Oxalic acid/phenols and oxalic acid/cholesterol co-crystals: a solid state ^{13}C CPMAS NMR study

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Dedicated to Professor Irina Beletskaya on the occasion of her 75th anniversary

Abstract
The structures of the crystals obtained by mixing oxalic acid (**1**) and five hydroxy derivatives, phenol (**2a**), *p*-cresol (**2b**), hydroquinone (**2c**), β-naphthol (**2d**), and cholesterol (**2e**) have been studied by ^{13}C CPMAS NMR. It has been proved that they are co-crystals of defined stoichiometry (oxalic/hydroxy derivative) 1:2 (**1**/**2a**, **1**/**2b**, **1**/**2e**), 2:2 (**1**/**2c**), and 1:4 (**1**/**2d**).

Keywords: Co-crystals, NMR, CPMAS, oxalic acid, phenols, cholesterol

Introduction

In 1916 Antonio Madinaveitia published two papers in the Spanish journal *Anales de Química* (*Productos de adición del ácido oxálico* and *Sobre la separación de la colesterina y la isocolesterina*.) where he discussed the structure of the compounds that are formed when oxalic acid (**1**) is mixed with phenols or cholesterol (*C*-hydroxy compounds **2**).[1,2] These papers were really in advance to Madinaveitia's time since they involve two fundamental concepts: hydrogen bonds and co-crystals. The concept of hydrogen bonding was introduced by Huggins and by Latimer and Rodebush in 1919.[3] The notion of co-crystals is much more difficult to date because this term includes a variety of situations, considering any system in which the molecule of interest can be crystallized with some other molecular species in order to yield a unique structure. There are a number of terms that describe this class of structures: solvate, salt, clathrate, host–guest compound, inclusion compound, 1:1 addition compound, binary or ternary crystal, hydrate, and coordination complex. All of these can be classified under the single term 'co-crystal' because all of them describe ways of creating unique crystal structures that contain a selected species plus some other molecular component.[4] Nevertheless, co-crystals and crystal

engineering are very important fields in 2008 but almost unknown in 1916.[5]

Madinaveitia doubted between two structures **3** and **4** (Chart 1), which today's knowledge of hydrogen bonds (HBs) allows to be reduced to **4** (O–H···O HB). A search for oxalic co-crystals provided many examples but the hydrogen bond acceptor (HBA) is either a nitrogen base[6] or another carboxylic acid derivative (often amides).[7]

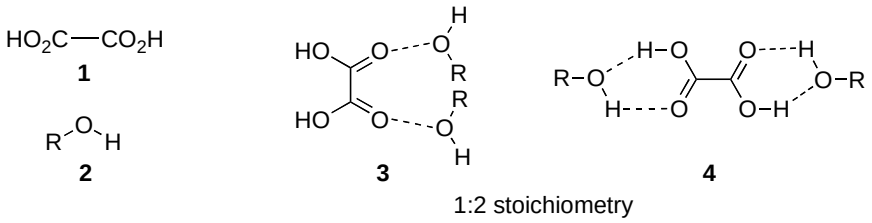

Chart 1. Structures **3** and **4** proposed by Madinaveitia in 1916 for the compounds obtained by mixing oxalic acid (**1**) and hydroxy derivatives **2**.

Examination of the Cambridge Structural Database (CSD),[8] led to the conclusion that there are no examples of co-crystals formed by oxalic acid and hydroxy derivatives (either alcohols or phenols), the closest structure are the hydrates (many structures, for an example see Chart 2).[9]

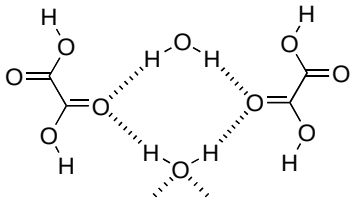

Chart 2. One of the oxalic hydrates.

Results and Discussion

Chart 3 shows the hydroxy derivatives studied by Madinaveitia.[1,2]

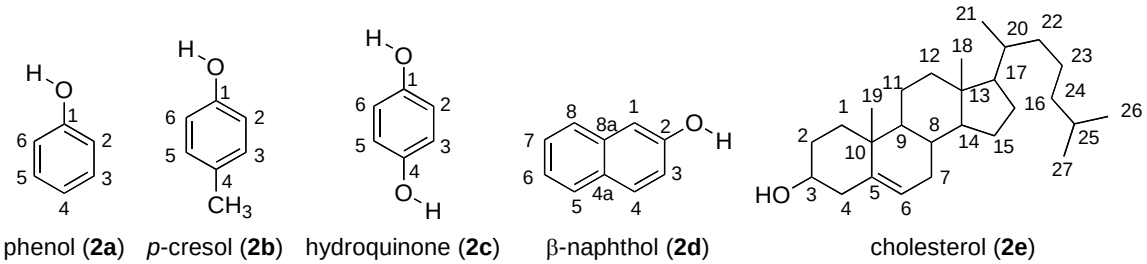

Chart 3. Compounds forming co-crystals with oxalic acid.

