X-Ray Diffraction and Solid-State NMR Structural Characterization of Isatin Derivatives

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Abstract: *The title compounds. have been synthesized and characterized by elemental analysis., IR and mass spectroscopy and their structures have been determined by single-crystal X-ray diffraction, solution and solid state ^{13}C NMR. For the ester derivative the conformer present is the S-cis, confirmed by both x-ray diffraction data and ^{13}C-CP/MAS spectrum. For the amide derivative, although according to X-ray data the conformer present is the S-trans, the results obtained with ^{13}C-CP/MAS showed that the two conformers S-cis and S-trans are present in the solid state. The solution NMR spectra of the ester and amide compounds showed that only one conformer seems to be present in solution.*

Introduction

The indole nucleus is a key structural feature of both natural and synthetic compounds.[1] Isatin and its derivatives have proved to be versatile starting materials for the synthesis of heterocyclic and acyclic compounds, natural products and analogues, including potentially important compounds with biological activity.[2] For example, isatin is a versatile molecule for the designing of potential antiviral agents.[3] Also, isatine oxindole derivatives have been shown to have antibacterial, antiprotozoan and anti-inflammatory activities.[4,5]

Some studies have been focused on the synthesis and characterization of intermediates for the preparation of new phenylethyl-amine derivatives that present adrenergic activity, analogues to R-(-) norepinefrin. We have prepared the compounds **1** (2-acetamidophenyl-glyoxamate) and **2** (2-acetamidophenyl-glyoxalate), which structures are shown in Figures 1 and 2, respectively. As can be seen , two different conformers, S-cis (Figure 1, A and Figure 2, C) or S-trans (Figure 1, B and Figure 2, D) can be present in solid state.

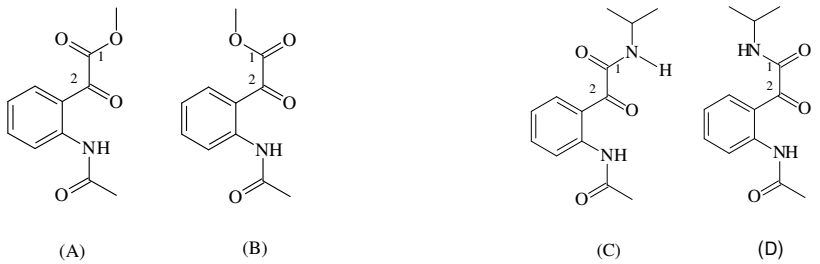

Figure 1. Structures for compound **1** (left), S-trans (A) and S-cis (B) conformations, and **2** (right), S-trans (C) and S-cis (D) conformations.

The literature reports on ^{1}H and ^{13}C data in solution state for some isatin derivatives[6], as well as some X-ray studies.[7] Cross-polarization (CP) combined with magic-angle spinning (MAS) is a powerful and frequently applied technique to obtain high-sensitivity, high-resolution solid-state nuclear magnetic resonance (NMR) spectra of nuclei with a low gyromagnetic ratio (e.g. ^{13}C) in the presence of abundant nuclei (^{1}H). In addition, this technique can be used for obtaining structural information and for assignment purposes.[8] To the best of our knowledge, this is the first report on the use of solid state NMR to investigate whether compounds **1** and **2** are able to exhibit different conformations in the solid state.

Experimental

Compounds **1** and **2** were prepared as reported elsewhere. [9] They were characterized by elemental analysis, Fourier transform infrared spectroscopy (FTIR) and mass spectrometry (MS) (results not shown). X-ray crystallographic data were obtained for compound **1** (ester derivative) by the following procedure: a prismatic crystal of 0.38 x 0.25 x 0.20 mm was mounted at random on an automatic CAD-4 Enraf-Nonius diffractometer. Cell dimensions were determined by least-squares fit to the setting angles for 25 reflections ($9<\theta<17^{o}$). Intensity measurements were carried out up to $\theta = 25^{o}$, using $\theta/2\theta$ scan mode and graphite-monochromated MoKα (0.71073 Å) radiation. X-ray data for compound **2** was published elsewhere.[7]

Solid state ^{13}C-CP/MAS spectra were recorded at 75.4 MHz on a Varian VXR-300 spectrometer (7.05 Tesla), using a Varian multinuclear CP-MAS probehead and a 7 mm zirconia rotors at spinning rate of 5.8 KHz. Spectra were obtained using cross-polarization with contact time in a range of .02 to 20 ms, sweep width 50kHz, 5.4μs $\pi/2$ pulse length for protons, relaxation delay of 5s and 500-800 scans. Chemical shifts were referenced externally to the CH_3 signal for hexamethyl benzene at 17.3 ppm.

