The Inclusion of Rhodium(II)α-Methyl-cinnamate in β-Cyclodextrin

R. D. SINISTERRA[1],* R. NAJJAR[2], O. L. ALVES[3], P. S. SANTOS[2],
C. A. ALVES DE CARVALHO[4] and A. L. CONDE DA SILVA[2]

[1]*Departamento de Química da Universidade Federal de Minas Gerais, P.O. Box 702, Belo Horizonte, Brazil CEP 30161-970.*
[2]*Departamento de Química Fundamental, Instituto de Química da Universidade de São Paulo, P.O. Box 26077, São Paulo, Brazil CEP 05599-970.*
[3]*Laboratório de Química do Estado Sólido, Instituto de Química da Universidade Estadual de Campinas, P.O. Box 6154, Campinas, Brazil CEP 13081-970.*
[4]*Departamento de Química do ICEB, Universidade Federal de Ouro Preto, Ouro Preto, MG, Brazil.*

Abstract. The preparation and characterization of the 1 : 1 inclusion compound of rhodium(II) α-methyl cinnamate in β-cyclodextrin is reported. Evidence of inclusion was obtained from X-ray powder diffraction results, Raman, IR and UV-Vis spectroscopic studies and thermal analysis. Given the potential antitumor activity of the rhodium(II) carboxylate and its virtual insolubility in water, its inclusion in β-cyclodextrin opens the possibility for its transference to the aqueous phase.

Key words: Rhodium(II)carboxylates, β-cyclodextrin inclusion compounds.

Introduction

The discovery of the antitumor activity of *cis*-platin [*cis*-Pt(NH$_3$)$_2$Cl$_2$] led to considerable effort in the development of new drugs based on platinum group metals [1]. The antitumor activity of rhodium(II)carboxylates was first demonstrated by Bear for rhodium(II)acetate in 1972 [2–4]. Several other rhodium(II)carboxylates have been prepared in an attempt to enhance antitumor activity and reduce toxicity. Rhodium citrate [5] proved to be particularly promising concerning the former aspect, whereas trifluoroacetate and its sulfadiazine adducts are particularly attractive concerning the latter [6].

Despite encouraging preliminary results, the extremely low solubility of rhodium(II)carboxylates is a serious drawback to their use as antitumor agents. As a strategy for circumventing this limitation we have investigated the possibility of including rhodium(II)carboxylates in cyclodextrins. The aqueous solubility of sparingly soluble molecules can be substantially increased by their inclusion in

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* Author for correspondence.

the cavity of various cyclodextrins. Many such guest–host inclusion complexes have been studied previously [7–10]. In the present work we report the inclusion compound of rhodium(II)-α-methyl-cinnamate in β-cyclodextrin.

Experimental

MATERIALS AND PREPARATION OF RHODIUM(II) α-METHYLCINNAMATE

β-cyclodextrin hydrate (β-CD) was purchased from Aldrich and used without further purification. Rhodium(II) α-methyl cinnamate was prepared by refluxing 1.0 g $RhCl_3 \cdot 3H_2O$ and 3.5 g of sodium α-methylcinnamate in 100 mL of absolute ethanol for 1.5 h. After cooling to room temperature a green solid was collected and washed with water. After drying in a dessicator for 24 h, the product was recrystallized from dichloromethane. The compound was virtually insoluble in water, but was soluble in most common organic solvents. Chemical analysis revealed the expected carbon and hydrogen content: C 56.4 (56.2 calc), H 4.2(4.0 calc).

PREPARATION OF THE INCLUSION COMPOUND

The inclusion compound was prepared by adding dropwise an aqueous solution of β-cyclodextrin (0.35 g in 25 mL of water) under constant stirring to an ethanolic solution of rhodium(II) α-methyl-cinnamate (0.25 g in 20 mL of EtOH). The reaction mixture was kept at ca. 40–50 °C for 24 h, the final volume being reduced to ca. 10 mL. The green solid produced was collected by filtration, washed with water and dried under vacuum at room temperature. The physical mixture of β-CD and rhodium(II) α-methylcinnamate in a 1 : 1 molar ratio was also prepared for comparison by gentle grinding of the components until a homogeneous powder was obtained.

PHYSICAL MEASUREMENTS

X-ray powder patterns were obtained using a Phillips model PW 1140 diffractometer fitted with a LiF monochromator and employing CuK_α radiation. The TG, DTG and DSC curves were obtained on a Shimadzu TGA-50 at a heating rate of 10 °C/min under a nitrogen atmosphere. IR spectra were obtained employing a Perkin–Elmer 1750 FTIR instrument, with the samples dispersed in fluorolube. Raman spectra were obtained with a Jobin-Yvon U1000 double monochromator Raman spectrometer, using the 514.5 nm radiation of an Ar^+ laser (Innova-90) and a rotatory disc to prevent thermal decomposition. The laser was operated at 150 mW and the spectral resolution was 5 cm^{-1}. Reflectance spectra were obtained by using a Fiber Optics Guide spectrophotometer.

