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The interactions of titanocene dihalides with α-, β- and γ-cyclodextrin host molecules

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Abstract. The inclusion of titanocene dihalides (X = F, Cl) into α-, β- and γ-cyclodextrin hosts was studied by NMR spectroscopy, thermal analysis and mass spectrometry. It was found that α-cyclodextrin does not form inclusion complexes with titanocene halides whereas β- and γ-cyclodextrin do form such complexes. According to the changes in NMR spectra we propose that there is a shallow penetration of a guest molecule of titanocene dihalide into the cavity in the case of β-cyclodextrin, but deeper penetration in the case of γ-cyclodextrin. The stability of the latter inclusion complexes was studied by NMR shift titration.

Key words: NMR spectroscopy, inclusion complexes, titanocene dihalides, CDs.

1. Introduction

Cyclodextrins (CDs) are a torus shaped family of cyclic oligosaccharides consisting of D-glucopyranose units (generally six (α-CD), seven (β-CD), or eight (γ-CD)) connected by α(1,4) interglucose bonds (Scheme 1) [1–4].

CDs act as molecular hosts towards a wide range of guests ranging from ions and very polar molecules to nonpolar molecules such as hydrocarbons [1–4]. Such inclusion complexes are especially interesting for pharmaceutical use due to the increased aqueous solubility of the drugs, better oral absorption and their improved stability towards heat, light, oxidising reagents and acidic conditions [5–10]. The binding forces that are present in such complexes are recognized as van der Waals attractions, ion pairing, hydrogen bonding, metal ion to ligand attractions, π-π attraction, along with hydrophobic and solvent liberation driving forces [1]. The preparation of an inclusion complex of CDs and a metallocene compound was first performed on ferrocene [11] and extended to ferrocene derivatives and metal clusters bearing aromatic ligands [12–14]. The increase in thermal stability of cobalt clusters included in CDs was observed [14].

It is well known that metallocene dihalides of the constitution Cp_2MX_2, where Cp = η^5-C_5H_5, M = Ti, V, Nb, Mo, X = F, Cl, Br, etc., are highly active against

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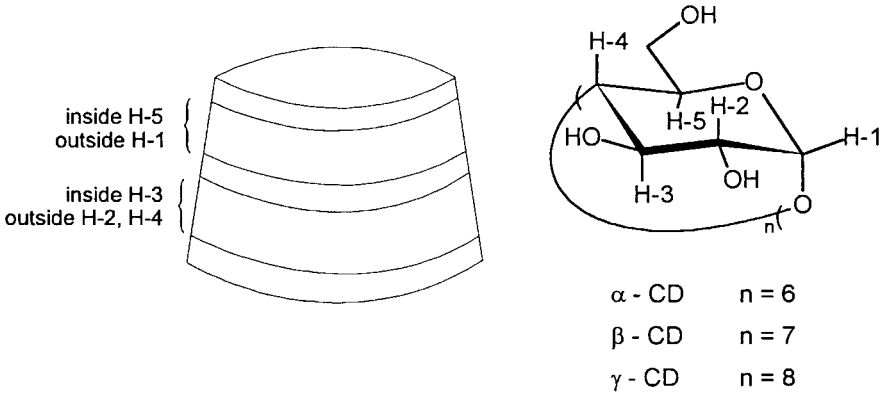


Scheme 1.

Ehrlich ascites tumour (EAT) cells, lymphoid leukemia L 1210, and thus represent a potent new class of organometallic antitumour agents [15–18].

Our aim was to study the inclusion of Cp_2TiCl_2 and Cp_2TiF_2 into α-, β- and γ-CD hosts and to determine properties of the inclusion complexes by NMR spectroscopy, thermal analysis and mass spectrometry. The inclusion of titanocene dihalides into CDs could also affect their toxicity, water solubility, hydrolysis and in final consequence their cytostatic properties and our study could serve as a preliminary insight into these interesting systems.

2. Experimental

2.1. SYNTHESIS OF SOLID STATE CD–Cp_2TiX_2 (X= F, Cl) INCLUSION COMPLEXES

Chemicals: α-CD and β-CD (Aldrich), γ-CD (Wacker) and Cp_2TiCl_2 (Alfa Products) were used as received. Cp_2TiF_2 was prepared from Cp_2TiCl_2 and Me_3SnF [19].