^{13}C solution NMR spectra were recorded on a Bruker Avance DRX-300 spectrometer operating at 75.4 MHz, with the samples dissolved in $CDCl_3$. Acquisition parameters were as follows: pulse width 3 μs ($\pi/6$), relaxation delay 1s, spectral width 10kHz, and 32768 data points. The chemical shifts are relative to TMS.

Results and Discussion

The crystal structure of compounds **1** and **2** (Figure 2) were determined by single crystal XRD data. It can be seen that for compound **1** the S-cis conformation is the preferred one, whereas for compound **2** the lowest energy corresponds to the S-trans conformation.

Proton decoupled ^{13}C NMR solution spectra are shown in Figures 3 and 4. Both presented three signals corresponding to carbonyl carbons in the 200-150 ppm range of chemical shifts.

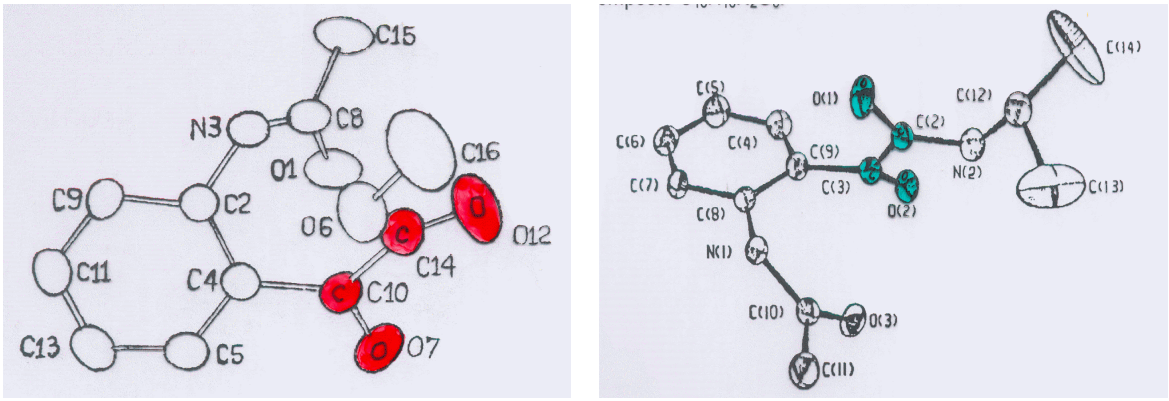

Figure 2. Crystal structures calculated for compounds **1** (left) and **2** (right).

For compound **1**, three carbonyl signals were observed at 163.72 ppm ($O=C_1$), at 169.40 ppm (O=C of acetyl group) and at 190.11 ppm ($O=C_2$). According to the XRD data, the signals at 163.72 ppm and at 190.11 ppm correspond to the S-cis conformation. For compound **2,** the signals were observed at 162.08 ppm ($O=C_1$), 169.22 ppm (O=C of acetyl group) and at 192.30 ppm ($O=C_2$). XRD data also suggest that the signals at 162.08 ppm and at 192.30 ppm correspond to S-trans conformation for that compound. The assignment was made based on some data reported for similar compounds.[6]

