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Spectroscopic and thermal characterization of the host–guest interactions between α-, β- and γ-cyclodextrins and vanadocene dichloride

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Host–guest interactions between α-, β- and γ-cyclodextrins and vanadocene dichloride (Cp_2VCl_2) have been investigated by a combination of thermogravimetric analysis, differential scanning calorimetry, powder X-ray diffraction and solid-state and solution electron paramagnetic resonance (EPR) spectroscopy. The solid-state results demonstrated that only β- and γ-cyclodextrins form 1 : 1 inclusion complexes, while α-cyclodextrin does not form an inclusion complex with Cp_2VCl_2. The β- and γ-CD–Cp_2VCl_2 inclusion complexes exhibited anisotropic electron-^{51}V ($I = 7/2$) hyperfine coupling constants whereas the α-CD–Cp_2VCl_2 system showed only an asymmetric peak with no anisotropic hyperfine constant. On the other hand, solution EPR spectroscopy showed that α-cyclodextrin (α-CD) may be involved in weak host–guest interactions in equilibrium with free vanadocene species. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: cyclodextrin; vanadocene dichloride; EPR; inclusion complex

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides that have α-1,4 linked D-glucose units. CDs are named according the number of the glucose units, α (six), β (seven) and γ (eight). They act as molecular hosts to a variety of guests: ions, metal complexes, polar and non-polar organic molecules.[1] These inclusion complexes have found pharmaceutical applications due to the increased aqueous solubility of the drugs, better oral absorption and their improved stability towards heat, light, oxidizing reagents and acidic conditions. CDs are known to form stable inclusion compounds with a variety of organometallic species including ferrocene and its derivatives,[2–5] and sandwich complexes of molybdenum.[6–8]

Metallocene dihalides and pseudo halides of general formula Cp_2MX_2 (M = Ti, V, Nb, Mo; X = Cl, Br, CN, SCN) have shown activity on a wide variety of murine and human tumors.[9–25] Although they belong to the same class of complexes, they have different chemical and biochemical behaviors. One of the major complications of these metallocene complexes is the low hydrolytic stability at physiological pH.[26,27] This has hindered the study of these complexes mechanistically and as a result has limited their pharmacological use. One way to protect these species from extensive hydrolysis is to encapsulate them into macromolecules such as cyclodextrins.

There are few reports on the encapsulation of metallocene dichlorides in cyclodextrins. For instance, the encapsulation of Cp_2TiCl_2 in cyclodextrins was reported in 1999 by Turel and coworkers.[28] This group has shown that the inclusion complexes are formed by the interaction of the metallocenes in the CD cavity and their penetration depends on the length of the cyclic oligosaccharides. According to this report, titanocene dichloride can be encapsulated in the larger β- and γ-cyclodextrins, and not in the smaller α-cyclodextrin. In another report, the β-CD–molybdenocene dichloride inclusion complex was characterized by physical methods and *ab initio* calculations.[29] The predicted geometry of β-CD–molybdenocene dichloride inclusion complex is that only one of the Cp ligands is inside the cavity of the cyclodextrin D-glucopyranose units.

More recently, the CD–Cp_2VCl_2 inclusion complexes have been studied by electron paramagnetic resonance (EPR) spectroscopic methods.[30] The g-tensor and the anisotropic hyperfine coupling constants (A_x, A_y, A_z) demonstrated that vanadocene dichloride and 1,1′-dimethylvanadocene dichloride were encapsulated in the β- and γ-cyclodextrins and the rhombic symmetry was distorted as expected for encapsulated vanadium species, while the α-cyclodextrin cannot encapsulate vanadocene complexes. In this regard, the anisotropic EPR spectral data demonstrated that only in the β- and γ-cyclodextrins the hyperfine interactions with the vanadium nucleus can be observed as a result of the vanadocene inclusion. However, no thermal analysis, powder X-ray diffraction (PXRD) and solution EPR spectroscopies were presented. Herein we report a more detailed thermal and spectroscopic characterization of the CD–Cp_2VCl_2 inclusion complexes. While in the previous report the α-cyclodextrin–Cp_2VCl_2 was completely ruled out as inclusion complex, we obtained different results in solution, using EPR spectroscopy. Herein we report our findings on the CD–Cp_2VCl_2 host–guest interactions.

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Table 1. Thermoanalytical data of the inclusion complexes, physical mixture and precursors

	Dehydration		Melting		
	Temperature range (°C)	Mass loss (%)	Temperature range (°C)	Mass loss (%)	DSC Eendothermic maximum (°C)
α-CD	25–100	9	245–496	88	76(D), 108(D), 136(D/glass transition), 289(M), 325(decomposition/exothermic)
β-CD	25–80	11	271–496	88	129(D/glass transition), 288(M), 325(decomposition/exothermic)
γ-CD	25–98	8	276–496	93	104(D/glass transition), 284 (M), 330(decomposition/exothermic)
Cp_2VCl_2	25–100	1	220–496	63	291(M/decomposition/exothermic)
α-CD–Cp_2VCl_2 FD	25–100	12	140–496	80	115 (D/glass transition), 170 (M) 243(decomposition/exothermic)
α-CD–Cp_2VCl_2 PM	25–100	8	139–496	83	83(D), 154 (D/glass transition), 186 (M), 239 (decomposition/exothermic)
β-CD–Cp_2VCl_2 FD	25–80	7	162–496	72	110(D/glass transition), 175(M), 215(decomposition/exothermic)
β-CD–Cp_2VCl_2 PM	25–100	12	130–496	81	144(D/glass transition), 206(M), 245 (decomposition/exothermic)
γ-CD–Cp_2VCl_2 FD	25–100	11	140–496	82	167(D/glass transition), 174(M), 230(decomposition/exothermic)
γ-CD–Cp_2VCl_2 PM	25–100	8	117–496	84	141(D/glass transition), 193(M), 274(decomposition/exothermic)

Note: D = dehydration and M = melting. FD = freeze-dried. PM = physical mixture.

Table 2. Powder X-ray diffraction spectral analysis of inclusion complexes (FD), physical mixtures and precursors

Compound	Major characteristic peaks at 2θ
α-CD	14.4 (strongest), 12.3, 21.8 (second), 5.4, 13.7, 15.8, 19.4, 22.9, 56.6
β-CD	4.5 (strongest), 12.6, 12.8 (second), 9.1, 10.7, 12.8, 17.2, 22.9, 27.3
γ-CD	5.1 (strongest), 16.5 (second), 4.5, 6.2, 9.2, 11.3, 12.3, 15.4, 15.9, 17.1, 17.8, 18.7, 22.5
Cp_2VCl_2	14.2 (strongest), 13.8, 15.5 (second), 20.2
α-CD–Cp_2VCl_2 FD	14.2 (strongest), 13.8, 15.5 (second), 20.2
α-CD–Cp_2VCl_2 PM	21.8 (strongest), 14.2, 15.5 (second), 12.3, 13.7
β-CD–Cp_2VCl_2 FD	12.3 (strongest), 6.0, 11.9, 17.8, 18.9, (second), 7.3, 15.8, 23.9
β-CD–Cp_2VCl_2 PM	12.7 (strongest), 15.5, 21.2, (second), 4.7, 9.2, 17.9, 19.0, 19.7, 25.9
γ-CD–Cp_2VCl_2 FD	12.1 (strongest), 16.6 (second), 7.4, 11.5, 14.2, 15.7, 20.4, 21.7, 22.4, 23.5
γ-CD–Cp_2VCl_2 PM	13.7 (strongest), 15.5 (second), 5.3, 16.5, 18.9

Note: FD = freeze-dried; PM = physical mixtures.

