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ORIGINAL ARTICLE

Supramolecular assemblies of Al^{3+} complexes with vitamin D_3 (cholecalciferol) and phenothiazine. Encapsulation and complexation studies in β-cyclodextrin

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Abstract Ternary assemblies of β-cyclodextrin with cholecalciferol (or vitamin D_3) or phenothiazine and Al^{3+} ions were studied. The stability constants of aluminium binary complexes with cholecalciferol or phenothiazine and of ternary assemblies (β-cyclodextrin, cholecalciferol or phenothiazine and Al^{3+}) were determined using potentiometric titrations at 25 °C ($I = 0.100$ M). The ^{13}C NMR spectra of the supramolecular structures in the solid state showed that ternary supramolecular structures associating β-cyclodextrin, cholecalciferol or phenothiazine and aluminium(III) ions were obtained. Finally, X-ray powder diffraction patterns showed that the ternary assemblies with phenothiazine are channel type inclusion complexes.

Keywords Ternary supramolecular assemblies · β-Cyclodextrin · Vitamin D · Phenothiazine · Aluminium

Introduction

Supramolecular binary or ternary assemblies are often used for various purposes. When organic compounds, like drugs, or inorganic cations are encapsulated in cyclodextrins as hosts, they may display new properties. Among cyclodextrins, β-cyclodextrins (β-CD) are the more often used mainly for studies in aqueous medium [1, 2]. So, β-CD are very common inclusion materials [3, 4] producing prodrugs able to deliver drugs under specific environmental conditions [5]. Modified cyclodextrins lead to inclusion complexes as well [6].

Binary assemblies where an organic substance is incorporated into the cyclodextrin cavity are the more often described and, for instance, there are some papers reporting inclusions complexes of vitamin D_3 or cholecalciferol (Vit D) [7]. On the opposite side, there are very few papers describing ternary supramolecular assemblies. Some articles dealt with ternary complexes associating β-CD, an organic molecule and a metal ion [8–11]. Recently, Marques et al. reported the inclusion of ruthenium(II) complexes in β-CD [12], while Ding et al. [13] published some ternary association with zinc(II). In this way, we have previously described the formation of ternary assemblies: β-CD:Vit D:metal ions (Co^{2+}, Cu^{2+}, Zn^{2+}), in which the molecular ratios were 5:1:1 or 10:1:1, respectively [14].

Al(III) compounds are involved in human health but they are also suspected in neurological disorders [15]. In

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the mean time, the Al^{3+} ion could be coordinated by cholecalciferol in ethanol–water medium [16]. In 2008, Dias et al. described ternary assemblies associating cyclodextrin and Al(III) with catechin or quercetin. Using IR and UV–Vis spectra, ^{1}H and ^{13}C NMR associated with TG and DTA, they concluded to 1:1 complex aluminium to β-cyclodextrin ratio [17].

Vitamin B_{10} could be included in β-CD, leading to 1:1 inclusion complex [18]. β-CD was also used to encapsulate hydrophobic drugs like indomethacin associated with water and ammonia [19, 20]. The complexation of an amphiphilic chiral derivative of phenothiazine (pheno) was described by Guerrero-Martinez et al. [21]. They concluded that the low flexibility of the cyclodextrin could lead to chiral recognition due to the existence of two binding sites on the β-CD molecules. Methylene blue and phenothiazine could also be included in β-cyclodextrin using sodium dodecyl sulfate micelles [22].

The aim of the present work was first to obtain prodrugs (using β-CD inclusion) able to deliver cholecalciferol or phenothiazine when useful. Phenothiazine is also an essential pharmacophore for some drug agents, especially tranquilizer drugs, and also may be a model of a polyaromatic substance, miming degradation products of some phytotoxic fertilizers. In the mean time, it should be efficient to complex aluminum to prevent environment from its contamination. The ternary assembly β-cyclodextrin, phenothiazine and Al^{3+} could be useful to extract toxic compounds from intensive agriculture and aluminium at once.

In this paper, we describe some new β-cyclodextrin ternary assemblies with aluminum(III) and cholecalciferol or phenothiazine. ^{13}C NMR spectra and XRD allowed us to determine the nature of these assemblies in the solid state. Using potentiometric titrations, the values of the binding constants of the various supramolecular binary and ternary assemblies were determined.

