Research Article

Magnetic Resonance in Chemistry

Received: 29 October 2008 Revised: 19 January 2009 Accepted: 20 January 2009 Published online in Wiley Interscience: 27 February 2009

(www.interscience.com) DOI 10.1002/mrc.2414

The behavior of Gliclazide in solution and in the solid state: a case of organic compound presenting a solid-solution structure

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The structure of the hypoglycemic agent Gliclazide has been studied by ^{1}H, ^{13}C, and ^{15}N NMR in solution ($CDCl_3$ and DMSO-d_6) and in the solid state. In the solid state, the compound crystallizes as an *EZ* isomer without dynamic properties. In $CDCl_3$ solution, the structure is still *EZ* but with a slow nitrogen inversion about the pyrrolidine nitrogen: two invertomers have been observed and characterized. In DMSO-d_6, the rate is faster and only averaged signals were observed. GIAO calculated absolute shieldings were used to confirm the nature of the observed species. In the solid state, Gliclazide presents the phenomenon of solid-solution with two disordered conformations present in the crystal at a 90 : 10 ratio. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords: urea; NMR; CPMAS; Gliclazide; GIAO; *E*/*Z* isomerism; nitrogen inversion

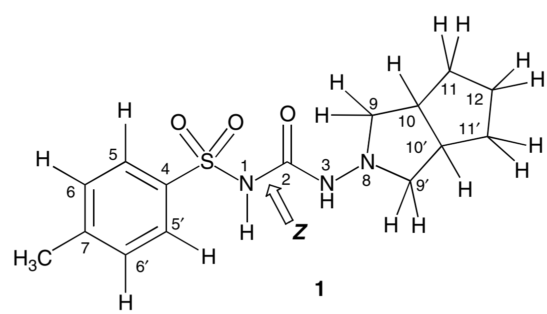
Introduction

We have been systematically reporting the characterization by NMR of relevant pharmaceutical and biological compounds: Omeprazole,[1,2] curcumin,[3] and biotin methyl ester.[4] We wish to describe now our studies of Gliclazide, 3-(7-azabicyclo[3.3.0]oct-7-yl)-1-(4-methylphenyl)sulfonylurea. Gliclazide **1** is an oral hypoglycemic (antidiabetic drug) belonging to the sulfonylurea family.

Sulfonylureas were discovered in 1942 by Marcel Janbon[5] and developed four years later by Auguste Loubatières both in Montpellier.[6,7] Servier Laboratories introduced Gliclazide under the name *Diamicron*. Gliclazide has a 2008 worldwide sale of around $30 million. The molecule is growing annually at the rate of 10–12% and numerous papers are devoted to its study.[8]

The X-ray structure of **1** is known,[9,10] CSD-refcode SUVGUL (Fig. 1).[11] Only the results of Ref. [10] were reported in the Cambridge Structural Database.[11] Note that, in the solid state, the N–H groups point to opposite directions (*EZ* isomer) and that the lone pair in the saturated 5,5-bicycle points toward the farthest N–H proton.

Although there is no detailed study of the NMR spectra of Gliclazide, there are several publications by Moyano *et al*. dealing with this compound included in β-cyclodextrine, in which ^{1}H, ^{13}C NMR in solution in NaOD/D_2O,[12–14] and ^{13}C CPMAS NMR data[15] of **1** were described. In no case the possibility of isomerism (see below) was considered.



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Scheme 1. Numbering of Gliclazide **1** both for *EZ* and *ZZ* isomers (two possible positions for N3H).

Results and Discussion

We have explored two different conformational possibilities of Gliclazide. One is the *E*/*Z* isomerism of the C2–N3 amide bond (Scheme 1), found in some ureas and thioureas,[16–19] that in the case of Gliclazide corresponds to an *EZ*/*ZZ* isomerism since the N1–C2 bond in sulfonylureas is always *Z*. The second one is related to the inversion of the bicyclic ring nitrogen atom (N8).

The relative energies calculated at the B3LYP/6-311++G** theoretical level (Fig. 2) indicate firstly that the structure (SUVGUL) found in the solid state is the most stable one and secondly that only *EZ* isomers are stable enough to be observed in solution.

NMR results are reported in Tables 1 and 2 with the atom numbering as in Scheme 1.