The general synthetic route described below was used to prepare all six possible products of CD (α-, β-, γ-) and titanocene dihalides (Cp_2TiCl_2, Cp_2TiF_2). CD (0.2 mmol) was dissolved in 30 mL of water and titanocene dihalide (0.2 mmol) was added. After stirring for 30 minutes clear solutions resulted that were frozen and dried under *vacuo* to obtain amorphous voluminous solid products. The colour of the products is yellow in the case of Cp_2TiF_2 and red in the case of Cp_2TiCl_2 inclusion complexes.

2.2. ELEMENTAL ANALYSIS

The C, H, N analysis was carried out on a Perkin Elmer 204 C microanalyser.

2.3. THERMAL ANALYSIS

The experiments were performed using a Mettler 2000 C instrument. The heating rate was 4 K/min, air atmosphere with a flow rate of 35 mL/min.

2.4. NMR MEASUREMENTS

The ^{1}H and ^{19}F NMR spectra were recorded on a Bruker Avance DPX 300 instrument at 302 K in D_2O (^{1}H NMR at 300.13 MHz and ^{19}F NMR at 282.40 MHz respectively). Chemical shifts are given on the δ scale (ppm) and are referenced to the H_2O/D_2O resonance (δ = 4.72) for ^{1}H and to an external sample of $CFCl_3$ for ^{19}F (δ = 0.00). The samples for NMR measurement were prepared as follows. 2.0 mL D_2O was added to 0.015 mmol titanocene dihalide and 0.015 mmol of CD. The resulting suspensions were stirred for 30 minutes to obtain clear solutions. The NMR spectra of fresh solutions were recorded. In the NMR shift titrations [20] the concentration of Cp_2TiX_2 was kept at 0.02 M and the γ-CD concentrations were 0.02, 0.04 and 0.08 M respectively.

2.5. MASS SPECTROMETRY

Mass spectra of CDs–titanocene dihalides (molar ratio 1 : 1) aqueous solutions were measured on a Finnigan MAT TSQ 7000 spectrometer by an electrospray atmospheric pressure chemical ionisation.

3. Results

3.1. ELEMENTAL ANALYSIS

The results of the elemental analyses with the corresponding formulas of the solid products are collected in Table I.

3.2. THERMAL ANALYSIS

Thermal analysis (TG-DSC) data of the solid state inclusion complexes and starting compounds are presented in Table II. The decompositions of the CD–titanocene dihalide complexes start at a lower temperature than the decomposition of CDs and titanocene halides respectively. The decomposition of all compounds under investigation is accompanied by exothermic effects.

3.3. NMR MEASUREMENTS

The reported assignments [5, 21, 22] of the ^{1}H NMR spectra of α-, β- and γ-CDs were confirmed by a series of homonuclear decoupling experiments.

Table I. The results of the elemental analysis for the solid products. The first values are calculated from the formulas given, the determined values are in parentheses.

	%C	%H	$\%H_2O$
α-CD–$Cp_2TiF_2 \cdot 9H_2O$	40.87 (40.74)	6.51 (6.01)	11.99
α-CD–$Cp_2TiCl_2 \cdot 7H_2O$	40.95 (41.06)	6.23 (6.21)	9.35
β-CD–$Cp_2TiF_2 \cdot 13H_2O$	39.37 (38.97)	6.69 (6.18)	14.76
β-CD–$Cp_2TiCl_2 \cdot 12H_2O$	39.00 (38.90)	6.50 (6.37)	13.50
γ-CD–$Cp_2TiF_2 \cdot 10H_2O$	41.11 (41.21)	6.49 (6.23)	10.63
γ-CD–$Cp_2TiCl_2 \cdot 9H_2O$	40.75 (40.99)	6.32 (5.98)	9.48

Table II. Thermoanalytical data for the investigated compounds.

	Dehydration		Decomposition		
	Temperature range (°C)	Mass loss (%)	Temperature range (°C)	Mass loss (%)	DSC exothermic maximum (°C)
α-CD	50–100	9	250–510	90	340; 460
β-CD	50–100	11	270–500	84	340; 470
γ-CD	40–100	7	260–480	88	345; 460
Cp_2TiF_2	–	–	220–450	60	240; 260; 290; 395
Cp_2TiCl_2	–	–	240–480	70	270; 325; 440
α-CD–Cp_2TiF_2	40–100	7	200–450	81	280; 375
α-CD–Cp_2TiCl_2	40–100	6	140–480	87	470
β-CD–Cp_2TiF_2	40–100	8	170–390	80	270; 380
β-CD–Cp_2TiCl_2	40–100	13	170–470	80	270; 375
γ-CD–Cp_2TiF_2	40–100	7	180–430	70	290; 410
γ-CD–Cp_2TiCl_2	40–100	8	180–440	84	280; 400

The NMR spectrum of α-CD remained unchanged after addition of Cp_2TiCl_2 or Cp_2TiF_2 respectively.

