in the average $\theta_{av} = -178.7^\circ$ of the 33 structures in Table S1.

The distortion of the carboxylic group to a flat asymmetric tetrahedron is induced by the (S) configuration at C_{α} and the (M_{ψ}) conformation of the $C_{\alpha}-C'$ bond. As for (S)-phenylglycine, there are no positive rotation angles ψ ; the selectivities $(S_{C_{\alpha}}) \rightarrow (R_{\theta}, S_{\theta})$ and $(M_{\psi}) \rightarrow (R_{\theta}, S_{\theta})$ are identical. In numbers, the overall selectivity for (S)-phenylglycine is $(M_{\psi}) \rightarrow (R_{\theta}) : (M_{\psi}) \rightarrow (S_{\theta}) = 27:6 = 4.6$. Thus, there is a considerable selectivity for the side of the (R_{θ}) configuration of the flat tetrahedron $O_{cis}O_{trans}C'C_{\alpha}$.

The height of the columns, the ψ/θ values, and the selectivity ratios in Figure 2 are experimental results, based on the available CSD structures. The best-fit line of the X-ray structural data in Figure 2, lower part, shows that the pyramidalization of the carboxylic group increases, when the rotation angles increase from $\psi = -4.0^\circ$ to higher negative rotation angles.

Figure 3. Upper part: rotation angle ψ_{calc} as a function of relative energy ($\circ$), calculated at the B3LYP/def2TZVP level in steps of 2.5° . Lower part: rotation angle ψ_{calc} as a function of pyramidalization angle θ_{calc} ($\triangle$). The dashed line is the best-fit line of the structures in Figure 2.

2.2. DFT Calculations of (S)-Phenylglycine

DFT calculations of the zwitterion of (S)-phenylglycine $\text{H}_3\text{N}-\text{C}_\alpha\text{HPh}-\text{C}'(\text{O}_{\text{cis}})\text{O}_{\text{trans}}$ were carried out, using the B3LYP/def2TZVP level, including dispersion (GD3BJ) and solvent effects (PCM; water) [10–18]. Details of the calculations and Table S2 with the numerical parameters are given in the Supplementary Materials. Figure 3, upper part, shows the rotation angle ψ_{calc} as a function of the relative energy. In 2.5° steps, the calculation extends from $\psi_{\text{calc}} = -90^\circ$ to 0° .

The relative energy of (S)-phenylglycine (open circles) is zero at $\psi_{\text{calc}} = -6.3^\circ$, which compares well with the average $\psi_{\text{av}} = -17.9^\circ$ of the 33 structures in Table S1. The small negative rotation angles are the result of the chiral induction from the (S) configuration at C_α to the (M_ψ) conformation of the $\text{C}_\alpha-\text{C}'$ bond in the first step of the chirality chain [1–4]. With increasing negative rotation angles, it rises slowly up to ψ_{calc} angles of -30° . Then, the increase becomes steeper, before it levels off at highly negative rotation angles ψ_{calc} . At $\psi_{\text{calc}} = -90^\circ$, the relative energy is 32.0 kJ/mol higher than in the minimum, a remarkable energy difference for a rotation around a single bond. On the side of positive rotation angles, the curve continues almost symmetrically.

Figure 3, lower part, shows the pyramidalization angles θ_{calc} as a function of the rotation angles ψ_{calc} (triangles). For the rotation angle $\psi_{\text{calc}} = 0^\circ$, the pyramidal angle $\theta_{\text{calc}} = -180.8^\circ$ is in the regime of (R_θ) configuration of the flat tetrahedron $\text{O}_{\text{cis}}\text{O}_{\text{trans}}\text{C}'\text{C}_\alpha$. Going to negative rotation angles, the curve steeply drops down to the minimum around $\psi_{\text{calc}} = -35^\circ$ in the area of (S_θ) configuration. At higher negative rotation angles, the curve passes about $\psi_{\text{calc}} = -70^\circ$, the state of a planar carboxylic group with a pyramidalization angle $\theta = -180^\circ$. Then, the curve continues into the area of the inverted (R_θ) configuration

of the carboxylic group. However, it must be kept in mind that structures with rotation angles between $\psi = -40^\circ$ and -90° have high relative energies, and for (*S*)-phenylglycine structures, such high rotation angles are absent. The remarkable and unexpected changes, which the pyramidalization of the carboxylic group does undergo during rotation around the $C_\alpha-C'$ bond, comes as a surprise. The region between 0° and $+90^\circ$ is almost symmetrical to the region between 0° and -90° .

