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Synthesis and Structural Study of Precursors of Novel Methylsilanediols by IR and Raman Spectroscopies, Single-Crystal X-Ray Diffraction and DFT Calculations

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SYNTHESIS AND STRUCTURAL STUDY OF PRECURSORS OF NOVEL METHYLSILANEDIOLS BY IR AND RAMAN SPECTROSCOPIES, SINGLE-CRYSTAL X-RAY DIFFRACTION AND DFT CALCULATIONS

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Abstract

On the way towards the development of a synthetic route aimed at obtaining new methylsilanediol derivatives with an aminocarbonyl group in β to silicon (which may have a potential biological interest), we have synthesized, isolated and purified five diphenylic possible precursors, namely chloromethyl(methyl)diphenylsilane, 2-[[methyl(diphenyl)silyl]methyl]-1H-isoindole-1,3(2H)-dione, *N*-[(methyl(diphenyl)silyl)-methyl]-benzamide, *N*-[(methyl(diphenyl)silyl)-methyl]-acetamide and *N*-[(methyl(diphenyl)silyl)-methyl]-formamide.

The conformational landscape of the five species in this study are explored by means of DFT calculations at the B3LYP/ 6-311++G** level. The theoretical molecular structures predicted are confirmed by the reproduction of their respective IR and Raman spectral profiles, that are completely assigned. Some evidence in the vibrational spectra points to the occurrence of conformational mixtures in the samples.

Further, single-crystal X-ray diffraction has allowed the elucidation of the crystalline structure of 2-[[methyl(diphenyl)silyl]methyl]-1H-isoindole-1,3(2H)-dione.

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1. Introduction

Silicon is the second most abundant element on earth and the one most similar to carbon. This close chemical analogy has been the inspiration for many studies of silicon as a potential replacement for carbon, particularly in biologically active molecules. [1,2] The most notable example of this is the claim of silanediols as bioisosteres of the hydrated amido group and their application in the development of peptidomimetics as protease inhibitors. [3,4] The *gem*-silanediol group is most stable in its tetrahedral configuration than the corresponding geminal carbinol that readily undergo dehydration and, therefore, interaction with active site of protease is favored through hydroxyl groups which are excellent hydrogen bond donors and acceptors. [5,6,7] Nevertheless, previous attempts to inhibit hydrolases with relatively simple silanediols found them to be inactive. [8] This may be attributed to the fact that dialkylsilanediols with small side chains are prone to fast polymerization while steric effects of the bulky groups prevent silanediols from this process through the screening of OH groups. The structure of silanediols successfully used as protease inhibitors, contains aminocarbonyl and amide groups in β and γ positions to silicon. [4,9]

Thus, a theoretical-experimental analysis of the molecular structure of this type of silanediol would help achieve a better understanding of the mechanisms of stabilization of the $\text{Si}(\text{OH})_2$ functionality, and which could be related to their potential biological role. For this task, we are working on the preparation of a significant set of relatively simple methylsilanediols which are structurally related to those that have proven biological activity.

We report our first efforts to synthesize a new set of these methylsilanediols, specifically those containing an aminocarbonyl group on the β position relative to the silicon (Figure 1). In this work, our goal has been to perform a thorough structural analysis of five diphenylsilyl intermediates, obtained synthetically and isolated and purified for the first time, which could be used as precursors of the mentioned silanediols.

We present the joint theoretical study and experimental characterization of the following structurally related species: chloromethyl(methyl)diphenylsilane (intermediate **2**), 2-[methyl(diphenyl)silyl]methyl]-1H-isoindole-1,3(2H)-dione (intermediate **3**), *N*-[(methyl(diphenyl)silyl)-methyl]-benzamide (intermediate **5a**), *N*-[(methyl(diphenyl)silyl)-methyl]-acetamide (intermediate **5b**) and *N*-[(methyl(diphenyl)silyl)-methyl]-formamide (intermediate **5c**). We have performed a thorough theoretical (DFT) conformational analysis of all the species. Further, the crystal structure of the so called intermediate **3** has also been determined using single crystal X-ray diffraction.

IR and Raman spectra of the five species have also been measured and the bands assigned showing, in some cases, evidence of conformational mixtures in the samples.

2. Materials and Methods

2.1. Synthesis

Reagents were purchased from commercial sources and used without further purification. Solvents were dried as described elsewhere. [10] Reactions were followed by thin layer chromatography (TLC). This was performed on Merck Silica Gel 60GF₂₅₄ aluminium precoated foils (0.2 mm) using fluorescent indicator and spots were visualized using ultraviolet radiation or using the ninhydrin test. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm). Melting points (m.p.) were determined in open capillaries in a Electrothermal IA9000 series digital melting point apparatus and are uncorrected. ¹H, ¹³C and ²⁹Si NMR spectra were recorded on a Bruker Avance 400 spectrophotometer operating at 400 MHz, 100 and 79.49 MHz respectively, using CDCl₃ and [D₆] DMSO as solvents and tetramethylsilane as the internal standard. The following abbreviations were used for the multiplicity of signals in ¹H-NMR: (s) singlet, (d) doublet, (m) multiplet, (bs) broad singlet. Mass spectra were run on a SHIMADZU-GCMS 2010-DI-2010 spectrometer (equipped with a direct inlet probe) operating at 70 eV. High resolution mass spectra were recorded using a Waters Micromass AutoSpec-Ultima spectrometer (equipped with a direct inlet probe) operating at 70 eV.