After the addition of Cp_2TiF_2 or Cp_2TiCl_2 to the solution containing β-CD, the upfield shifts of proton H-3 were observed (Figure 1). In the complexes the H-3 multiplet is superimposed on the H-6 signals. It could be seen that the H-5 protons are only slightly affected and are not well separated from the H-6 signals. Minor differences between the spectra of titanocene difluoride and titanocene dichloride inclusion complexes could also be observed in this region (see Figure 1b and Figure 1c). The signals of other CD protons are virtually not affected.

The most pronounced changes were found in the γ-CD–Cp_2TiCl_2 and γ-CD–Cp_2TiF_2 systems as shown by NMR shift titrations (Figures 2 and 3). Whereas

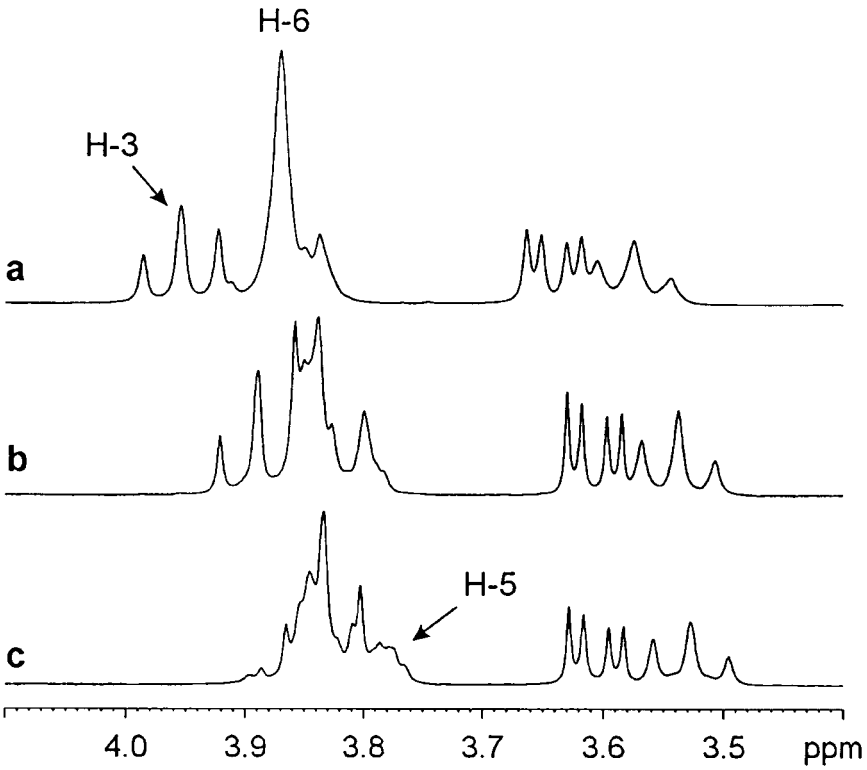


Figure 1. A part of the β-CD ^{1}H NMR spectrum showing the effect of titanocene dihalide addition to the aqueous solution of CD ((a)β-CD; (b) β-CD–Cp_2TiF_2; (c) β-CD–Cp_2TiCl_2). The molar ratio β-CD: Cp_2TiX_2 was 1 : 1.

the shift of the H-3 signals is somehow similar to the β-CD–Cp_2TiX_2 (X = F, Cl) examples (Figure 1), there is an additional upfield shift of the H-5 multiplet which is now totally separated from the H-6 signals. The H-5 and H-3 multiplets shift further upfield as the ratio metallocene: CD is increased. The resonances of other CD protons are only slightly shifted while their shapes remain unchanged. On the other hand the resonances of Cp_2TiX_2 protons are almost nonsensitive to changing the metallocene: CD ratio. The concentrations-ratio dependent shift of the H-3 and H-5 resonances indicates that the system is in the chemical-shift fast-exchange limit. The resonances appear at the population-averaged chemical shift of free and complexed γ-CD. The dissociation constants (K_D) for the equilibrium γ-CD–$Cp_2TiX_2 \leftrightarrow \gamma$-CD + Cp_2TiX_2 were calculated. According to a modified Benesi–Hildebrand equation [23], using the shifts of the H-3 and H-5 resonances, the values of K_D are 0.0020(2) mol/L for γ-CD–Cp_2TiF_2 and 0.013(2) mol/L for γ-CD–Cp_2TiCl_2.

