Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 9179–9186

TETRAHEDRON

Synthesis and study of novel fulleropyrrolidines bearing biologically active 1,4-dihydropyridines☆

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Received 1 July 2003; revised 4 September 2003; accepted 15 September 2003

Abstract—New fulleropyrrolidines endowed with chlorine-containing biological active 1,4-dihydropyridines (1,4-DHPs) have been synthesised from the respective formyl substituted 1,4-DHPs by following Prato's procedure. The presence of the chlorine atom on C2 of the 1,4-DHP ring brings about important spectroscopical and structural differences in compounds **10a–f** related to the parent hydrogen-containing **11a**. The mass spectroscopy study reveals different fragmentation patterns for fulleropyrrolidines **10a–f** and their precursors 1,4-DHPs, as well as with **11a**. Semiempirical calculations (AM1 and PM3) predict a most stable stereoisomer in all cases (*RS* for **10a–f**) and the same *RR* for **11a**. The presence of chlorine atom in **10a–f** is responsible for the higher calculated conformational energy barriers in comparison with **11a**. The geometry of the 1,4-DHP shows that the presence of fullerene unit does not significantly alter the required conformation for biological activity.

1. Introduction

Fullerenes and their derivatives have shown a broad range of promising biological activities,[1,2] especially in the fields of photodynamic therapy,[3] inhibition of HIV-protease,[4,5] neuroprotection,[6] and apoptosis.[1,2] However, an important feature when dealing with fullerenes is the lack of solubility in polar solvents for their biological study. This problem can be overcome by means of chemical modification of fullerenes (**1**–**3**) in such a way that they acquire solubility in polar media. In this regard, Prato et al.[7] have recently shown that the covalent attachment of polyether chains to [60]fullerene (**4**) brings about the formation of water soluble fulleropyrrolidines (see Chart 1)

On the other hand, 1,4-dihydropyridine derivatives (1,4-DHPs) such as nifedipine (**5**) form a class of heterocyclic compounds which present interesting pharmacological and biological properties. Thus, they have been used as effective calcium channel modulators for the treatment of cardiovascular disorders.[8] Much effort has been devoted to the synthesis of 1,4-DHPs with different substituents[9] or heteroatoms,[10] and it is well-established that the calcium

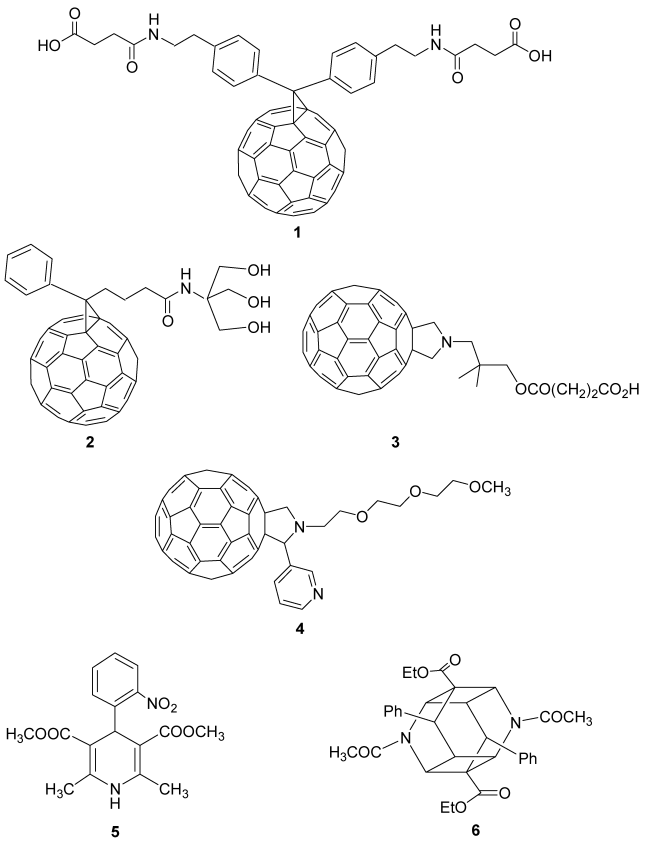

Chart 1.

☆ Supplementary data associated with this article can be found at doi: 10.1016/j.tet.2003.09.047

Keywords: fulleropyrrolidines; 1,4-dihydropyridines; [60]fullereno.
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doi:10.1016/j.tet.2003.09.047

modulator activity of members of this family is determined by structural requirements.[11] Thus, it is necessary that the substituted phenyl ring on C-4 occupies an axial position perpendicularly bisecting the boat-like 1,4-DHP ring with the substituent in a synperiplanar orientation.[12] Structure activity studies have demonstrated that flattening of the boat conformation correlates with increased activity, presumably due to the concurrent change in the position of the phenyl ring on C-4.[13] A *cis* carbonyl ester orientation with respect to the olefinic double bond is also needed for high activity.[14] It has been proposed that the antagonist or agonist activity in 1,4-DHPs is dependent on the absolute configuration at C-4 (*R* versus *S*-enantiomer) acting as a molecular switch.[15]

In spite of the widely developed chemistry of the 1,4-DHPs along the last 30 years,[16] the design and study of novel 1,4-DHPs remain desirable nowadays.[17] Recent papers have reported novel 1,4-DHP derivatives as calcium channel modulators[18] and the protective effects of dihydropyridine Ca-blockers against endothelial cell oxidative injury due to combined nitric oxide and superoxide.[19] It has been also determined that 1,4-dihydropyridines containing NO-donor furoxan moieties at the 3-positioned basic lateral chain present vasodilating activity.[20]

Very recently, it has been reported the development of dimeric 4-aryl-1,4-dihydropyridine (**6**) as a third class of nonpeptide HIV-1 protease inhibitors.[21] Additionally, the crystal structure of this protease inhibitor derived by simple solid-state dimerization of 4-aryl-1,4-dihydropyridine was also determined[22] (see Chart 1).