2.1.1. Chloromethyl(methyl)diphenylsilane (**2**):

Dichloro(chloromethyl)methylsilane (6 mL, 0.041 mol) was added drop-wise over a period of 30 min under an argon atmosphere to a stirred solution of commercial phenylmagnesium bromide in diethyl ether (41 mL, 0.123 mol). The mixture was then refluxed for 16 h and subsequently poured into ice water (150 mL). The mixture was extracted with diethyl ether (2 x 100 mL) and the extract washed with three 100 mL portions of water and then dried over anhydrous sodium sulfate. Finally, the solvent was removed *in vacuo* and the residue was purified by Flash chromatography (n-hexane) producing **2** as colourless oil (8.13 g, 80 %). ¹H NMR (400 MHz, CDCl₃, 25°C) δ (ppm): 7.65-7.62 (m, 4H, Ar), 7.49-7.42 (m, 6H, Ar), 3.31 (s, 2H, -CH₂), 0.78 (s, 3H, -CH₃); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 134.6, 134.2, 129.9, 128.0, 28.8 (-CH₂), -5.6 (-CH₃); ²⁹Si NMR (79.49 MHz, CDCl₃) δ (ppm): -8.95; MS (EI, 70 eV): 246 (M⁺, 1), 197 (100), 165 (7), 105 (8); HR-MS (EI): C₁₄H₁₅ClSi calculated 246.0632, found. 246.0624. Anal. Calcd for C₁₄H₁₅ClSi (246.81): C, 68.13; H, 6.13. Found: C, 68.16; H, 6.17.

2.1.2. 2-([methyl(diphenyl)silyl]methyl)-1*H*-isoindole-1,3(2*H*)-dione (**3**):

Potassium phtalamide (8.14 g, 43.96 mmol) was added to a solution of **2** (7.23 g, 29.31 mmol) in anhydrous DMSO (100 mL) at room temperature and the solution was then heated to 100 °C until no starting material was visible by TLC (ca: 18 h. Eluent: hexane/ethyl acetate 8:2 v/v). After the mixture was cooled to room temperature it was

subsequently poured into ice water (300 mL). The solid was filtered off, washed with water and n-hexane and recrystallized from EtOH to produce compound **3** as a yellow solid (7.54 g, 72 %). M.p. 91-93 °C; ¹H NMR (400 MHz, DMSO-*d*₆, 25°C) δ (ppm): 7.73 (m, 4H, Ar), 7.52 (m, 4H, Ar), 7.34 (m, 6H, Ar), 3.61 (s, 2H, -CH₂), 0.68 (s, 3H, -CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 167.7 (C=O), 134.6, 134.2, 134.1, 131.4, 129.6, 127.8, 122.6, 26.6 (-CH₂), -4.2 (-CH₃); ²⁹Si NMR (79.49 MHz, DMSO-*d*₆) δ (ppm): -8.65; MS (EI, 70 eV): 356 (M-H⁺, 9), 342 (8), 280 (100), 266 (31), 197 (66), 105 (11); HR-MS (EI): C₂₂H₁₈NO₂Si-H calculated 356.1107 [M-H], found 356.1112 [M-H]. Anal. Calcd for C₂₂H₁₉NO₂Si (357.48): C, 73.92; H, 5.36; N, 3.92. Found: C, 73.89; H, 5.40; N, 3.88.

2.1.3. [(Methyl(diphenyl)silyl)]-methanamine (**4**):

Hydrazine monohydrate (5.9 mL, 78.67 mmol) was added to a solution of **3** (3.00 g, 8.39 mmol) in a mixture of THF and methanol (40 ml, 1:1, v/v) under an argon atmosphere. The solution was heated to 65°C until no starting material was observable using TLC (ca: 4 h. Eluent: hexane/ethyl acetate 8:2, v/v) and then was cooled, filtered, washed with THF and finally concentrated *in vacuo*. The residue was washed with water and extracted with four 20 mL portions of toluene. Organic extract was dried over Na₂SO₄, filtered and the solvent removed *in vacuo* to give compound **4** as a colourless oil (1.73 g, 90 %). ¹H NMR (400 MHz, DMSO-*d*₆, 25°C) δ (ppm): 7.49 (m, 4H, Ar), 7.36 (m, 6H, Ar), 2.55 (s, 2H, CH₂), 0.53 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 136.1, 134.3, 129.2, 127.8, 28.4 (-CH₂), -5.9 (-CH₃); ²⁹Si NMR (79.49 MHz, DMSO-*d*₆) δ (ppm): -9.51.

2.1.4. *N*-[(methyl(diphenyl)silyl)-methyl]-benzamide (**5a**):

Benzoyl chloride (0.8 mL, 7.26 mmol) in dry toluene (5mL) was added drop-wise to a solution of freshly obtained **4** (1.10 g, 4.85 mmol) and Et₃N (6.1 mL, 43.54 mmol) in dry toluene (10 mL) at 0 °C under an argon atmosphere. The mixture was stirred and warmed to reflux until no starting material was observable using TLC (ca: 5 h. Eluent: CH₂Cl₂/MeOH 9:1, v/v) and then, 20 % aqueous K₂CO₃ (20 mL) was added at room temperature. The organic layer was separated and aqueous layer extracted twice with toluene (10 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried over Na₂SO₄, and finally the solvent was removed *in vacuo*. Flash chromatography (CH₂Cl₂/MeOH, 99:1, v/v) resulted in **5a** as a pure pale yellow solid (0.52 g, 32 %). M.p. 82-84 °C; ¹H NMR (400 MHz, CDCl₃, 25°C) δ (ppm): 7.60-7.24 (m, 15H, Ar), 5.85 (bs, 1H, -NH), 3.48 (d, *J* = 5.6 Hz, 2H, -CH₂), 0.67 (s, 3H, -CH₃); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 167.8 (C=O), 134.8, 134.6, 134.3, 133.9, 131.1, 130.0, 129.8, 128.5, 128.3, 127.8, 126.6, 27.6 (-CH₂), -5.0 (-CH₃); ²⁹Si NMR (79.49 MHz, CDCl₃) δ (ppm): -8.54; MS (EI, 70 eV): 331 (M, 13), 330 (M-H, 43), 316 (14), 254 (93), 240 (69); 197 (100), 105 (42), 77 (29); HR-MS (EI): C₂₁H₂₀NOSi-H calculated 330.1314 [M-H], found 330.1320 [M-H].