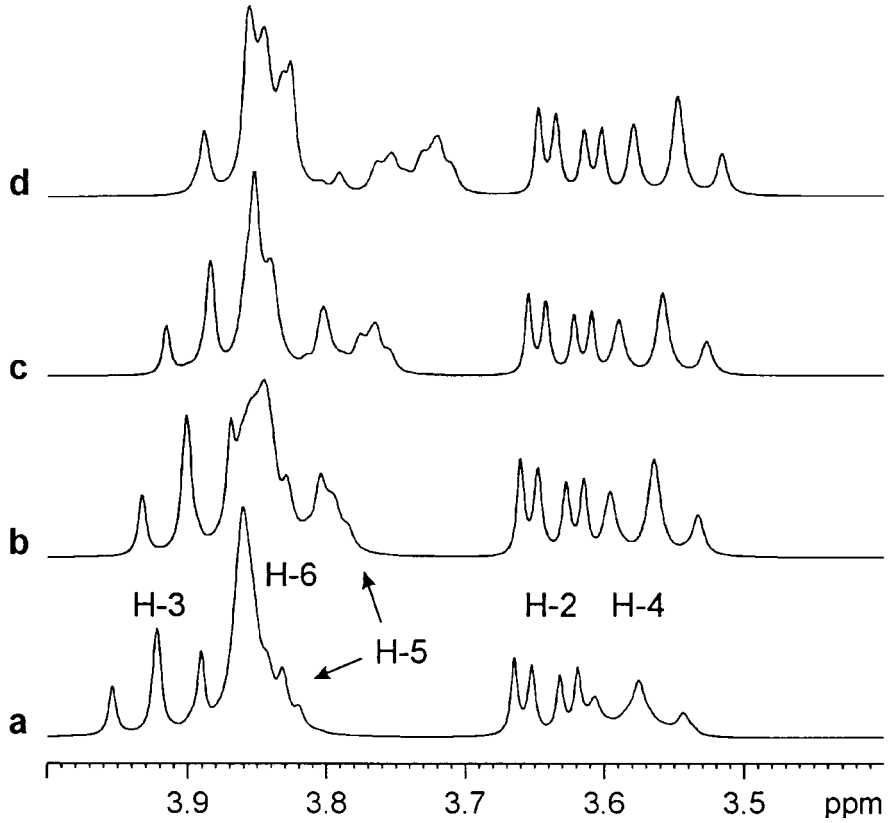


Figure 2. The NMR shift titration in the γ-CD–Cp_2TiF_2 system. The starting concentration of Cp_2TiF_2 was 0.02 M ((a) γ-CD; (b) γ-CD–Cp_2TiF_2 = 4:1; (c) γ-CD–Cp_2TiF_2 = 2 : 1; (d) γ-CD–Cp_2TiF_2 = 1 : 1).

3.4. MASS SPECTROMETRY

The development of soft ionisation methods in mass spectrometry allows the study of noncovalent interaction in molecular recognition processes [24]. We have used atmospheric pressure chemical ionisation as a soft ionisation method. Besides the molecular CD ions we were also able to observe the ions of two inclusion complexes. In the β-CD–Cp_2TiF_2 system the peak at m/z 1369 (intensity 40%) and in the γ-CD–Cp_2TiF_2 system the peak at m/z 1532 (intensity 25%) were observed. Both peaks could be ascribed to the $[CD + H_2O + Cp_2TiF_2]^+$ ion. No corresponding peaks were found in all other products prepared.

