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# Spectral Assignments and Reference Data

## Total assignment of the $^{1}H$ and $^{13}C$ NMR data for felodipine and its derivatives

**Jihyun Jung,[1] Laehee Kim,[1] Chang Sik Lee,[2] Yoon Hwan Cho,[2] Seung-Ho Ahn[2] and Yoongho Lim[1]***

[1] Department of Applied Biology and Chemistry, Konkuk University, Seoul 143-701, Korea
[2] Central R&D Center, Korea United Pharm Inc., Chungnam 339-840, Korea

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**The $^{1}H$ and $^{13}C$ NMR data for felodipine and its derivatives were completely assigned. Felodipine has 3-ethyl and 5-methyl esters which make the 1,4-dihydropyridine asymmetric. It is, however, difficult to distinguish 2,6-dimethyl groups in the NMR spectra. With the help of NOESY and computer-aided molecular modeling, these groups can be assigned. Whereas the 1,4-dihydropyridine of felodipine is connected through a methine carbon to a dichlorophenyl ring, the aromatic pyridine of felodipine derivatives is connected through a quaternary carbon. As a result, the three-dimensional conformations between the pyridine ring and the phenyl ring have important implications. Copyright © 2001 John Wiley & Sons, Ltd.**

**KEYWORDS:** NMR; $^{1}H$ NMR; $^{13}C$ NMR; felodipine; structure

### INTRODUCTION

Felodipine is a calcium channel blocker that is used for management of hypertension.[1] As shown in Fig. 1, felodipine (**1**) is a 1,4-dihydropyridine derivative belonging to the same group as the calcium channel blocking drugs nifedipine, amlodipine, isradipine and nimodipine.[2] Felodipine can be constructed through organic

*Correspondence to: Y. Lim, Department of Applied Biology and Chemistry, Konkuk University, Hwayang-Dong 1, Kwangjin-Ku, Seoul 143-701, Korea. E-mail: yoongho@konkuk.ac.kr