We have recorded the ^{13}C CPMAS NMR spectra of those hydroxy compounds that are solids: oxalic acid (**1**), hydroquinone (**2c**), β-naphthol (**2d**) and cholesterol (**2e**). Phenol (**2a**) melts at 40.5 ºC and *p*-cresol (**2b**) at 34.8 ºC, making them unsuitable for solid-state NMR at room temperature (the probe heats up during the experiment). Most of these compounds have been studied in solution and their signals have been assigned.[9–11] Oxalic acid (**1**) presents a single signal at δ 160.6 (Figure 1; in solution δ 160.1),[11] but hydroquinone (**2c**) shows a complex splitting pattern with signals at δ 152.0, 149.3, 148.8, 147.9, 120.0, 119.0, 118.0, 117.0 and 116.0 (shoulder) (Figure 2; in solution δ 151.5 and 118.5).[10]

The spectrum of β-naphthol (**2d**) (Figure 3) is very similar to that described in solution:[10] δ 111.8 and 109.0 (C1), 152.4 (C2), 116.0 (C3), 129.0 (C4), 128.1 (C5), 125.0 and 123.4 (C6), 128.1 (C7), 128.1 (C8), 128.1 (C4a) and 135.2 (C8a), some signals being clearly splitted.

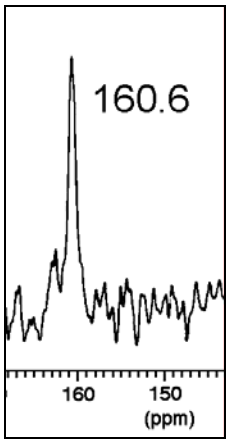

Figure 1. Oxalic acid (**1**).

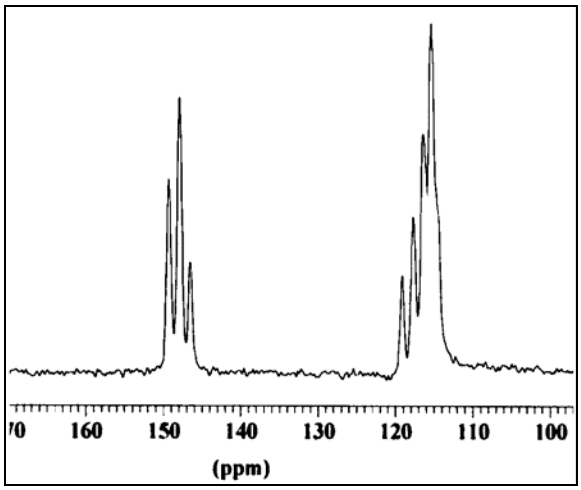

Figure 2. Hydroquinone (**2c**).

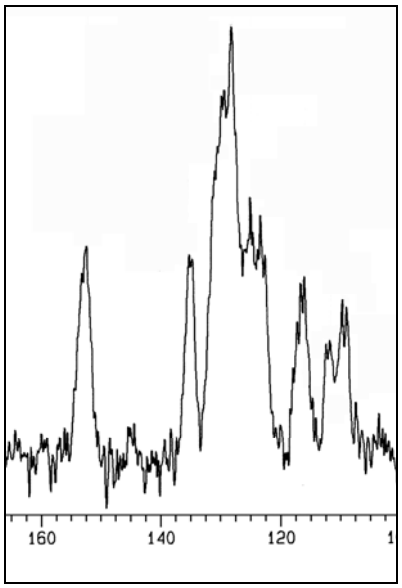

Figure 3. β-Naphthol (**2d**).

^{13}C CPMAS NMR data for cholesterol (**2e**) have already been published;[13] our spectrum is reported in Figure 4 and the chemical shifts in Table 1.

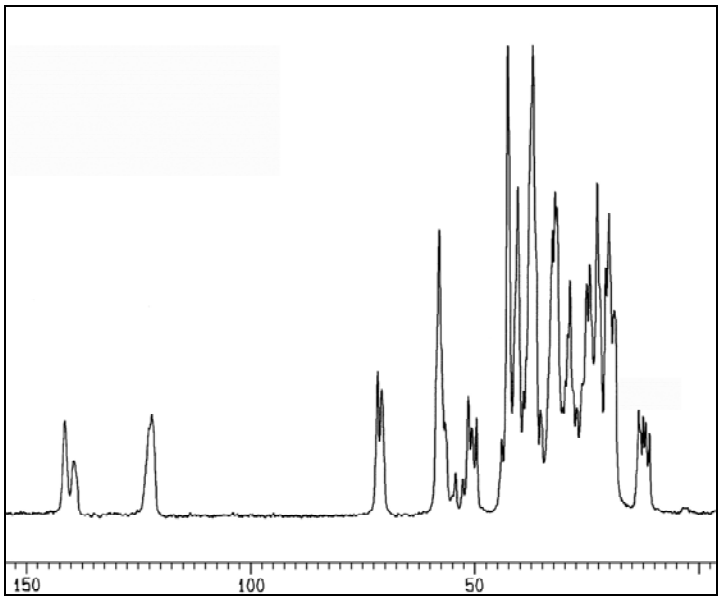

Figure 4. Cholesterol (**2e**).