In previous works, we have described the synthesis and structural study by X-ray crystallographic methods and quantum chemical calculations, of several 1,4-DHP derivatives, and we found that, in general, the conformational features reported for 1,4-DHP calcium modulators are preserved for these compounds.[23]

In a previous recent paper,[24] we reported the synthesis of new fulleropyrrolidines bearing DHPs as a biologically active substituent related to the well-known nifedipine [3,5-dimetoxycarbonyl-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine] (**5**). The fullerene derivatives were synthesised by 1,3-dipolar cycloaddition of the in situ generated azomethine ylides to C_{60}, by reaction of the corresponding formyl substituted 1,4-DHPs with sarcosine and [60]fullerene by following Prato's protocol.[25]

As a part of our studies aimed at synthesising 1,4-dihydropyridines with the substitution patterns required for a biological chemical programme, and continuing our interest in the chemistry and properties of organofullerene derivatives, in this work we apply our approach to the synthesis of novel pyrrolidino[3′,4′:1,2][60]fullerenes containing the less known 1,4-DHP moiety bearing a chlorine atom on C2 in the DHP ring.[26]

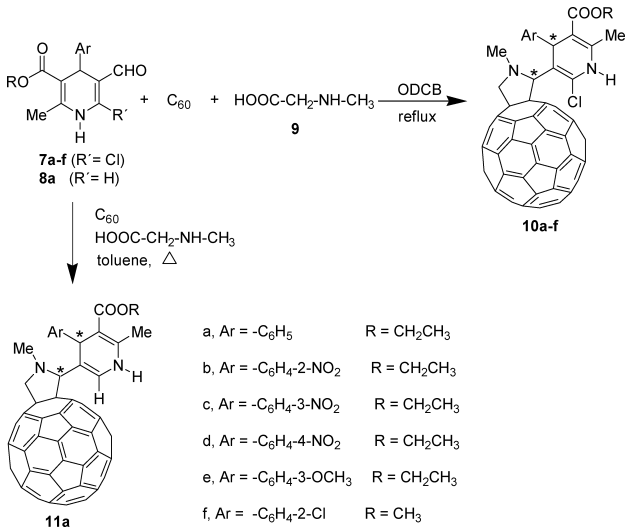
In addition, these chlorine containing organofullerenes are suitably functionalized for further chemical transformations on the chlorine substituted DHP.

Since the determination of the favoured conformation has been used to account for the pharmacological effect of different compounds with similar structures,[27] and in order to predict the biological activity of the compounds synthesised herein, we have carried out a structural study of these compounds using semiempirical AM1[28] and PM3[29] methods. These two theoretical calculations have been widely used for the determination of the minimum energy conformation of some fullerene derivatives with good results.[30]

2. Results and discussion

6-Chloro-5-formyl 1,4-DHPs **10a–f** were prepared according to the procedure described by us,[26] by reaction of the corresponding alkyl 2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylate[31] with the Vilsmeier–Hack reagent ($POCl_3$, DMF). The new fulleropyrrolidines **10a–f** were synthesised according to Prato's procedure[25] by refluxing in *o*-dichlorobenzene (ODCB) a mixture of the corresponding 3-alkoxycarbonyl-4-aryl-6-chloro-5-formyl-2-methyl-1,4-dihydropyridine (1 equiv.), C_{60} (1 equiv.) and sarcosine (*N*-methylglicine) (4 equiv.) during 24 h (see Scheme 1). After purification by column chromatography on silica gel, and repetitive precipitation and centrifugation using hexane, methanol and ethyl ether as solvents, the structure of compounds **10a–f** was confirmed by spectroscopic methods.

The novel compounds showed in the IR spectra the bands corresponding to the carbonyl group at ~1700 cm^{-1} and a band typical of organofullerene derivatives, around 526 cm^{-1}. The ^{1}H-NMR spectra showed the presence of the pyrrolidine protons as one singlet (~5.2 ppm) and two doublets (~4.9 and ~4.1 ppm) with a coupling constant of 9.2–10.4 Hz. The proton attached to the C4 of de 1,4-DHP ring gives rise to a singlet around 5.4–5.8 ppm, and the NH proton appears as a singlet at 5.8–6.5 ppm. It is important to note that in all cases these compounds were isolated as a diastereomeric mixture in different rates, which could not be separated by column chromatography.



Scheme 1.

The number of signals in the ^{13}C NMR spectra show the lack of symmetry in these compounds. The ester carbonyl group appears at 165–167 ppm and the signals for the sp^3 carbons of the pyrrolidine ring and those at the 6,6-ring junction of the C_{60} cage are observed at $\delta\sim76-81$ and $\delta\sim69-71$, respectively.

Compound **11a** was synthesised by following a similar route to that followed for compounds **10a–f**, by 1,3-dipolar cycloaddition reaction of the in situ generated azomethyne ylide from **8a** and sarcosine, to [60]fullerene.[32] The spectroscopic data found for **11a** are quite similar to those of **10a–f**, showing the proton on C-6 of the 1,4-DHP ring as a doublet (J=5.1 Hz) at δ=6.77. This coupling takes place with the NH proton which is observed as a broad doublet (J=5.1 Hz) at δ=5.34.