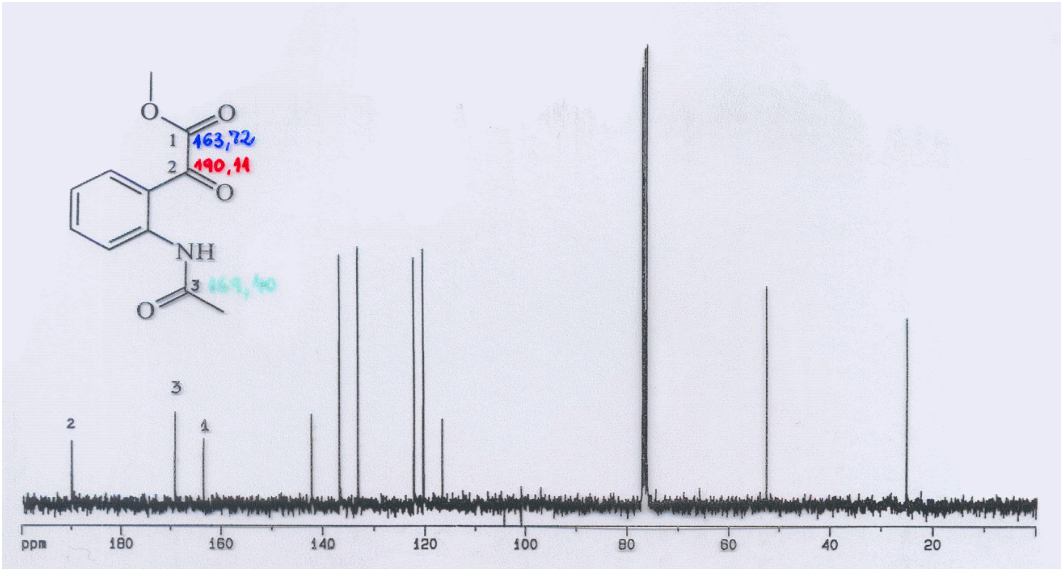

Figure 3. $^{13}C\{H\}$ solution NMR spectrum obtained for compound **1.**

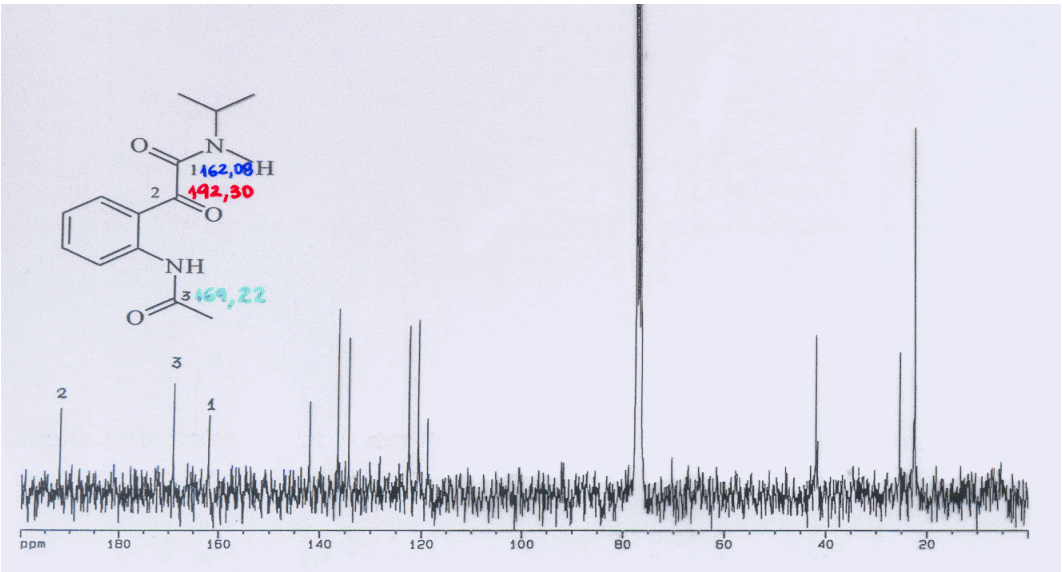

Figure 4. $^{13}C\{H\}$ solution NMR spectrum obtained for compound **2**.

As has been stated, NMR solid-state chemical shifts generally are very similar to those found in solution. Thus, CP/MAS can be a complementary analysis, filling in the gaps between data obtained by diffraction techniques on solid-state structures and on those in solution.[10] Figures 5 and 6 show ^{13}C-CP/MAS spectra obtained with a contact time of 2 ms for compounds **1** and **2**.