The ^{1}H NMR chemical shifts in $CDCl_3$ in the 213–330 K range are similar in position save the N3–H chemical shift, which is very sensitive to the temperature. The proportions change and a considerable broadening is observed when the temperature increases (Fig. 3).

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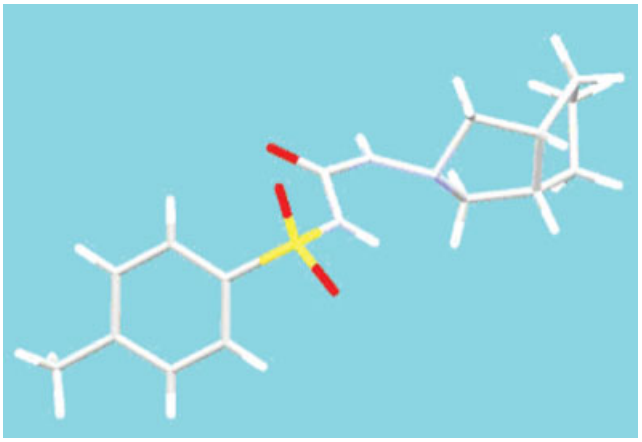

Figure 1. X-ray structure (SUVGUL) of Gliclazide.

In DMSO-d_6 at 345 K (^{1}H NMR) only one group of signals is observed, which should correspond to a fast exchange between two isomers. In the solid state, the CPMAS spectrum must correspond to **1a** since this is the conformation observed in SUVGUL. The different signals were assigned using conventional 2D experiments.

Although there is no doubt that the major isomer observed in $CDCl_3$ corresponds to **1a**, we decided to calculate the absolute shieldings of the four isomers, shown in Fig. 2, at the GIAO//B3LYP/6-311++G** level using the Gaussian 03 facilities[22–25] that we are currently using in this kind of studies.[20,21] To this aim and starting from the X-ray structure (SUVGUL), an optimization leads for **1a** to a geometry (Fig. 2) only slightly modified. From this one and the other three optimized geometries, we calculated the corresponding absolute shieldings, σ, that we transformed into chemical shifts, δ, using the equations reported in Tables 1 and 2.

We have carried out a series of regressions to select the most correlated structures. In ^{13}C NMR, we have to exclude the carbon linked to the SO_2 group, C4, and in ^{1}H NMR both NH groups, too sensitive to solvent effects. Using ^{15}N NMR, chemical shifts does not allow selecting a particular structure, because there are not enough points and because the correlation coefficients are nearly identical (always $r^2 > 0.99$). Using ^{13}C chemical shifts, the correlation coefficients are also very similar for the four conformers. In any case, the calculated value for C4, ~142 ppm, is much higher than the experimental value of 134.9 ppm. We have already noted that at the calculated level used, some carbon atoms are overestimated, such as C–Br[26,27] and C–S.[28] The results are more significant using the ^{1}H NMR data, the r^2 values are for the major isomer: **1b** (0.999) > **1a** (0.997) > **1c** (0.976) > **1d** (0.971) and for the minor isomer: **1c** (0.992) > **1a** (0.986) > **1d** (0.985) > **1b** (0.979). Taking into account the energy calculations, we conclude that the major isomer is **1a** and the minor one **1c**. Treating together both isomers, the following equations are obtained (they include the references, nitromethane and TMS):

$$^{15}\mathrm{N}: \delta^{15}\mathrm{N}\ \mathrm{exp.} = (1.3 \pm 10.1) + (1.00 \pm 0.04)\,\delta^{15}\mathrm{N\ calc.} \quad n = 7,\ r^2 = 0.992 \tag{1}$$

$$^{13}\mathrm{C}: \delta^{13}\mathrm{C}\ \mathrm{exp.} = -(1.5 \pm 0.9) + (1.02 \pm 0.01)\,\delta^{13}\mathrm{C\ calc.} \quad n = 19,\ r^2 = 0.999 \tag{2}$$

$$^{1}\mathrm{H}: \delta^{1}\mathrm{H}\ \mathrm{exp.} = -(0.02 \pm 0.07) + (0.996 \pm 0.018)\,\delta^{1}\mathrm{H\ calc.} \quad n = 21,\ r^2 = 0.994 \tag{3}$$