Compound **11a** was isolated as a diastereomeric mixture (60:40) which we were not able to separate by column chromatography. Therefore, the ^{13}C NMR spectrum showed 117 signals corresponding to both diasteroisomers, which did not allow a clear assignment of the respective signals.

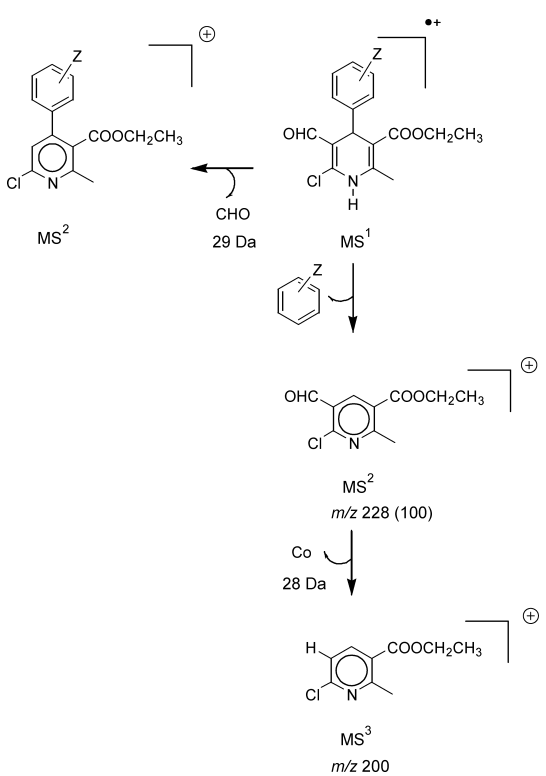
In order to determine unambiguously the structure of these compounds as well as to establish the fragmentation pathway of the new fulleropyrrolidines bearing a dihydropyridine group (**10a–f**), we have recorded the mass spectra generated under electrospray ionization (ESI) conditions. We have also recorded the mass spectra of the starting 1,4-DHPs (**7a–f**)[26] in order to compare their spectra and to determine the influence of the C_{60} moiety in their fragmentation pattern. We have described earlier the fragmentation pattern of fulleropyrrolidines bearing pyrazine groups and we demonstrated that the main fragmentation is the formation of a stable methanofullerene.[33]

The electron impact ionization (EI) mass spectra of substituted dihydropyridines (**7a–f**) show as the main fragmentation the loss of the substituent attached at the C4 position forming a very stable pyridinium cation (Scheme 2). This fragmentation is similar to that observed for the related hexahydroquinolines.[34] However, while for hexahydroquinolines the stability of this fragment prevents subsequent fragmentation, for the 1,4-DHPs the pyridinium ion, which is the base peak at m/z 228, undergoes a decarbonylation process affording the fragment at m/z 200. The elimination of the formyl group takes also place directly from the molecular peak although in a lower extension. Loss of the chlorine atom was not detected.

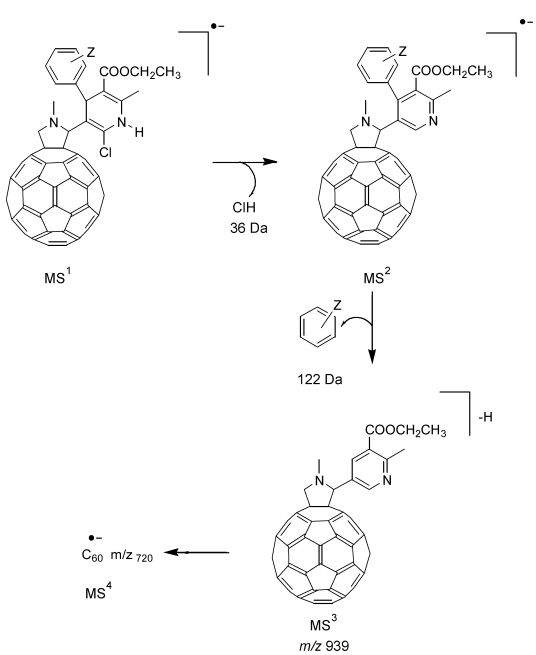
Compounds **10a–f** show a total different mass spectrometric behaviour under ESI conditions. The first remarkable characteristic of compounds **10a–f** is the formation of odd-electron molecular ions in contrast with that observed for other fulleropyrrolidines which form even-electron molecular ions.[33] The lack of protonation in positive mode or deprotonation in negative mode under ESI conditions can be explained assuming a different electrochemical behaviour toward the ESI source. Although the presence of heteroatoms like oxygen or nitrogen is important in the protonation process, the possibility to form odd-electron ions is due to the electrochemical properties of the compound to be ionised.

The molecular ions derived from **10a–f** undergo at the first stage of fragmentation the loss of a hydrogen chloride molecule (Scheme 3). Subsequent elimination of the substituent at the C4 position affords a deprotonated fulleropyrrolidine which finally yields C_{60}.

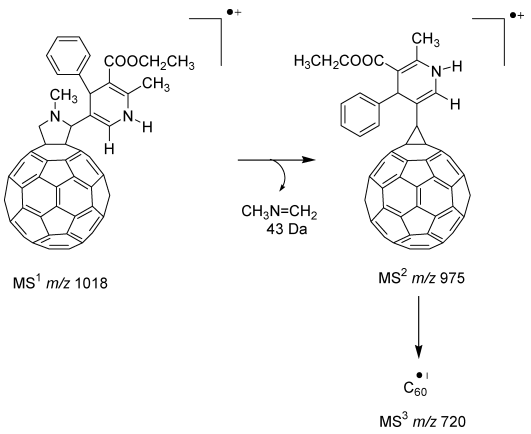
The main fragmentation of the fulleropyrrolidines is a loss



Scheme 2.



