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A ^{13}C NMR study of the structure of four cinnamic acids and their methyl esters

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Abstract

The ^{13}C NMR spectra, both in DMSO solution and in the solid state of four cinnamic acids (*p*-methoxy, *p*-hydroxy, *p*-methyl, *p*-chloro) and their corresponding methyl esters have been recorded. The two main results in the solid state are: (i) the only significant difference between acids and esters chemical shifts concerns the C=O group which, on average, appears at 173 ppm in the acids and 168 ppm in the esters; (ii) the signals of the *ortho* and *meta* carbons both in the acids and the esters are splitted. The two 'anomalies' disappear in DMSO solution. These observations can be rationalized using simple GIAO/B3LYP/6-31G* calculations.

Keywords: Cinnamic acids; Cinnamic esters; Solid state NMR; ^{13}C NMR; GIAO calculations

1. Introduction

We selected for a structural study using ^{13}C NMR spectroscopy (in solution and in the solid state, CPMAS) four cinnamic acids whose X-ray structures were known [1]: **1a** *p*-methoxy (MXCINN) [2], **2a** *p*-hydroxy (COUMAC01) [3], **3a** *p*-methyl (JADVUF) [4] and **4a** *p*-chloro (PCTCIN) [5]. All these compounds crystallize as dimers **I**, often with dynamic proton disorder, as usually carboxylic acids do [6]. Compounds **1a** and **4a** are disordered, while compounds **2a** and **3a** exist in the ***IZZ*** conformation, at least predominantly. When the *para*-substituent can adopt two conformations, namely methoxy and hydroxy, it is planar and on the same side as the acrylic chain with regard to the phenyl ring. We have also synthesized and studied the corresponding methyl esters, **1b**–**4b**, for comparative purposes: no X-ray structure of the esters has been reported [1]. The eight compounds have been and still are the subject of great interest mainly for their properties (note that compound **2b** is known as methyl *p*-coumarate). Related to these compounds are BSB, used for imaging Azheimer's plaque [7], and the *trans*-cinnamides used for control of solid state photodimerizations [8].

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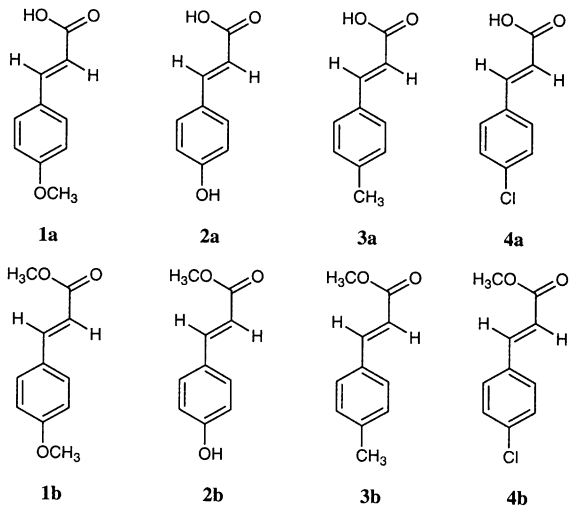
Table 1
^{13}C chemical shifts of cinnamic acids (in ppm). In bold, splitted signals and splitting in ppm

Compound	Cond.	CO_2H	CH(CO)	CH(Ar)	C_{ipso}	C_{ortho}	$C_{ortho'}$	C_{meta}	$C_{meta'}$	C_{para}	*p*-R
1a	Solid	173.4	117.9	144.6	125.5	**128.6**	**132.9**	**111.9**	**117.9**	162.1	55.5 (MeO)
	splitting, $\Delta\delta$					**4.3**		**6.0**			
1a	DMSO	167.9	116.5	143.8	126.9	130.0	130.0	114.4	114.4	161.0	55.3 (MeO)
2a	Solid	172.1	117.0	146.8	127.3	**127.3**	**136.2**	**114.4**	**117.0**	157.1	–
	splitting, $\Delta\delta$					**8.9**		**2.6**			
2a	DMSO	168.0	115.4	144.3	125.3	130.2	130.2	115.8	115.8	159.7	–
3a	Solid	173.2	117.2	146.1	130.8	**126.6**	**132.3**	**129.7**	**130.8**	142.3	21.6 (Me)
	splitting, $\Delta\delta$					**5.7**		**1.1**			
3a	DMSO	167.8	118.1	144.0	131.6	128.3	128.3	129.6	129.6	140.2	21.1 (Me)
4a	Solid	174.7	117.2	146.1	131.2	**128.4**	**133.6**	**128.4**	**128.4**	133.6	–
	splitting, $\Delta\delta$					**5.2**		**0.0**			
4a	DMSO	167.5	120.1	142.6	133.2	130.0	130.0	129.0	129.0	134.8	–