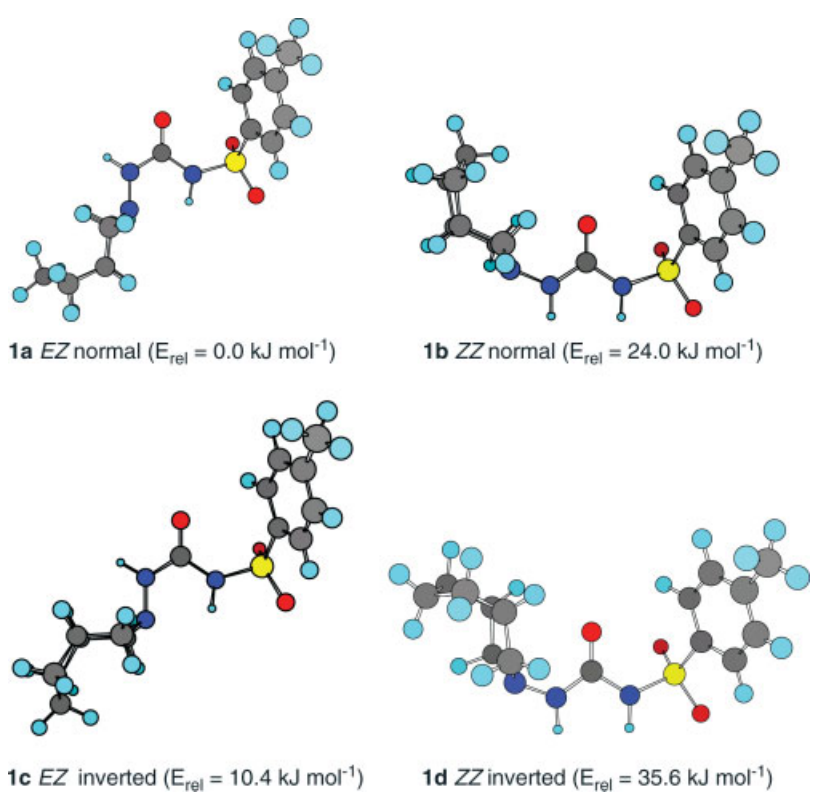

Figure 2. The four minimum energy conformations of Gliclazide.

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Table 1. Chemical shifts (δ, ppm) and coupling constants (J, Hz) of Gliclazide in solution. Values in italics are identical (or at least very similar to the point of being indistinguishable) in the major and minor isomers

$CDCl_3$ at 213 K			DMSO-d_6 at 345 K		GIAO calc. δ			
Atom	Major isomer	Minor isomer	Only ^{1}H and ^{13}C	[52/48]	*EZ* normal **1a**	*ZZ* normal **1b**	*EZ* inverted **1c**	*ZZ* inverted **1d**
N1	−246.2	−246.5	–	–	−238.9	−240.2	−237.8	−240.6
	$^1J = 90.4$	$^1J = 89.7$						
C2	152.3	*152.3*	152.6	–	149.5	148.0	149.5	149.1
N3	−248.1	*−248.1*	–	–	−260.3	−274.3	−256.0	−256.0
	$^1J = 90.4$	$^1J \approx 97$						
C4	134.9	*134.9*	137.4	–	[142.2	142.7	141.9	142.8]
C5	128.0	128.1	127.0	–	127.2	129.0	128.7	128.9
C6	129.2	*129.2*	128.9	–	127.7	127.8	127.7	127.8
C7	144.8	*144.8*	143.1	–	144.3	144.7	143.8	144.7
C–Me	21.8	*21.8*	20.5	–	21.2	21.6	21.0	21.7
N8	−293.4	−291.8	–	–	−300.8	−307.0	−290.7	−303.5
C9	62.0	62.4	61.3	–	63.4	57.6	64.8	67.4
C10	39.3	39.7	39.7	–	44.2	44.2	44.8	49.5
C11	30.5	33.9	31.9	–	32.1	32.7	32.7	33.6
C12	23.5	27.0	25.2	–	25.7	26.0	25.3	26.4
N1–H	9.00	8.73	9.36	8.87	[7.74	5.56	7.75	5.55]
N3–H	7.07	7.04	7.72	7.06	[3.88	5.11	4.95	5.51]
H5	7.92	*7.92*	7.81	7.92	8.07	7.98	8.08	7.98
H6	7.28	*7.28*	7.38	7.28	7.19	7.18	7.21	7.18
C–Me	2.41	2.42	2.39	2.41	2.36	2.38	2.29	2.39
H9 ax	1.88	2.74	2.42	2.29	1.81	1.81	2.98	3.13
H9 eq	3.19	2.49	2.90	2.85	2.88	3.22	2.70	3.18
H10	2.51	*2.51*	2.50	2.51	2.63	2.53	2.70	3.18
H11 ax	1.47	1.88	1.62	1.65	1.46	1.45	1.58	1.58
H11 eq	1.43	1.23	1.39	1.33	1.44	1.39	1.39	1.39
H12 ax	1.67	1.23	1.63	1.34	1.56	1.82	1.49	1.49
H12 eq	1.44	1.35	1.47	1.52	1.56	1.52	1.56	1.56