Experimental

Chemicals

All reagents were analytical grade and were used as received. Aluminium chloride standard solution, potassium chloride and absolute ethanol were Merck (Germany). Cholecalciferol, β-cyclodextrin hydrate and phenothiazine were Sigma-Aldrich (USA). Nitric acid, potassium hydroxide and potassium hydrogen phthalate were Riedel-de-Häen (Germany). KCl was Carlo Erba (Italy), Na_2EDTA was Reagen (Brazil), hexadeuterated dimethyl sulphoxide DMSO-D_6 (99.9 %) and TMS (sodium-3-trimethylsilylpropionate) were Cambridge Isotope Laboratories, Inc. (USA). $ZnSO_4$ and dithizone were Merck (Germany). Water used was bidistilled in a quartz bidistillator (Tecnal, Brazil) and deionized in a cationic exchange column and freshly boiled.

Synthesis of the supramolecular assemblies of β-cyclodextrin

An amount of 0.02 or 0.04 mmol of Vit D or phenothiazine (pheno) were dissolved in absolute EtOH (25 mL). 0.2 mmol of β-CD previously dissolved in water (25 mL) were mixed with magnetic stirring under N_2 atmosphere whenever Vit D were present, for at least 4 h. When the synthesis were made in the presence of Al^{3+}, the same ratios used for the previous reagents were maintained and the metal ion quantity was identical to the quantity of added guest (0.02 or 0.04 mmol) and the pH set to the 4.5–5.5 range [14]. The obtained complex assemblies were then β-CD:pheno:Al^{3+} or β-CD:Vit D:Al^{3+} with the following molar ratios: 10:1:1 and 5:1:1 when 0.04 or 0.02 mmol were added of both pheno or Vit D and Al^{3+}, respectively.

The supramolecular assemblies were dried in a rotary evaporator (Fisatom, Brazil) under vacuum until the solids were completely dried. They were finally stocked in small closed glasses, in a dessiccator.

Potentiometric titrations

Potentiometric titrations were carried out in triplicate under N_2 atmosphere and at constant temperature 25.0 ± 0.1 °C (Thermostated bath MQBTC 99–20, Microquímica, Brazil) and constant ionic strength (I = 0.100 M, KCl). The calculations of millimols of reagents and the binding constants were done with the help of Hyperquad program [23] and the species distribution diagrams were drawn with HYSS program [24]. All information required for the proper input for the program were provided or calculated, as the concentration of all reagents, the hydrolysis constants for Al^{3+} taken from literature [25] and concentration of KOH (potassium hydrogen phthalate standardization with phenolphthalein) and the Al^{3+} solution acid content, by Gran's Plot [26, 27]. The metal ion was determined by complexometric back titration with $ZnSO_4$ and dithizone as indicator (standardized final concentrations of $AlCl_3$ solution were $[H^+] = 0.1334$ and $[Al^{3+}] = 0.01045$ M). An Orion pH meter (model 420A, USA) with H^+ and Ag/AgCl (Orion, Switzerland) reference electrodes was calibrated to differences no higher than 0.005 pH units in acidic region and 0.015 pH units in basic region. KCl was the supporting electrolyte used to maintain the ionic strength of all system at 0.100 M, with $pK_w = 13.78$ for the aqueous conditions and 14.71 for 70 % v/v ethanol/water solutions for the experiments done with Vit D [9]. A Sigma Techware (USA) piston burette was used to deliver the titrant, free CO_2 standard KOH (~0.1 M, 0.02 ± 0.01 mL).

^{13}C NMR experiments

Proton decoupled ^{13}C-NMR spectra of binary and ternary synthesized solid complexes (10 mg) were recorded on a Bruker Advance DRX400 spectrometer (100.61 MHz, Germany) on samples in DMSO-D_6 (0.5 mL) solution in quartz tubes for 2 h. Samples (5 mg mL^{-1}) were analyzed using a 5 mm inverse probe at 30 °C. The pulse sequence was used with a delay (D1) and acquisition time (AQ) of 0.10 and 0.59 s respectively, using a spectral width of 31.0 kHz, 32 K data points, 90° pulse (7.1 μs), and 8,000–10,000 scans. The chemical shifts (ppm) were measured relative to an internal TMS standard set at 0.0 ppm.

X-ray diffraction analysis

The solid complexes used in ^{13}C NMR spectra were analyzed in a glass holder by X-ray diffraction (XRD) employing a Shimadzu diffractometer XRD6000 (Japan), with a CuKα monochromator (1.5418 Å), in the 10–80° 2θ range, with a 2° min^{-1} sweep rate.

Results and discussion

The structure of β-CD is given in Fig. 1 while the chemical structures of cholecalciferol and phenothiazine are shown in Fig. 2.