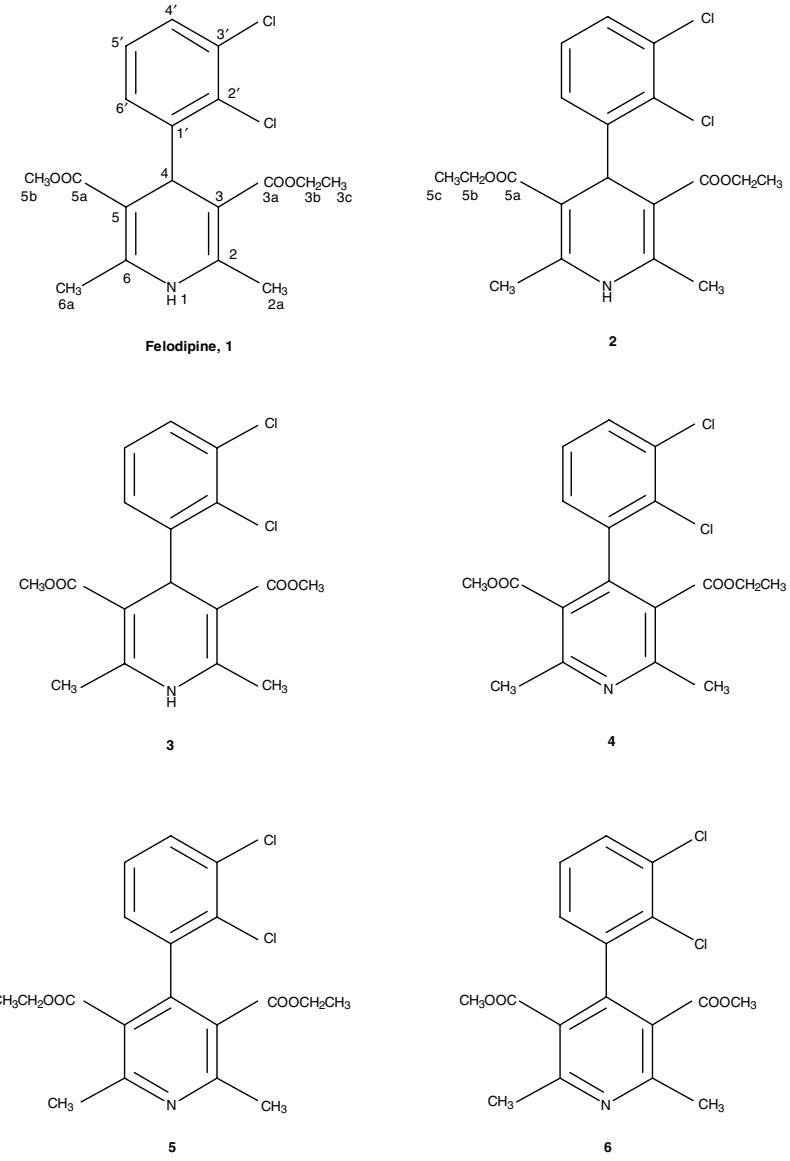


**Figure 1.** Structures and nomenclature of felodipine and its derivatives.

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synthesis.[3] Several impurities, which are all felodipine derivatives (Fig. 1), are produced during this synthesis. Whereas felodipine has 3-ethyl and 5-methyl ester groups, derivatives **2** and **3** have a 3,5-diethyl and a 3,5-dimethyl group, respectively. Unlike felodipine, derivatives **4**, **5** and **6** contain the aromatic pyridine instead of 1,4-dihydropyridine. Even though felodipine contains the asymmetric functional groups 3-ethyl ester and 5-methyl ester, there is only a one carbon difference. Therefore, it is difficult to assign the $^{1}H$ and $^{13}C$ NMR data completely. Yiu and Knaus[3] reported $^{1}H$ NMR data for felodipine but could not distinguish the 2,6-dimethyl groups. Here, these groups were completely assigned with the help of NOESY and computer-aided molecular modeling (CAMM). The $^{13}C$ NMR data for felodipine were also completely assigned. In addition, the $^{1}H$ and $^{13}C$ NMR data for the five felodipine derivatives **2**–**6** present as impurities were determined.

Whereas the 1,4-dihydropyridine group of felodipine and derivatives **2** and **3** is connected through a methine carbon to the dichlorophenyl ring, the aromatic pyridine of derivatives **4**, **5** and **6** is connected through a quaternary carbon. As a result, the three-dimensional conformations between the pyridine ring and the phenyl ring become significant. These conformations were studied using CAMM.

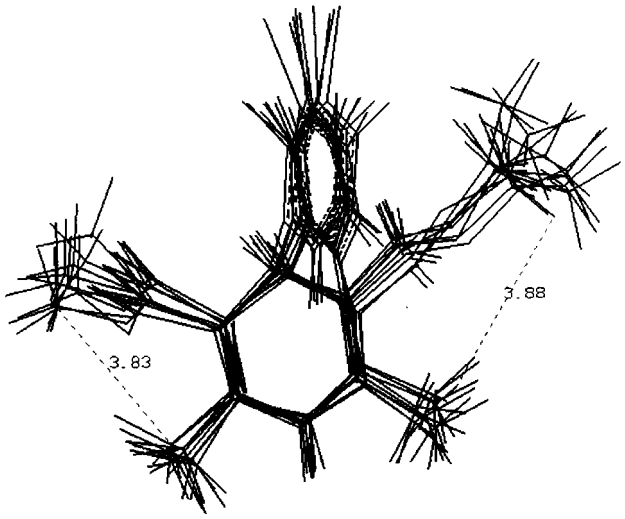


**Figure 2.** Distances between H-3b and H-2a and between H-5b and H-6a obtained from CAMM calculation.

## RESULTS AND DISCUSSION

Felodipine has two esters, one of which is a methyl group and the other an ethyl group. Two $^{13}C$ peaks at 50.97 and 59.30 ppm belong to these groups. The former is a quartet that is determined by DEPT and the latter is a triplet. Therefore, the peaks at 50.97 and 59.30 ppm are assigned to C-5b and C-3b, respectively. In HMQC, the $^{13}C$ signal at 59.30 ppm is correlated with the $^{1}H$ signal at 3.94 ppm, which must be H-3b. H-3c is determined by COSY because a cross peak between 3.94 and 1.06 ppm is observed. The peak at 166.98 ppm is assigned to C-3a based on the vicinal coupling between C-3a and H-3b observed in HMBC. Among 18 signals in the $^{13}C$ NMR spectrum, that at 167.51 ppm should be C-5a, which is another carboxylic group. The $^{13}C$ doublet peak observed at 38.30 ppm must be C-4.