1a **2a** **3a** **4a**

1b **2b** **3b** **4b**

2. Experimental

The cinnamic acids **1a**–**4a** are commercially available (Aldrich). The esters **1b**, **3b** and **4d** were prepared by methylation (methyl sulfate, K_2CO_3, acetone at reflux) of the corresponding cinnamic acids **1a**, **3a** and **4a**. Ester **2b** was prepared from 4-hydroxycinnamic acid **2a** by a sequence of transformations: benzylation (benzyl chloride, K_2CO_3, DMF at reflux), saponification (aqueous NaOH and methanol heated at 70°C), methylation (methyl sulfate, K_2CO_3, acetone at reflux) and debenzylation (3:1 mixture of acetic/concentrated hydrochloric acid heated at 70°C) reactions.

The one-dimensional ^{13}C NMR spectra were obtained in DMSO-d_6 solutions at room temperature on a Bruker AMX 300 spectrometer working at 75 MHz. All the chemical shifts are expressed in parts per million reported to external TMS. ^{13}C assignments were made using HETCOR and HMBC experiments (delay for long-range *J* C/H couplings were optimized for 7 Hz). ^{13}C NMR CPMAS spectra were recorded at 100 MHz on a Bruker MSL 400 spectrometer using 5 s of recycle delay, a 90° pulse of 4.2 μs, SW = 300 ppm and AQ = 41 ms.

All the calculations have been performed with the GAUSSIAN 98 package [9]. Full geometry optimization has been carried out at the B3LYP/6-31G* level [10–12] maintaining a symmetry plane for all the systems considered. The absolute NMR shieldings have been calculated with the GIAO method [13,14] at the mentioned computational level.

3. Results and discussion

The ^{13}C chemical shifts of the eight compounds are gathered in Tables 1 (acids) and 2 (esters). The two CH carbons of esters **1b**, **3b** and **4b** have already been reported by Brazilian authors [15]. Leaving aside, for the moment, the splitting observed in the solid state for *ortho* and *meta* carbons of almost all compounds (only the *meta* carbons of **4a** and **4b** coincide), the

Table 2
^{13}C chemical shifts of methyl cinnamates (in ppm). In bold, splitted signals

Compound	Cond.	CO_2Me	CH(CO)	CH(Ar)	C_{ipso}	C_{ortho}	$C_{ortho'}$	C_{meta}	$C_{meta'}$	C_{para}	*p*-R and CO_2Me
1b	Solid	167.4	116.8	143.0	126.7	**127.3**	**134.6**	**109.7**	**117.7**	161.0	54.8 (MeO)
	splitting, $\Delta\delta$					**7.3**		**8.0**			
1b	DMSO	167.1	115.1	144.4	126.7	130.2	130.2	114.4	114.4	161.2	55.3 (MeO)
											51.4 (CO_2Me)
2b	Solid	169.8	115.5	145.7	127.3	**124.8**	**134.2**	**113.8**	**115.5**	159.1	–
	splitting, $\Delta\delta$					**9.4**		**1.7**			
											53.8 (CO_2Me)
2b	DMSO	167.2	114.0	144.9	125.1	130.5	130.5	115.9	115.9	160.0	51.4 (CO_2Me)
3b	Solid	167.5	116.7	146.8	131.7	**125.7**	**131.7**	126.5	131.7	140.8	21.1 (Me)
	splitting, $\Delta\delta$					**6.0**		**5.2**			
											50.8 (CO_2Me)
3b	DMSO	166.9	116.7	144.7	131.3	128.5	128.5	129.6	129.6	140.6	21.1 (Me)
											51.5 (CO_2Me)
4b	Solid	167.7	118.0	144.5	132.8	**127.4**	**136.9**	**127.4**	**127.4**	136.9	–
	splitting, $\Delta\delta$					**9.5**		**0.0**			
											53.9 (CO_2Me)
4b	DMSO	166.6	118.7	143.2	133.0	130.2	130.2	129.0	129.0	135.1	–
											51.6 (CO_2Me)

Table 3
^{13}C absolute shieldings σ and estimated ^{13}C chemical shifts δ (both in ppm) of cinnamic acids. The predicted values are in italics