Table 3. Anisotropic hyperfine coupling constants and *g* factors of the inclusion complexes

Complex	A_i	A_{ii}	g_i	g_{ii}
Cp_2VCl_2	Single	Asymmetric	Peak	
α–CD–Cp_2VCl_2	Single	Asymmetric	Peak	
β-CD–Cp_2VCl_2	74.7 G	197.1 G	1.980	1.937
γ-CD–Cp_2VCl_2	74.0 G	198.8 G	1.980	1.936

Table 4. Isotropic hyperfine coupling constants and g factors inclusion complexes

Complex	A_{iso}	g_{iso}
Cp_2VCl_2	78.4 G	1.978
α–CD–Cp_2VCl_2	79.6 G (62%), 115.7 G (35%), 68 G (3%)	1.967, 1.979, 1.980
β-CD–Cp_2VCl_2	114.4 G	1.967
γ-CD–Cp_2VCl_2	115.1 G	1.966

Experimental

Material and methods

α-CD (Sigma-Aldrich), β-CD (Aldrich) and γ-CD (Fluka) were obtained commercially. The water contents of cyclodextrins were determined by thermal gravimetric analysis (TGA): α-CD, 9.3%; β-CD, 13.95%; and γ-CD, 8.5%. Cp_2VCl_2 was purchased from Aldrich and used as received. The inclusion complexes were prepared using CDs (α-, β-, and γ corrected for water content) and vanadocene dichloride.

Elemental analyses were performed by Atlantic Microlab. The thermal analysis experiments were performed using a TAQ100 (differential scanning calorimetry, DSC) and TAQ500 (TGA) instrument. The heating rate was 3 °C/min for DSC analysis and 10 °C/min for TGA analysis. A DSC interfaced to a PC was used to measure the thermal properties of the inclusion compounds. The calorimetry operated with a nitrogen flow of 50 mL/min. The temperature of the calorimeter was calibrated from the observed melting points of indium. Powder X-ray diffraction (PXRD) data were collected on a Siemens D5000 diffractometer using Cu K_α radiation = 1.5418 Å. The diffractograms were acquired between 2θ angles of 2° and 60° with a step of 0.020° and step time of 2 s at 25 °C.

FTIR data were collected on a Nexus 670 spectrometer using Thunderdome ATR. EPR spectra were recorded with an Elexsys E 500 spectrometer with an ER 4122SHQE resonator. Magnetic fields were measured with an E036 TM Teslameter. Solid sample spectra were acquired with 3 mm i.d. sample tubes. Solution samples were acquired with ER 106FC-Q flat cells. Simulations were optimized with XSophe version 1.114.

Synthesis of CD–Cp_2VCl_2 Inclusion Complexes

An aliquot of 0.2 mmol of CD (corrected for water content) was dissolved in 30 mL of deionized water and 0.2 mmol of solid Cp_2VCl_2 was added. After stirring for 30 min, the green solution was filtered in a fritted funnel of fine porosity and the resulting solution was lyophilized to obtain an amorphous voluminous solid product.

Anal. calcd for 'α-CD–$Cp_2VCl_2\cdot 13H_2O$' [($C_{36}H_{60}O_{30}$)–($C_{10}H_{10}VCl_2$)$\cdot$13H_2O]: C, 37.86; H, 6.63; Cl, 4.86. Found: C, 37.41; H, 5.98; Cl, 4.28. IR(KBr) cm^{-1}: 3272(bm), 2928(w), 1685(vw), 1330(w), 1151(m), 1076(m), 1024(s), 950(w), 937(w), 825(w).

Anal. calcd for β-CD–$Cp_2VCl_2\cdot 14H_2O$ [($C_{42}H_{70}O_{35}$)–($C_{10}H_{10}VCl_2$)$\cdot$14H_2O: C, 38.10; H, 6.64; Cl, 4.33. Found: C, 37.90; H, 6.24; Cl, 3.90. IR(KBr) cm^{-1}: 3278(bm), 2929(w), 1686(w), 1331(w), 1151(m), 1076(s), 1024(s), 950(w), 938(w), 826(w).

Anal. calcd for γ-CD–$Cp_2VCl_2\cdot 10H_2O$ [($C_{48}H_{80}O_{40}$)–($C_{10}H_{10}VCl_2$)$\cdot$10H_2O]: C, 40.29; H, 6.41; Cl, 4.10. Found: C, 40.65; H, 5.94; Cl, 3.92. IR(KBr) cm^{-1}: 3279(bm), 2930(w), 1331(w), 1151(m), 1076(m), 1024(s), 950(w), 938(w), 826(w).

Physical mixtures were prepared by mixing equimolar amounts of cylodextrin and Cp_2VCl_2 in a bench top tumbler blender.

Results and Discussion

Vanadocene dichloride slowly hydrolyzes in water, at low pH, to form $[Cp_2V(OH_2)_2]^{2+}$.[31] However, the inclusion complexes in solution and solid states have shown that Cp_2VCl_2 is the predominant species, as corroborated by a series of spectroscopic and analytical techniques. First, we will discuss the solid-state results. The inclusion complexes were characterized by elemental analysis, TGA, DSC, IR, PXRD and EPR spectroscopies.