Table 1. ^{13}C Chemical shifts of cholesterol (**2e**) and its adduct with oxalic acid (**1**)

Atom	Solution[10]	Solution[11]	CPMAS	**1**/**2e** (1:2)
1	37.8	37.5	37.3	39.1 and 38.4 (1:1)[a]
2	31.9	31.6	32.9, 32.4 and 32.0 (1:2:1)[a]	32.3 and 33.0 (3:1)
3	71.6	71.3	71.8 and 70.9 (1:1)	72.9 and 71.8
4	42.7	42.4	42.9	42.3 and 42.7
5	141.5	141.2	141.5 and 139.4 (2:1)	139.9
6	121.6	121.3	122.8 and 122.0 (1:1)	123.5 and 123.1 (1:1)
7	32.3	32.0	32.9, 32.4 and 32.0 (1:2:1)	32.3 and 33.0 (3:1)
8	32.3	160.5[b]	32.9, 32.4 and 32.0 (1:2:1)	32.3 and 33.0 (3:1)
9	50.8	50.5	51.6, 50.8 and 49.8 (2:1:2)	52.2 and 51.2 (1:1)
10	36.8	36.5	36.6 (two peaks)	37.9
11	21.5	21.2	21.2 and 22.4	22.1
12	28.6	28.3	29.0	29.9 and 30.7 (1:1)
13	42.7	42.4	42.9	42.3 and 42.7
14	57.2	56.9	58.1 and 57.6 (3:1)	57.1 and 58.1 (1:1)
15	24.6	24.3	25.3 and 24.6 (1:1)	26.9 and 27.2 (2:1)
16	40.3	40.0	40.7	41.5 and 41.0 (1:3)
17	56.8	56.5	58.1, 57.6, 56.7 (3:1:1)	58.2 and 57.1 (1:1)
18	12.3	12.0	13.7, 13.2, 12.7, 12.1, and 11.2	13.2 and 12.8 (1:1)
19	19.7	19.4	20.0 and 21.2 (1:2)	18.6 and 19.0 (1:1)
20	36.1	35.8	36.6 (two peaks)	36.9 and 36.4 (1:1)
21	19.1	18.8	18.8 (three peaks)	18.6 and 19.0 (1:1)
22	36.7	36.4	36.6 (two peaks)	37.5
23	24.4	24.1	24.6	24.3 and 24.7 (1:2)
24	39.9	39.6	39.3 and 38.8 (1:1)	40.3
25	28.3	28.0	29.0	28.7 and 29.5 (1:1)
26	22.8	22.5	23.0	23.5
27	23.1	22.8	24.5 and 25.3 (1:3)	23.5
Oxalic acid	166.3	160.1[12]	——	162.4 and 161.6

[a]Relative intensity of peaks. [b]Erroneous value in reference 11.

The methyl group at position 18 of cholesterol appears as a five-peak multiplet in the solid state (Figure 5) that probably corresponds to six different molecules with slightly different conformations (one of the methyl groups being under another signal). Other signals show lesser splitting, but considering the relative intensities the same explanation accounts. Cholesterol exhibits polymorphism[13] making it difficult to assign the CPMAS spectrum to a particular polymorph, one of them has $Z' = 8$ (eight independent molecules, codename CHOEST).[8]

Similarly, hydroquinone splitting (Figure 2) is also related to its polymorphism and the number of independent molecules (Z' = 3 for some of the polymorphs, codename HYQUIN).[8]

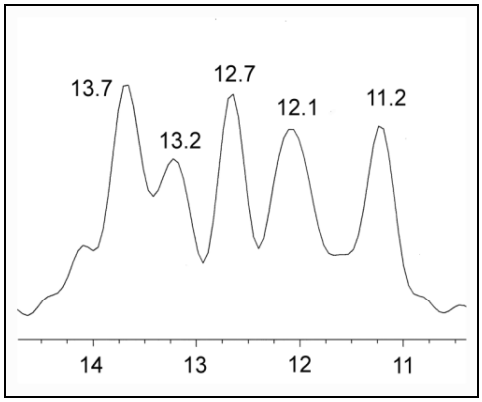

Figure 5. Signals of CH_3 at position 18 in **2e**.