In Figure 3, we added the best-fit line of the structural data of (*S*)-phenylglycine. It follows the decrease of the calculated curve of negative rotation angles in remarkable agreement.

2.3. Analysis of (*S*)- α -Phenylpropionic Acid Structures

Replacement of the NH_3 group in (*S*)-phenylglycine by a CH_3 group results in (*S*)- α -phenylpropionate, which is the parent compound of important drugs. Is the two-step chirality chain, operative in amino acids, also working for (*S*)- α -phenylpropionic acid? We analyzed α -phenylpropionic acid (*S*)- $H_3C-CHPh-C'(O)OH$ and its derivatives (*S*)- $H_3NC-CHPh-COO(R/M)$ esterified or coordinated at the carboxylic group in a CSD search. Similar to Table S1 of (*S*)- α -phenylglycine, Table S3 contains 87 structures of (*S*)- α -phenylpropionic acids, ordered according to decreasing negative rotation angles ψ . Structures with (*R*) configurations were inverted to (*S*) configurations.

The rotation angles ψ of (*S*)- α -phenylpropionic acid in Table S3 range between -84.2° and 81.6° . Similar to (*S*)-phenylglycine, the rotation angles ψ accumulate in the area of small negative values. However, in contrast to (*S*)-phenylglycine, there are some highly negative and also some positive rotation angles. Therefore, the induction field $(S_{C_\alpha}) \rightarrow (M_\psi)$ of (*S*)-phenylglycine in Figure 2 doubles to the two halves $(S_{C_\alpha}) \rightarrow (M_\psi)$ and $(S_{C_\alpha}) \rightarrow (P_\psi)$ in Figure 4, upper part. The preference of small negative rotation angles for a given (*S*) configuration shows up in the average $\psi_{av} = -22.1^\circ$ of the 87 structures in Table S3. In the upper part of Figure 4 the rotation angles ψ are given as a function of their frequency of occurrence in percent in a column representation with the envelope corresponding to the energy minimum.

Figure 4. Upper part: the rotation angles ψ of the (*S*)- α -phenylpropionic acids in Table S3 as a function of their frequency of occurrence in percent in a column representation with the envelope corresponding to the energy minimum. Lower part: the rotation angles ψ as a function of the pyramidalization angles θ , including the best-fit curve.

Table S3 shows that the (S) configuration of α -phenylpropionic acid confers a high chiral induction to the torsional system $\psi = \text{OC}'\text{C}_\alpha\text{N}$. The columns in Figure 4, upper part, visualize the high $(S_{C_\alpha}) \rightarrow (M_\psi)$ selectivity. Thus, 73 of a total of 87 structures adopt (M_ψ) conformation with respect to the $\text{C}_\alpha\text{-C}'$ bond. Only 14 structures have (P_ψ) conformation, resulting in a selectivity $(S_{C_\alpha}) \rightarrow (M_\psi) : (S_{C_\alpha}) \rightarrow (P_\psi) = 73:14 = 5.2$ in the first step of the chirality chain.

According to Table S3 and Figure 4, lower part, the pyramidalization angles θ concentrate below -180° , indicating (S_θ) configuration in the flat tetrahedron $\text{O}_{\text{cis}}\text{O}_{\text{trans}}\text{C}'\text{C}_\alpha$, in particular for small negative rotation angles ψ . The concentration of the pyramidalization angles θ below -180° appears in the average $\theta_{\text{av}} = -178.9^\circ$ of the 87 structures of Table S3. In the lower part of Figure 4, the $(\psi)/(\theta)$ representation expands to a four-field system with four different chiral inductions. The two fields on the left side of Figure 4 show the two diastereomers (M_ψ, S_θ) and (M_ψ, R_θ) . The induction according to the second step of the chirality chain results in a diastereoselectivity $(M_\psi) \rightarrow (S_\theta) : (M_\psi) \rightarrow (R_\theta) = 49:24 = 2.0$. (M_ψ, S_θ) in the bottom left field and (P_ψ, R_θ) in the top right field are enantiomers. Therefore, the inductions $(M_\psi) \rightarrow (S_\theta)$ and $(P_\psi) \rightarrow (R_\theta)$ should be the same. However, the ratio $(M_\psi) \rightarrow (S_\theta) : (P_\psi) \rightarrow (R_\theta)$ is $49:10 = 4.9$, the deviation from 1:1 reflecting the contribution of the (S) configuration at C_α .