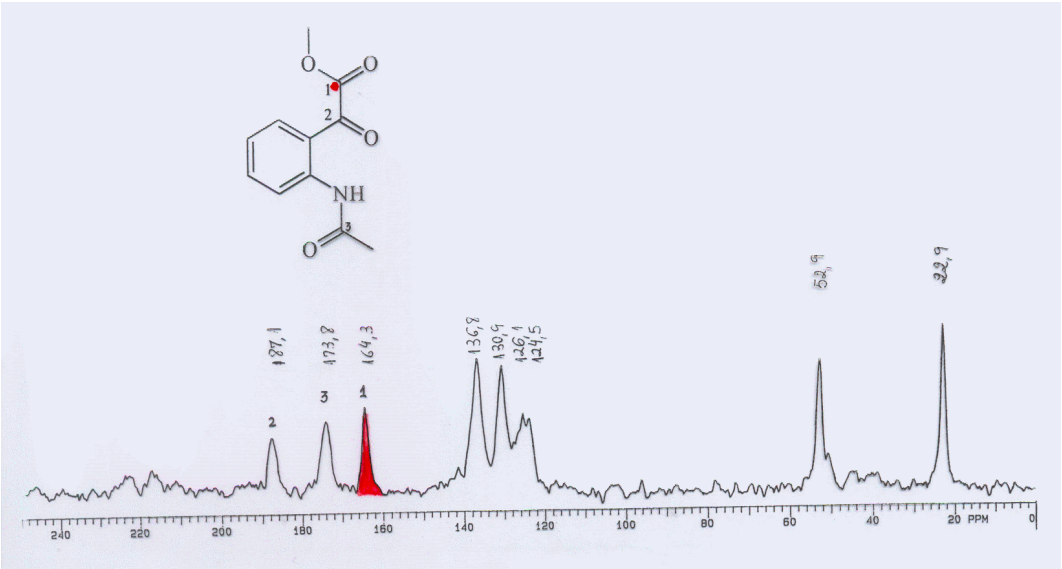

Figure 5. ^{13}C CPMAS solid state NMR spectrum obtained for compound **1.**

The ^{13}C CPMAS spectrum of **1** shows three signals in the region 160-190 ppm, corresponding to the three carbonyl groups presence. The difference of the chemical shifts measured in solution and in solid state, lower than 4 ppm indicates that for compound **1** the same conformation would be present in the liquid and solid state. An interesting result is revealed in the 200-150 ppm spectral region for compound **2**. In contrast with the result obtained for compound **1**, the ^{13}C CPMAS spectrum showed four signals (Figure 6).