The assignment of ^{13}C NMR signals to individual molecules of the unit cell is a difficult task that we have undertaken for camphopyrazole based on a pure statistical approach[14] or using GIAO calculated chemical shifts.[15]

Madinaveitia has carried out a large exploration on hydroxy derivatives in search for those that form co-crystals with oxalic acid; those that do not form addition compounds are primary, secondary, and tertiary aliphatic alcohols, thymol, eugenol, α-naphthol, pyrocatechol, resorcinol, orcin, pyrogallol, salicylic acid, *p*-hydroxybenzoic acid, *p*-hydroxybenzaldehyde, *p*-bromo-phenol, *o*-nitrophenol, *p*-nitrophenol, picric acid.[1] He has also reported that oxalic acid can be used to separate cholesterol (**2e**) (he named it "colesterin") from isocholesterol ("isocolesterin") because only the first one yields addition products with oxalic acid.[2]

We followed Madinaveitia's procedure:[1,2] both components were dissolved in diethyl ether, and the ether solutions were mixed. We used two stoichiometries, 1:2 (oxalic acid/C-hydroxy compound) and 2:2 (equimolar). Only in the case of **1**/**2c** (1:2) a solid precipitated. In the other cases, a solid was obtained by evaporating the solvent. Save for hydroquinone (**2c**), the 2:2 mixtures correspond to the sum of the 1:2 co-crystal + free oxalic acid, proving that the most stable stoichiometry is 1:2 for mono-OH compounds. Chart 4 presents the structures we propose for the identified complexes on the basis of the CPMAS NMR experiments.

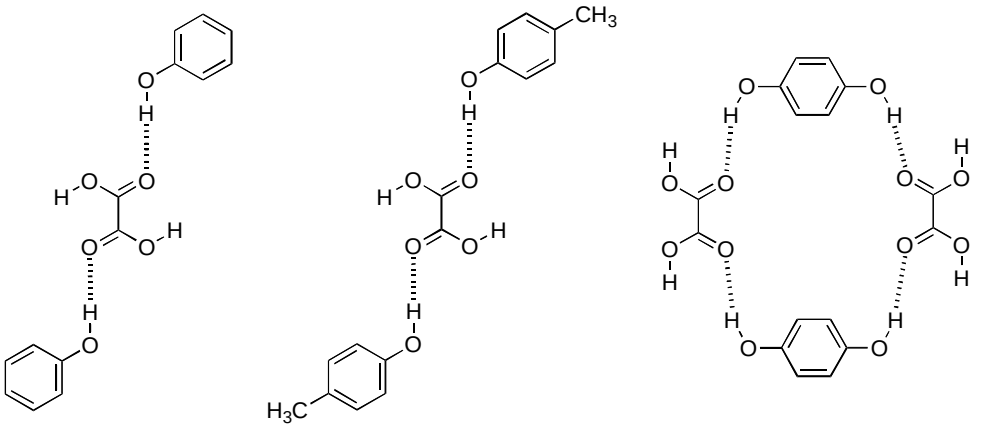

Chart 4. Proposed structures for the identified complexes.

Oxalic acid (**1**)/phenol (**2a**). ^{13}C CPMAS NMR spectra of 1:2 and 2:2 stoichiometries are shown in Figures 6 and 7, respectively. Oxalic acid exhibits two signals (free and complexed); this is of fundamental importance to establish the co-crystal nature of the 1:2 complex. The signals (Figure 6) appear at δ 160.3 (oxalic acid), 153.1 (C_{ipso}, in solution 155.1),[11] 129.2 (C_{meta}, in solution 130.1),[11] 120.9 (C_{para}, in solution 121.4)[11] and 115.0 (C_{ortho}, in solution 115.7).[11]

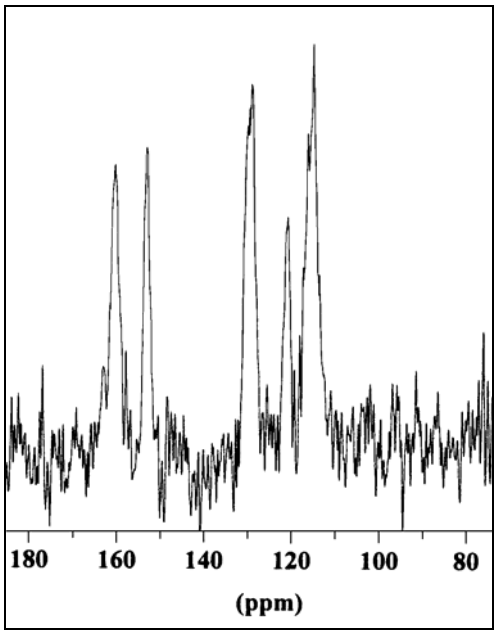

Figure 6. Oxalic acid (**1**)/phenol (**2a**) 1:2.