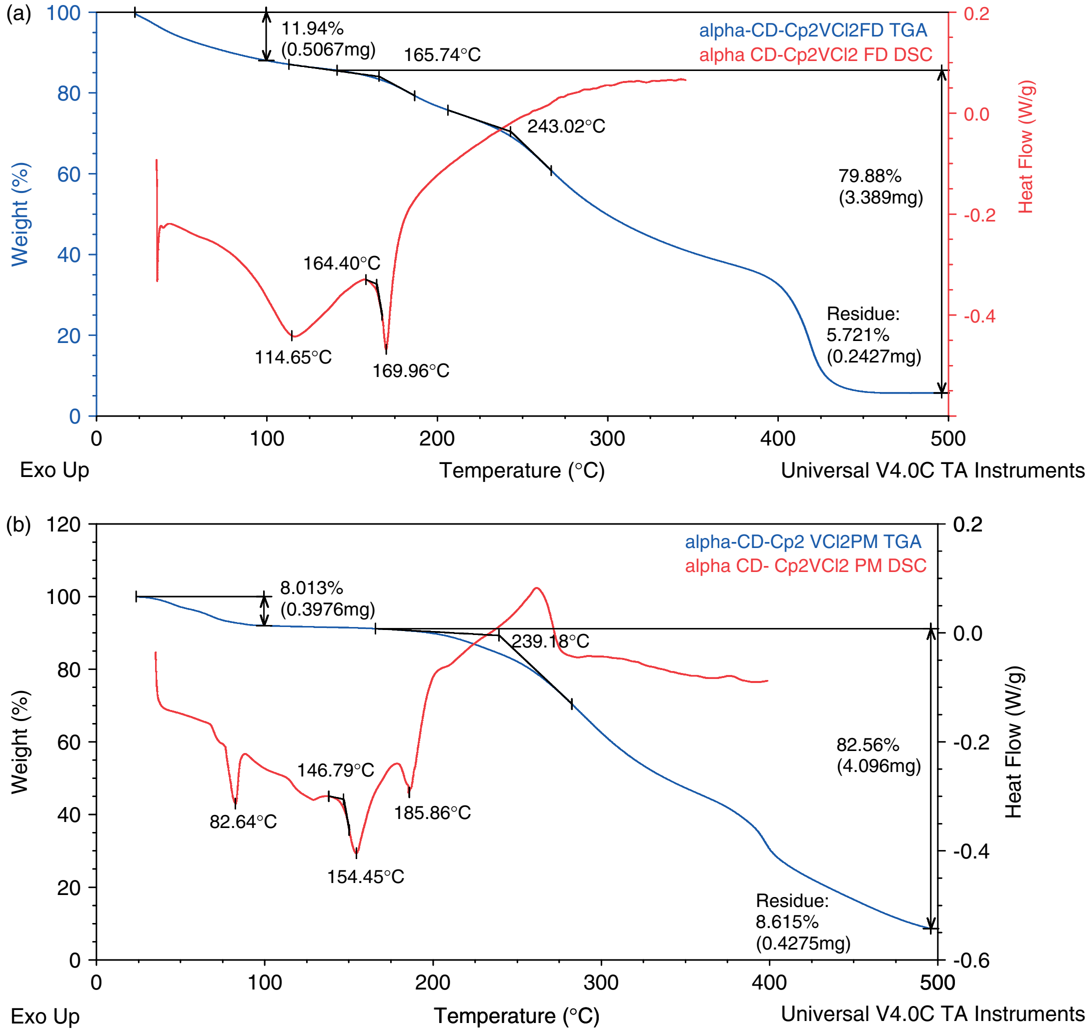


Figure 1. TGA and MDSC curves of (a) α-CD–Cp_2VCl_2 FD; (b) α-CD–Cp_2VCl_2 PM. TGA (red); (c) β-CD–Cp_2VCl_2 FD; (d) β-CD–Cp_2VCl_2 PM. TGA (red), MDSC (blue). FD = freeze-dried (EM = enclosed mixture), PM = physical mixture.

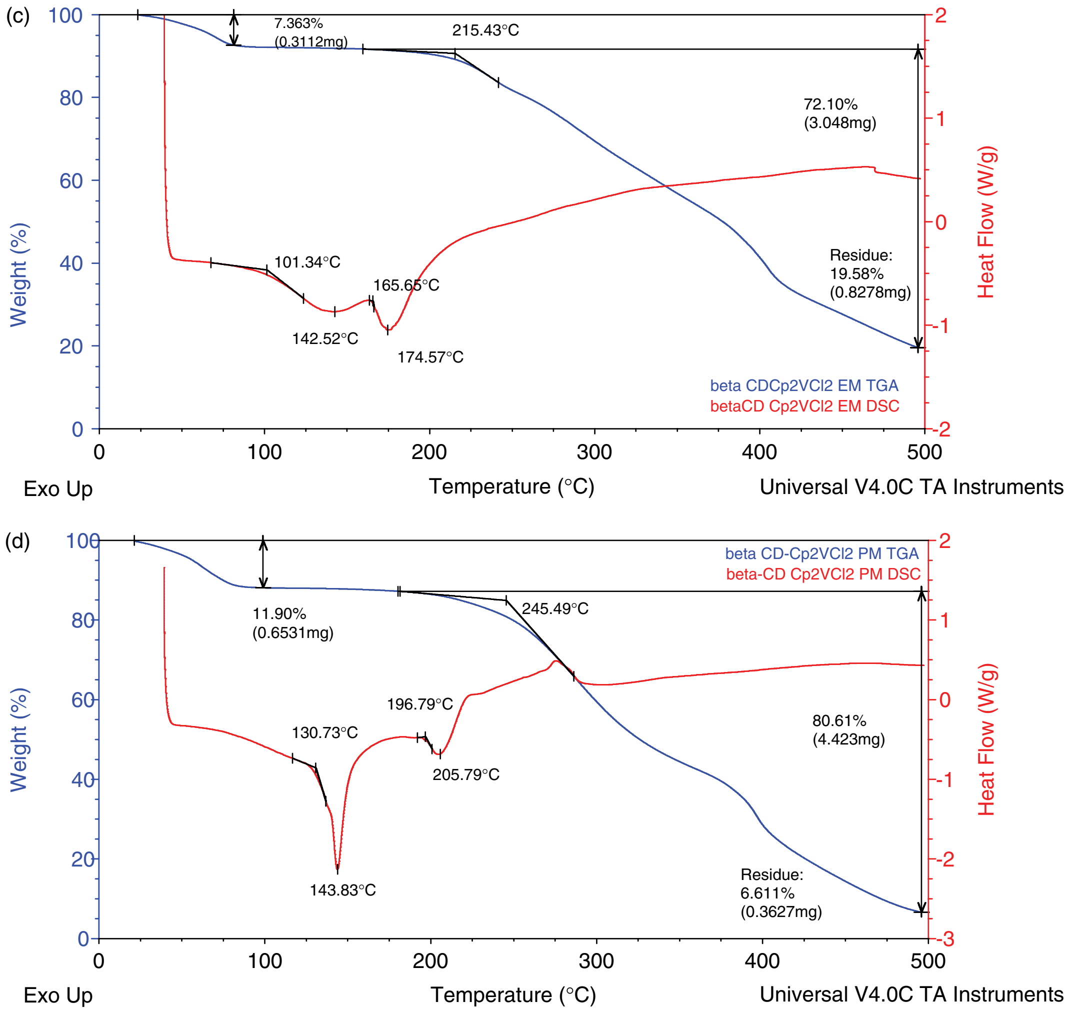


Figure 1. (*Continued*).

Table 1 summarizes the thermal properties (TGA and DSC) of the drug, cyclodextrins and the inclusion complexes and Fig. 1 and Fig. 1S (Supplementary Material) show representative TGA and DSC thermograms for α-, β- and γ-cyclodextrin complexes. In general, pure α-, β- and γ-cyclodextrins loose 8–11% of mass in the range 25–108 °C (see Supplementary Material), indicating loss of hydrated water in the cyclodextrins. The TGA and DSC thermograms of the inclusion complexes demonstrated mass loss of 7–12% between 25 and 100 °C, also indicating loss of water from the cyclodextrin inclusion complexes. Although we are aware that elemental analysis of lyophilized samples could be meaningless at some point, we compared the water calculated with elemental analysis and TGA for the new complexes. It can be observed that there is a discrepancy between the water content calculated by elemental analysis and the water content determined by thermal analysis. This suggests that, in the thermal analysis, at low temperature (25–100 °C) only the weakly bound water molecules are released. The more tightly bound water molecules are lost at higher temperatures and this process could be overlapped by other thermal events such as the melting/decomposition of the inclusion complexes. Similar results were obtained in the CD–Cp_2TiX_2 inclusion complexes reported by Turel and co-workers[28] and in CD–Cp_2NbCl_2 inclusion complexes by our group.[32]

According to the DSC analysis, the melting points of the cyclodextrins (284–289 °C), Cp_2VCl_2 (291 °C) and the physical mixtures (186–206 °C) are substantially higher than those of the inclusion complexes (lyophilized samples, 170–175 °C). Similarly, the decomposition temperatures of the free cyclodextrins, the physical mixtures and Cp_2VCl_2 are higher than those of the inclusion complexes. These thermal behaviors initially suggest that the lyophilized samples are inclusion complexes due to their distinct thermal behaviors.