Scheme 3.



Scheme 4.

of 43 Da corresponding to the elimination of a *N*-methyl-*N*-methyleneamine molecule affording a methanofullerene derivative.[33] However, in this case the presence of a chlorine atom near to the fullerene moiety changes dramatically this tendency. To determine exactly the effect of the chlorine atom at the C6 position of the DHP ring and the influence of the fullerene cage, we have recorded the ESI mass spectra of compound (**11a**) in which the chlorine atom is replaced by a hydrogen atom (Scheme 4).

In this case, the fragmentation takes place with loss of 43 Da affording a substituted methanofullerene. We can conclude that the proximity of chlorine atom and the C_{60} moiety is fundamental to explain these differences in the fragmentation pathway of the substituted fulleropyrrolidines.

In order to gain a better understanding of the novel compounds, we have calculated their structures at the semiempirical level (AM1 and PM3) by using Gaussian 98. Although all compounds **10a**–**f** were calculated, we will focus our discussion on the differences between **10a** and **11a** in order to determine the impact that the chlorine atom has on the structural properties.

Firstly, we determined the heat of formation for the four expected stereoisomers resulting from the two stereogenic centers present in compounds **10** and **11**. Interestingly, stereoisomer *RS* in **10a** was predicted to be 4.3 kcal/mol more stable than *RR*, and 5.2 kcal/mol than *SS*, being 9.1 kcal/mol more stable than *SR*, using the AM1 method. The same trend, with similar energy differences, was observed using the PM3 method. A similar behaviour was observed for compound **11a** bearing the vinyl H atom instead of the chlorine one, resulting predicted the *RR* stereoisomer to be the most stable with significant lower energy differences than those found for **10a** (see Table 1).

Table 1. ΔH_f[a] for all possible stereoisomers of **10a** and **11a**

Stereoisomer	Compound **10a**		Compound **11a**	
	AM1	PM3	AM1	PM3
RS	**919.6**	743.6	924.5	749.0
RR	923.9	747.4	**922.7**	747.0
SS	924.8	747.5	933.9	757.4
SR	928.7	749.8	930.8	756.5

[a] in kcal/mol (AM1 semiempirical level).

Figure 1 shows the minimum energy conformation found for compounds **10a** and **11a** calculated at the AM1 level. Both stereoisomers are structurally equivalents and the *RR* notation is simply a consequence of the atomic priority of the CIP rules.

In order to determine the effect of the substitution of the H atom by the Cl atom, we calculated the rotational barrier around the C2–C8 bond linking the DHP ring to the fulleropyrrolidine (Fig. 2).

As expected, chlorine containing **10a** shows the minimum energy at the torsional angle of C7–C8–C2–C3 of −85.6°,

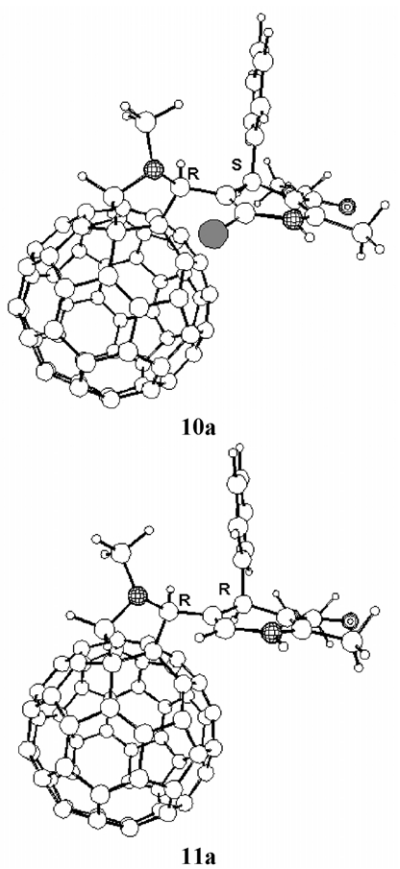


Figure 1. Minimum energy conformations for **10a** and **11a**.

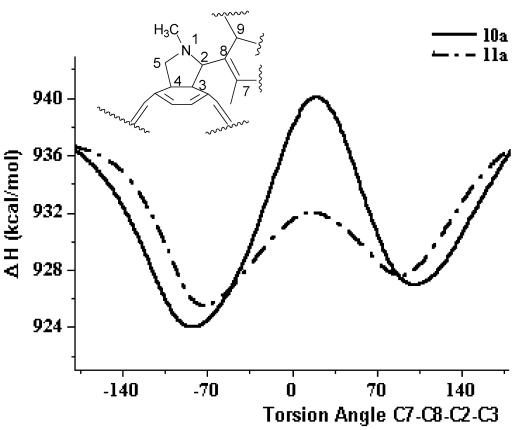


Figure 2. Conformational analyses for **10a** and **11a** around C2–C8 bond.

corresponding to the conformation shown in Figure 1. Similarly, the torsional angle found for **11a** was −89.3°. However, important differences were observed for the predicted barriers found between the two energy minima, being around 11 kcal/mol for **10a** and only 4 kcal/mol for **11a**. These data can be accounted for by the difference in the van der Waals radii for the Cl and H atoms, resulting in a higher steric hindrance between the chlorine atom and the fullerene cage. To support these findings the calculated distances from the Cl and H atoms to the C_{60} surface were 1.934 and 2.570 Å, respectively (AM1), and 1.879 and 2.312 Å by using the PM3 method. The most relevant geometrical data calculated by AM1 and PM3 methods are collected in the Supplementary Material.