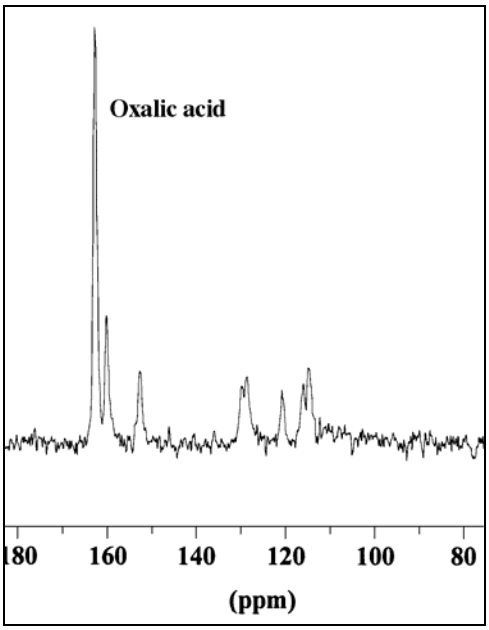

Figure 7. Oxalic acid (**1**)/phenol (**2a**) 2:2.

Oxalic acid (**1**)/*p*-cresol (**2b**). ^{13}C CPMAS NMR spectra (Figures 8 and 9) of the 1:2 and 2:2 stoichiometries are similar to the previous example. The signals in Figure 8: δ 159.9 (oxalic acid), 151.3 (C_{ipso}, in solution 152.6),[11] 129.4 (C_{para}, in solution 130.5)[11] 127.6 (C_{meta}, in solution 130.2),[11] 116.9 and 114.8 (C_{ortho}, in solution 115.3)[11] and 21.1 (methyl, in solution 20.6).[11]

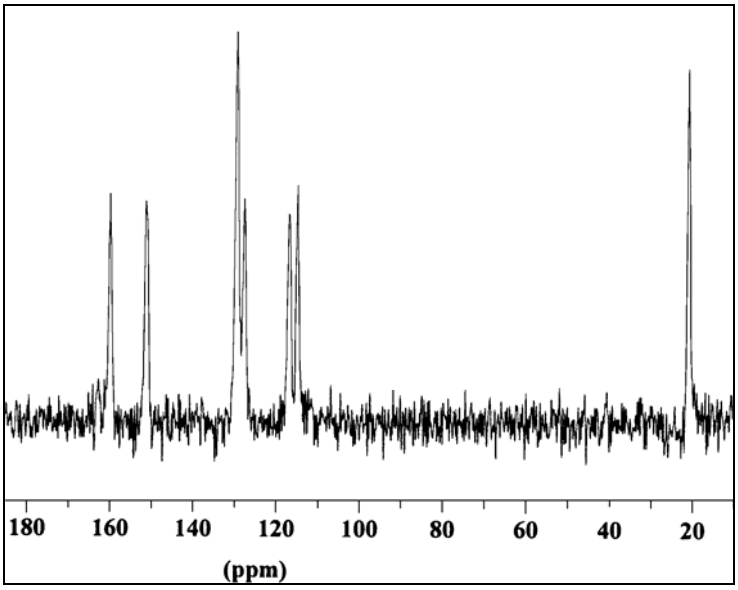

Figure 8. Oxalic acid (**1**)/*p*-cresol (**2b**) 1:2.

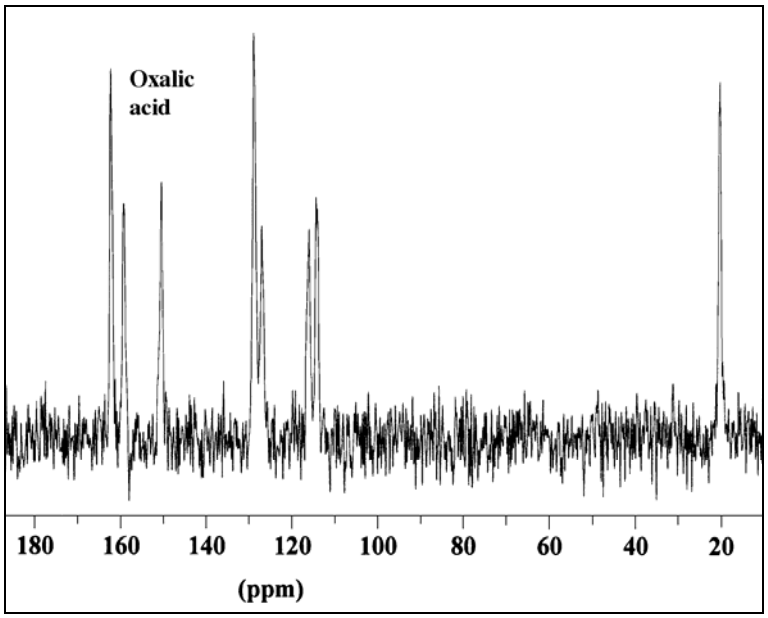

Figure 9. Oxalic acid (**1**)/*p*-cresol (**2b**) 2:2.