Results and Discussion

The first evidence for the inclusion of the rhodium(II) α-methylcinnamate comes from the solubilization of the complex in the β-cyclodextrin aqueous solution, as is observed by visual inspection. Chemical analysis indicates that the product isolated from the β-CD/rhodium(II) α-methylcinnamate solution has a 1 : 1 stoichiometry. The product shows moderate solubility in water as compared with the virtual insolubility of the pure carboxylate.

More stringent evidence for the formation of the inclusion compound comes from the X-ray results, as can be seen from the diffractograms displayed in Figure 1. The diffractogram of the physical mixture of the components (Figure 1) is simply the superposition of the diffractogram of the carboxylate and β-cyclodextrin, whereas the diffractogram of the product isolated from the rhodium(II)carboxylate/β-CD solution (Figure 1) shows new peaks at 9.6 and 10.15°, with other peaks characteristic of the individual components now being absent. Such results strongly suggest the formation of a new phase that can be associated with the inclusion compound. On the other hand, this diffractogram reveals appreciable crystallinity, in contrast to the majority of the CD inclusion compounds described in the literature [7, 9].

TG, DTG and DSC curves for β-cyclodextrin, the rhodium(II) α-methylcinnamate complex, the inclusion compound and the physical mixture (molar ratio 1 : 1) are shown in Figures 2 and 3, respectively. The TG/DSC results show that dehydration of β-CD occurs in the 80–90 °C region; this is not observed in the TG curve of the inclusion compound. The behaviour of the physical mixture in this respect parallels that of neat β-CD. This is again very strong evidence for the formation of the inclusion compound, indicating that the water molecules normally occupying the β-CD cavity were removed by the inclusion of the carboxylate. In addition, the behaviour of the TG/DSC curves for the inclusion compound and physical mixture at 250–300 °C is also different, with the latter showing a thermal behaviour that is a superposition of the curves observed for the isolated components.

The IR and Raman spectra are shown in Figures 4 and 5, respectively. The IR spectrum of the inclusion compound in the 3300–3400 cm^{-1} region, indicates the absence of the characteristic strong and broad band of water, which, on the other hand, is observed in β-CD and physical mixture. These results support the thermal analysis results. In general only small shifts in the vibrational frequencies of the guest molecules are observed revealing that the host : guest interaction is not particularly strong, as has already been observed for several CD inclusion compounds [8]. Changes in the relative intensities of modes assigned to the aromatic moiety suggest its inclusion in the β-CD cavity.