Theoretical calculations reveal a planar boat conformation for the 1,4-DHP ring in **10a** and **11a**. The planarity of the heterocyclic ring is defined by the sum of the modular values of the six internal dihedral angles of the DHP ring ($\sum|\rho|$).[12] Semiempirical calculations (AM1) predict values of $\sum|\rho|$=73.3 for **10a** and $\sum|\rho|$=57.3 for **11a**, thus showing that de 1,4-DHP ring is slightly more planar in organofullerene **11a**. This finding could be accounted for by the larger volume of chlorine atom related to the hydrogen atom.

In all cases, the phenyl group on C9 appears in a pseudoaxial orientation (torsion angle values C11–C10–C9–C12 of 104.7 and 109° for **10a** and **11a**, respectively), bisecting the plane containing the DHP ring [torsion angle for C13–C12–C9–C10: −84.3° (**10a**) and −90.3° (**11a**)]. These values are in good agreement with those obtained theoretically (AM1 and HF/3-21G) and experimentally (X-ray diffraction) for related heterocyclic systems, thus validating the reliability of AM1 and PM3 methods for predicting conformational features on these compounds.[23]

Similarly to other related DHPs, the nitrogen atom shows a sp^2 hybridisation [valence angles C7–N6–C11=119.7° (**10a**) and 120.1° (**11a**)], whereas the pyrrolidine nitrogen exhibits a sp^3 hybridisation with a valence angle C5–N1–C2 of 109.9° (**10a**) and 109.3 (**11a**). The remaining structural features for the 1,4-DHP ring are similar to those expected for related systems.[23]

The remaining synthesised compounds (**10b–f**) were also studied by using the AM1 method and the calculations reveal that, in all cases, stereoiomer **RS** resulted to be the most stable, regardless of the substitution pattern on the phenyl group on C4 of the 1,4-DHP ring. In Table 2 the heats of formation calculated for the four stereoisomers of compounds **10b–f** are collected, showing energy differences quite similar to those found for the parent compound **10a**. The most relevant geometrical data calculated for these compounds (**10b–f**) are collected in the Supplementary Material.

Table 2. ΔH_f[a] for all possible stereoisomers of **10b–f**

Stereoisomer	10b	10c	10d	10e	10f
RR	941.2	934.3	934.3	893.6	927.4
RS	934.0	929.9	929.8	889.1	922.3
SR	946.0	938.9	939.4	898.5	933.8
SS	940.1	935.2	935.2	894.3	929.0

[a] in kcal/mol (AM1 semiempirical level).

3. Conclusions

A new series of fulleropyrrolidines have been synthesised bearing biologically active 1,4-DHPs by dipolar 1,3-cycloadition reaction. Important differences were observed in spectroscopic (MS) and structural properties depending upon the presence of a chlorine atom on C2 of the 1,4-DHP ring. According to the semiempirical (PM3 and AM1) theoretical calculations, we conclude that the geometrical parameters (bond distances, valence and torsion angles) predicted for the most stable stereoisomers calculated by semiempirical methods (AM1 and PM3) reveal that the presence of the fullerene unit does not significantly alter the conformation of the 1,4-DHPs required for biological activity.

4. Experimental

4.1. General

All EI mass spectra were recorded on a HP 8990A (Hewlett–Packard, Palo Alto, CA, USA) quadrupole instrument at 70 eV using a source temperature of 250°C. The ESMS spectra were carried out using an ESQUIRE-LC™ (Bruker Daltonics, Bremen, Germany) ion trap spectrometer. A syringe pump was used to deliver the fullerene solutions (chloroform/acetonitrile/formic acid 50:48:2, v/v/v). Nitrogen was used as nebulizer gas (flow: 4 L min^{-1}), the ionisation potential was 5.0 kV and the chamber temperature 150°C. MS/MS were carried out with helium after isolation of the appropriate precursor using an isolation width of 0.4 *m/z*, fragmentation voltage amplitude of 0.60 V and fragmentation time of 40 ms. NMR spectra were recorded on a Bruker Advance-300, a Bruker Avance AV500 and in a Bruker AMX 500. Chemical shifts are given as δ values against tetramethylsilane as the internal standard and *J* values are given in Hz. The IR spectra were measured with a Shimadzu FTIR 8300 instrument as potassium bromide pellets. The reactions were monitored by TLC and performed on silica-gel plates (Merck $60F_{250}$) using hexane/ethyl acetate (8:2) as the eluent.

Chromatography was performed using Merck silica gel (70–230 mesh). Commercially available starting materials and reagents were purchased from commercial sources (BDH and Fluka) and were used without further purification. All solvents were dried according to standard procedures. Full geometry optimisation was carried out using semiempirical AM1[28] and PM3[29] calculations with the aid of Hyperchemn 5.02[35] and Gaussian 98[36] programs. Calculations were carried out on an IBM RS/6000 workstation.

4.1.1. Synthesis of 1,4-dihydropyridines (7a–f and 8a). Alkyl 4-aryl-6-chloro-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**7a–f**) were prepared following the procedure previously reported in our laboratory.[26a]

Ethyl 5-formyl-4-phenyl-2-methyl-1,4-dihidropyridine-3-carboxylate (**8a**) was prepared according to the following method: to a solution of phenylmethylenemalonaldehyde (66 mg, 0.41 mmol) in ethanol (8 mL) ethyl 3-aminocrotonate (59 mg, 0.45 mmol) was added. The mixture was refluxed for 72 h light protected. The solvent was removed under reduced pressure and the residue was chromatographed over silica gel using hexane/ethyl acetate 19/1 as the eluent, obtaining compound **8a** as an oil. 10% yield; IR (KBr): 3350, 3020, 2910, 2850, 1700, 1640, 1550, 1490, 1365, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.20 (s, 1H), 7.31–7.12 (m, 5H), 6.87 (d, 1H, J=5.7 Hz), 6.60 (broad s, 1H), 5.03 (s, 1H), 4.04 (q, 2H), 2.38 (s, 3H), 1.16 (t, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.78, 167.13, 146.19, 143.32, 141.82, 128.07, 127.94, 126.42, 120.62, 105.98, 59.97, 36.69, 19.44, 14.09; EM *m/z* (%) 271 (M^+, 37), 270 (10), 242 (18), 226 (10), 194 (100), 166 (51), 120 (7), 77 (4), 59 (11); Anal. calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.50; H, 6.09; N, 5.35.