Oxalic acid (**1**)/hydroquinone (**2c**). The ^{13}C CPMAS NMR spectrum corresponding to the 2:2 stoichiometry is shown in Figure 10 with signals at δ 159.6 (oxalic acid), 147.0 (C_{ipso}, in solution 151.5)[11] and 116.2 and 114.7 ppm (C_{ortho}, in solution 118.5 ppm).[11] It is noteworthy that the five signals of C_{ortho} in hydroquinone (Figure 2) are reduced to only two, proving that the crystal structure has been modified in the co-crystal.

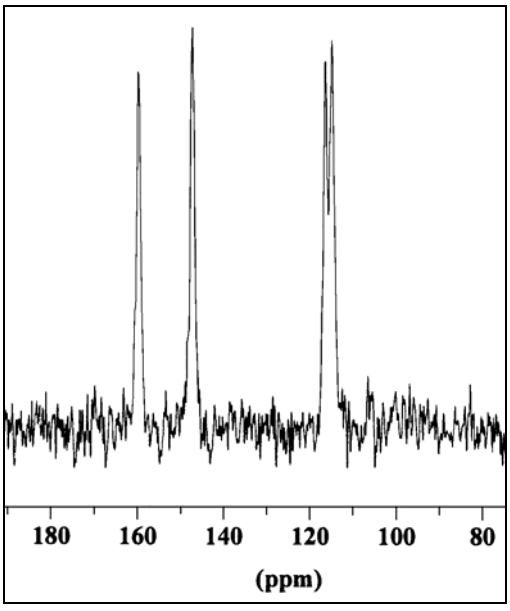

Figure 10. Oxalic acid (**1**)/hydroquinone (**2c**) 2:2.

Oxalic acid (**1**)/cholesterol (**2e**). The isolated complex has a 1:2 stoichiometry and probably a structure similar to one of those represented in Chart 4. The spectrum is reported in Figure 11 and the chemical shifts in Table 1.

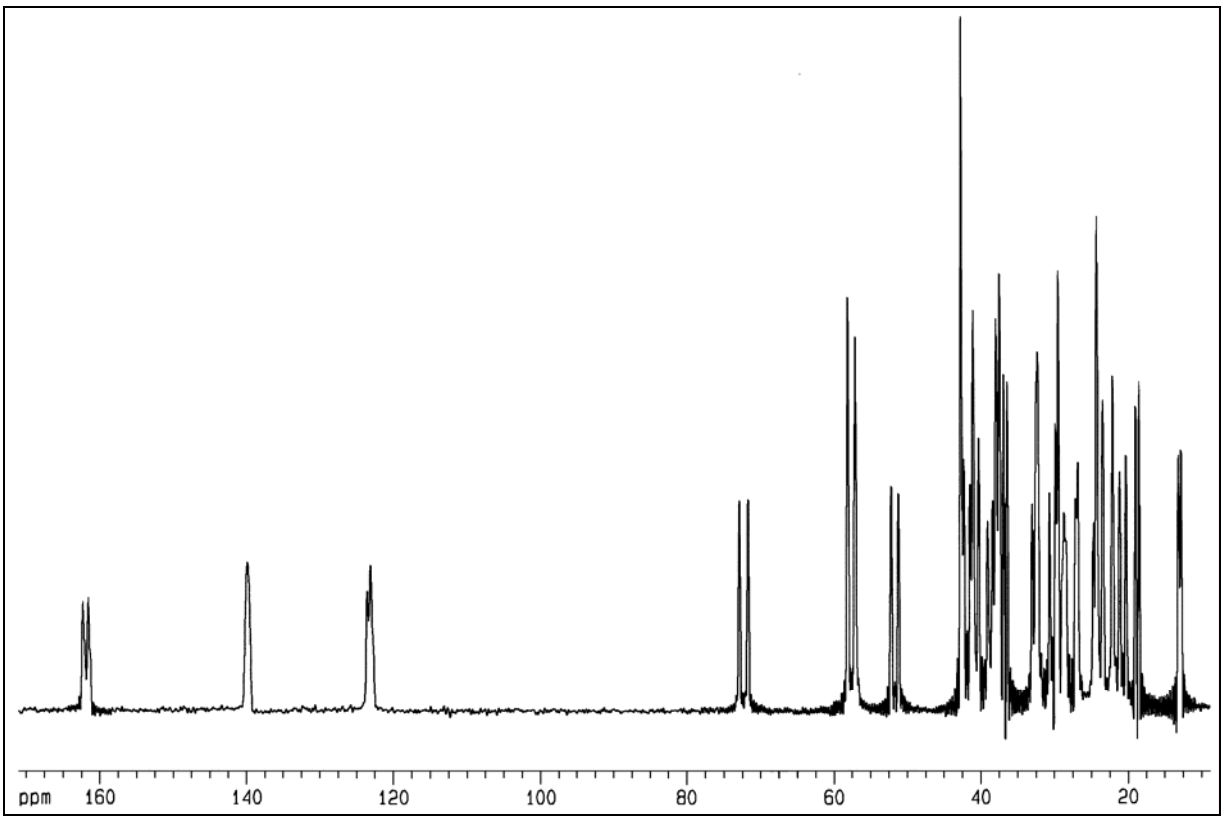

Figure 11. Oxalic acid (**1**)/cholesterol (**2e**) 1:2.