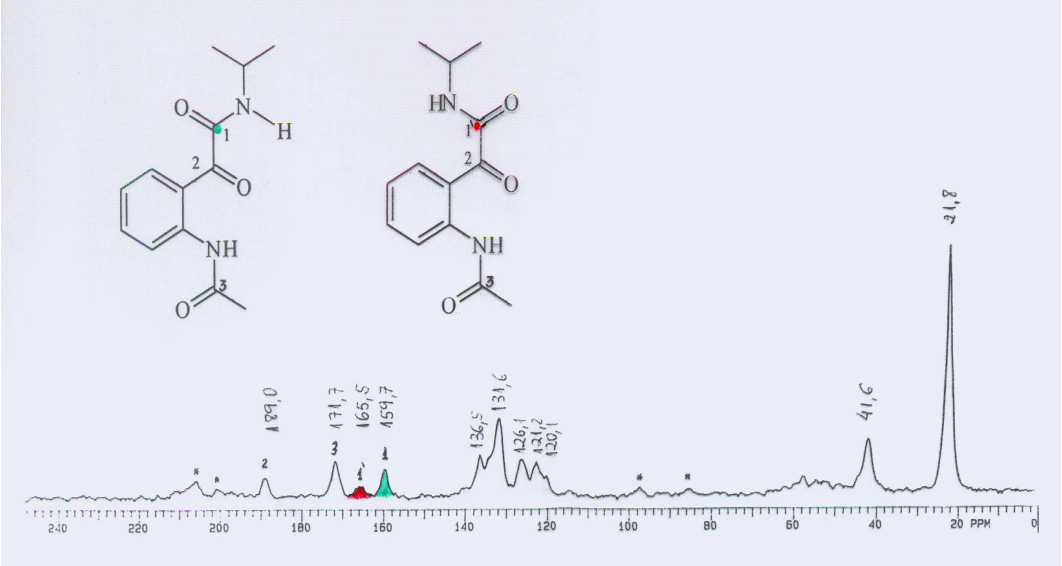

Figure 6. ^{13}C CPMAS solid state NMR spectrum obtained for compound **2.**

There is no change in the chemical shifts of these signals when the spinning speed was varied, and variation of the intensity of the four signals with the contact time (Figure 7) is a support for the assumption that we are observing four non-equivalent carbonyl signals, contrary to what is found for the solution NMR spectrum. The presence of these different carbonyl resonances reflects the existence of at least two distinct conformers for this compound. ^{13}C NMR chemical shifts values for carbonyls of compounds **1** and **2** in the solid state and in solution state are shown in Table 1.

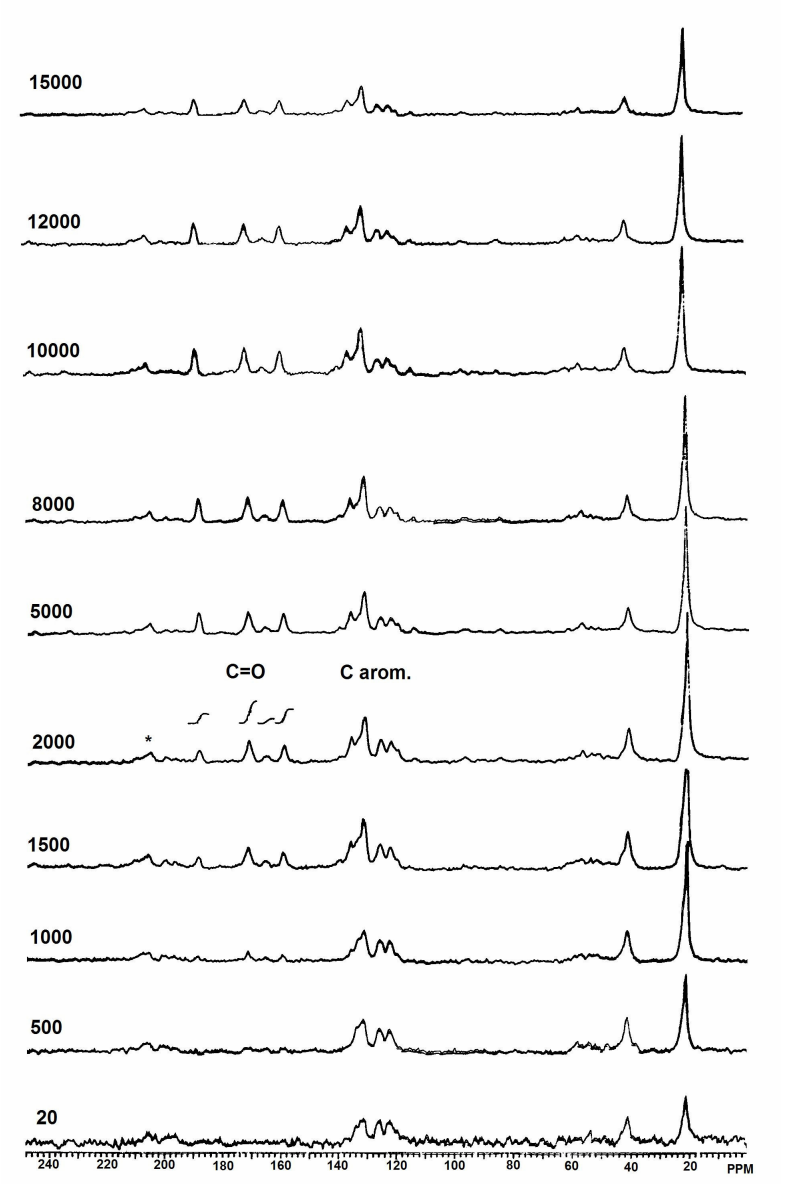

Figure 7. Solid state ^{13}C CPMAS spectra obtained with variation in contact time (μs) for compound **2**.