Equilibrium constants

The potentiometric pH profiles of β-CD, pheno and Vit D on one hand and β-CD:pheno and β-CD:Vit D on the other hand, are shown in Figs. 3 and 4. These curves show the changes in the different ligand to metal ratios studied profiles for both binary and ternary systems, in the presence of Al^{3+} ions.

Figure 3 shows the titration profiles of pheno alone and in the presence of Al^{3+} (with increasing ligand to metal ratio 1:1, 2:1 and 3:1). Figure 4 depicts the pH profiles of supramolecular assembly β-CD:pheno and β-CD:pheno with Al^{3+} (ligand to metal ratios of 1:1 and 2:1). In Fig. 5, are drawn the experimental and the calculated pH profiles of the supramolecular assembly β-CD:Vit D in the presence of Al^{3+} in ligand to metal ratios of 5:1:1 and we note a good fit between the two curves, owing us to validate the model used in our calculations. In all potentiometric profiles, the inorganic acid added to the Al^{3+} solution was previously discounted.

These pH data were used to determine the complexed species present in the system using calculations performed with Hyperquad program [23]. The logarithms of the binding constants, calculated as previously described

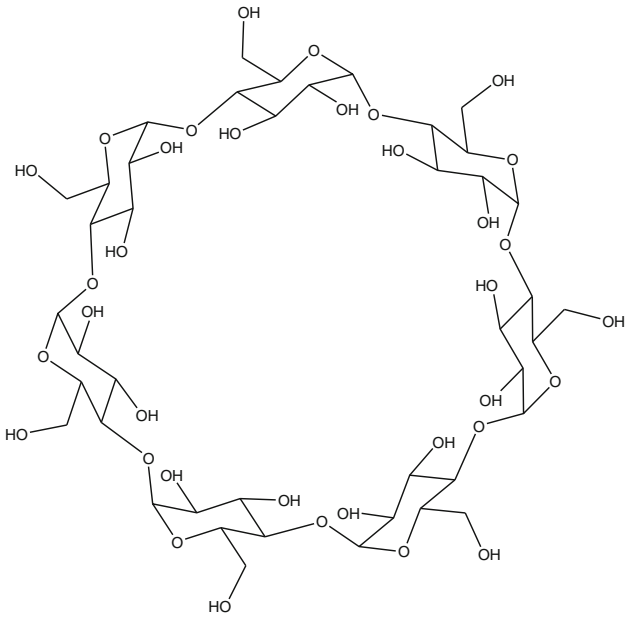

Fig. 1 Molecular structure of β-CD

[16, 28], in all present systems are listed in Table 1. The simulation procedure was made in all experiments and calculations but it was only shown in the ternary systems (Fig. 5) in order to validate the binding constants calculated. All calculated values were done for species with a percentage higher than 10 % in the equilibrium, assuming that the total metal concentration is 100 %.

The log β_1 for binary systems β-CD:Al^{3+}, pheno:Al^{3+} are 14.48 and 10.02 respectively, while its value is 12.4 for Vit D:Al^{3+} [16]. Looking at the logarithmic values for the ternary systems (Table 1), we remark that high values are observed. Lower values were observed in similar supramolecular complexes combining β-CD, copper(II) and functionalized adamantyl ethylene diamine [29]. Our results are explained by the fact that the supramolecular assembly binds the metal ion in a conjugated way, using all possible basic centers (electrons pair donors) in both host β-CD and guest ligands (pheno or Vit D).

The species distribution curves of the binary and ternary systems (not shown) indicated that at least one complex species was present, with a minimal percentage of 50 % in the 5–8 pH range. However, there was a variation in the formation of complexed species depending upon the ligand studied. For physiological pH value (7.4) there was the presence of, at least, one complexed species in all studied systems.