The TGA and DSC curves of the α-CD–Cp_2VCl_2 freeze-dried sample [α-CD–Cp_2VCl_2 FD, Fig. 1(a), top trace] showed some features different from the free α-cyclodextrin and vanadocene dichloride as well as from the α-CD–Cp_2VCl_2 physical mixture (α-CD–Cp_2VCl_2 PM). This suggests that α-CD might be able to encapsulate Cp_2VCl_2. However, this is not a conclusive analysis to determine if the inclusion complex exists, as this thermal behavior could be the result of a fine dispersion rather than an inclusion complex or a mixture of inclusion complex and free vanadocene dichloride, as will be shown below with EPR spectroscopy. Likewise, the β-CD–Cp_2VCl_2 FD (Fig. 1, bottom traces) and the γ-CD–Cp_2VCl_2 FD (Supplementary Material) exhibited thermal behaviors different to the free CD, Cp_2VCl_2 or CD–Cp_2VCl_2 physical mixtures. In this regard, for β-CD–Cp_2VCl_2 (β-CD–$Cp_2VCl_2 \cdot 14H_2O$) to be a 1 : 1 inclusion compound, 69.3% of the mass must belong to β-CD, while 15.4% must be Cp_2VCl_2. Upon analysis of Fig. 1(d), there is a major mass loss of 72% above 215 °C, which we believe belongs to the β-CD. There is a mass loss of 7.5% between 165 and 230 °C which could involve more tightly bound water molecules and 19.6% residue that must belong to some sort of vanadium compound. For a 2 : 1 β-CD–Cp_2VCl_2 inclusion compound, about 90% of the total must belong to β-CD. Such evidence is not observed into the TGA and DSC curves. In any event, for the β- and γ-CDs cases, EPR spectroscopy demonstrated unambiguously that they can indeed form inclusion complexes with Cp_2VCl_2.

In the infrared spectral data of the inclusion complexes, the weak shoulder about 3100 cm^{-1} attributed to Cp ν (C–H) vibration is most likely overlapped by the broad peak of OH vibrations and cannot be observed. Only a new peak at 825 cm^{-1} is observed in the inclusion compounds which belong to the Cp_2VCl_2 ν (C–H) out of plane vibration.[33] The KBr IR spectrum of Cp_2VCl_2 shows a peak at 820 cm^{-1}. In any event, all the α-, β-, γ-CD–Cp_2VCl_2 samples exhibited this ν (C–H) vibration. Therefore, we explored other analytical techniques to determine inclusion compounds.

PXRD analysis was undertaken on the investigated compounds. This is an important technique to characterize inclusion complexes of cyclodextrins in the solid state. Table 2 shows the PXRD peaks of the hosts, guests, physical mixtures and inclusion complexes. Figures 2 and 3 and Figure 2S (Supplementary Material) depict PXRD spectra of CD–vanadocene complexes.

Upon analysis of Fig. 2 and Table 2, it is evident that the PXRD of the free α-CD, Cp_2VCl_2, physical mixture and freeze-dried samples have some common features. In particular, the lyophilized sample has features corresponding mainly to free Cp_2VCl_2. This is supported by the fact that the α-CD–Cp_2VCl_2 freeze-dried sample has X-ray diffraction peaks at 2θ (13.8, 14.2, 15.5 and 20.2) corresponding to free Cp_2VCl_2. This evidence suggests that the α-CD–Cp_2VCl_2, freeze-dried sample is not an inclusion complex. For β- and γ-CD–Cp_2VCl_2 freeze-dried samples, diffraction peaks

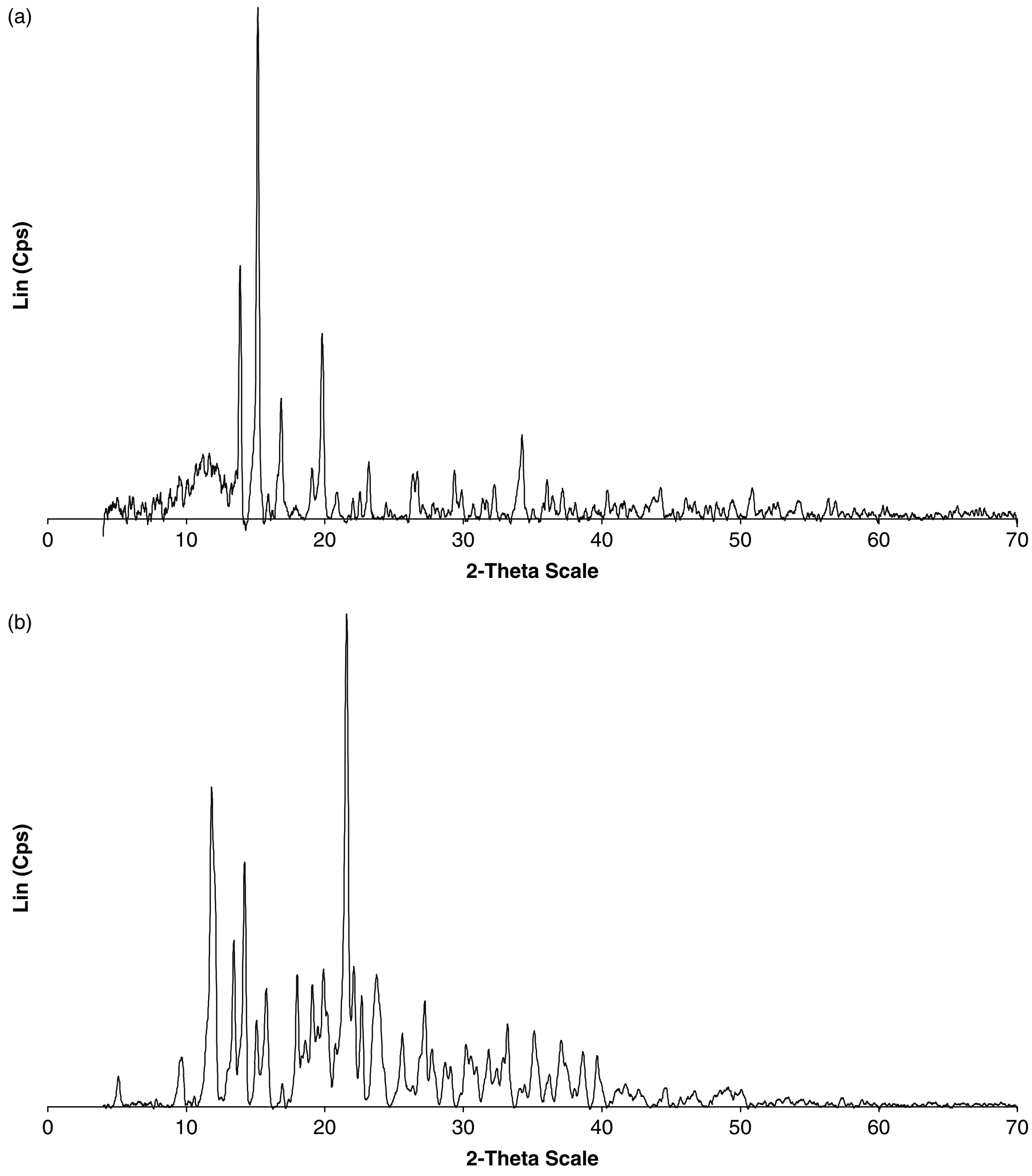


Figure 2. PXRD of (a) Cp_2VCl_2; (b) α-CD; (c) α-CD–Cp_2VCl_2 FD; (d) α-CD–Cp_2VCl_2 PM. FD = freeze dried and PM = physical mixture.