2.1.5. *N*-[(methyl(diphenyl)silyl)-methyl]-acetamide (**5b**):

A mixture of freshly obtained compound **4** (0.63 g, 2.77 mmol) and acetic anhydride (6 mL) was stirred at room temperature until no starting material was observable using TLC (ca: 2 h. Eluent: CH₂Cl₂/MeOH 9:1, v/v) and then CH₂Cl₂ (15 mL) and water (15 mL) were added. The aqueous layer was extracted twice with CH₂Cl₂ (15 mL) and then all the organic extracts were put together, washed with 20 % aqueous K₂CO₃ (20 mL) and dried over MgSO₄. Finally, the solvent was removed *in vacuo* and the residue was purified by Flash chromatography (CH₂Cl₂/MeOH, 95:5, v/v) to give **5b** as a colourless oil (0.45 g, 60 %).

¹H NMR (400 MHz, CDCl₃, 25°C) δ (ppm): 7.51 (m, 4H, Ar), 7.38 (m, 6H, Ar), 5.19 (bs, 1H, NH), 3.29 (d, *J* = 5.6 Hz, 2H, CH₂), 1.88 (s, 3H, CH₃), 0.61 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 170.3 (C=O), 134.5, 134.3, 129.9, 128.2, 27.3 (-CH₂), 23.1 (-CH₃), -5.1 (-CH₃); ²⁹Si NMR (79.49 MHz, CDCl₃) δ (ppm): -8.99; MS (EI, 70 eV): 268 (M-H, 7), 254 (17), 197 (94), 192 (100), 178 (58), 137 (28); 105 (21), 43 (7). HR-MS (EI): C₁₆H₁₈NOSi-H calculated 268.1158 [M-H], found 268.1163 [M-H]

2.1.6. *N*-[(methyl(diphenyl)silyl)-methyl]-formamide (**5c**):

A mixture of freshly obtained compound **4** (1.00 g; 4.40 mmol), aqueous 95 % formic acid (0.67 mL, 17.59 mmol) and sodium formate (0.072 g, 0.88 mmol) in toluene (10 mL) was heated under reflux using MS 3Å until no starting material was observable using TLC (ca: 24 h. Eluent:) and then, 30 % aqueous K₂CO₃ (20 mL) was added. The organic layer was separated and the aqueous layer extracted twice with toluene (10 mL). The combined organic extracts were washed with saturated aqueous NaCl and dried over MgSO₄. Finally, the solvent was removed *in vacuo* and the residue was purified by Flash chromatography (CH₂Cl₂/MeOH 95:5, v/v) to give **5c** as a yellow oil (0.60 g, 53 %).

¹H NMR (400 MHz, CDCl₃, 25°C) δ (ppm): 8.10 (s, 1H, CH), 7.52-7.38 (m, 10H, Ar), 5.28 (bs, 1H, NH), 3.32 (d, *J* = 5.8 Hz, 2H, CH₂), 0.62 (s 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 161.4 (C=O), 134.5, 134.0, 130.0, 128.3, 25.8 (-CH₂), -5.2 (-CH₃); ²⁹Si NMR (79.49 MHz, CDCl₃) δ (ppm): -9.08. MS (EI, 70 eV): 254 (M-H, 4), 240 (9); 197 (100); 178 (66); 164 (37); 137 (16), 105 (18). HR-MS (EI): C₁₅H₁₆NOSi-H calculated 254.1001 [M-H], found. 254.0995 [M-H].

2.2. Infrared and Raman spectra

IR spectra of the samples were recorded in the MIR and FIR regions using a FT-IR Bruker Vertex 70 spectrophotometer equipped with a ceramic internal air cooled source, KBr optics (for MIR) and polyethylene optics (for FIR) and a DLaTGS detector.

Raman spectra of the samples were recorded using a MultiRAM Stand Alone FT-Raman Spectrometer, equipped with an Nd:YAG laser (excitation line at 1064 nm) and a Ge detector cooled at liquid nitrogen temperature. All spectra were recorded with a resolution of 1 cm⁻¹ and 100 scans.