Equations used to transform σ into δ (including ^{1}H TMS $\sigma = 31.97$ ppm, ^{13}C TMS $\sigma = 184.75$ ppm, ^{15}N $MeNO_2$ $\sigma = -154.43$ calculated at the same level).
^{15}N NMR: $\delta^{15}N = -154 - 0.98\,\sigma^{15}N$, $n = 3$, $r^2 = 0.995$.
^{13}C NMR: $\delta^{13}C = 175.7 - 0.963\,\sigma^{13}C$, from Ref. [20].
^{1}H NMR: $\delta^1H = 31.0 - 0.97\,\sigma^1H$, from Ref. [21].

Temperature variation modifies the percentages of isomers **1a** and **1c**. In $CDCl_3$ the values are: 51.4/48.6 (300 K), 53.6/46.4 (288 K), 58.3/41.7 (263 K), 65.8/34.2 (238 K), 74.4/25.6 (213 K), and 76.9/23.1 (203 K). The equilibrium constant $K_e = [\mathbf{1c}]/[\mathbf{1a}]$, and since $\Delta G = -RT \ln K_e = \Delta H - T\Delta S$, a simple regression ($R^2 = 0.995$) affords $\Delta H = (6.1 \pm 0.2)$ kJ mol^{-1} and ΔS (20.7 ± 0.7) J K^{-1} mol^{-1}.

In DMSO-d_6 at 345 K, only a set of ^{1}H chemical shifts was observed. Using the experimental values in $CDCl_3$ at 213 K, the best fit is obtained for a mixture of 52% of **1a** and 48% of **1c**. Probably, the results obtained by Moyano *et al*. in NaOD/D_2O also correspond to mixtures of conformers in rapid equilibrium.

The most interesting results are those obtained in the solid state, where signals are not averaged (Table 2). In the part of the spectrum where the signals of the sp^3 carbons are located between 16 and 68 ppm (see Fig. 4), a series of small signals appear that are independent on the conditions used to prepare the sample. They correspond to an amount of about 10%. In the paper of Winters, Shields, Timmins, and York there is a ^{13}C CPMAS NMR spectrum of Gliclazide at 75.4 MHz (their Fig. 2 on page 301),[9] and looking carefully at their spectrum one can see the signals of the minor compound.

The signals of the major isomer were adjusted to the structure present in the crystal, i.e. **1a**.

$$^{15}\mathrm{N}:\ \delta^{15}\mathrm{N}\ \mathrm{exp.} = -(1.1 \pm 10.3) + (0.99 \pm 0.05)\,\delta^{15}\mathrm{N\ calc.}\quad n = 4,\ r^2 = 0.996 \tag{4}$$

$$^{13}\mathrm{C}:\ \delta^{13}\mathrm{C}\ \mathrm{exp.} = -(1.8 \pm 1.2) + (1.03 \pm 0.01)\,\delta^{13}\mathrm{C\ calc.}\quad n = 15,\ r^2 = 0.998 \tag{5}$$

If one analyzes the five sp^3 carbons (Me, C9, C10, C11, and C12) of **1a** and one of the other three possibilities **1b, 1c,** and **1d** to find the best fit one obtains:

$$\mathbf{1a} + \mathbf{1b}:\ \delta^{13}\mathrm{C\ CPMAS} = -(2.7 \pm 2.0) + (1.06 \pm 0.05)\ \delta^{13}\mathrm{C\ calc.}\ n = 17,\ r^2 = 0.970 \tag{6}$$

$$\mathbf{1a} + \mathbf{1c}:\ \delta^{13}\mathrm{C\ CPMAS.} = -(1.1 \pm 1.1) + (1.00 \pm 0.02)\ \delta^{13}\mathrm{C\ calc.}\ n = 17,\ r^2 = 0.993 \tag{7}$$

$$\mathbf{1a} + \mathbf{1d}:\ \delta^{13}\mathrm{C\ CPMAS} = -(0.9 \pm 1.4) + (0.96 \pm 0.03)\ \delta^{13}\mathrm{C\ calc.}\ n = 17,\ r^2 = 0.983 \tag{8}$$