4. Discussion

From the thermal analysis results we are not able to conclude whether the solid state CD–Cp_2TiX_2 (X = F, Cl) products are the inclusion complexes or only a

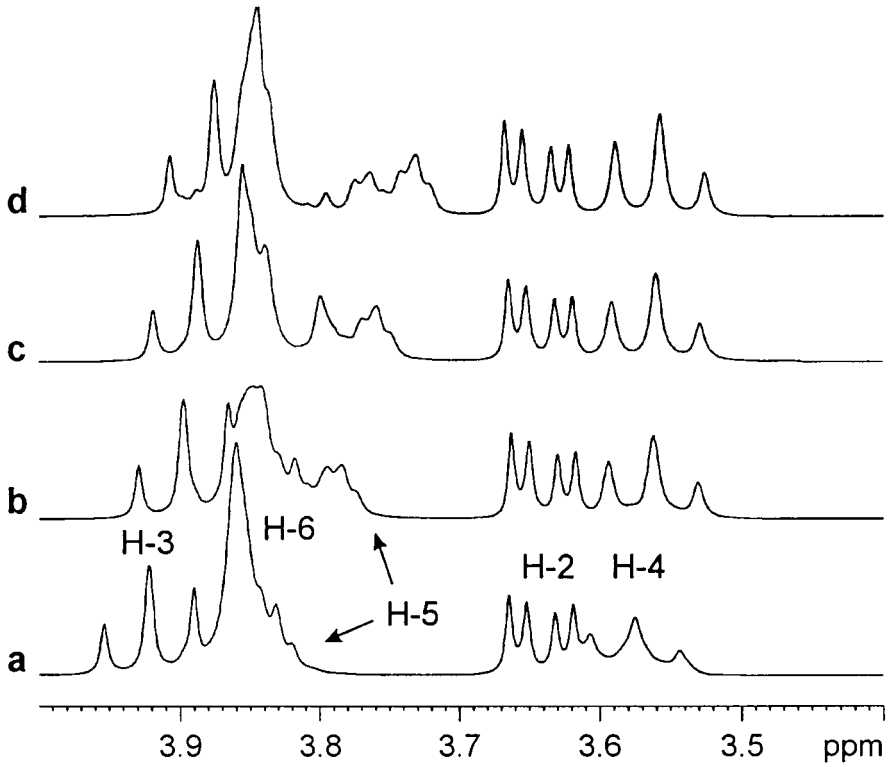


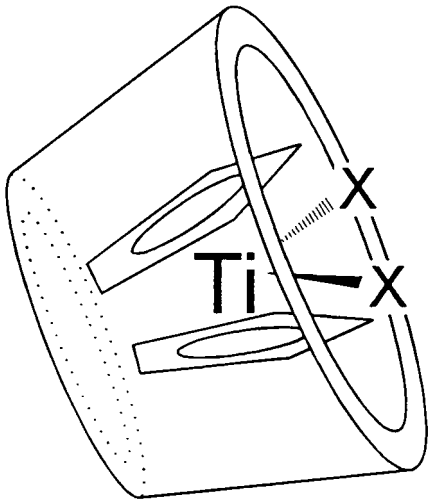
Figure 3. The NMR shift titration in the γ-CD–Cp_2TiCl_2 system. The starting concentration of Cp_2TiCl_2 was 0.02 M ((a) γ-CD; (b) γ-CD–Cp_2TiCl_2 = 4 : 1; (c) γ-CD–Cp_2TiCl_2 = 2 : 1; (d) γ-CD–Cp_2TiCl_2 = 1 : 1).

fine dispersion of titanocene dihalides and cyclodextrins [25], since the thermal decompositions of Cp_2TiX_2 and CDs occur in the same temperature range.

There are some differences in the water content in the solid products determined from thermal analysis (dehydration) and the water content calculated from the formulas derived from elemental analysis data (Tables I and II). We assume that all water molecules are not equivalent in the structure; the weakly bonded molecules are lost at lower temperatures whereas some water molecules are tightly bonded and are lost at higher temperatures. The latter process is overlapped by the thermal decomposition of the substance.

It is obvious from the ^{1}H NMR spectra that both titanium compounds used in this study do not form inclusion complexes with α-CD since there were no changes in the NMR spectrum of the cyclodextrin after the addition of titanium compounds. We propose that there is not enough space in the cavity of α-CD to enable appropriate interactions.

The changes in the β-CD–Cp_2TiF_2 and β-CD–Cp_2TiCl_2 spectra (Figure 1) suggest that there is an interaction of the H-3 proton that is directed towards the interior



Scheme 2. The model of the incorporation of the Cp_2TiX_2 in the CD cavity.

of the CD cavity (Scheme 1), and the titanocene residue. According to the proposed models of incorporation of ferrocene we could suggest that the metallocene is incorporated only shallowly in the interior of the torus.