^{13}C NMR spectra

The carbon numbering scheme for β-cyclodextrin used in this paper was previously proposed by several authors [14, 30–32], the numbering scheme for pheno was given by

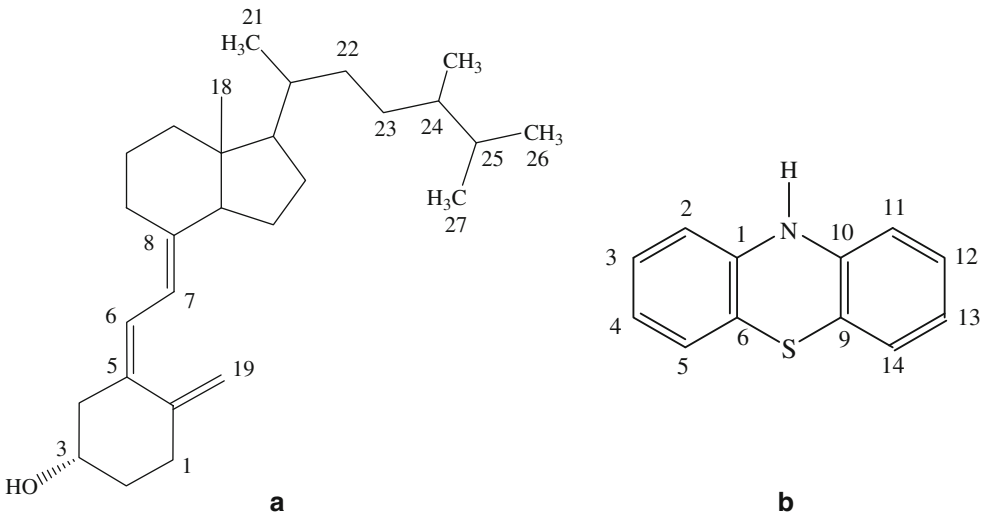

Fig. 2 Chemical structures of vitamin D_3 (**a**) and phenothiazine (**b**) with carbon numbering schemes

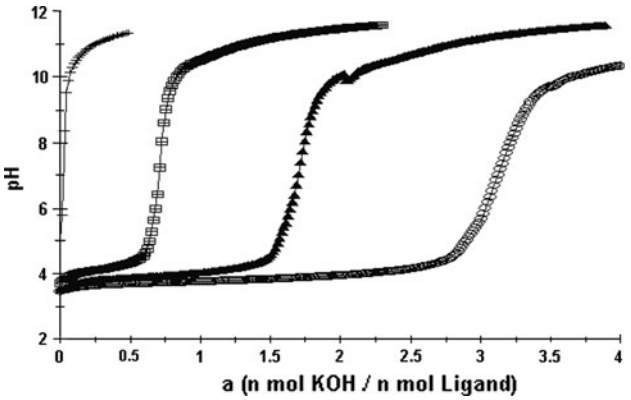

Fig. 3 Potentiometric pH profile (25.0 °C, $I = 0.100$ M, KCl) of pheno (*black line*), pheno:Al 1:1 ratio (*circles*), 2:1 ratio (*triangles*) and 3:1 ratio (*squares*)

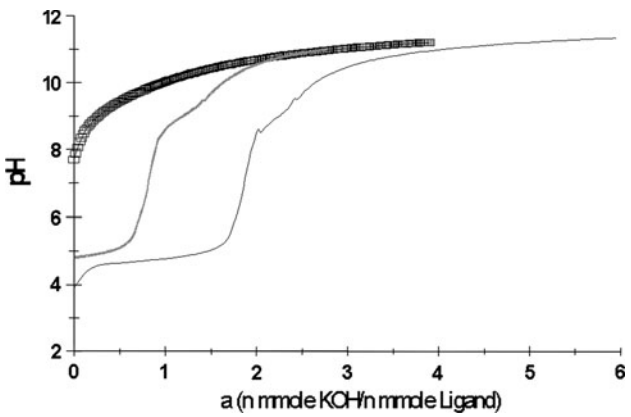

Fig. 4 Potentiometric pH profile (T = 25.0 °C, $I = 0.100$ M, KCl) of β-CD:pheno alone (*squares*), and with Al^{3+} in 1:1 ratio (*black line*) and in 2:1 ratio (*grey line*)

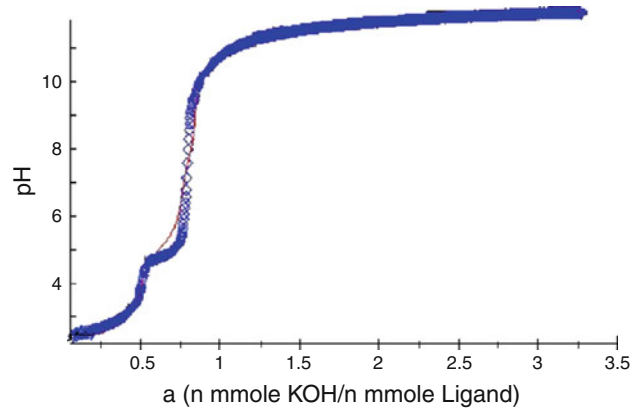

Fig. 5 Experimental (*diamond*) and calculated (*line*) potentiometric pH data of supramolecular assembly β-CD:Vit D with Al^{3+} in 5:1:1 ratio (25.0 °C, $I = 0.100$ M, KCl)

Palafox [33]. The chemical shifts of the complexed species are listed in Tables 2, 3 and 4 and experimental spectra are shown in Figs. 6, 7 and 8.