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Table 2. Chemical shifts (δ, ppm) in the solid state (CPMAS experiments)

Atom	Exp. major	Exp. minor[a]	*EZ* normal **1a**	*ZZ* normal **1b**	*EZ* inverted **1c**	*ZZ* inverted **1d**
N1	−241.5	–	−230.3	−231.6	−229.2	−231.9
C2	154.9	–	149.5	148.0	149.5	149.1
N3	−241.5	–	−251.1	−264.6	−246.9	−246.9
C4	136.2	–	[142.2	142.7	141.9	142.8]
C5	128.3	–	126.1	126.3	126.1	126.3
C5′	129.4	–	131.3	131.7	131.2	131.5
C6	129.4	–	127.1	127.3	127.2	127.4
C6′	131.0	–	128.4	128.2	128.1	128.2
C7	146.9	–	144.3	144.7	143.8	144.7
C−Me	21.8	–	21.2	21.6	21.0	21.7
N8	−288.6	–	−290.3	−296.3	−270.9	−292.8
C9	65.1	–	63.1	57.6	64.8	67.7
C9′	61.9	64.1	63.7	57.6	64.8	67.2
C10	40.5	43.9	44.1	43.9	44.5	49.7
C10′	39.5	42.3	44.7	44.6	45.0	49.4
C11	32.6	31.8	32.1	32.7	32.4	33.5
C11′	29.3	28.2	32.2	32.7	33.1	33.7
C12	24.3	–	25.7	26.0	25.3	26.4

[a] For the minor isomer only the signals that are not under those of the major isomer are reported.
Equations used to transform σ into δ (including ^{1}H TMS $\sigma = 31.97$ ppm, ^{13}C TMS $\sigma = 184.75$ ppm, ^{15}N $MeNO_2$ $\sigma = -154.43$ calculated at the same level).
^{15}N NMR: CPMAS: $\delta^{15}N = -148-0.95\,\sigma^{15}N$, $n = 4$, $r^2 = 0.996$.
^{13}C NMR: $\delta^{13}C = 175.7-0.963\,\sigma^{13}C$, from Ref. [20].
^{1}H NMR: $\delta^1H = 31.0-0.97\,\sigma^1H$, from Ref. [21].

The conclusion is that the small signals belong to **1c** (Eqn 7) that have not been detected in crystallography due to their small abundance.

The values for N1 and N3 chemical shifts in Table 2 (CPMAS: −241.5 and −241.5 ppm, $\Delta\delta = 0.0$ ppm) and Table 1 ($CDCl_3$: −246.2 and −248.1 ppm, $\Delta\delta = 1.9$ ppm) are very close, showing that the anomaly is not related to the solid state (intermolecular HBs, ring current effects on solid-state NMR) but most probably to the calculations: −230.3 and −251.1 ppm in solid-state ($\Delta\delta = 20.8$ ppm); −238.9 and −260.3 ppm in $CDCl_3$ ($\Delta\delta = 21.4$ ppm).

In conclusion, Gliclazide shows a dynamic situation in solution that involves not an *E*/*Z* equilibrium of the amide bond but a nitrogen inversion. Nitrogen inversion in N–R pyrrolidines is generally too fast to observe separate signals for both invertomers but the barrier increases considerably when the N atom bears an amino substituent[29,30] and when the pyrrolidine is fused to another ring (the bicyclic effect[31]). Also, it is known that the barrier is higher in chloroform than in other solvents.[30,32] In the case of Gliclazide, the signals of both invertomers being only slightly broad in $CDCl_3$ at 213 K and the average signals in DMSO-d_6 at 345 K showing broadness only for those signals that are most different in **1a** and **1c** means that the barrier to nitrogen inversion is about 40–60 kJ mol^{-1} in $CDCl_3$ and about 20–40 kJ mol^{-1} in DMSO-d_6.[33]

In the solid-state, Gliclazide is an example of substitutional solid-solution, i.e. a homogeneous crystalline phase in which some of the constituent molecules are substituted by foreign molecules that possess sufficient similarity that the lattice dimensions are changed only slightly.[34–39] That is the case of **1a** and **1c**. We imagine that in solution there are both **1a** and **1c** (according to the calculations in the gas phase there is 98% of **1a** and 2% of **1c**) and when the crystal starts to grow it is formed by **1a** molecules and, from time to time, a **1c** molecule is inserted in the lattice.