Compound	CO_2H	CH(CO)	CH(Ar)	C_{ipso}	C_{ortho}(C=C)	$C_{ortho'}$(CH)	C_{meta}(C=C)	$C_{meta'}$(CH)	C_{para}	*p*-R	
1a*E*	σ	33.31	84.07	48.68	69.12	68.78	60.87	85.65[a]	78.03	36.72	137.20 (MeO)
	δ	164.6	111.1	148.4	126.8	*127.2*	*135.5*	*109.4*	*117.4*	161.0	55.1
	$\Delta\delta$					**8.3**		**8.0**			
	$\delta_{average}$					131.4		113.4			
2a*E*	σ	33.39	84.03	48.99	69.14	68.97	59.95	81.90[a]	80.69	39.58	–
	δ	164.5	111.1	148.0	126.8	*127.0*	*136.5*	*113.4*	*114.6*	158.0	
	$\Delta\delta$					**9.5**		**1.2**			
	$\delta_{average}$					131.8		114.0			
3a*E*	σ	33.35	82.12	48.20	64.41	70.70	62.32	66.35	66.98	54.85	167.57 (Me)
	δ	164.5	113.1	148.9	131.8	*125.2*	*134.0*	*129.7*	*129.1*	141.9	23.1
	$\Delta\delta$					**8.8**		**0.6**			
	$\delta_{average}$					129.6		129.4			
3a*Z*	σ	34.74	80.20	50.44	64.27	70.80	62.83	66.60	67.02	54.97	167.61 (Me)
	δ	164.2	114.9	147.4	131.9	*125.1*	*133.5*	*129.5*	*129.0*	141.7	23.0
	$\Delta\delta$					**8.4**		**0.5**			
	$\delta_{average}$					129.3		129.2			
4a*E*	σ	33.67	80.43	49.60	63.66	70.05	61.84	66.76	66.74	50.22	–
	δ	164.2	114.9	147.4	132.6	*125.8*	*134.5*	*129.3*	*129.3*	146.7	
	$\Delta\delta$					**8.7**		**0.0**			
	$\delta_{average}$					130.2		129.3			

[a] Same side as the Me (or H) of the OMe (or OH) group.

chemical shifts in solution and in the solid state are very similar. If we average the calculated absolute shieldings of *ortho* and *meta* carbons, the only differences affect the C=O carbon of the carboxylic groups (not that of the ester groups). If these four signals are excluded, Eq. (1) is obtained.

$$\delta^{13}C_{solid} = (1.0025 \pm 0.0016)\delta^{13}C_{solution}, \qquad n = 54, \quad R^2 = 0.9999 \tag{1}$$

This equations predicts for the carboxylic groups in the solid state values close to 168.2 ppm, that is, 5.2 ppm higher field than the average experimental values (173.4 ppm).

Therefore, both acids and esters behave normally in the solid state and only two aspects of the CPMAS spectra deserve further study: (i) the 'anomalous' C=O chemical shift *of acids*; (ii) the splitting of carbons *ortho* and *meta both in acids and esters* as well as their assignment; note that the average value of the splitted signals coincides with the value in solution.

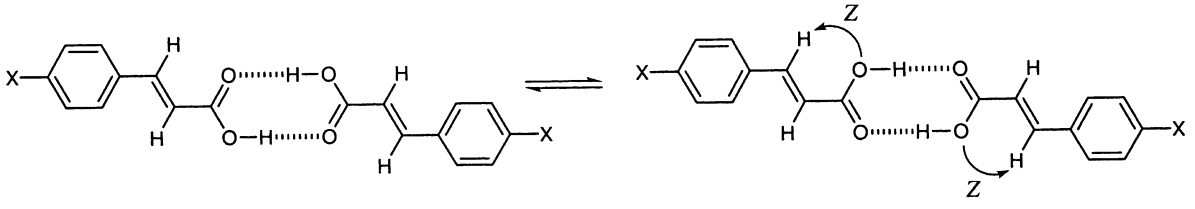
With this aim we carried out a series of GIAO/B3LYP/6-31G* calculations on compounds **1a**, **2a**, **3a** and **4a**. This level is sufficient for our purposes. For compounds **1a**, **2a** and **4a** we used the ***E*** conformations while for compound **3a** we calculated the two conformations, **3a*E*** and **3a*Z***. In the case of **1a*E*** and **2a*E*** the calculated conformation of the methoxy and hydroxy groups are as represented (Me and H on the same side as the CH=CH–CO_2H moiety) because they are like this in the crystal (MXCINN [2] and COUMAC01 [3]). The absolute shieldings are reported in Table 3.