Table 1. ^{13}C chemical shifts (ppm) for the carbonyl region, obtained for compounds **1** and **2**, in solution and in the solid state.

compound	chemical shift (δ, ppm) solution	solid state	assignment
1	163.72	164	O=C_1 (S-trans)
	169.40	174	O=C acetyl group
	190.11	187	O=C_2
2	162.08	160	O=C_1 (S-cis)
	-	166	O=C_1 (S-trans)
	169.22	172	O=C acetyl group
	192.30	189	O=C_2

The existence of different conformational forms for compound **2** is also shown in the region corresponding to phenyl ring carbons (145-120 ppm). Although resolution is poor, at least five signals could be observed for this compound (but only four for compound **1**). The variation of signal intensities with contact time permitted us to stablish the the carbonyl $O=C_1$ (Figure 8, data **X**) presented a higher signal intensity than the $O=C_2$ carbonyl (Figure 8, data ◆), and similar to the O=C from acetal carbonyl (Figure 8, data ■). On the other hand, for compound **2** (Figure 9, data **X**), the same $O=C_1$ carbonyl signal showed lower intensity, compared with the signal from the acetyl carbonyl group (Figure 9, data ■).

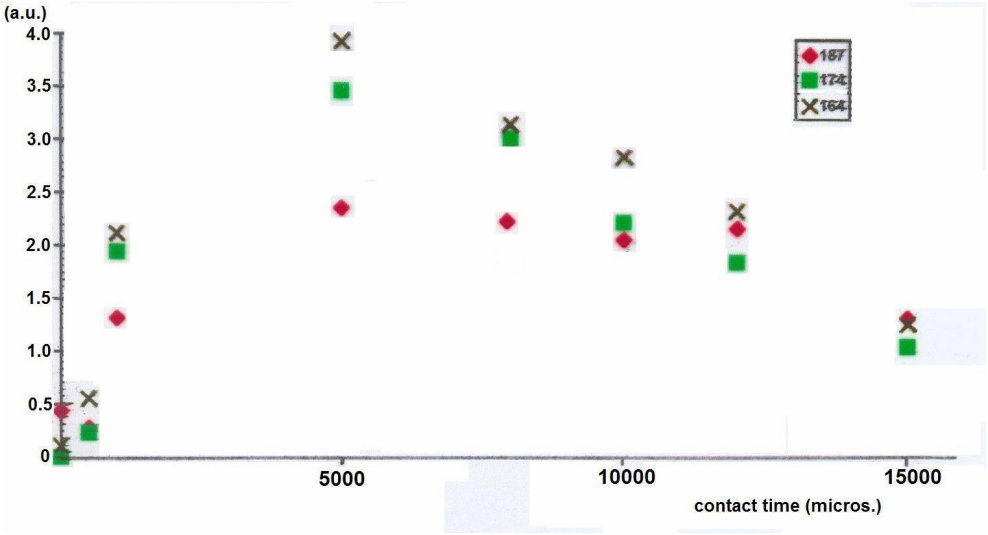

Figure 8. Variation in the intensity signal (arbitrary unities) in function of contact time (in μs), obtained for compound **1**.