Raman spectroscopy is ideal for observing pertubations in the vibrational spectrum of the guest in CD inclusion compounds, since CDs are very poor Raman scatterers. In fact, the Raman spectrum of the inclusion compounds displays virtu-
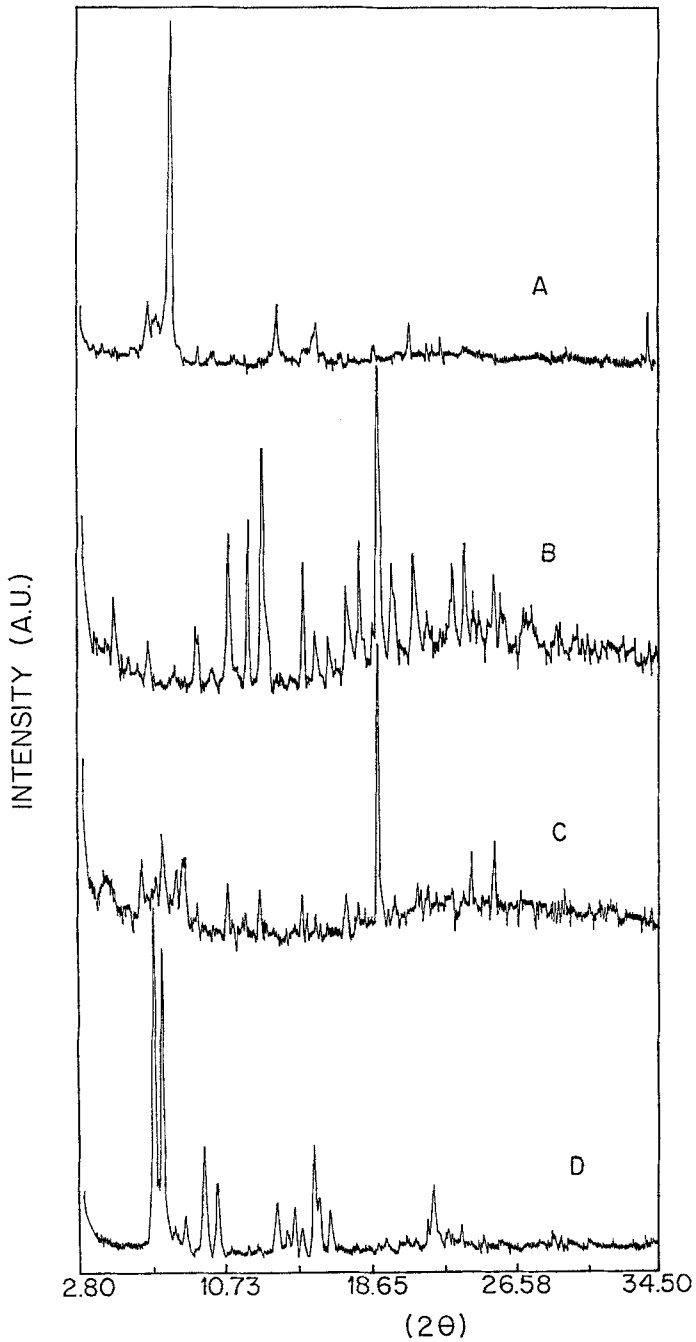
Fig. 1. X-ray diffraction pattern of (A) rhodium(II) α-methyl-cinnamate, (B) β-cyclodexterin, (C) the physical mixture and (D) the inclusion compound.
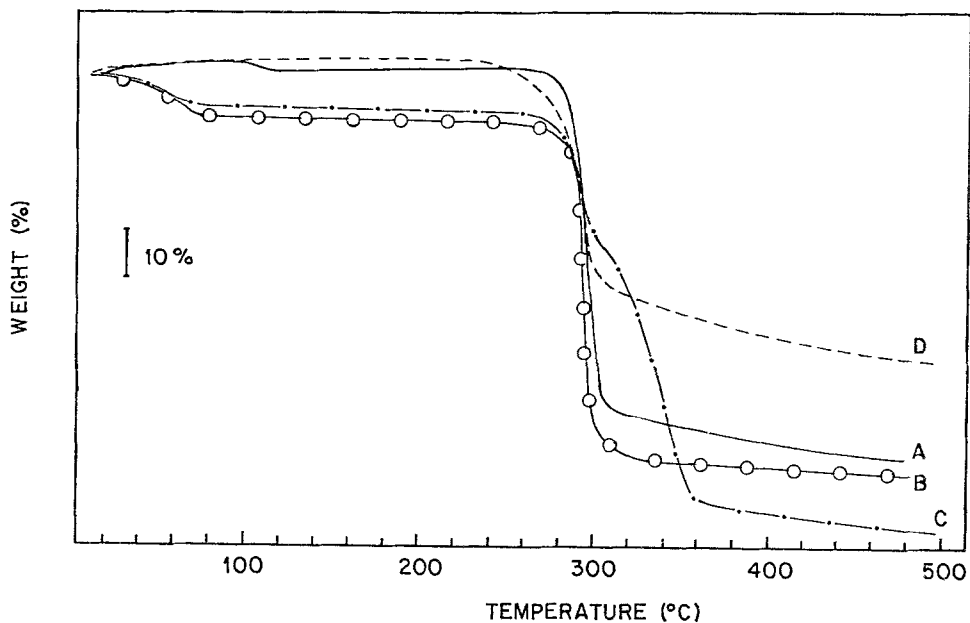
Fig. 2.   TG curves of (A) rhodium(II) α-methyl-cinnamate, (B) β-cyclodextrin, (C) the physical mixture and (D) the inclusion compound.
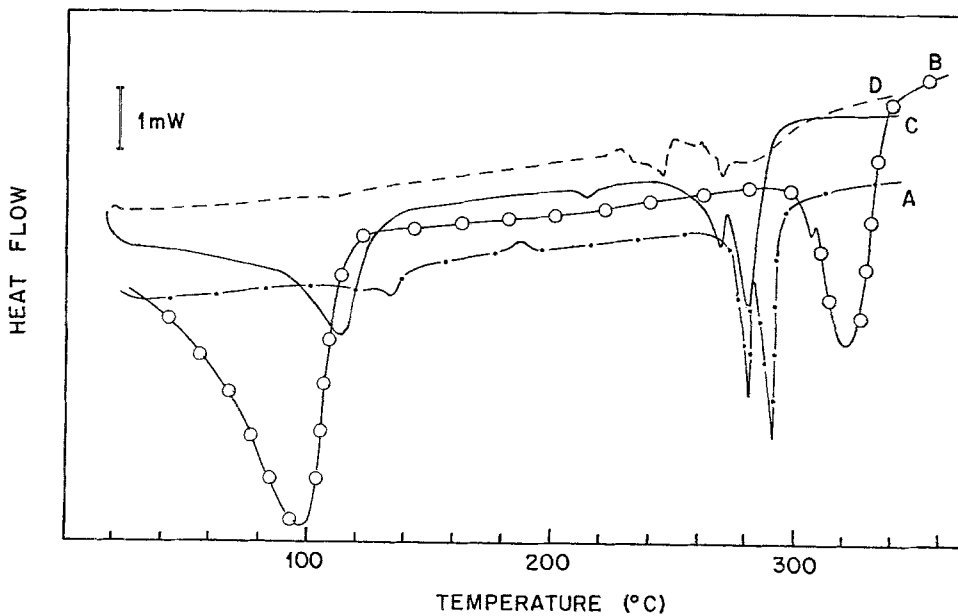