The best-fit curve in Figure 4, lower part, starts in the field (M_ψ, R_θ) with (R_θ) configuration of the flat tetrahedron $\text{O}_{\text{cis}}\text{O}_{\text{trans}}\text{C}'\text{C}_\alpha$. Then, the majority of structures with small negative rotation angles adopts (S_θ) configuration. At rotation angles above $\psi = -70^\circ$, the curve again enters the area of (R_θ) configuration of the flat tetrahedron. Thus, the curve progression parallels the curve of the DFT calculation of (S)-phenylglycine in Figure 3.

The 87 structures of (S)- α -phenylpropionic acids in Table S3 accumulate at small negative rotation angles around the average $\psi_{\text{av}} = -22.1^\circ$, indicating an energy minimum. For (S)-phenylglycine, there had been no CSD structures with higher negative rotation angles than $\psi = -40^\circ$, which increasingly rise in energy content according to Figure 3. However, Figure 4 shows that a few structures of (S)- α -phenylpropionic acids accept high-energy conformations with rotation angles of $\psi_{\text{av}} = -80^\circ$ to -90° , probably due to strong packing forces and/or hydrogen bond networks. Interestingly, at these high conformational energies, the configuration of the flat tetrahedron tends to move from $(M_\psi) \rightarrow (S_\theta)$ to the regime of $(M_\psi) \rightarrow (R_\theta)$.

2.4. Analysis of the (S)-Ibuprofen Structures

Ibuprofen is the 4-isobutyl derivative of α -phenylpropionic acid. We searched for $\text{H}_3\text{C-CH}(4\text{-}^i\text{BuC}_6\text{H}_4)\text{-C}'(\text{O})\text{OH}$ and its derivatives $\text{H}_3\text{C-CH}(4\text{-}^i\text{BuC}_6\text{H}_4)\text{-COO(R/M)}$ esterified or coordinated at the carboxylic group. Table S4 comprises 80 structures, in which (S)-ibuprofen crystallizes with different co-crystallization partners. Ordering is done according to decreasing negative rotation angles ψ . Structures with (R) configurations were inverted to (S) configurations.

Similar to the (S)- α -phenylpropionic acids, the rotation angles ψ of the (S)-ibuprofens in Table S4 span a wide range from -92.7° to 71.6° . The rotation angles ψ accumulate in the area of small negative values. As for the (S)- α -phenylpropionic acids, there are some positive and also some highly negative rotation angles. The average $\psi_{\text{av}} = -28.0^\circ$ of the 80 points in Table S4 emphasizes the preference of small negative rotation angles for a given (S) configuration. The upper part of Figure 5 shows the rotation angles ψ versus their frequency of occurrence in percent. The envelope enwrapping the columns corresponds to the energy minimum.

Figure 5. Upper part: the rotation angles ψ of the (S)-ibuprofen structures in Table S4 versus their frequency of occurrence in percent in a column representation with the envelope corresponding to the energy minimum. Lower part: the rotation angles ψ versus the pyramidalization angles θ , including the best-fit curve.

Table S4 and Figure 5 confirm the high chiral induction from the (S_{Cα}) configuration of the (S)-ibuprofens to the (M_ψ) conformation of the C_α-C' bond. The columns in Figure 5 visualize the high (S_{Cα}) → (M_ψ) selectivity. Indeed, 71 of the 80 structures adopt (M_ψ) conformation with respect to the C_α-C' bond. Only nine structures have (P_ψ) conformation, resulting in a selectivity of (S_{Cα}) → (M_ψ):(S_{Cα}) → (P_ψ) = 71:9 = 7.9 in the first step of the chirality chain.

As for the (S)-α-phenylpropionic acids, the pyramidalization angles θ in Table S5 and Figure 4, lower part, accumulate below -180° , indicating (S_θ) configuration in the flat tetrahedron O_{cis}O_{trans}C'C_α, in particular for small negative rotation angles ψ . Similar to the (S)-α-phenylpropionic acids, the diastereoselectivity in the second step of the chirality chain is (M_ψ) → (S_θ):(M_ψ) → (R_θ) = 49:24 = 2.0. Due to the chiral induction of the (S) configuration at C_α, the ratio of the two enantiomers (M_ψ) → (S_θ):(P_ψ) → (R_θ) is 47:6 = 7.8. The best-fit curve in Figure 4, lower part, resembles the curves of the (S)-α-phenylpropionic acid derivatives.