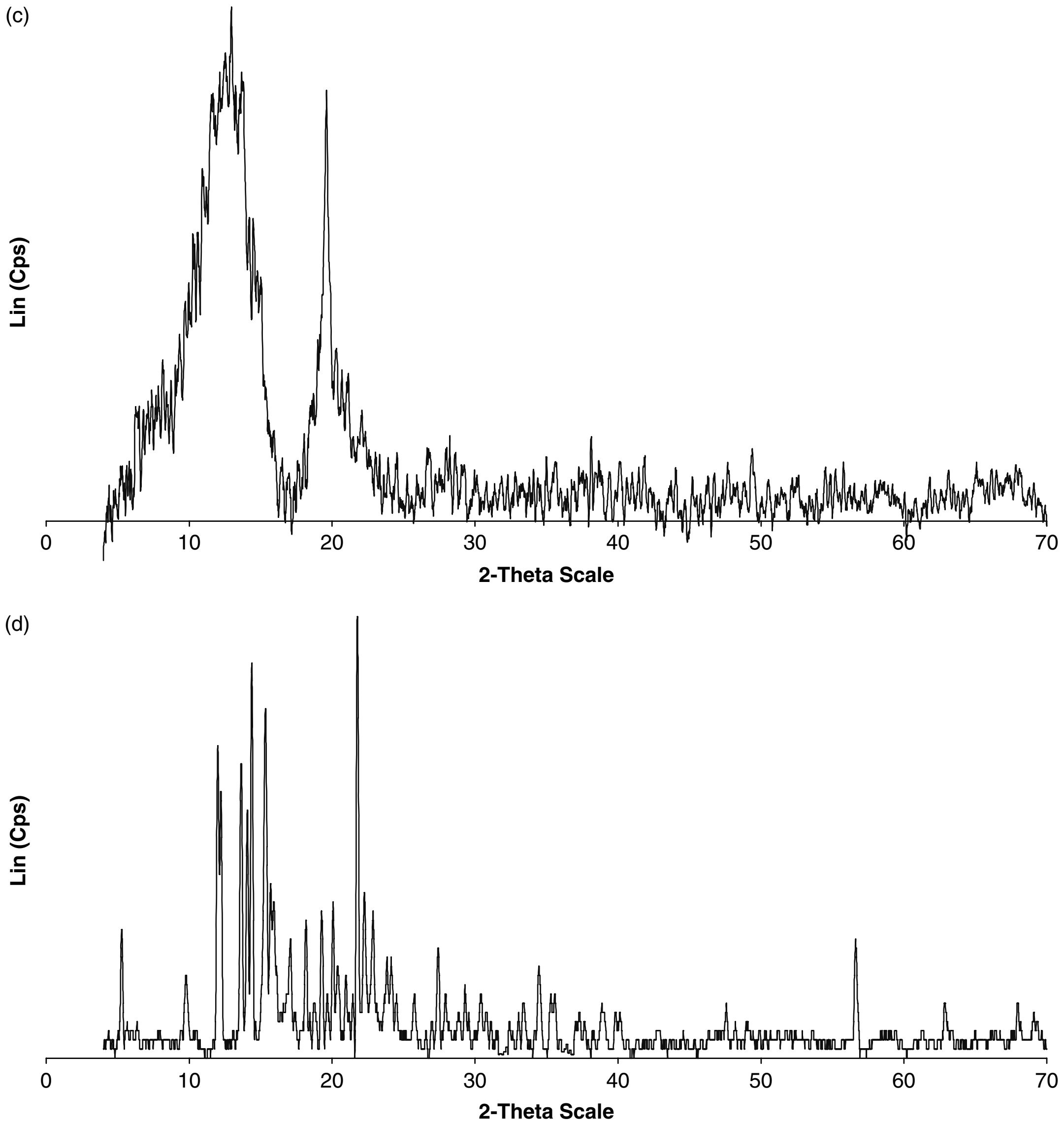


Figure 2. (*Continued*).

corresponding to the free Cp_2VCl_2 and CDs are not observed. In this regard, the PXRD spectra of the β- and γ-CD–Cp_2VCl_2 freeze-dried samples have diffraction patterns (see Fig. 3 and Fig. 2S, Supplementary Material) completely different from their initial components and the physical mixtures. These new diffraction patterns observed in the PXRD spectra can only be explained as new, more amorphous solid materials containing the Cp_2VCl_2 encapsulated into their CD hydrophobic cavities.

To explore the possibility of other types of inclusion compounds with α-CD, we studied the diffraction patterns of 1 : 2 and 2 : 1 α-CD–Cp_2VCl_2 systems (Supplementary Material). None of these systems exhibited diffraction patterns that can be attributed to an inclusion compound.

EPR spectroscopy in the solid state has been used to elucidate the electronic and magnetic environments around the vanadium (d^1) metal center and determine if Cp_2VCl_2 is encapsulated into the CD cavity.[30] We have pursued solution and solid-state EPR experiments to determine the inclusion complexes in both states (see Tables 3 and 4).

The solid-state EPR spectra of the α- and β-CD–Cp_2VCl_2 host–guest interactions are depicted in Figs 4 and 5. Figure 4 presents the EPR spectra of the α-CD–Cp_2VCl_2 physical mixture, α-CD–Cp_2VCl_2 freeze-dried sample and the subtraction of both spectra. It is evident that in the α-CD–Cp_2VCl_2 freeze-dried sample, the major species present is free Cp_2VCl_2 since only a single asymmetric peak with no electron-^{51}V ($I = 7/2$) anisotropic hyperfine coupling is observed. This spectrum has identical features to the solid-state EPR spectrum of Cp_2VCl_2. There is a second species but its concentration is too low to determine the anisotropic hyperfine coupling accurately. Thus, this is evidence that the major component in the α-CD–Cp_2VCl_2 is mainly free vanadocene and the EPR spectrum (Fig. 4) is mainly a dispersion mixture rather than an inclusion complex. On the hand, the β- and γ-CD–Cp_2VCl_2 freeze-dried samples exhibited anisotropic hyperfine coupling on their EPR spectra (Table 3). Similar results were obtained by Vinklárek and co-workers.[30] These results can be rationalized in terms of dilution of the paramagnetic d^1 center. In this regard, magnetically diluted samples arise from the inclusion of Cp_2VCl_2 into the β- and γ-CD cavities. In other words, the d^1 (Cp_2VCl_2) center has been diluted into the diamagnetic matrix, β-CD or γ-CD.