The case of β-naphthol is different from other mono-hydroxy compounds. The latter compounds crystallize as 1:2 complexes; however, the spectrum obtained with a 1:2 stoichio–metry of oxalic acid (**1**)/β-naphthol (**2d**) (Figure 12) shows the presence of free oxalic acid. It was only when a 1:4 stoichiometry was reached (Figure 13) that all oxalic acid was associated with **2d**. The signals shown in Figure 13 are reported in Chart 5 together with those in solution.[11]

Several structures can be conceived for a 1:4 complex of oxalic acid (**1**) and β-naphthol (**2d**), Chart 6 representing one of them.

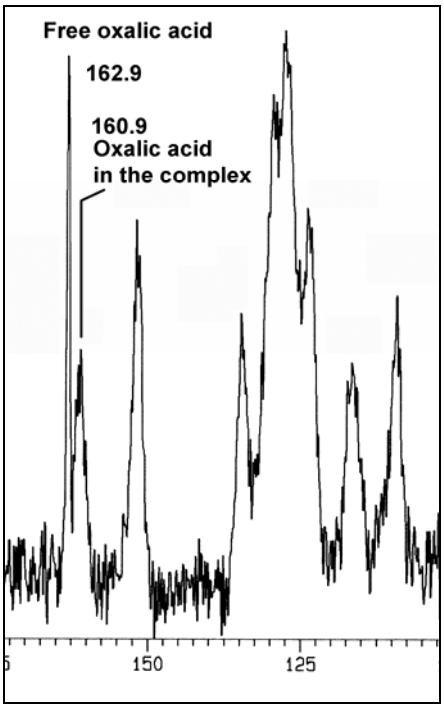

Figure 12. Oxalic acid (**1**)/β-naphthol (**2d**) (1:2).

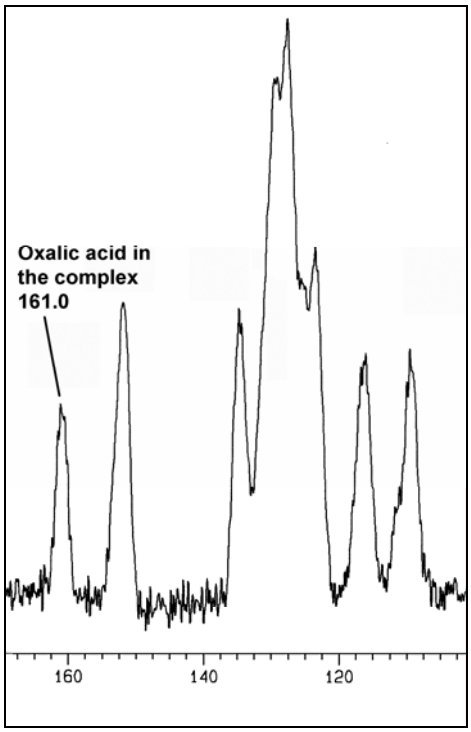

Figure 13. Oxalic acid (**1**)/β-naphthol (**2d**) (1:4).

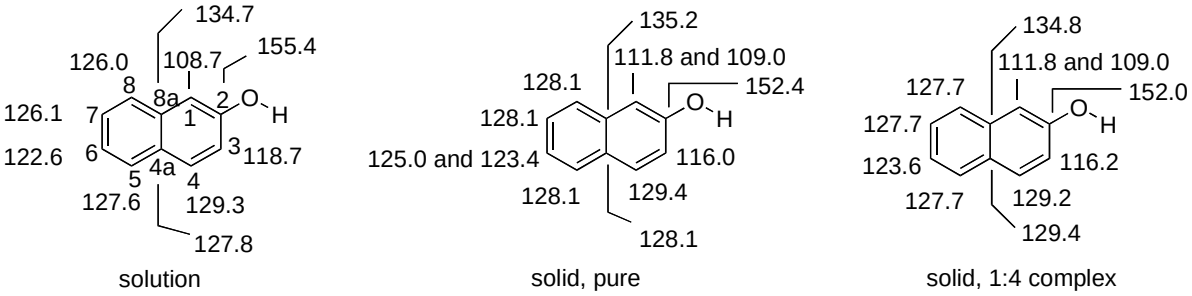

Chart 5. ^{13}C chemical shifts of β-naphthol (**2d**) in different states (the values in solution are those determined in DMSO-d_6 (100 mg in 0.6 mL), similar to those reported in the literature).[11,12]