The results obtained for the (S)-ibuprofen structures closely resemble those of the (S)-α-phenylpropionic acids. The features established for the low-energy (M_ψ) conformations of the C_α-C' bond and the (S_θ) configurations of the flat tetrahedron O_{cis}O_{trans}C'C_α should persist in the solution, where ibuprofen performs its effectiveness.

3. Conclusions

(S)-Phenylglycine, (S)-α-phenylpropionic acid, and (S)-ibuprofen derivatives follow the two-step chirality chain, in which three elements of chirality selectively interact within the molecules. In the first step, (S) configuration at C_α preferentially induces (M_ψ) conformation at the C_α-C' bond, tantamount to small negative rotation angles ψ . In the second step, there is a preferred formation of (S_θ) configuration in the four-atom system of the carboxylic group, which is distorted to a flat tetrahedron. The chirality chain in a

drug such as ibuprofen reveals structural details, important for approach and binding to its receptor.

4. Materials and Methods

The Cambridge Structural Database ver. 5.41 [19] (update August 2020) was used for a search of phenylglycine, α -phenylpropionic acid, and ibuprofen derivatives. The programs OLEX² [20], Mercury CSD ver. 2020.2.0 [21], and ConQuest ver. 2020.2.0 [22] were applied for the structure analyses. Single crystal preparation and X-ray diffraction analysis of (R)/(S)-, (R)-, and (S)-phenylglycine, (R)/(S)-, (R)-, and (S)-methyl phenylglycinate hydrochloride, as well as (R)-ethyl phenylglycinate hydrochloride are described in the Supplementary Materials.

Supplementary Materials: Available online at <https://www.mdpi.com/2073-8994/13/1/55/s1>: Table S1: Phenylglycine (S)-NH₃CH(Ph)COO and its derivatives (S)-NH₃CH(Ph)COO(H/R/M) protonated, esterified, and coordinated at the carboxylic group (structures with R factors >10% excluded). Table S2: (S)-Phenylglycine: relative energy as a function of the rotation angle $\psi = \text{O}_{\text{cis}}-\text{C}'-\text{C}_{\alpha}-\text{N}$ and the pyramidalization angle $\theta = \text{O}_{\text{trans}}-\text{C}'-\text{C}_{\alpha}-\text{O}_{\text{cis}}$, calculated at the B3LYP/def2-TZVP level, including dispersion (GD3BJ) and solvent effects (PCM; water). Table S3: α -Phenylpropionic acid (S)-CH₃CH(Ph)COOH and its derivatives (S)-CH₃CH(Ph)COO(R/M) esterified and coordinated at the carboxylic group (structures with R factors >10% excluded). Table S4: Ibuprofen (S)-CH₃CH(C₆H₄Buⁱ-4)COOH and its derivatives (S)-CH₃CH(C₆H₄Buⁱ-4)COO(R/M) esterified and coordinated at the carboxylic group (structures with R factors >10% excluded). Table S5: Crystallographic data for (R)/(S)-, (R)-, and (S)-phenylglycine, (R)/(S)-, (R)-, and (S)-methyl phenylglycinate hydrochloride, and (R)-ethyl phenylglycinate hydrochloride. Figure S1: ORTEP drawing of conglomerate (R)/(S)-phenylglycine: CCDC1981269. Figure S2: ORTEP drawing of (R)-phenylglycine: CCDC1981270. Figure S3: ORTEP drawing of (S)-phenylglycine: CCDC1981271. Figure S4: ORTEP drawing of racemate (R)/(S)-methyl α -phenylglycinate hydrochloride: CCDC1981272. Figure S5: ORTEP drawing of (R)-methyl α -phenylglycinate hydrochloride: CCDC1981273. Figure S6: ORTEP drawing of (S)-methyl α -phenylglycinate hydrochloride: CCDC1981274. Figure S7: ORTEP drawing of (R)-ethyl α -phenylglycinate hydrochloride: CCDC2049622. The crystallographic data for this paper (CCDC1981269, 1981270, 1981271, 1981272, 1981273, 1981274, and 2049622) can also be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033.

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