The differences between the calculated absolute shieldings of **3a*Z*** and **3a*E*** are too small to be relevant for our purpose; therefore for the other compounds we have calculated only the ***E*** isomers. At this level of the theory, $\sigma_{TMS} = 189.69$ ppm while, experimentally, Jameson has measured $\sigma_{TMS} = 188.1 \pm 0.9$ ppm [16,17]. A linear regression of experimental values in DMSO solution against absolute shieldings (for *ortho* and *meta* carbons, average values), leads to Eq. (2).

$$\delta^{13}C_{solution} = (199.7 \pm 1.2) - (1.054 \pm 0.015)\sigma^{13}C, \qquad n = 39, \quad R^2 = 0.992 \tag{2}$$

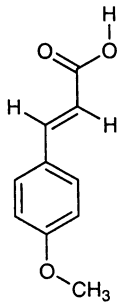
In Table 3 we have also reported the fitted and predicted (underlined) values using Eq. (2). Concerning the fitted values, they reproduce reasonably well the values in solution (compare Tables 1 and 3). There are some differences that can be assigned to the moderate level of the calculations, for instance, C_{para} of **4a** appears at about 135 ppm (Table 1) whilst the calculations correspond to 147 ppm, obviously the *ipso* chlorine effect is not well reproduced. Three carbon atoms deviate systematically: C=O (~3 ppm), CH(CO) (~5 ppm) and CH(Ar) (~ − 5 ppm).

To discuss the chemical shifts of the –CH=CH–CO_2H moiety, we need to take into account the dimerization of carboxylic acids in the solid state as well as their strong hydrogen bonds with DMSO in solution [18]. First we have compared the absolute shieldings of formic acid **5** and its dimer **5/5** and transformed them into δ values by means of Eq. (2). On dimerization, the carbon of formic acid moves from 154.3 to 163.7 ppm ($\Delta\delta = 9.4$ ppm). This explains why the calculated values (monomers, Table 3) are about 163–164 ppm and the solid state data (dimers, Table 1) are close to 173 ppm in the solid state. In solution, an intermediate situation is found (168 ppm) which should correspond to hydrogen bonds with DMSO.

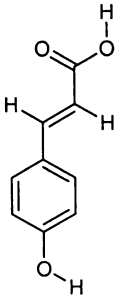


I*EE* **I*ZZ***

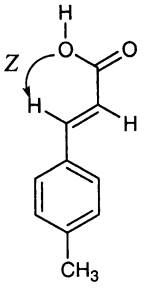
Then, we have studied the effect of the dimerization on acrylic acid **6** to find out if the effect of its dimerization, **6/6**, extends over the olefin moiety. According to the calculations (σ values transformed into δ through Eq. (2)), the C=O moves from 161.8 to 169.3 ppm ($\Delta\delta = 7.5$ ppm), the CH(CO) from 125.2 to 127.9 ($\Delta\delta = 2.7$ ppm) and the terminal CH_2 remains unchanged (134.0 and 133.8 ppm). Although, qualitatively, these effects correspond to those observed when Tables 1 and 3 are compared, we decided to study a more related model: a dimer of cinnamic and formic acids, **3a*E*/5**. The effects (again transformed into δ values through Eq. (2)) are +7.7 ppm for the C=O and +2.0 ppm for the CH(CO); all other signals are affected by less than 1 ppm.



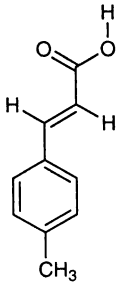
1a*E*



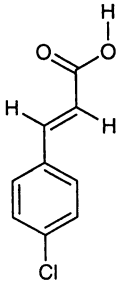
2a*E



3a*Z*



3a*E*



4a*E*

According to the calculations, the splitting of *ortho* and *meta* carbons can be analyzed, in a first approximation, as coming independently from the acrylic substituent (C_{ortho}) and from the *p*-substituent (C_{meta}). The *ortho* carbon which is on the same side as the $-CH=CH-CO_2R$ residue appears at 125–127 ppm and that on the other side at 134–136 ppm ($\Delta\delta = 8$–9 ppm) independently of the *p*-substituent (because *meta* effects are usually small). The *meta* carbon chemical shifts depend on the *p*-substituent (because *ortho* effects are large). In that case, two situations are possible: (i) the X substituent has an axial symmetry (CH_3 **3**, Cl **4**) and both *meta* carbons are very similar ($\Delta\delta$ null or very small); (ii) the substituent has two planar conformations with regard to the phenyl ring (OCH_3 **1**, OH **2**). According to the calculations, the difference is large in the case of the methoxy ($\Delta\delta = 8.0$ ppm) and small in the case of the OH ($\Delta\delta = 1.2$ ppm). All these conclusions agree fairly well with the experimental observations.

4. Conclusions

Simple GIAO calculations allow to rationalize the splittings observed for *ortho* and *meta* carbons of cinnamic acids in the solid state. In solution, the free rotation about the single bonds linking the phenyl ring to $CH=CH-CO_2R$ and X substituents suppresses the splitting averaging the signals. Moreover, the calculations allow an assignment of the splitted signals, thus offering an alternative to a problem of great experimental difficulty since it requires very large monocrystals (several millimeters) and an NMR instrument provided with a goniometer.

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