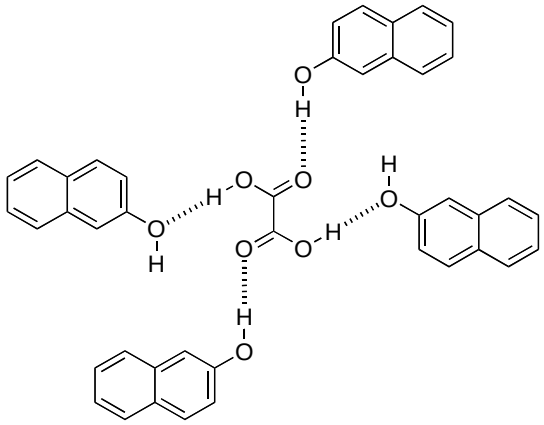

Chart 6. Possible structure of the 1:4 complex of **1** and **2d**.

Conclusions

^{13}C CPMAS NMR allows to determine two important features of the oxalic acid co-crystals: i. the fact that they are new supramolecular entities and not mixtures, and ii. the stoichiometries are (2:2, 1:2 and 1:4). On the other hand, in the absence of X-ray structures, the hydrogen bonds in Charts 4 and 6 are tentative.

Experimental Section

Materials. Commercially available oxalic acid (**1**), phenol (**2a**), *p*-cresol (**2b**), hydroquinone (**2c**), β-naphthol (**2d**) and cholesterol (**2e**) were used without further purification.

General Procedures. Diethyl ether solutions of components **1** and **2** were mixed, and the solvent was evaporated; the stoichiometry of the white solid obtained was checked by ^{1}H NMR in $CDCl_3$ solution (7–10 mg in 0.6 mL).

Oxalic acid (1)/phenol (2a) (1:2). By mixing solutions of **1** (90 mg, 1 mmol) in diethyl ether (3 mL) and **2a** (188.1 mg, 2 mmol) in diethyl ether (5 mL) followed by evaporation of the solvent.
Oxalic acid (1)/phenol (2a) (2:2). By mixing solutions of **1** (90.0 mg, 1 mmol) in diethyl ether (3 mL) and **2a** (94 mg, 1 mmol) in diethyl ether (5 mL) followed by evaporation of the solvent.
Oxalic acid (1)/p-cresol (2b) (1:2). By mixing solutions **1** (45 mg, 0.5 mmol) in diethyl ether (3 mL) and **2b** (108 mg, 1 mmol) in diethyl ether (5 mL) followed by evaporation of the solvent.
Oxalic acid (1)/p-cresol (2b) (2:2). By mixing solutions of **1** (90 mg, 1 mmol) in diethyl ether (3 mL) and **2b** (108 mg, 1 mmol) in diethyl ether (5 mL) followed by evaporation of the solvent.
Oxalic acid (1)/hydroquinone (2c) (2:2). By mixing solutions of **1** (90 mg, 1 mmol) in diethyl ether (3 mL) and **2c** (110 mg, 1 mmol) in diethyl ether (5 mL) followed by solvent evaporation.
Oxalic acid (1)/β-naphthol (2d) (1:2). By mixing solutions of **1** (45.0 mg, 0.5 mmol) in diethyl ether (3 mL) and **2d** (144 mg, 1 mmol) in diethyl ether (5 mL) followed by solvent evaporation.
Oxalic acid (1)/β-naphthol (2d) (1:4). By mixing solutions of **1** (45.0 mg, 0.5 mmol) in diethyl ether (3 mL) and **2d** (289 mg, 2 mmol) in diethyl ether (5 mL) followed by solvent evaporation.
Oxalic acid (1)/cholesterol (2e) (1:2). By mixing solutions of **1** (45.0 mg, 0.5 mmol) in diethyl ether (3 mL) and **2e** (386 mg, 1 mmol) in diethyl ether (5 mL) followed by solvent evaporation.

NMR parameters
Solution. The spectra were recorded in $CDCl_3$ at 300 K on a Bruker DRX 400 (9.4 Tesla, 400.13 MHz for ^{1}H) spectrometer with a 5-mm inverse-detection H-X probe equipped with a z-gradient coil for ^{1}H, ^{13}C and ^{15}N.
Solid state. ^{13}C (100.73 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 4-mm diameter cylindrical zirconia rotors 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 Me_4Si (for C atom $\delta_{glycine}$ 176.1). To assign the C atom signals in the solid state, non-quaternary suppression (NQS) experiments were run by conventional cross-polarization. Typical acquisition parameters for ^{13}C CPMAS were: spectral width, 40 kHz; recycle delay, 5 s; acquisition time, 30 ms; contact time, 2 ms and spin rate, 12 kHz.

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