4.1.2. Synthesis of *N*-methyl-2-(4-aryl-3-alkoxycarbonyl-2-chloro-6-methyl-1,4-dihydropyridin-3-yl)pyrrolidino[3′,4′:1,2][60]fullerenes (10a–f) and *N*-methyl-2-(3-ethoxycarbonyl-6-methyl-4-phenyl-1,4-dihydropyridin-3-yl)pyrrolidino[3′,4′:1,2][60]fullerene (11a). A mixture of C_{60} (0.15 mmol), *N*-methylglycine (0.76 mmol), and the corresponding alkyl 6-chloro-5-formyl-4-aryl-2-methyl-1,4-dihydropyridine-3-carboxylate (0.15 mmol) in ODCB (220 mL) (for compounds **10a–f**) or ethyl 5-formyl-4-phenyl-2-methyl-1,4-dihydropyridine-3-carboxylate (0.15 mmol) in toluene (250 mL) (for compound **11a**), was refluxed for 24 h. The solvent was removed under reduced pressure and the solid residue thus obtained was purified by column chromatography on silica gel, using CS_2 to elute unreacted C_{60} and cyclohexane/toluene 1/1 to elute the corresponding pyrrolidino[3′,4′:1,2][60]fullerene. Additional purification of these compounds was carried out by repetitive precipitation and centrifugation using hexane, methanol and diethyl ether as solvents.

4.1.3. *N*-Methyl-2-(4-phenyl-3-ethoxycarbonyl-2-chloro-6-methyl-1,4-dihydropyridin-3-yl)pyrrolidino[3′,4′:1,2][60]fullerene (10a). This compound was obtained in 28% yield (42% based on recovered C_{60}). Diastereomeric relationship: 95/5; IR (KBr): 3421, 2925, 2852, 2760, 1701, 1654, 1560, 1496, 13500, 1255, 1107, 526 cm^{-1}; ^1H NMR ($CDCl_3/CS_2$ 1/1, 500 MHz) δ 7.62 (2H, m), 7.34 (3H, m), 5.79 (1H, s, NH), 5.51 (1H, s), 5.25 (1H, s), 4.89 (1H, d, J=9.64 Hz), 4.12 (1H, d, J=9.64 Hz), 3.91 (2H, q, CH_2), 2.26 (3H, s, CH_3), 2.14 (3H, s, CH_3), 0.99 (3H, t, CH_3); ^{13}C NMR ($CDCl_3/CS_2$ 1/1, 500 MHz) δ 165.95, 154.23, 154.11, 154.30, 154.23, 148.78, 147.15, 147.11, 146.76, 146.51, 146.27, 146.14, 146.12, 145.99, 145.94, 145.86, 145.79, 145.78, 145.52, 145.37, 145.32, 145.29, 145.28, 145.24, 145.18, 145.15, 145.12, 145.11, 144.95, 144.60, 144.23, 144.19, 143.10, 142.98, 142.97, 142.95, 142.94, 142.93, 142.92, 142.91, 142.89, 142.52, 142.49, 142.44, 142.10, 142.05, 142.00, 141.97, 141.93, 141.90, 141.55, 141.43, 141.11, 139.99, 139.96, 139.11, 136.89, 136.33, 135.14, 134.84, 130.37, 128.88, 128.39, 128.16, 128.10, 127.47, 126.67, 108.69, 102.59, 80.68, 76.25, 70.39, 69.21, 59.68, 40.87, 29.81, 19.31, 14.41; MS (ESI): 1052 $[M]^{\cdot -}$.

4.1.4. *N*-Methyl-2-(4-(2-nitrophenyl-3-ethoxycarbonyl-2-chloro-6-methyl-1,4-dihydropyridin-3-yl)-pyrrolidino[3′,4′:1,2][60]fullerene (10b). This compound was obtained in 18% yield (34% based on recovered C_{60}). Diastereomeric relationship: 80/20; IR (KBr): 3421, 2922, 2848, 2783, 1701, 1654, 1610, 1529, 1508, 1425, 1350, 1263, 1199, 1178, 1091, 1039, 526 cm^{-1}; ^1HNMR ($CDCl_3/CS_2$ 1/1, 300 MHz) δ 7.90 (1H, d, J=8.00 Hz), 7.80 (1H, d, J=7.85 Hz), 7.61 (1H, t, J=7.80 Hz), 7.42 (1H, t, J=7.85 Hz), 6.52 (1H, s, NH), 5.78 (1H, s), 5.21 (1H, s), 4.86 (1H, d, J=9.70 Hz), 4.04 (1H, d, J=9.70 Hz), 3.95 (2H, q, CH_2), 2.37 (3H s, CH_3), 2.16 (3H s, CH_3), 1.13 (3H, t, CH_3); ^{13}C NMR ($CDCl_3/CS_2$ 1/1, 500 MHz) δ 166.65, 159.13, 159.03, 156.23, 155.48, 155.38, 155.05, 151.81, 149.23, 148.47, 147.74, 147.72, 146.76, 146.71, 146.67, 146.53, 146.49, 146.45, 146.38, 146.35, 146.20, 146.00, 145.94, 145.90, 145.81, 145.73, 145.69, 145.66, 145.61, 145.59, 145.44, 145.31, 145.24, 145.14, 144.88, 144.72, 144.60, 143.73, 143.49, 143.11, 143.07, 143.05, 142.96, 142.94, 142.69, 142.64, 142.56, 142.54, 142.44, 142.05, 142.01, 140.69, 140.63, 140.52, 140.01, 139.83, 138.97, 135.06, 134.32, 134.10, 133.27, 131.92, 131.89, 128.87, 128.45, 127.95, 125.13, 108.51, 101.12, 81.09, 76.16, 70.90, 69.70, 60.75, 41.56, 32.70, 19.98, 14.92; MS (ESI): 1097 $[M]^{\cdot -}$.