2.3. Single-crystal X-ray diffraction analysis

Crystals of 2-{methyl(diphenyl)silyl}methyl}-1H-isoindole-1,3(2H)-dione (intermediate **3**) were grown by slow evaporation (at 40°C) of dissolutions of the sample in diethylether/hexane (1:1) mixtures. Small, pale orange block crystals of the sample were obtained. X-ray diffraction data were collected at 100K on a Rigaku R-axis/RAPID image plate diffractometer equipped with an Oxford cryosystems N₂ low temperature device, using graphite monochromated MoK α radiation ($\lambda = 0.71075 \text{ \AA}$). The crystal structure was solved using direct methods and the program SHELXS-97 [11] and refined using SHELXL-97 [12] against $|F^2|$ using all data, as implemented in the WinGX program suite. [13] Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were identified in a Fourier difference map and were allowed to refine freely. Crystal data at 100K: formula C₂₂H₁₉NO₂Si, M= 357.48 g/mol, X-Ray (100K): Monoclinic, space group P2₁/c, $a = 7.8360(6)$, $b = 29.6480(3)$, $c = 7.9145(8) \text{ \AA}$, $\alpha = 90$, $\beta = 92.247(7)$, $\gamma = 90$, $V = 1837.3(3) \text{ \AA}^3$, $Z = 4$, $\rho = 1.292 \text{ g cm}^{-3}$, $\mu = 0.144 \text{ mm}^{-1}$, $F(000) = 752$. A total of 20901 reflections ($3.3^\circ < \theta < 27.5$) were collected, 4199 unique ($R_{int} = 0.0352$), $R = 0.0381$ for 3452 reflections with $I > 2\sigma(I)$, and $R = 0.0488$ for all reflections, $wR2 = 0.0992$, ρ_{el} (max, min) = 0.389 and $-0.273 \text{ e \AA}^{-3}$, $GOOF(S) = 1.069$. All other refinement details are available in the CIF (CCDC: 922163).

2.4. Computational Details

All DFT calculations were performed using the Gaussian 09 suite of programs [14]. Geometry optimizations and frequency calculations were carried out using the Becke's three-parametric hybrid exchange functional (B3) [15] combined with the Lee-Yang-Parr correlation functional (LYP) [16] in conjunction with the 6-311++G** basis set [17]. Each stationary point obtained was characterized by the computation of the harmonic vibrational spectra at the same level of theory.

3. Results and Discussion

3.1. Synthesis

Along the synthesis route towards **6** (see Figure 1S in the supplemental material) with an aminocarbonyl group in β to silicon, five apparently simple silanodiol derivatives have been generated from the common starting point of treating commercial chlorosilane **1** with 1.5 eq of phenylmagnesium bromide in diethyl ether according with the procedure reported by Hu *et al* [18] and improved by Larson *et al*. [19]

The preparation of any silanol typically requires that the hydroxyl groups be masked or protected along the synthetic route in order to avoid self-condensation. Phenyl groups were selected for this purpose because of their ability to assist in stabilizing intermediates and the possibility of removing these groups at the end under

acid conditions compatible with amide groups. Then, the nitrogen was introduced as a phthalimide. Treatment of chloromethylsilane **2** with potassium phthalimide gave **3** in 72 % and removal of the phthalimide group with hydrazine under standard Gabriel conditions gave the corresponding amine **4** as a colourless oil in an excellent yield. [9] This amine decomposes easily, and therefore must be stored in a dark place and under inert atmosphere and fresh samples used in further synthesis steps.

Treatment of this amine freshly obtained with benzyl chloride, acetic anhydride and formic acid under inert atmosphere, provided several representative amide moiety on the left-hand side of the structure **5a-c** in moderate yielded using classical substitution chemistry. [20-24]

With compounds **5** in hand, we are now working in the optimization of the final key deprotection of phenyl groups. In this respect, a review of the literature reveals that phenyls groups could be removed afterwards using an excess of triflic acid –TfOH– in methylene chloride at 0°C, followed by addition of ammonium hydroxide. [3,24-26]

3.2. Theoretical conformational analysis and molecular structure

The search for the conformers of the five intermediates (compounds **2**, **3**, **5a**, **5b** and **5c**) was performed considering the relative orientation of the side chain with respect to the Si-CH₃ bond. The positions of the phenyl groups were not fixed during optimization since their relative orientations have been proven to be fairly influenced by the positions adopted by the side chains.

Three different conformations were found to be real minima (for which no imaginary frequencies were computed) on the PES of the corresponding molecules, which differ in the relative orientation of the substituents on the silicon center. The side chains of the mentioned systems can be arranged in *anti* (A, 180°), *gauche+* (*g+*, +60°) and *gauche-* (*g-*, -60°) geometry respect to the Si-CH₃ bond. The case of intermediate **3** is noteworthy, for which the *anti* conformation was not a real minima but an eclipsed (*e*) arrangement of the phthalimide and phenyl groups was found instead. The *e* conformation of intermediate **3** was confirmed by *ab initio* calculations (MP2/ 6-31+G*) performed for this system. Figure 2S (reported as supplemental material) shows the different structures isolated from the corresponding PES of the intermediates under study.

Table 1 shows the relative energies (ΔE_0 , kcal mol⁻¹) for the three conformers of each intermediate along with their relative populations in gas phase (at room temperature) calculated from ΔE_0 values (B3LYP/ 6-311++G**) using the Boltzmann distribution equation. As shown in the table, conformer *g-* is the global minimum for intermediate **2** and conformer *e* is the most stable for intermediate **3**. For each of the remaining species (**5a**, **5b** and **5c**), conformer *a* represents the global minimum. Nevertheless, the relative energy differences (ΔE_0) among the three described conformers of each intermediate are less than 1 kcal/ mol, showing that the contribution

to the theoretical total sample composition of each conformer is very similar within a given set of conformers of each system.