Solution EPR spectra were recorded on the α-, β- and γ-CD–Cp_2VCl_2 host–guest interactions to further investigate the possible species that may exist, in solution and not in the solid state, between vanadocene species and cyclodextrins (Table 4). In aqueous solution, the EPR spectrum of the α-CD–Cp_2VCl_2 host–guest interaction (Fig. 6) is a superposition of three paramagnetic species. The major component (62%) has an isotropic hyperfine coupling constant of 79.6 G. Based on previous report, the isotropic hyperfine coupling constant of Cp_2VCl_2 in aqueous solution is 75 G (there is a slight pH dependence).[31] Our EPR spectrum of Cp_2VCl_2 in aqueous solution showed an isotropic hyperfine coupling constant (A_{iso}) of 78.4 G. Since it is known that Cp_2VCl_2 dissolved in water, at low pH, forms $[Cp_2V(H_2O)_2]^{2+}$,[27,31] we believe that the major species present in the α-CD–Cp_2VCl_2 system is free $[Cp_2V(H_2O)_2]^{2+}$. The second component (35%) has an A_{iso} of 115.7 G. Upon comparison with the solution EPR spectra of the β- and γ-CD–Cp_2VCl_2 host–guest interactions we found that these inclusion complexes have A_{iso} values of 114.4 G and 115.1 G respectively. Since these CDs form host–guest inclusion complexes with Cp_2VCl_2, we believe that some sort of host–guest interactions exist between the α-CD and Cp_2VCl_2, albeit weak. However, to pinpoint what type of interaction is present, we analyze the EPR spectrum of $[Cp_2V(MeOH)]_2Cl_2$ in water. Surprisingly the A_{iso} of this complex, which involves V–O (V–MeOH) coordination, is 114 G. Therefore, it seems that, in solution, vanadocene is being coordinated weakly by the secondary alcohols (C-2 and C-3 OHs) on the wider edge of the cavity and that this interaction also exists in the β- and γ-CD–Cp_2VCl_2 host–guest interactions when the inclusion complexes are dissolved in water and the

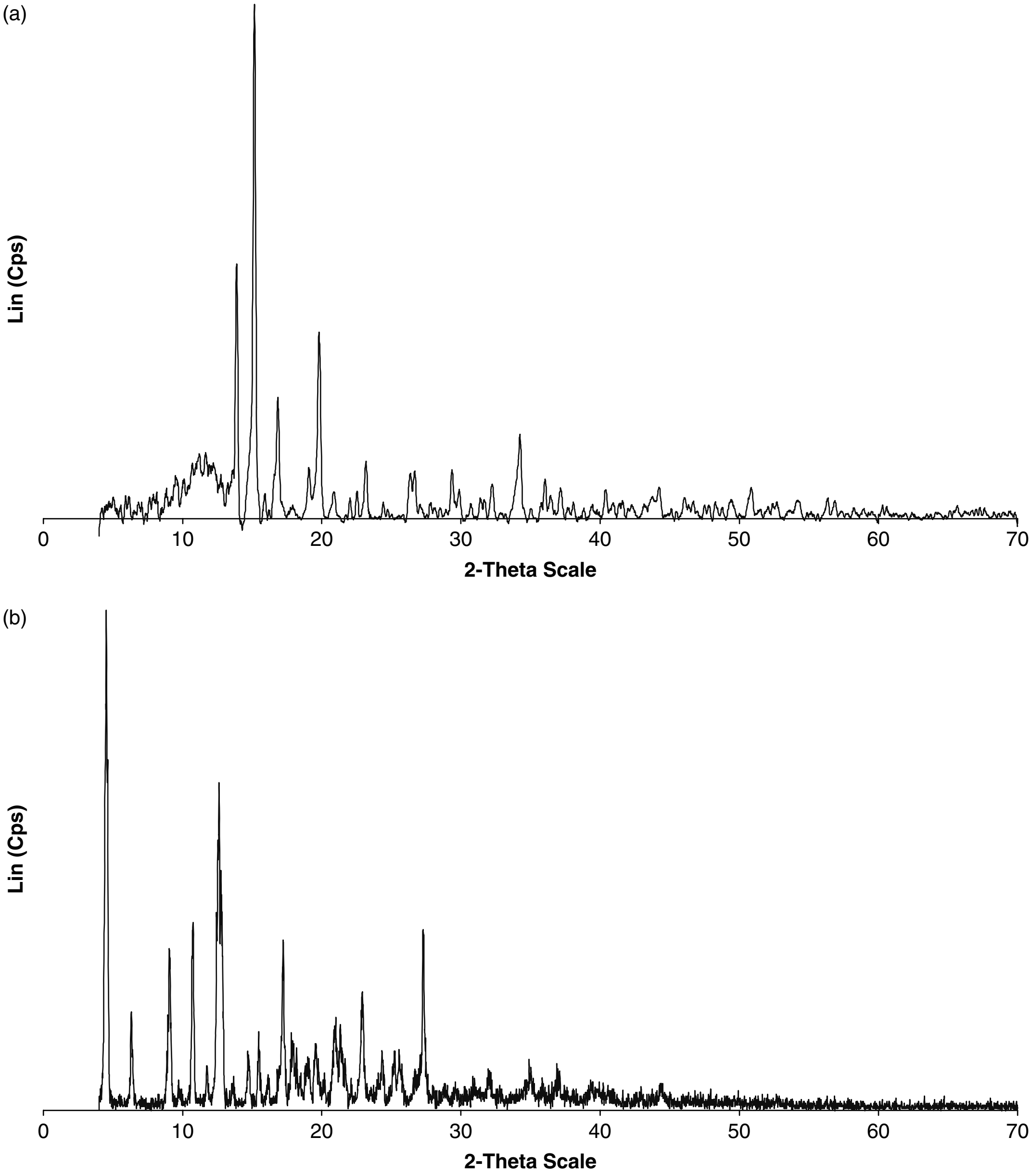


Figure 3. PXRD of (a) Cp_2VCl_2; (b) β-CD; (c) β-CD–Cp_2VCl_2 FD; (d) β-CD–Cp_2VCl_2 PM. FD = freeze dried and PM = physical mixture.