4.1.5. *N*-Methyl-2-(4-(3-nitrophenyl-3-ethoxycarbonyl-2-chloro-6-methyl-1,4-dihydropyridin-3-yl)-pyrrolidino[3′,4′:1,2][60]fullerene (10c). This compound was obtained in 22% yield (36% based on recovered C_{60}). Diastereomeric relationship: 85/15; IR (KBr): 3394, 2922, 2850, 2781, 2329, 1701, 1685, 1654, 1618, 1527, 1461, 1419, 1345, 1271, 1215, 1195, 1088, 526 cm^{-1}; ^1H NMR ($CDCl_3/CS_2$ 1/1, 500 MHz) δ 8.36 (1H, br.s), 8.07 (1H, dd, J=7.9 Hz, J=1.5 Hz), 7.96 (1H, d, J=7.4 Hz), 7.46 (1H, t, J=7.9 Hz), 5.96 (1H, s, NH), 5.67 (1H, s), 5.24 (1H, s), 4.85 (1H, d, J=9.85 Hz), 3.99 (1H, d, J=9.85 Hz), 3.84 (2H, q, CH_2), 2.36 (3H, s, CH_3), 2.17 (3H, s, CH_3), 1.11 (3H, t, CH_3); ^{13}C NMR ($CDCl_3/CS_2$ 1/1, 500 MHz) δ 165.89, 155.65, 153.66, 151.38, 148.43, 147.35, 146.93, 146.16, 146.14, 146.09, 145.97, 145.93, 145.67, 145.54, 145.48, 145.46, 145.34, 145.32, 145.29, 145.25, 145.23, 145.18, 145.13, 144.87, 144.71, 144.69, 144.60, 144.58, 144.42, 144.39, 144.32, 144.29, 143.25, 143.16, 143.07, 142.73, 142.67, 142.64, 142.59, 142.32, 142.20, 142.19, 142.17, 142.15, 142.12, 142.11, 142.09, 142.07, 142.04, 142.02, 141.98, 141.84, 141.70, 141.57, 141.15, 140.16, 139.25, 137.42, 136.63, 135.02, 134.07, 129.24, 128.77, 123.65, 123.11, 122.03, 106.40, 101.99, 80.97, 76.71, 70.93, 69.78, 60.60, 41.64, 30.30, 19.46, 14.43; MS (ESI): 1097 $[M]^{\cdot -}$.

4.1.6. *N*-Methyl-2-(4-(4-nitrophenyl-3-ethoxycarbonyl-2-chloro-6-methyl-1,4-dihydropyridin-3-yl)-pyrrolidino[3′,4′:1,2][60]fullerene (10d). This compound was obtained in 24% yield (44% based on recovered C_{60}). Diastereomeric relationship: 98/2; IR (KBr): 3413, 2922, 1701, 1654, 1595, 1525, 1423, 1342, 1309, 1244, 1197, 1091, 526 cm^{-1}; ^1H NMR ($CDCl_3/CS_2$ 1/1, 300 MHz) δ 8.21 (2H, d, J=8.80 Hz), 7.80 (2H, d, J=8.80 Hz), 5.93 (1H, s, NH), 5.70 (1H, s), 5.28 (1H, s), 4.92 (1H, d, J=9.81 Hz), 4.14 (1H, d, J=9.81 Hz), 3.91 (2H, q, CH_2), 2.36 (3H, s, CH_3), 2.15 (3H, s, CH_3), 1.20 (3H, t, CH_3); ^{13}C NMR ($CDCl_3/CS_2$ 1/1, 500 MHz) δ 166.10, 157.49, 153.39, 148.53, 147.36, 147.12, 147.02, 146.92, 146.75, 146.50, 146.16, 146.14,

146.05, 146.02, 145.99, 145.94, 145.68, 145.50, 145.48, 145.42, 145.35, 145.32, 145.27, 145.25, 145.23, 145.15, 145.12, 144.92, 144.77, 144.70, 144.68, 144.62, 144.52, 144.29, 144.00, 143.89, 143.55, 143.36, 142.85, 142.70, 142.62, 142.59, 142.36, 142.33, 142.25, 142.27, 142.21, 142.17, 142.15, 142.12, 142.11, 142.08, 142.07, 142.04, 142.02, 141.82, 141.72, 141.55, 137.75, 135.73, 135.21, 135.07, 129.36, 129.06, 125.35, 123.71, 111.61, 101.71, 80.57, 76.52, 70.45, 69.27, 60.21, 41.29, 29.90, 19.55, 14.56; MS (ESI): 1097 $[M]^{\cdot -}$.