3.3. Single crystal X-ray study

Only intermediate **3** was suitable for study by mean of single crystal X-ray diffraction. 2-[[methyl(diphenyl)silyl]methyl]-1H-isoindole-1,3(2H)-dione (intermediate **3**) crystallizes in space group $P 2_1/c$ with both the $g+$ and $g-$ forms present in the crystal packing of the sample, as shown in Figure 3S of the supplemental material. Comparison between the experimental and theoretical (gas-phase, B3LYP/ 6-311++G**) molecular structures reveals a good match (RMS=0.0240) between theory and experiment (see Figure 4S reported as supplemental material). As shown, there is a high level of similarity between the two molecular structures with a slight difference in one of the phenyl rings. This fact confirms the suitability of using the corresponding optimized theoretical structure (B3LYP/ 6-311++G**) for the computation of the vibrational spectra and carrying out the subsequent vibrational analysis and spectral assignment of the sample. The slight differences found between the experimentally and theoretically determined structures can be attributed to effects of the crystal packing. The most noteworthy dissimilarity between the experimental and theoretical (DFT) structures is related to the arrangement of one of the phenyl groups attached to the silicon center. In the DFT structure the plane containing one of the phenyl groups is 14° twisted with respect to the plane containing the same phenyl ring in the experimental molecular structure. The associated experimental value for the Si-C-C angle is $122.0^\circ(1)$ whereas in the theoretical model it is calculated to be 119.7° .

The crystal packing of the structure is dominated by CH- π (*edge-to-face* π stacking) and *offset* π - π stacking interactions, which commonly are the main forces governing the crystal structure of aromatic systems [27]. These two types of interactions are established by both phenyl rings and the phthalimide group. Each phthalimide group interacts through *offset* π - π stacking with another phthalimide group of a neighboring molecule, with a distance of 3.369\AA between the planes containing each heterocycle. On the other hand, both phenyl groups interact through CH *edge-to-face* π stacking with adjacent molecules. However, each phenyl group interacts in a different manner within a given molecular unit. One of the phenyl groups acts as H donor making a CH *edge-to-face* π stacking interaction with a neighboring phenyl ring of an adjacent molecule, measuring 3.267\AA between the centroid of the charge donor ring and the hydrogen atom involved in the interaction. On the contrary, the other phenyl group within the same molecular unit acts as double H acceptor and interacts through CH *edge-to-face* π stacking simultaneously with a phthalimide aromatic unit (2.720\AA between the centroid of the ring and the hydrogen atom) and a phenyl group (3.267\AA between the centroid of the ring and the hydrogen atom) of two adjacent molecules, resulting in a double *T-shape* π -stacking interaction. This *double T-shape* interaction corresponds to the phenyl ring with the most significant deviation from the calculated molecular structure, which was performed under the isolated molecule approximation in which crystal packing effects such as this were not taken into account.

3.4. Vibrational Study

The IR and Raman spectra of the five compounds under study are shown in Figures 2 and 3, while Tables 1S-5S (that can be found as supplemental material) outline the proposed vibrational assignments for intermediates **2**, **3**, **5a**, **5b** and **5c**, respectively. Note that, while in the case of compounds **2**, **5a**, **5b** and **5c** the vibrational analyses have been carried out considering all the possible molecular conformations predicted for the species in the gas phase, for compound **3**, only conformers *g+* and *g-* were taken into account; those which were confirmed to be present in the crystal packing, as reported above. Figure 4 shows the experimental IR and Raman spectra profile of this species in comparison with the theoretical spectra calculated for both conformers. As shown, the theoretical spectra are in quite good agreement with the experimental profiles of the sample since most of the experimental features are reproduced by the computed spectra for both conformers.

Theoretical wavenumbers have been scaled using the scale factors recommended elsewhere [28] for harmonic vibrational frequencies computed at the B3LYP/6-311++G** level in the low and high frequency regions (1.0019 and 0.9673 respectively). As can be seen, we have found a good correlation among the scaled values of the computed harmonic frequencies and the observed vibrational bands in the whole spectral range for all the species under study, especially in the spectral region above 700 cm^{-1} . Nonetheless, below 700 cm^{-1} , some features appearing in the vibrational spectra of **2**, **5a**, **5b** and **5c** may point to the occurrence of conformational mixtures in these samples.

In the case of intermediate **2**, the medium intensity band centered at 623 cm^{-1} (IR) can be assigned to the symmetric stretching of the SiC bond in conformers *g+* and *g-*. However, the band at 617 cm^{-1} (IR) can be attributed to the same vibrational mode in conformer *a*, in accordance with its calculated value. Similarly, the medium intensity band centered at 368 cm^{-1} (IR) can be assigned to the scissoring of the SiC₂ group in conformer *a* while the peak observed at 373 cm^{-1} (IR) can be assigned indistinctly to the same motion in conformers *g+* and *g-* (Table 1S, in bold).

On the other hand, for **5a** the most interesting feature in its vibrational spectra is the band centered at 350 cm^{-1} (IR) which have been assigned to the SiC₂ scissoring vibrational mode of conformer *a*, while the band centered at 312 cm^{-1} (IR) has been assigned to the same vibrational mode of conformer *g+* (Table 3S, in bold), according to their computed values.

Also suggesting the presence of more than one conformer, the band observed at 345 cm^{-1} in the Raman spectrum of compound **5b** can be attributed to the scissoring of the SiC₂ group in conformer *a*. Nevertheless, the bands observed at 317 (Raman) and 307 (IR) cm^{-1} can only be assigned to the same vibrational mode in conformers *g+* and *g-* (Table 4S, in bold).

Finally, in the case of the so-called compound **5c**, the band observed at 437 cm^{-1} in the IR spectrum is assigned to the CC out-of-plane deformation mode of phenyl rings in conformer *a*, in agreement with its calculated value (Table 5S, in bold), whilst the same vibration is calculated at 453 and 450 cm^{-1} for conformers *g+* and *g-* and observed at 465 cm^{-1} , also in the IR spectrum.