Although no example has been reported, the results presented in this study point out to the probable existence of conformational polymorphism in Gliclazide.

Experimental

Solution NMR spectra were recorded on a Bruker DRX 400 (9.4 T, 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C, and 40.56 MHz for ^{15}N) spectrometer with a 5-mm inverse-detection H-X probe equipped with a z-gradient coil. Chemical shifts (δ in ppm) are given from

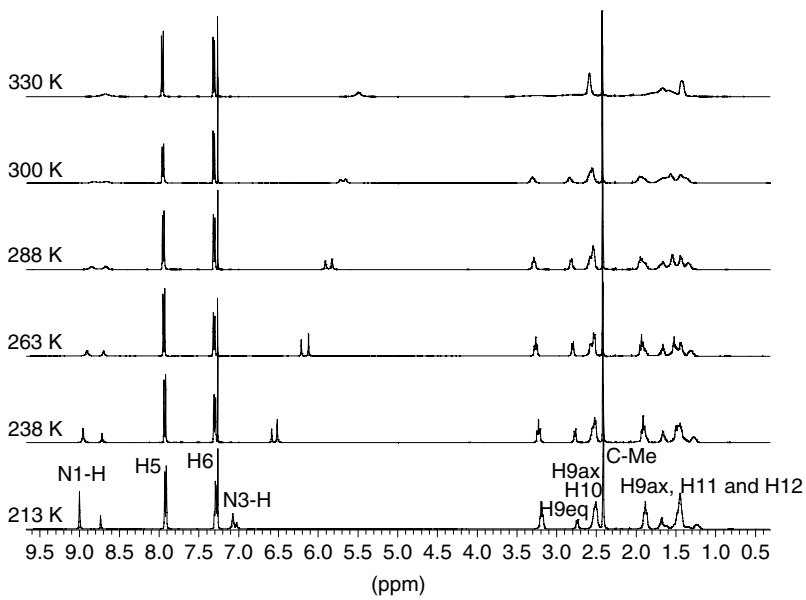

Figure 3. ^{1}H NMR spectra in $CDCl_3$ between 213 and 330 K.

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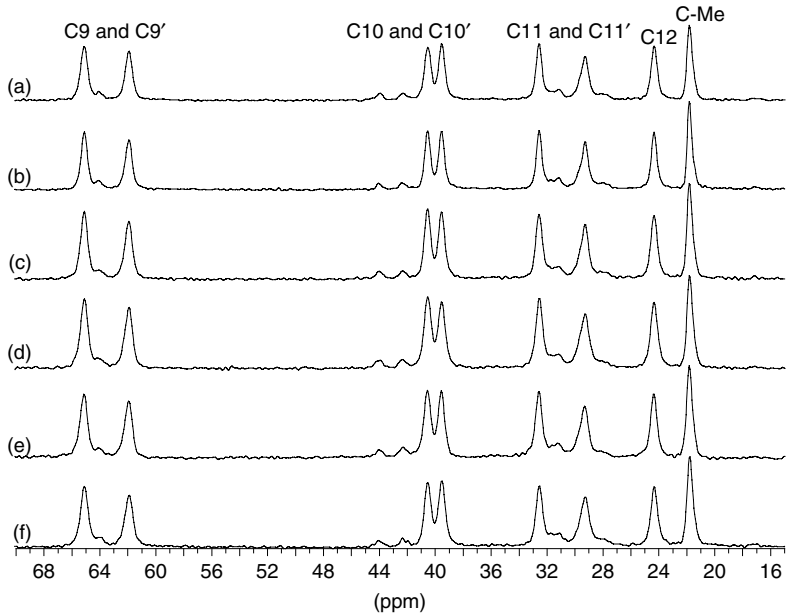

Figure 4. ^{13}C CPMAS NMR spectra of **1**. Region of sp^3 carbon atoms. (a) Commercial product without crystallization; (b) dissolved in methanol and evaporated; (c) crystallized in methanol; (d) crystallized in chloroform/hexane; (e) crystallized in acetone; and (f) crystallized in DMF.

internal solvent: $CDCl_3$ 7.26 for ^{1}H and 77.0 for ^{13}C, DMSO-d_6 2.49 for ^{1}H and 39.5 for ^{13}C, and for ^{15}N NMR nitromethane (0.00) was used as external standard. Variable temperature: a Bruker BVT3000 temperature unit was used to control the temperature and an exchanger to reach low temperatures. To avoid problems at low temperatures caused by air moisture, pure nitrogen was used as cooling gas stream.