4.1.7. *N*-Methyl-2-(4-(3-metoxiphenyl-3-ethoxycarbonyl-2-chloro-6-methyl-1,4-dihydropyridin-3-yl)-pyrrolidino [3′,4′:1,2][60]fullerene (10e). This compound was obtained in 12% yield (28% based on recovered C_{60}). Diastereomeric relationship: 98/2; IR (KBr): 3421, 2922, 2848, 2779, 1700, 1654, 1560, 1498, 1170, 1091, 526 cm^{-1}; ^1H NMR ($CDCl_3/CS_2$ 1/1, 300 MHz) δ 7.20 (3H, m), 6.79 (1H, d, J=7.88 Hz), 5.83 (1H, s, NH), 5.49 (1H, s), 5.27 (1H, s), 4.90 (1H, d, J=10.4 Hz), 4.13 (1H, d, J=10.4 Hz), 4.04 (2H, q, CH_2), 3.87 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.22 (3H, s, CH_3), 1.15 (3H, t, CH_3); ^{13}C NMR ($CDCl_3/CS_2$ 1/1, 300 MHz) δ 166.58, 159.96, 153.37, 148.58, 147.75, 147.71, 147.14, 146.80, 146.73, 146.63, 146.56, 146.47, 146.38, 146.12, 145.95, 145.93, 145.88, 145.71, 145.67, 145.55, 145.51, 145.48, 145.45, 145.30, 145.27, 145.18, 145.12, 145.09, 144.82, 144.78, 144.72, 144.62, 144.51, 143.68, 143.52, 143.48, 143.36, 143.10, 143.04, 142.99, 142.71, 142.62, 142.58, 142.53, 142.45, 142.32, 142.17, 142.13, 142.11, 142.04, 142.01, 141.82, 141.72, 141.68, 141.59, 140.62, 140.56, 140.53, 139.67, 137.60, 135.41, 135.30, 129.63, 121.39, 115.18, 112.00, 102.97, 81.20, 76.62, 70.83, 69.72, 60.33, 55.54, 41.55, 31.16, 19.95, 15.05; MS (ESI): 1082 $[M]^{\cdot -}$.

4.1.8. *N*-Methyl-2-(4-(2-chlorophenyl-3-methoxycarbonyl-2-chloro-6-methyl-1,4-dihydropyridin-3-yl)-pyrrolidino [3′,4′:1,2][60]fullerene (10f). This compound was obtained in 16% yield (30% based on recovered C_{60}). Diastereomeric relationship: 95/5; IR (KBr): 3413, 2923, 2785, 1670, 1654, 1560, 1541, 1498, 1425, 1261, 1097, 1020, 526 cm^{-1}; ^1H NMR ($CDCl_3/CS_2$ 1/1, 300 MHz) δ 7.68 (1H, d, J=8.00 Hz), 7.37 (1H, d, J=8.00 Hz), 7.19 (2H, m), 6.01 (1H, s, NH), 5.75 (1H, s), 5.19 (1H, s), 4.89 (1H, d, J=9.6 Hz), 4.07 (1H, d, J=9.6 Hz), 3.50 (3H, s, CH_3), 2.34 (3H, s, CH_3), 2.01 (3H, s, CH_3); ^{13}C NMR ($CDCl_3/CS_2$ 1/1, 500 MHz) δ 167.16, 156.97, 155.32, 154.84, 152.71, 148.99, 147.75, 147.70, 146.95, 146.74, 146.67, 146.63, 146.58, 146.54, 146.49, 146.45, 146.38, 146.36, 146.35, 146.27, 146.12, 146.03, 146.00, 145.91, 145.84, 145.80, 145.78, 145.73, 145.68, 145.56, 145.40, 145.37, 145.24, 145.17, 144.84, 144.80, 144.45, 144.38, 144.22, 143.71, 143.52, 143.40, 143.13, 143.10, 143.05, 142.97, 142.84, 142.71, 142.66, 142.60, 142.58, 142.55, 142.48, 142.12, 142.03, 141.59, 140.72, 140.67, 140.52, 139.90, 135.50, 135.48, 129.97, 128.57, 128.45, 127.8, 127.3, 112.32, 102.21, 81.37, 76.34, 71.11, 69.94, 51.19, 40.68, 31.74, 14.89; MS (ESI): 1072 $[M]^{\cdot -}$.

4.1.9. *N*-Methyl-2-(3-ethoxycarbonyl-6-methyl-4-phenyl-1,4-dihydropyridin-3-yl)pyrrolidino[3′,4′:1,2][60] fullerenes (11a). This compound was obtained in 30% yield (60% based on recovered C_{60}). Diastereomeric relationship: 60/40; 30% yield; IR (KBr) 3360, 3060, 2957, 2890, 1698, 1565, 1446, 1377, 1365, 1332, 1321, 1217, 1105, 526 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.47–7.33 (m, 5H), 6.77 (d, 1H, J=5.1 Hz, major), 5.34 (broad s, 1H, major), 4.95 (s, 1H, major), 4.73 (d, 1H, J=9.3 Hz, major), 4.22 (s, 1H, major), 3.99 (d, 1H, J=9.3 Hz, major), 3.89 (m, 2H), 2.39 (s, 3H), 2.30 (s, 3H, major), 1.02 (t, 3H); MS (ESI): 1080 $[M]^{\cdot +}$.

Acknowledgements

Supports of this work by Proyectos Alma Mater (CUBA) and MCyT of Spain (BQU2002-00855 and BQU2000-0790) are gratefully acknowledged. M. Suárez is indebted to Programa de Cooperación Científica con Iberoamérica, (PR158/01-10051), M.E.C. Spain, 2001.

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