4. Conclusions

- On the way towards a synthetic route to obtain a series of new methylsilanediol derivatives with an aminocarbonyl group β to silicon, five diphenylic derivatives, candidate precursors of these species, have been prepared, isolated and purified.
- A conformational analysis was performed at the B3LYP/6-311++G** level for the five diphenylic compounds yielding up to three different molecular conformations for each system, which differ in the arrangement of the side chain, that can adopt either *gauche* (*g+* and *g-*) or *anti* orientation with respect to the Si-CH₃ bond in the case of compounds **2**, **5a**, **5b** and **5c**. As concerns compound **3**, the *eclipsed* orientation was discarded following X-ray structural analysis, albeit it was found to be the global minimum in gas phase.
- Only intermediate (**3**) was suitable for study by single-crystal X-ray diffraction. The so-called conformers *gauche* + and *gauche* – are both present in the crystal structure of the sample, whose packing is dominated by π - π stacking interactions (*edge-to-face* and *offset*). The eclipsed conformation (global minimum in the gas phase) was not detected in the crystalline phase.
- The Raman and infrared spectra of the five species under study were recorded and completely assigned for each species with the support of the DFT calculations. We have found some evidences of the occurrence of conformational mixture in the samples, since some of the experimental features are only justified if different conformers are considered to be present.

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Table 1. Calculated molecular population and zero point corrected relative energies (ΔE_0 / kcal mol⁻¹) for the molecular conformations of intermediates **2**, **3**, **5a**, **5b** and **5c** at the B3LYP/ 6-311++G** level of theory.

Intermediate 2			
	A	G+	G-
ΔE_0^a (kcal/mol)	0.74	0.00	0.06
Population(%) ^b	27.3	36.8	35.9
Intermediate 3			
	E	G+	G-
ΔE_0 (kcal/mol)	0.00	0.21	0.21
Population(%)	35.3	32.4	32.3
Intermediate 5^a			
	A	G+	G-
ΔE_0 (kcal/mol)	0.00	0.14	0.80
Population(%)	37.5	35.4	27.1
Intermediate 5b			
	A	G+	G-
ΔE_0 (kcal/mol)	0.00	0.17	0.80
Population(%)	37.6	35.1	27.3
Intermediate 5c			
	A	G+	G-
ΔE_0 (kcal/mol)	0.00	0.15	0.80
Population(%)	37.5	35.3	27.1

^a ΔE_0 stand for zero point corrected relative energy. ^b Theoretical population calculated using the Boltzmann equation and taking T=298.16K.

FIGURE CAPTIONS

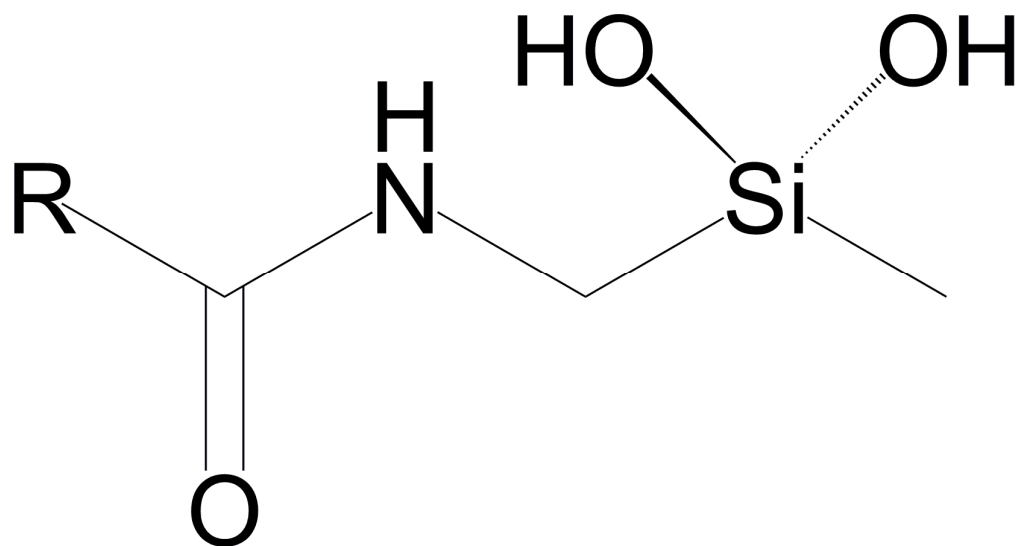
Figure 1. Molecular scheme of methylsilanediols with an aminocarbonyl group in the β position relative to the silicon.

Figure 2. Experimental IR spectra of the five intermediates in this study: (a) intermediate (**2**), (b) intermediate (**3**), (c) intermediate (**5a**), (d) intermediate (**5b**), (e) intermediate (**5c**).