In our experiments, the ^{13}C NMR chemical shifts for β-CD in DMSO-D_6 are (Fig. 6): C1 = 103.356, C2 = 73.827, C3 = 74.469, C4 = 83.003, C5 = 73.456 and C6 = 61.384 ppm [34]. The chemical shifts for ^{13}C NMR of vitamin D_3 were previously reported [14, 35, 36]. The ^{13}C chemical shifts for pheno are C2 and C11 = 115.953, C6 and C9 = 117.884, C4 and C13 = 123.252, C5 and C14 = 127.718, C3 and C12 = 129.012 ppm and C1 and C10 at 143.620 ppm and these values agree with those reported in the literature [33, 37, 38].

We have calculated the difference between the chemical shifts of β-CD alone and for the same carbon atom in binary and ternary systems (Tables 2, 3, 4). In binary

Table 1 Logarithms of the binding constants for the binary and ternary systems, T = 25.0 °C and $I = 0.100$ M (KCl)

Equilibrium	β-CD + Al^{3+}	pheno + Al^{3+}	β-CD:pheno + Al^{3+}	β-CD:Vit D + Al^{3+}
[ML]/[M]·[L]	14.48 ± 0.07	10.02 ± 0.03	19.6 ± 0.1	31.3 ± 0.3
$[ML_2]$/[ML]·[L]	14.1 ± 0.4	n.d.	18.5 ± 0.5	20.3 ± 0.5
[MLOH]/[M]·[L]·[OH]	n.d.	n.d.	16.9 ± 0.1	n.d.
$[M_2LH]/[M]^2$·[L]·[H]	n.d.	n.d.	25.7 ± 0.2	n.d.

Table 2 Chemical shifts of the ^{13}C NMR in DMSO-D_6 of β-CD and Al^{3+} and the differences $\delta = \delta$ (β-CD)—δ (β-CD + Al)

	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)
β-CD	103.356	73.827	74.469	83.003	73.456	61.384
β-CD + Al (5:1)	103.271	73.762	74.388	82.890	73.378	61.275
β-CD + Al (10:1)	103.300	73.783	74.417	82.919	73.405	61.303
$\Delta\delta$ (1:5)	0.085	0.065	0.081	0.113	0.078	0.109
$\Delta\delta$ (1:10)	0.056	0.044	0.052	0.084	0.051	0.081

Table 3 ^{13}C NMR chemical shifts of β-CD, and the supramolecular assembly β-CD:pheno in the absence and in the presence of Al^{3+}, ligands to metal ratios of 5:1:1 and 10:1:1

	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)
a-β-CD	103.356	73.827	74.469	83.003	73.456	61.384
b-β-CD:pheno(5:1)	103.354	73.832	74.451	83.068	73.449	61.378
c-β-CD:pheno:Al (5:1:1)	103.369	73.826	74.479	82.967	73.459	61.354
d-β-CD:pheno(10:1)	103.316	73.799	74.417	83.008	73.413	61.338
e-β-CD:pheno:Al (10:1:1)	103.391	73.844	74.502	82.992	73.482	61.385
$\Delta\delta$ (a–b)	0.002	−0.005	0.018	−0.065	0.007	0.006
$\Delta\delta$ (b–c)	−0.015	0.006	−0.028	0.101	−0.010	0.024
$\Delta\delta$ (a–d)	0.040	0.028	0.052	−0.005	0.043	0.046
$\Delta\delta$ (d–e)	−0.075	−0.045	−0.085	0.016	−0.069	−0.047

Table 4 ^{13}C NMR chemical shifts of β-CD and the supramolecular assembly β-CD:Vit D and with Al^{3+}, β-CD:Vit D:Al, in ligands to metal ratios of 5:1:1 and 10:1:1

	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)
a-β-CD	103.356	73.827	74.469	83.003	73.456	61.384
b-β-CD:Vit D 5:1	103.379	73.851	74.477	83.049	73.469	61.383
c-β-CD:Vit D:Al 5:1:1	103.325	73.811	74.446	82.948	73.427	61.339
d-β-CD:Vit D:Al 10:1:1	103.335	73.817	74.445	82.974	73.435	61.340
$\Delta\delta$ (a–b)	−0.023	−0.024	−0.008	−0.046	−0.013	0.001
$\Delta\delta$ (a–c)	0.031	0.009	0.023	0.055	0.029	0.045
$\Delta\delta$ (b–c)	0.054	0.040	0.031	0.101	0.042	0.044
$\Delta\delta$ (b–d)	0.044	0.034	0.032	0.075	0.034	0.043

β-CD:Al^{3+}, all differences appeared to be positive like in the case of copper binary system [14] and higher for 1:5 system that for 1:10 assembly.