It is known that if only the H-3 resonance undergoes a shift in the presence of a substrate then the cavity penetration is shallow, whereas if the H-5 resonance also shifts the penetration is deep [3]. According to these facts there is no doubt that titanocene is deeply incorporated in the framework of γ-CD (Figures 2 and 3). Both protons affected (H-3 and H-5) are shifted upfield thus suggesting interactions with a titanocene host molecule. Only marginal shifts are observed for protons H-1, H-2 and H-4, which are all located on the exterior of the CD torus (Scheme 1).

A possible explanation for the difference in dissociation constants of γ-CD–Cp_2TiX_2 (X= F, Cl) could be the different hydrolytic behaviour of Cp_2TiCl_2 and Cp_2TiF_2 (see below) giving ionic hydrolysed $Cp_2Ti(H_2O)Cl^+$ and molecular non-hydrolysed Cp_2TiF_2 as the major species in solution.

It is interesting to compare our NMR results with some studies for other metal–CD inclusion complexes reported in the literature.

In the $Pt(NH_3)_2$(CBDCA)–α-CD (CBDCA = cyclobutane-1,1-dicarboxylato) complex [5] the H-5 resonance was shifted upfield, similar to the observation in our system, whereas H-3 was shifted downfield which is in contrast to the result found in our system.

In the alkyl(aqua)cobaloxime–α-CD complex [22] both H-3 and H-5 resonances were shifted upfield; H-3 from 3.98 to 3.87 ppm and H-5 from 3.83 to 3.78 ppm. The X-ray structure of this complex revealed that the alkyl groups of the guest molecules are located in the α-CD cavities and the planes involving dimethylglyoxime and Co atoms are near the wide opening of the α-CD cavities.

In our systems the H-5 proton is shifted more than the H-3 proton and this could again be proof that the metallocene is incorporated deep in the cavity.

Another interesting part of the proton spectra (where inclusion was observed) is the region between 6.50–6.70 ppm assigned to the protons of the cyclopentadienyl residue of the titanocene halides molecules.

It was found [16] that for Cp_2TiCl_2 the dissociation of the first Cl^- in water is instantaneous whereas the approximate half-life for the loss of the second chloride is 50 minutes. Regarding this data we assume that $Cp_2Ti(H_2O)Cl^+$ is the species incorporated in the CD cavity when the starting material is Cp_2TiCl_2. Only one strong resonance was observed in the NMR spectra of γ-CD–Cp_2TiCl_2 (at 6.68 ppm) in the range 6.50–6.70 ppm if the spectra were recorded 30 minutes after the solutions were prepared. This resonance could be ascribed to $Cp_2Ti(H_2O)Cl^+$. An additional resonance (at 6.49 ppm) was detected in the spectrum recorded after 150 minutes and could be ascribed to $Cp_2Ti(H_2O)_2^{2+}$. The integration ratio of the peaks is approximately 10 : 1.

The ^{19}F spectra of D_2O solutions of free titanocene difluoride and β- and γ-CD mixtures were also recorded. The ^{19}F signal in Cp_2TiF_2 found at 3.56 ppm was shifted to 15.08 ppm in the β-CD–Cp_2TiF_2 solution and to 14.14 ppm in the γ-CD–Cp_2TiF_2 solution. Since we did not detect the hydrogen fluoride resonance in ^{19}F NMR spectra we suggest that the hydrolysis of Cp_2TiF_2 results in the cleavage of the Ti-Cp bond. The observed ^1H NMR resonances of aromatic protons could be ascribed to Cp_2TiF_2 (6.60 ppm) and to the hydrolysis product C_5H_5D (6.62 and 6.49 ppm). The detailed study dealing with these processes is in progress.

In conclusion, it is well known [25] that although the complex formation is convincingly proved in solution (by different techniques), sometimes a well-defined crystalline material is not isolated, but instead a solid-state product of unknown degree of complexation is obtained. We have proved the formation of inclusion complexes of Cp_2TiX_2 (X = F, Cl) with β- and γ-CD in solutions. The isolation of the crystals, which could allow the determination of the structure, was unsuccessful presumably due to hydrolysis of the titanocene halides. Unfortunately the degree of the complexation in the solid state products isolated by liophilisation, could not be unequivocally determined from the results of the solid state techniques used in the study.

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