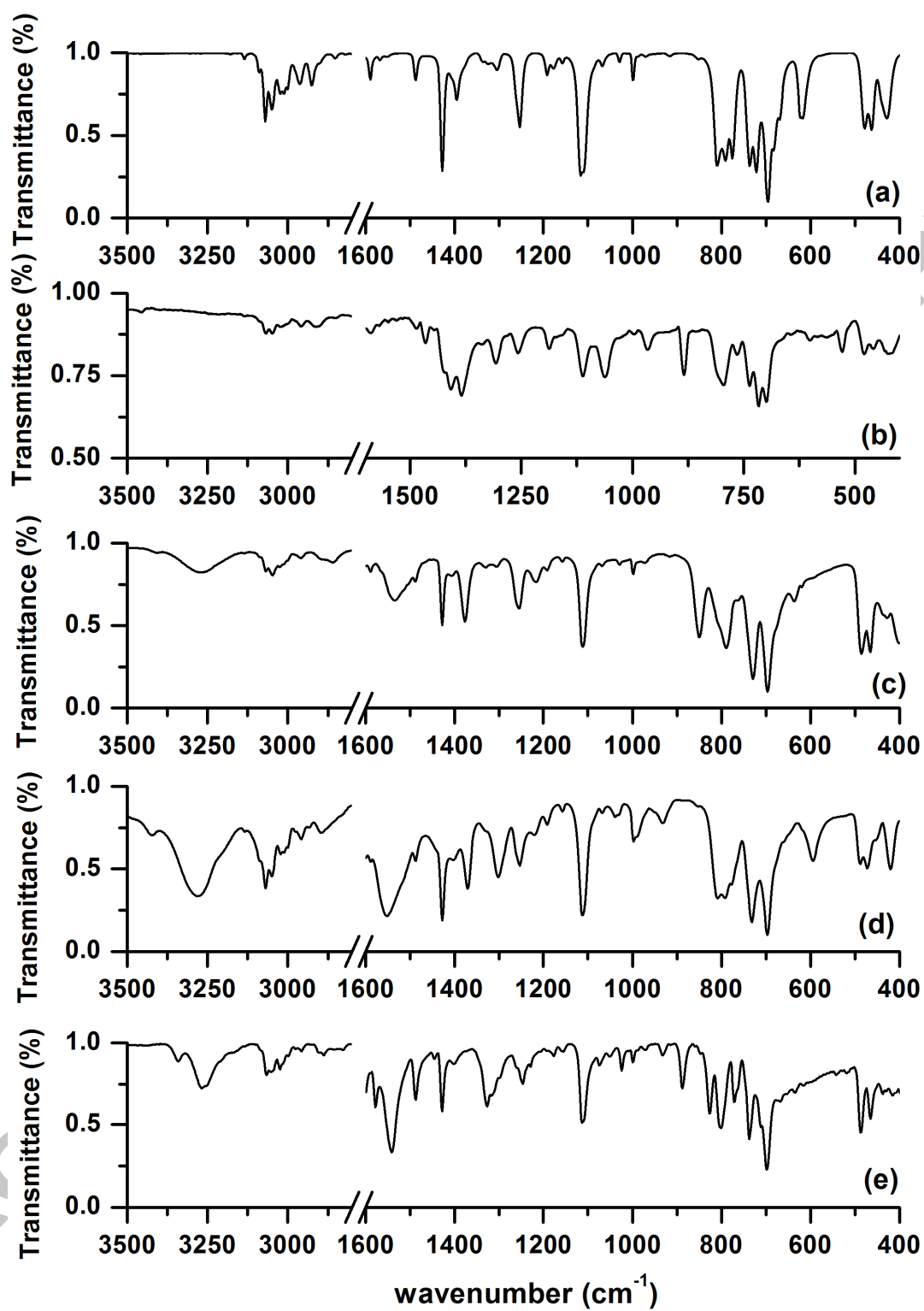
Figure 3. Experimental Raman spectra of the five intermediates in this study: (a) intermediate (**2**), (b) intermediate (**3**), (c) intermediate (**5a**), (d) intermediate (**5b**), (e) intermediate (**5c**).

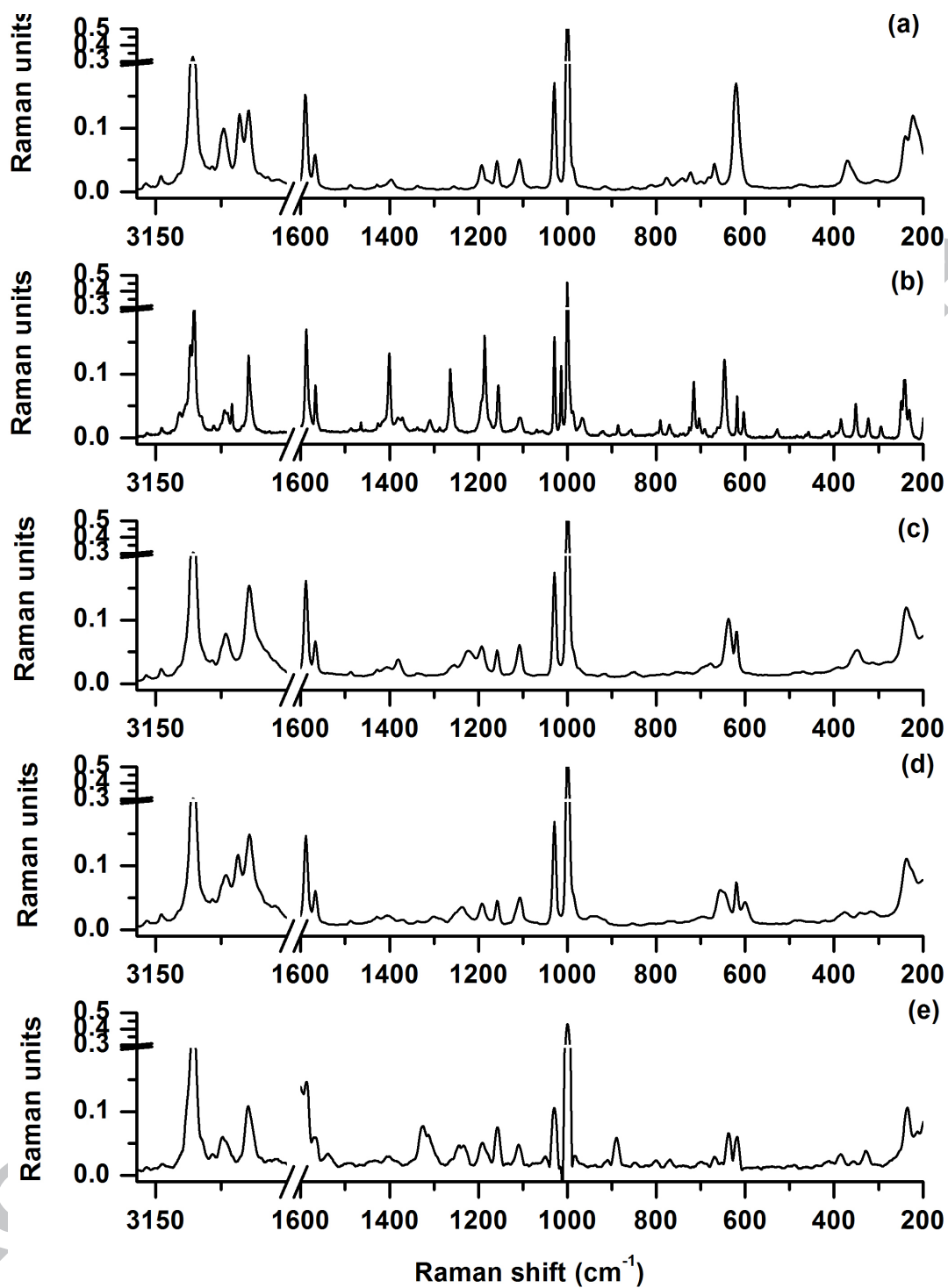
Figure 4. Comparison of the IR (right) and Raman (left) theoretical (B3LYP/6-311++G**) and experimental spectra of intermediate **3**.