The signal of the C4 atom is shifted in the β-CD:Al binary system and this shift is higher for 1:5 ratio. The calculated δ for C6 carbon (external hydroxyl) were the highest in binary system β-CD:Al whatever the molecular ratio. This difference is not observed with pheno or Vit D alone. These results are consistent with a coordination of Al^{3+} ions through the external hydrophilic wall of β-CD while Vit D or pheno are included in the internal hydrophobic cavity of the cyclodextrin molecule [39]. In the mean time, the shifts of the internal C2 and C3 atoms are higher in ternary systems.

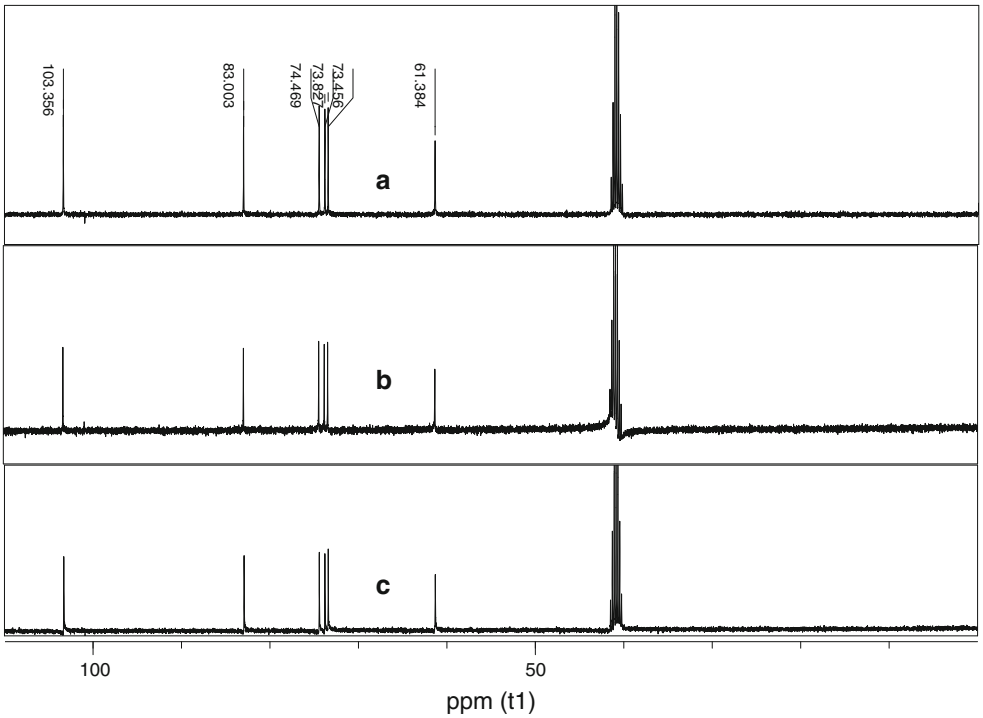

Fig. 6 ^{13}C NMR spectra: **a** β-CD, **b** β-CD:Al^{3+}, 5:1 ligand to metal ratio, **c** β-CD:Al^{3+}, 10:1 ratio