The 1,4-dihydropyridine ring is neither magnetically nor structurally equivalent, but rather is quasi-symmetric because only one methylene group in the esters imparts an asymmetric character. As a result, it is difficult to distinguish C-2a from C-6a, C-3 from C-5 and C-2 from C-6. Two $^{13}C$ quartet peaks at 18.42 and 18.48 ppm can be assigned to C-6a and/or C-2a. Based on HMQC, the two $^{1}H$ peaks at 2.24 and 2.25 ppm can be assigned to H-6a and/or H-2a. In order to distinguish these two, a CAMM calculation was performed. As shown in Fig. 2, the distance between H-3b and H-2a is 3.88 Å and that between H-5b and H-6a is 3.83 Å. Therefore, NOEs should be observed. When the $^{1}H$ peak at 3.49 ppm (H-5b) is saturated, the peak at 2.24 ppm shows an NOE value of 0.4% [Fig. 3(a)]. In this manner, an NOE value of 0.6% between 3.94 ppm (H-3b) and 2.25 ppm is observed [Fig. 3(b)]. These results are informative for H-6a and H-2a, which are located at 2.24 and 2.25 ppm, respectively. C-6a and C-2a are assigned to the signals at 18.42 and 18.48 ppm, respectively, from the HMQC data. Since the geminal coupling between H-2a and C-2 is observed in HMBC, the $^{13}C$ chemical shift of C-2 is 146.11 ppm. The $^{13}C$ peak at 146.14 ppm should be C-6. C-3 is determined based on the vicinal coupling between H-2a and C-3 in HMBC, which is 102.10 ppm. The $^{13}C$ singlet peak at 101.72 ppm must be C-5. As a result, with the help of NOESY and CAMM, C-2a, C-6a, C-3, C-5, C-2 and C-6 are completely determined.

Since C-4 is coupled with H-6′ in HMBC, the $^{1}H$ peak at 7.30 ppm is assigned to H-6′. H-5′ and H-4′ can be determined from the COSY spectrum and C-6′, C-5′ and C-4′ can be determined from HMQC. H-4′ is coupled with two $^{13}C$ peaks at 129.80 and 131.72 ppm in HMBC, indicating C-3′ and/or C-2′. However, they cannot be distinguished from these data. Because H-4 is coupled with the $^{13}C$ peak at 129.80 ppm in HMBC, however, the peak must be C-2′. The peak at 131.72 ppm is automatically assigned to C-3′. Seventeen $^{13}C$ signals were determined, with the exception of 149.43 ppm, which is assigned to C-1′. In HMBC the couplings of C-1′ with H-4 and H-5′ clarify the assignment. The $^{1}H$ signal observed at 8.90 ppm is not correlated with any $^{13}C$ peak in HMQC. However, the peak is coupled with C-2a in HMBC. As a result, the $^{1}H$ peak at 8.90 ppm should be H-1. The complete assignments of the $^{1}H$ and $^{13}C$ NMR data of felodipine are listed in Table 1.

Felodipine derivatives **2** and **3** have symmetric 1,4-dihydropyridine rings. Therefore, C-3a exhibits the same chemical shift as C-5a. Likewise, the pairs C-3b and C-5b, C-3c and C-5c, C-3 and C-5, C-2 and C-6, and C-2a and C-6a show the same chemical shifts. Derivatives **2** and **3** have the same dichlorophenyl group as felodipine. Therefore, their chemical shifts are expected to be nearly identical with those of felodipine. The complete assignments of the $^{1}H$ and $^{13}C$ NMR data for derivatives **2** and **3** are listed in Tables 2 and Table 3, respectively.

Unlike felodipine and derivatives **2** and **3**, derivative **4** has an aromatic pyridine ring. The $^{1}H$ and $^{13}C$ chemical shifts of its dichlorophenyl group are expected to be the same as those for felodipine. However, the chemical shifts of the pyridine ring should be assigned separately. C-3a, C-3b, C-3c, C-5a and C-5b can be assigned in the same manner as used for felodipine. Based on the long-range coupling between H-6′ and C-4 in HMBC, the C-4 peak is 143.81 ppm. Among the six carbons of the dichlorophenyl ring, C-1′ exhibits a different chemical shift but can be assigned by the long-range coupling between H-5′ and C-1′ in HMBC.