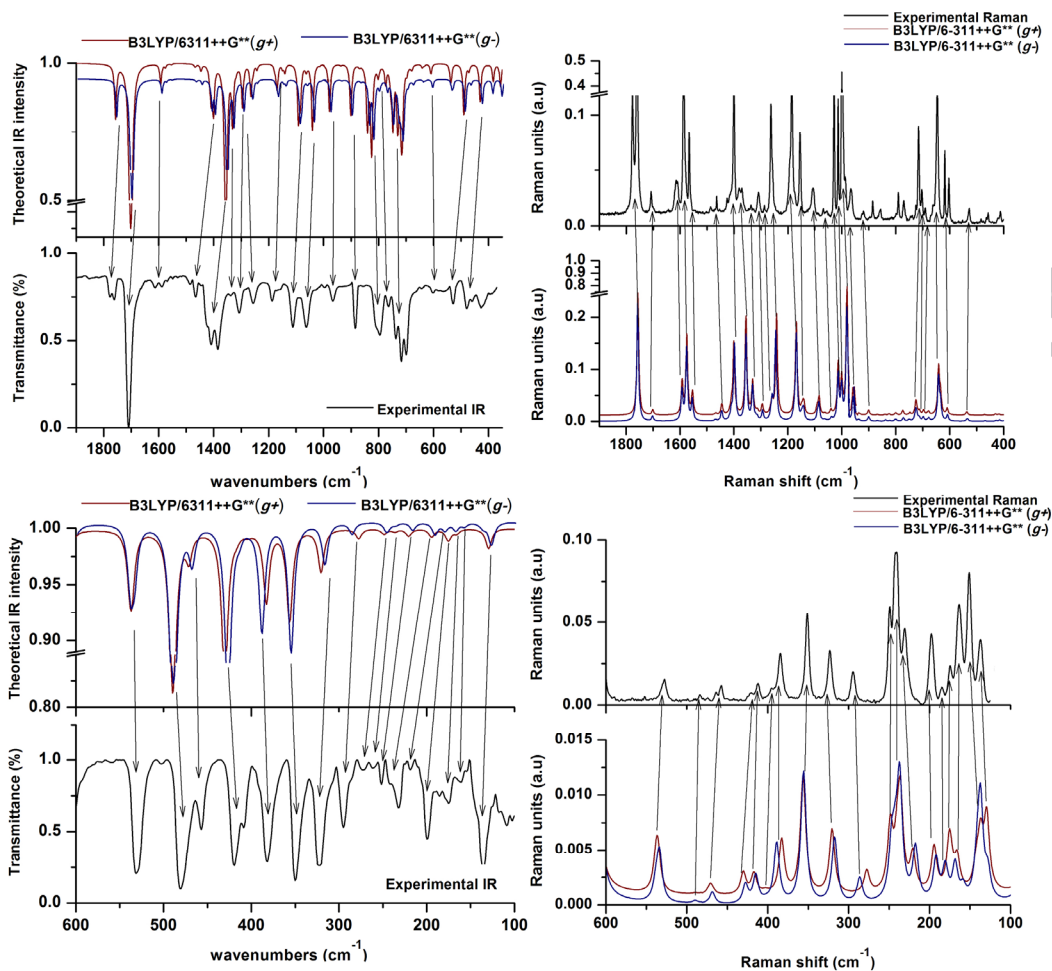
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HIGHLIGHTS

Five diphenylic precursors of methylsilanediols derivatives were synthesized.

Their molecular structures were studied using IR, Raman and single crystal XRD.

Their vibrational spectra were assigned with the support of DFT calculations.

Some experimental features gave evidence of the conformational mixture in the samples.

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Graphical abstract