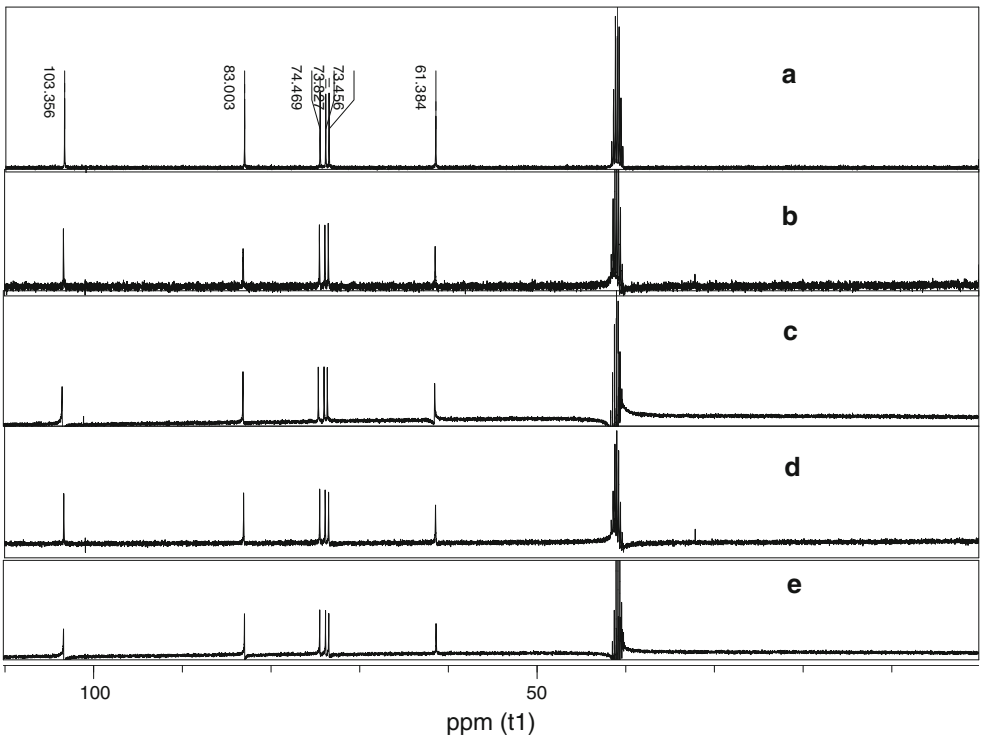

Fig. 7 ^{13}C NMR spectra: **a** β-CD, **b** β-CD:pheno, **c** β-CD:pheno:Al 5:1:1, **d** β-CD:pheno 10:1, **e** β-CD:pheno:Al 10:1:1

The shielding effect in the obtained supramolecular structures were higher when the metal ion were not present for β-CD:Vit D and on the contrary when the system were with pheno, when in the presence of metal ion, the supramolecular assembly was more shielded. The ligands to metal ratios also showed differences in the chemical shifts