The pairs C-2a and C-6a, C-3 and C-5, and C-2 and C-6 must now be distinguished. NOESY analysis and CAMM calculations were performed. According to the CAMM calculation, the distance between H-3b and H-2a is 3.88 Å and that between H-5b and H-6a is 3.83 Å. Therefore, NOEs are expected to be observed. When the $^{1}H$ peak at 3.51 ppm (H-5b) is saturated, the peak at 2.55 ppm shows an NOE value of 0.7%. In this manner, an NOE value of 0.7% between 3.97 ppm (H-3b) and 2.56 ppm is observed. The results are indicative regarding H-6a and H-2a, which are located at 2.55 and 2.56 ppm, respectively. In addition, from HMQC, C-6a and C-2a are assigned to 23.29 and 23.36 ppm, respectively. Since geminal coupling between H-2a and C-2 is observed in HMBC, the $^{13}C$ chemical shift of C-2 is 156.44 ppm. The $^{13}C$ peak at 156.61 ppm should be C-6. C-3 is determined based on the vicinal coupling between H-2a and C-3 in HMBC, which is 125.99 ppm. The $^{13}C$ singlet peak at 126.04 ppm must be assigned to C-5. The complete assignments of the $^{1}H$ and $^{13}C$ NMR data for derivative **4** are listed in Tables 2 and 3, respectively. Derivatives **5** and **6** have symmetric pyridine rings so their assignments can be finished based on the results for derivative **4**.

The three-dimensional structures of felodipine and derivative **4** were studied using CAMM. For felodipine, C-4 has a tetrahedral structure. The dichlorophenyl ring is placed in front of the pyridine ring by 125° and H-4 is placed at the back of the pyridine ring by 117°. For derivative **4**, however, the dichlorophenyl ring is twisted in relation to the pyridine ring by 179°, and C-4′, C-1′, C-4′ and N-1 are placed on the same central axis because of the aromatic pyridine ring.

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# Spectral Assignments and Reference Data