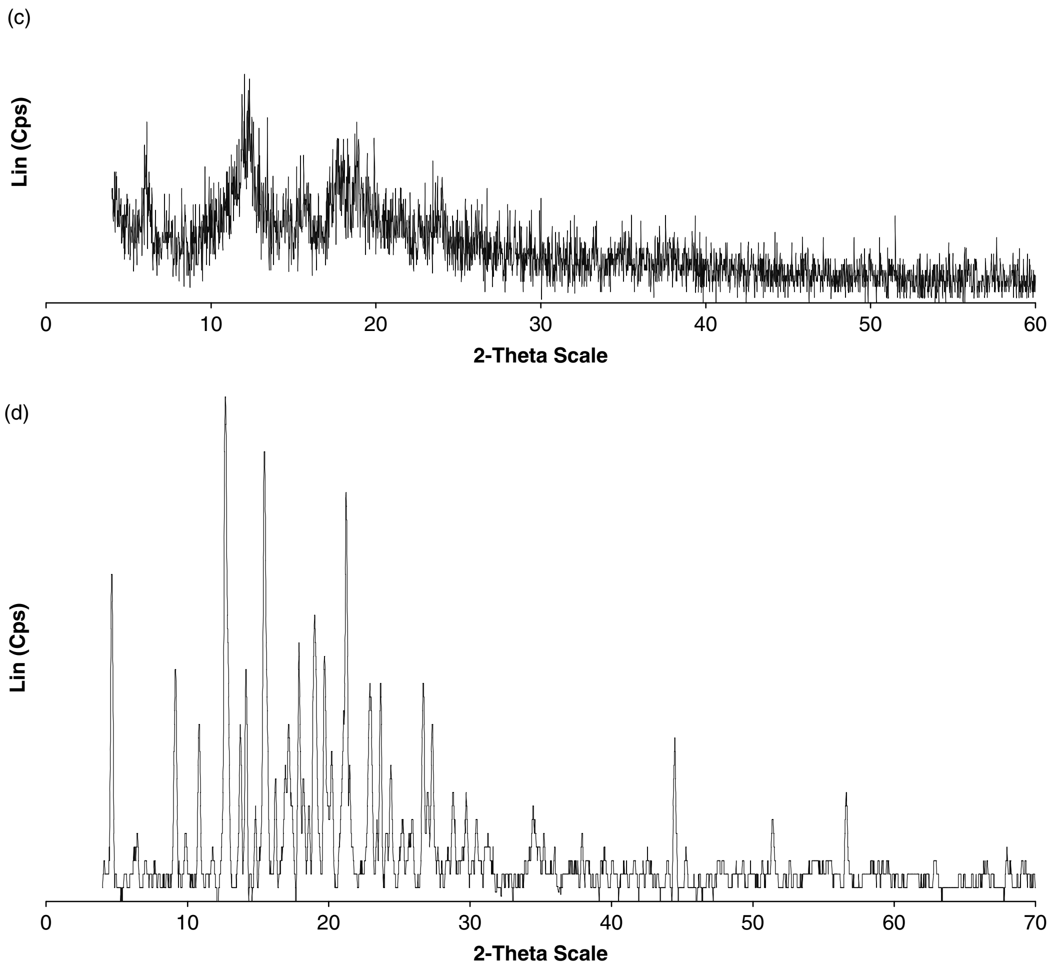


Figure 3. (*Continued*).

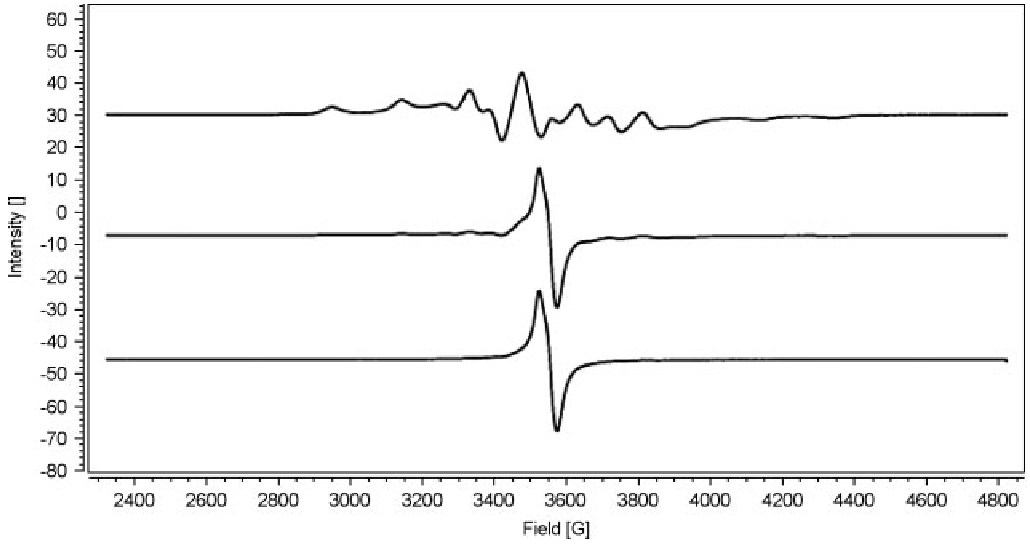


Figure 4. Solid-state EPR spectra of α-CD–Cp_2VCl_2. Physical mixture (top trace, green), freeze-dried sample (middle trace, red) and subtraction of the top spectrum to the middle spectrum (bottom, blue).

cyclodextrin releases the vanadocene species into the aqueous media. On the other hand, once the water is removed from the medium (lyophilized sample), the vanadocene is enclosed into the β-CD and γ-CD but not into the smaller α-CD cavity. There is a third species (in the Cp_2VCl_2–α-CD solution) in about 3% with isotropic hyperfine coupling constant of 68 G. It is not clear what

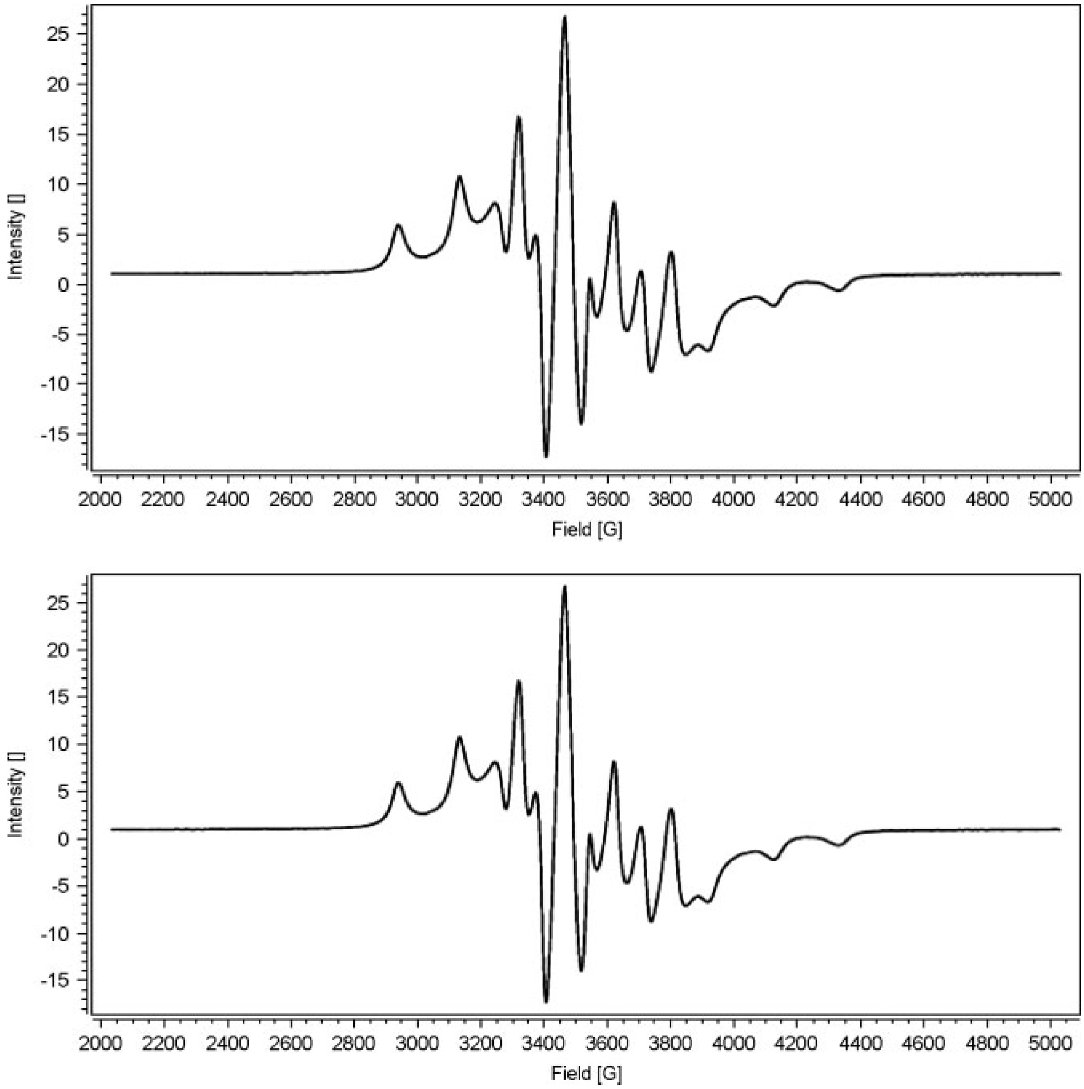
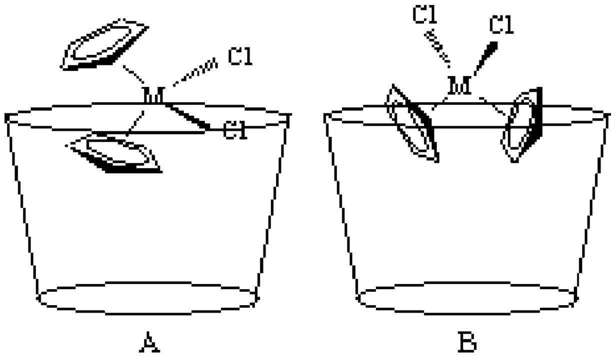