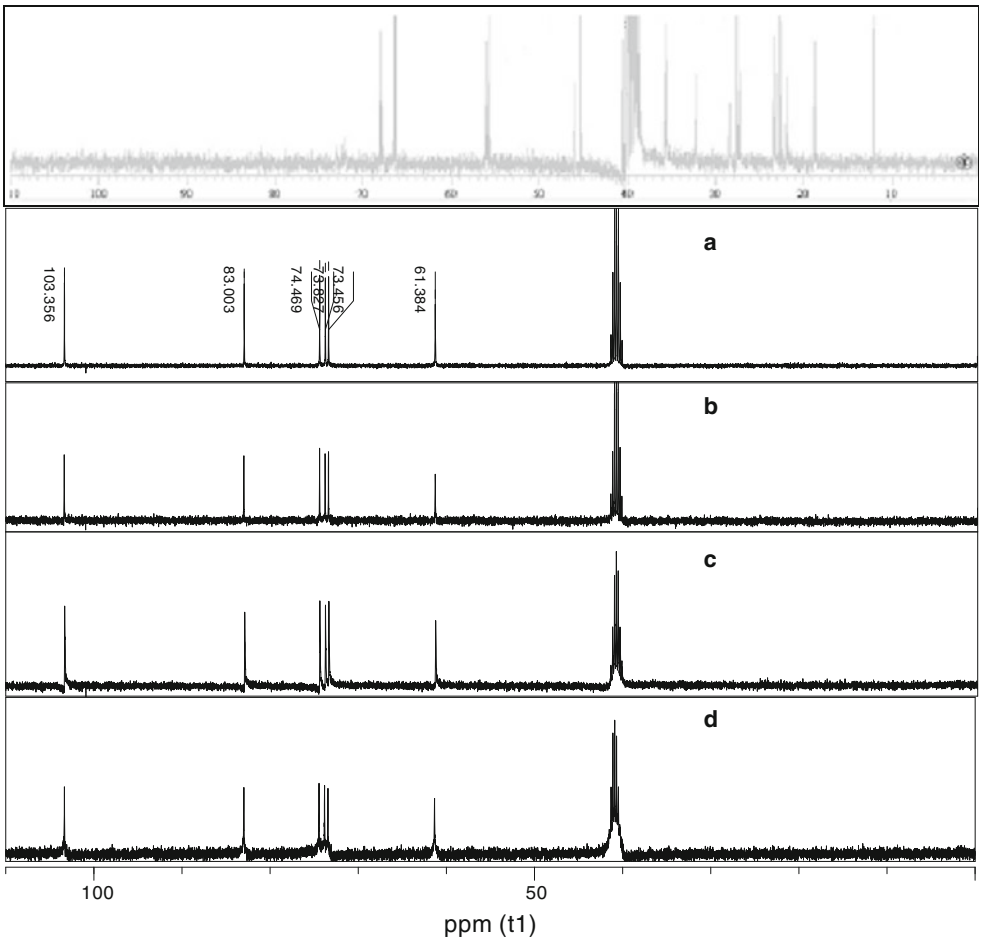

Fig. 8 ^{13}C NMR spectra: Vit D alone (*grey line*) and **a** β-CD, **b** β-CD:Vit D, **c** β-CD:Vit D:Al 5:1:1, **d** β-CD:Vit D:Al 10:1:1

when compared to one another suggesting different conformations when the quantity of the host and the metal ion were changed.

X-ray powder diffraction

In Fig. 9, are shown the diffraction patterns of pheno, β-CD:pheno and β-CD:pheno:Al.

In the XRD spectra of pheno there are very few lines. In the cases of β-CD:pheno 5:1 and β-CD:pheno:Al 5:1:1, respectively we remark the absence of the lines due to pheno when it is encapsulated in β-CD (Fig. 9). For example, the peak at ca. $2\theta = 28°$ disappeared in the case of β-CD:pheno 5:1 but it was present in the case of the ternary assembly β-CD:pheno:Al 5:1:1. In the cases of β-CD, β-CD:Vit D 10:1 and β-CD:Vit D:Al 10:1:1 (not shown), the same diffraction figures are observed, but the lines for the assemblies are not so sharp and intense than in the case of β-CD alone. This fact shows that there are no significant changes in the crystallinity of the β-CD after inclusion even with or without Al^{3+} in the complexes.

According to Saenger et al. [31] the arrangement is not the same in the supramolecular structures presented.

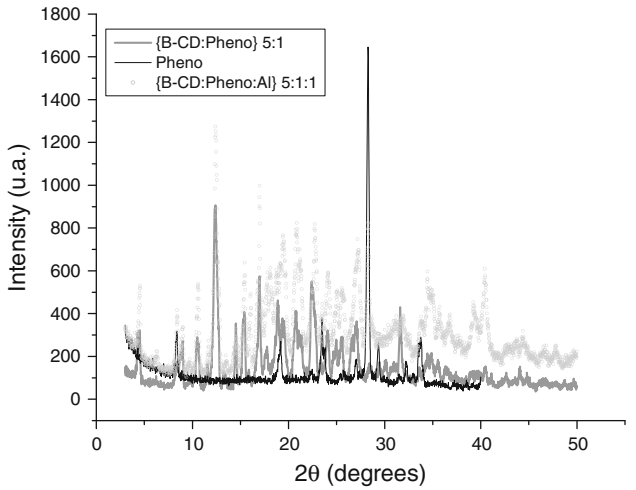

Fig. 9 XDR spectra of pheno, β-CD:pheno 5:1 and β-CD:pheno:Al 5:1:1

β-CD:Vit D inclusion complexes showed, according to previously reported results [14, 40], employing XRD that these complexes are channel type inclusion complexes also with Al^{3+}, with a number of diffraction peaks lower than pure β-CD. On the opposite side, the inclusion complexes

of pheno, β-CD formed a cage type structure with or without Al^{3+}: the lines at $2\theta = 9.5$, 12.8, 13.3 (less intense in our diagrams) and 18.1° are typical of a cage type structure [31, 40].

Conclusion

New supramolecular assemblies of β-CD and phenothiazine or vitamin D_3 were synthesized in this work with Al^{3+} employing previously successfully tested ligands to metal ratios of 10:1:1 and 5:1:1 [14]. They were characterized by studying the solid complexes extracted from aqueous or aqueous ethanol solutions, depending on guest being phenothiazine or vitamin D_3, respectively, by ^{13}C NMR. The X-ray diffraction of ternary assemblies showed that they are channel type inclusion complexes. The solution systems were studied by potentiometric titrations and the binding constants were calculated and the speciation according to variation of pHs were also obtained.

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