Typical parameters for ^{1}H NMR spectra were spectral width 3700–4700 Hz, pulse width 7.5 µs at an attenuation level of 0 dB, and resolution 0.23–0.29 Hz per point. Typical parameters for ^{13}C NMR spectra were spectral width 20 576 Hz, pulse width 10.6 µs at an attenuation level of −6 dB, and resolution 0.63 Hz per point; WALTZ-16 was used for broadband proton decoupling; the FIDS were multiplied by an exponential weighting (lb = 1 Hz) before Fourier transformation.

2D (^{1}H–^{1}H) gs-COSY and inverse proton detected heteronuclear shift correlation spectra, (^{1}H–^{13}C) gs-HMQC, (^{1}H–^{13}C), gs-HMBC and (^{1}H–^{15}N) gs-HMBC, were acquired and processed using standard Bruker NMR software and in nonphase-sensitive mode. Gradient selection was achieved through a 5% sine truncated shaped pulse gradient of 1 ms.

Selected parameters for (^{1}H–^{1}H) gs-COSY were spectral width 3700–4700 Hz, the acquisition data size 1024 points and one transient accumulated per increment, with a 1 s relaxation delay, for a total of 512 experiments, data processing using zero filling in the F1 domain and shifted sine-bell apodization of factor 0 in both dimensions.

Selected parameters for (^{1}H–^{13}C) gs-HMQC and gs-HMBC spectra were spectral width 3700–4700 Hz for ^{1}H and 20.6 kHz for ^{13}C, 1024 × 256 data set, number of scans 2 (gs-HMQC) or 4 (gs-HMBC), and relaxation delay 1 s. The FIDs were processed using zero filling in the F1 domain and a sine-bell window function in both dimensions was applied prior to Fourier transformation. In the gs-HMQC experiments, GARP modulation of ^{13}C was used for decoupling.

Selected parameters for (^{1}H–^{15}N) gs-HMBC spectra were spectral width 3700 Hz for ^{1}H and 15.0 kHz for ^{15}N, 1024 × 512 data set, number of scans 2, relaxation delay 1 s, and 60 ms delay for the evolution of the ^{15}N–^{1}H long-range coupling. The FIDs were processed using zero filling in the F1 domain and a sine-bell window function in both dimensions was applied prior to Fourier transformation.

Solid state ^{13}C (100.73 MHz) and ^{15}N (40.60 MHz) CPMAS NMR spectra were obtained on a Bruker WB 400 spectrometer at 300 K using a 4 mm DVT probehead. Samples were carefully packed in a 4-mm diameter cylindrical zirconia rotor with Kel-F end-caps. Operating conditions involved 3.2 µs 90° ^{1}H pulses and decoupling field strength of 78.1 kHz by TPPM sequence. ^{13}C spectra were originally referenced to a glycine sample and then the chemical shifts were recalculated to the Me_4Si (for the carbonyl atom δ (glycine) = 176.1 ppm) and ^{15}N spectra to $^{15}NH_4Cl$ and then converted to nitromethane scale using the relationship: δ ^{15}N(nitromethane) = δ ^{15}N(ammonium chloride) − 338.1 ppm. The typical acquisition parameters for ^{13}C CPMAS were: spectral width, 40 kHz; recycle delay, 15 s; acquisition time, 30 ms; contact time, 2 ms; and spin rate, 12 kHz. And for ^{15}N CPMAS the typical acquisition parameters were: spectral width, 40 kHz; recycle delay, 15 s; acquisition time, 35 ms; contact time, 7 ms; and spin rate, 6 kHz.

For the theoretical calculations see any of our previous papers.[20,21,27,28]

Acknowledgements

This work has been financed by the Spanish MEC (CTQ2007-62113 and CTQ2007-61901/BQU) and Comunidad Autónoma de Madrid (Project MADRISOLAR, ref. S-0505/PPQ/0225).

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