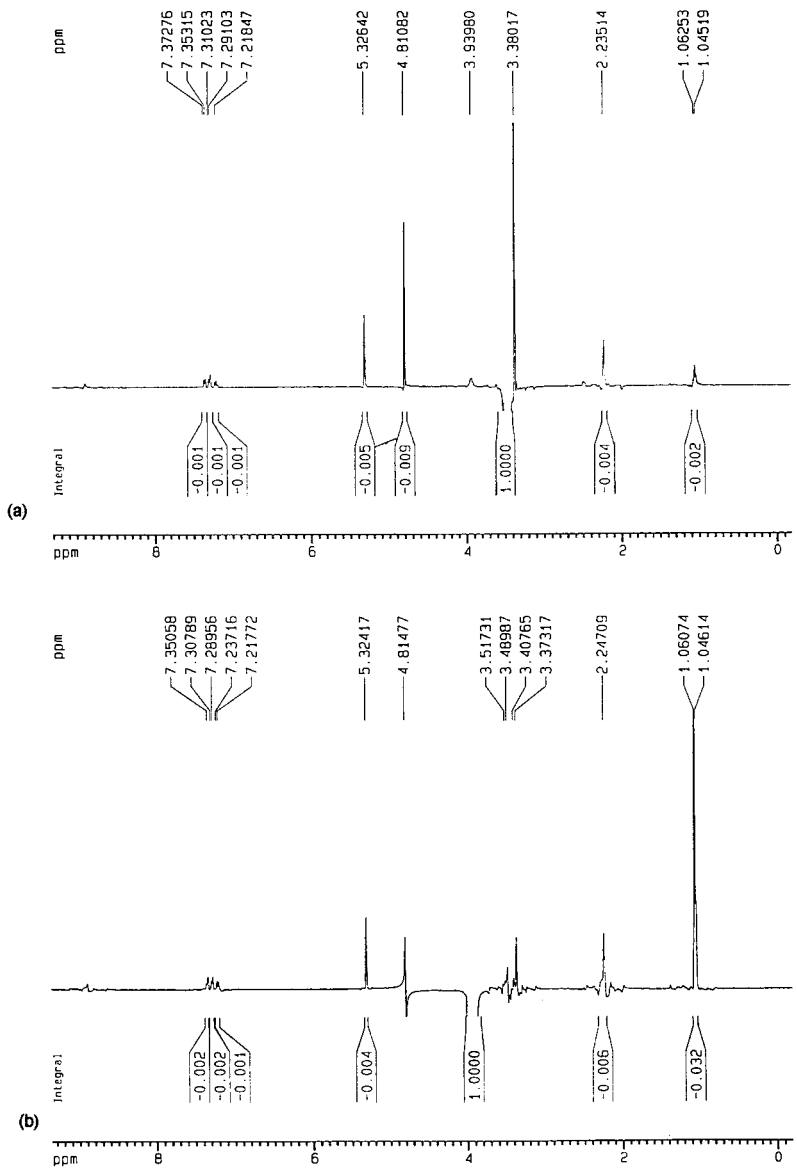


**Figure 3.** (a) NOE spectra between H-3b and H-2a and (b) H-5b and H-6a of felodipine.

**Table 1.** Assignments of the NMR data of felodipine

| $\delta^{13}$C | CH*n* | $\delta^{1}$H (*J*, Hz) | HMBC | COSY | Assignment |
|---|---|---|---|---|---|
| 14.43 | q | 1.06 (t, 7.1) | | H-3c/H-3b | C-3c |
| 18.42 | q | 2.24 (s) | | | C-6a |
| 18.48 | q | 2.25 (s) | C-2a/H-1 | | C-2a |
| 38.30 | d | 5.33 (s) | C-4/H-6′ | | C-4 |
| 50.77 | q | 3.49 (s) | | | C-5b |
| 59.30 | t | 3.94 (m) | C-3b/H-3c | H-3b/H-3c | C-3b |
| 101.72 | s | — | C-5/H-4 | | C-5 |
| 102.10 | s | — | C-3/H-2a, C-3/H-1 | | C-3 |
| 128.32 | d | 7.22 (t, 7.8) | C-5′/H-6′ | H-5′/H-4′, H-5′/H-6′ | C-5′ |
| 128.42 | d | 7.37 (dd, 1.7, 7.7) | | H-4′/H-5′ | C-4′ |
| 129.80 | s | — | C-2′/H-4 | | C-2′ |

(*continued overleaf*)

**Table 1.** (*Continued*)

| $\delta^{13}$C | CH*n* | $\delta^{1}$H (*J*, Hz) | HMBC | COSY | Assignment |
|---|---|---|---|---|---|
| 129.93 | d | 7.30 (dd, 1.7, 7.9) | C-6′/H-4′ | H-6′/H-5′ | C-6′ |
| 131.72 | s | — | C-3′/H-4′, C-3′/H-5′ | | C-3′ |
| 146.11 | s | — | C-2/H-2a, C-2/H-4 | | C-2 |
| 146.14 | s | — | | | C-6 |
| 149.43 | s | — | C-1′/H-4, C-1′/H-5′ | | C-1′ |
| 166.98 | s | — | C-3a/H-4, C-3a/H-3b | | C-3a |
| 167.51 | s | — | C-5a/H-5b | | C-5a |
| — | — | 8.90 (s) | | | N-1 |

**Table 2.** Assignments of $^{1}$H NMR data for felodipine and its derivatives

| | **1** | **2** | **3** | **4** | **5** | **6** |
|---|---|---|---|---|---|---|
| 3c | 1.06 (t, 7.1) | 1.07 (t, 7.1) | — | 0.83 (t, 7.1) | 0.77 (t, 7.1) | — |
| 5c | — | | — | — | | — |
| 6a | 2.24 (s) | 2.24 (s) | 2.25 (s) | 2.55 (s) | 2.50 (s) | 2.48 (s) |
| 2a | 2.25 (s) | | | 2.56 (s) | | |
| 4 | 5.33 (s) | 5.32 (s) | 5.34 (s) | — | — | — |
| 5b | 3.49 (s) | 3.95 (m) | 3.49 (s) | 3.51 (s) | 3.91 (m) | 3.44 (s) |
| 3b | 3.94 (m) | | | 3.97 (m) | | |
| 5′ | 7.22 (t, 7.8) | 7.22 (t, 7.8) | 7.23 (t, 7.8) | 7.41 (t, 8.0) | 7.34 (t, 7.9) | 7.34 (t, 7.9) |
| 4′ | 7.37 (dd, 1.7, 7.7) | 7.37 (dd, 1.7, 7.8) | 7.36 (dd, 1.7, 7.8) | 7.69 (dd, 1.5, 8.0) | 7.64 (dd, 1.2, 8.1) | 7.61 (dd, 1.4, 8.1) |
| 6′ | 7.30 (dd, 1.7, 7.9) | 7.30 (dd, 1.7, 7.8) | 7.29 (dd, 1.7, 7.8) | 7.16 (dd, 1.5, 8.0) | 7.1 (dd, 1.2, 7.7) | 7.09 (dd, 1.4, 7.7) |
| N1 | 8.90 (s) | 8.87 (s) | 8.94 (s) | — | — | — |