Figure 5. Solid-state EPR spectra of β-CD–Cp_2VCl_2 FD (top) and γ-CD–Cp_2VCl_2 FD (bottom). FD = freeze-dried sample.

species is present but based on the A_{iso} it is possible that a sort of vanadocene complex (perhaps $[Cp_2VCl(H_2O)]^+$]) is present in the solution as a free species.



Scheme 1.

Conclusion

The host–guest interactions between α-, β-, and γ-CDs and Cp_2VCl_2 have been characterized by a combination of solid-state physical methods and solid and solution EPR spectroscopy. The formation of a true inclusion complex in a 1 : 1 ratio has been detected unequivocally for β- and γ-cyclodextrins. In the solid state, α-CD does not form stable 1 : 1 inclusion complex. For the α-CD, solution EPR spectral data showed it to have three species. Two of them should be free vanadocene species (A_{iso} = 68–79 G), while the third one has an A_{iso} = 115.7 G, which suggests some type of weak coordination between secondary alcohols of cyclodextrin and vanadocene. On the other hand, solution EPR spectroscopy showed that the vanadocene species involved in the β- and γ-CDs have only one species with high isotropic hyperfine coupling constants (A_{iso} 114–115 G). This should involve, must likely, some sort of intermediate species between free and encapsulated vanadocene, coordinated by the secondary alcohols analogous to α-CD. But upon removal of water, only β- and γ-CDs are able to enclose vanadocene.

Two possible geometries for these inclusion complexes can be envisioned, A and B. According to the ^{13}C CP MAS NMR spectral

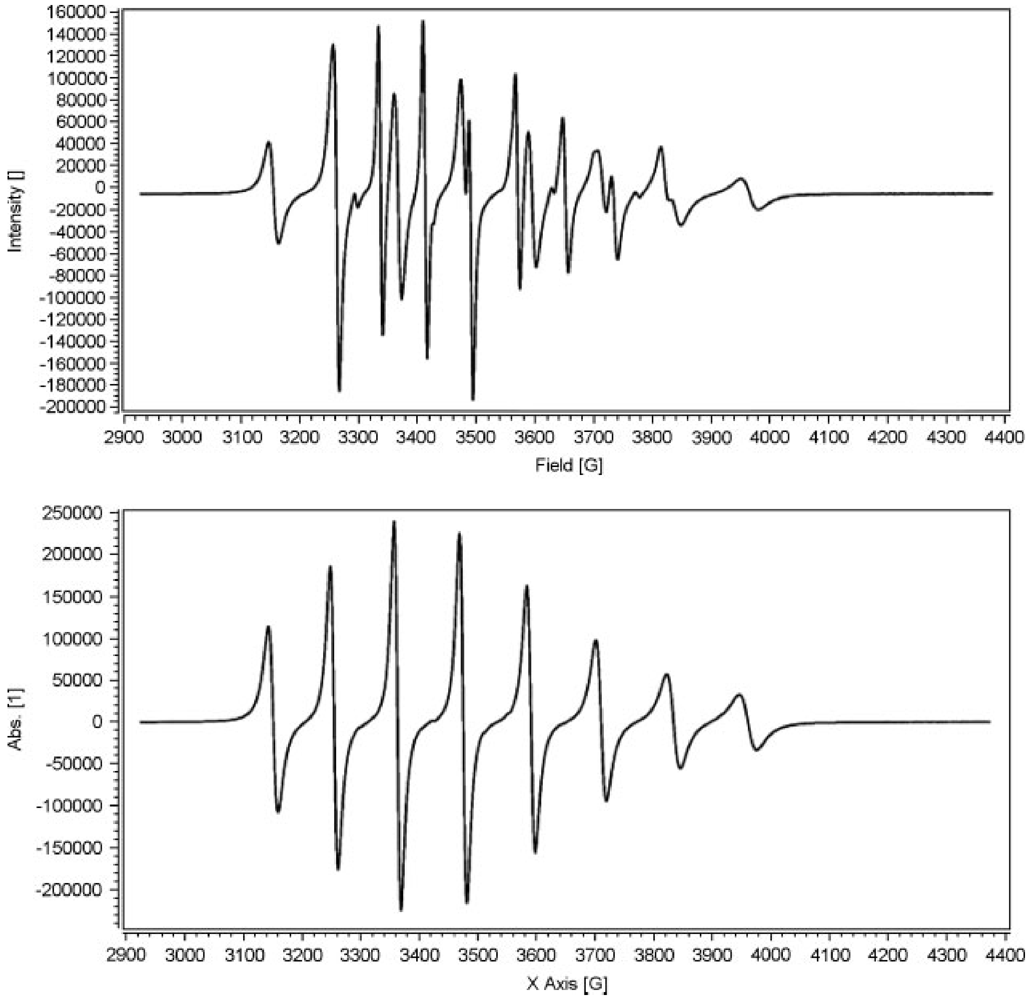


Figure 6. EPR spectra of α-CD–Cp_2VCl_2 mixture (top) and Cp_2VCl_2 in water (bottom).

data on CD–niobocene[32] and CD–molybdenocene host–guest interactions,[29] geometry A is the most likely conformation. On a recent study, Goncalves and co-workers found, using *ab initio* calculations, that geometries A and B as well as a third geometry where the chloride is inserted into the cavity with a shallow penetration of the Cp rings could exist at room temperature.[34] The most likely geometry of the CD–Cp_2VCl_2 host–guest complex will be investigated by molecular mechanics calculation.

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