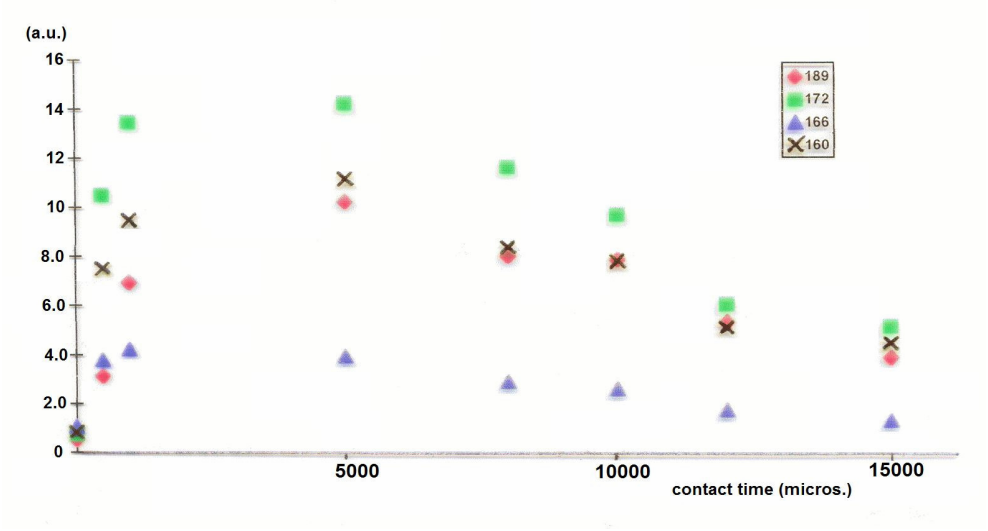

Figure 9. Variation in the intensity signal (arbitrary unities) in function of contact time (in μs), obtained for compound **2**.

In order to confirm that for compound **2** two different conforms are in fact present, we added the areas corresponding to S-cis and S-trans signals (Figure 9, data ◆ plus data ▲, equals data **X** in Figure 10). The polarization dynamic curves resulted similar to that observed for the polarization dynamic for compound **1** (comparison of Figures 8 and 10). Considering that carbonyl carbons of comformers S-cis and S-trans cross-polarize at the same rate, we were able to determine the amount of S-cis and S-trans conformer by measuring the area of the corresponding resonance lines. The proportions of the corresponding carbonyl groups, deduced from the line areas, indicate that the carbonyl group corresponding to S-trans isomer is aprox. 25% of the total present in the sample of compound **2** in solid state.

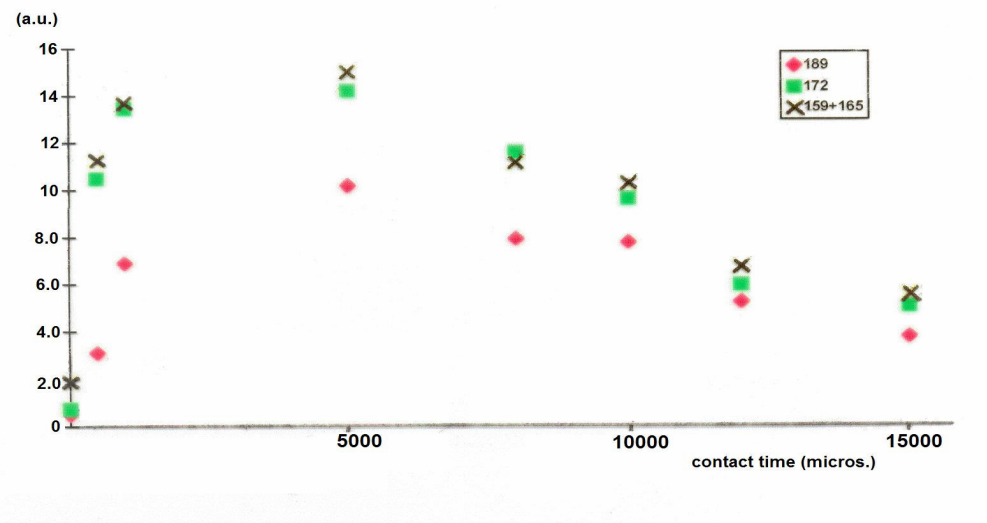

Figure 10. Variation in the intensity signal (arbitrary unities) in function of contact time (in μs), obtained for compound **2**; the areas of the signals at 160 and 166 ppm (S-cis and S-trans) were added.

Conclusion

The conformation of substituted isatins revealed by ^{13}C solid state NMR depends upon the nature of the substituent. In the ester derivative, only one kind, S-cis conformer, is present, both in solution and in solid state. In the amide derivative, two kinds of conformer, S-cis and S-trans are present at room temperature. In contrast, the X-ray crystal structure of compounds **1** and **2** shows only one conformer, S-cis for **1** and S-trans for **2**.

Acknowledgements

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