**Table 3.** Assignments of $^{13}$C NMR data for felodipine and its derivatives

| | **1** | **2** | **3** | **4** | **5** | **6** |
|---|---|---|---|---|---|---|
| 3c | 14.43 | 14.5 | — | 13.51 | 13.5 | — |
| 5c | — | | — | — | | — |
| 6a | 18.42 | 18.5 | 18.4 | 23.29 | 23.2 | 23.4 |
| 2a | 18.48 | | | 23.36 | | |
| 4 | 38.30 | 38.4 | 38.2 | 143.81 | 143.7 | 143.9 |
| 5b | 50.77 | 59.3 | 50.8 | 52.63 | 61.4 | 52.6 |
| 3b | 59.30 | | | 61.43 | | |
| 5 | 101.72 | 101.9 | 101.9 | 126.04 | 126.1 | 125.9 |
| 3 | 102.10 | | | 125.99 | | |
| 5′ | 128.32 | 128.26 | 128.3 | 128.19 | 128.1 | 128.2 |
| 4′ | 128.42 | 128.39 | 128.5 | 130.98 | 130.87 | 131.0 |
| 2′ | 129.80 | 129.9 | 129.7 | 130.59 | 130.85 | 130.4 |
| 6′ | 129.93 | 130.1 | 129.8 | 129.09 | 129.2 | 128.9 |
| 3′ | 131.72 | 131.7 | 131.8 | 132.07 | 132.2 | 132.0 |
| 2 | 146.11 | 146.0 | 148.2 | 156.44 | 156.5 | 156.6 |
| 6 | 146.14 | | | 156.61 | | |
| 1′ | 149.43 | 149.6 | 149.5 | 137.46 | 137.6 | 137.4 |
| 3a | 166.98 | 167.1 | 167.5 | 166.28 | 166.3 | 166.9 |
| 5a | 167.51 | | | 166.90 | | |

MRC

# Spectral Assignments and Reference Data

Even though felodipine contains the asymmetric functional groups 3-ethyl ester and 5-methyl ester, these groups differ from each other by only one methylene group. It is, therefore, difficult to assign the $^{1}H$ and $^{13}C$ NMR data completely. The $^{1}H$ NMR data were completely assigned by Yiu and Knaus,[3] but H-2a and H-6a were not distinguished. The $^{13}C$ NMR data were also determined. In addition, the NMR data for impurities occurring in felodipine synthesis were completely assigned.

## EXPERIMENTAL

### Materials

Felodipine (**1**) was prepared according to a published procedure.[3] Derivatives **2–6** were synthesized according to published procedures.[4,5]

### NMR spectra

All NMR measurements were performed on a Bruker Avance 400 spectrometer system (9.4 T) at 298 K. The $^{1}H$ NMR, $^{13}C$ NMR, DEPT, COSY, HMQC, HMBC, and NOESY spectra were collected in DMSO-$d_6$ with TMS as an internal reference. The concentration of the samples was 50 mM. For $^{1}H$ NMR analysis, 32 transients were acquired with a 1 s relaxation delay using 32K data points. The 90° pulse was 9.7 μs with a spectral width of 4000 Hz. $^{13}C$ NMR and DEPT spectra were obtained for a spectral width of 8000 Hz, collecting 64K data points. The 90° pulse was 9.6 μs. Two-dimensional spectra were acquired with 2048 data points for $t_2$ and 256 for $t_1$ increments.

### Calculations

All calculations were performed using software from MSI (San Diego, CA, USA) on a Silicon Graphics INDY R4400 workstation. The potentials and partial charges were arranged using a consistent-valence force field and the calculations were performed for 500 ps. Among 500 calculated structures, 10 structures with the lowest total energy were superimposed.

### Acknowledgements

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