Fig. 3.   DSC curves of (A) rhodium(II) α-methyl-cinnamate (—), (B) β-cyclodextrin (o-o-o), (C) the physical mixture (·-·-·-·), (D) the inclusion compound (- - - -).
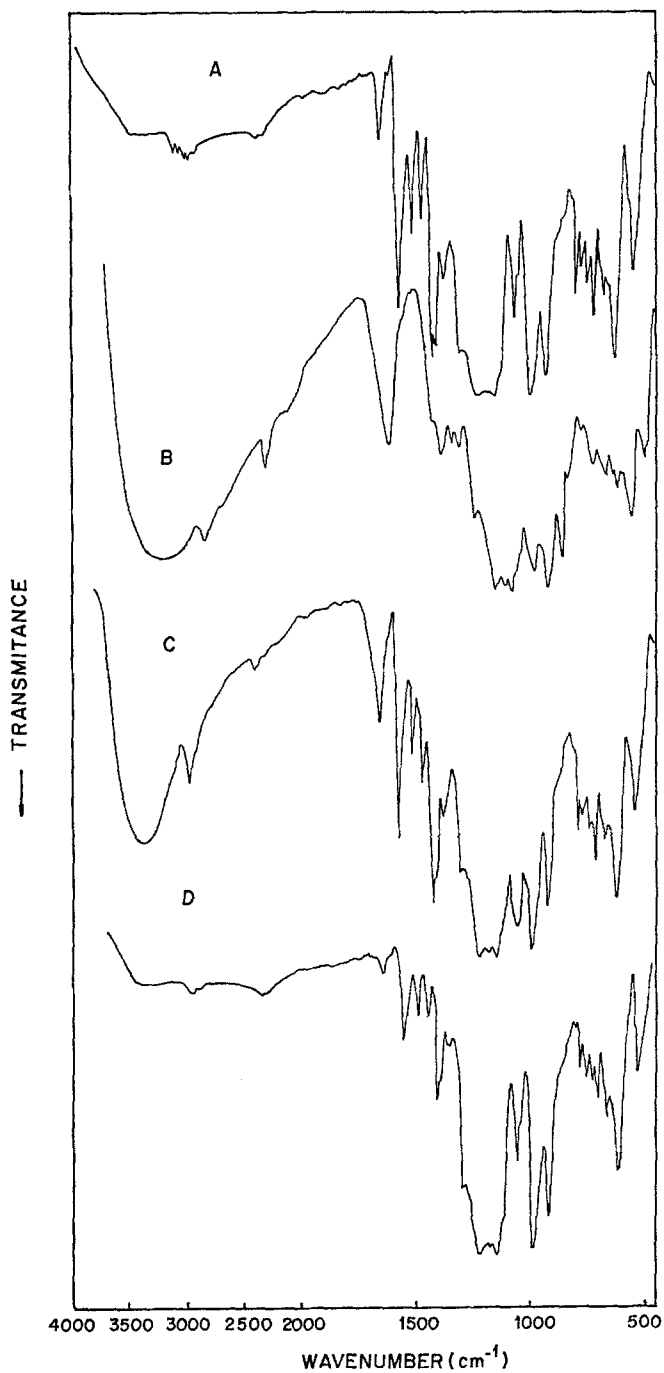
Fig. 4.   Infrared spectra in fluorolube dispersions of (A) rhodium(II) α-methylcinnamate, (B)-β-cyclodextrin, (C) the physical mixture and (D) the inclusion compound.
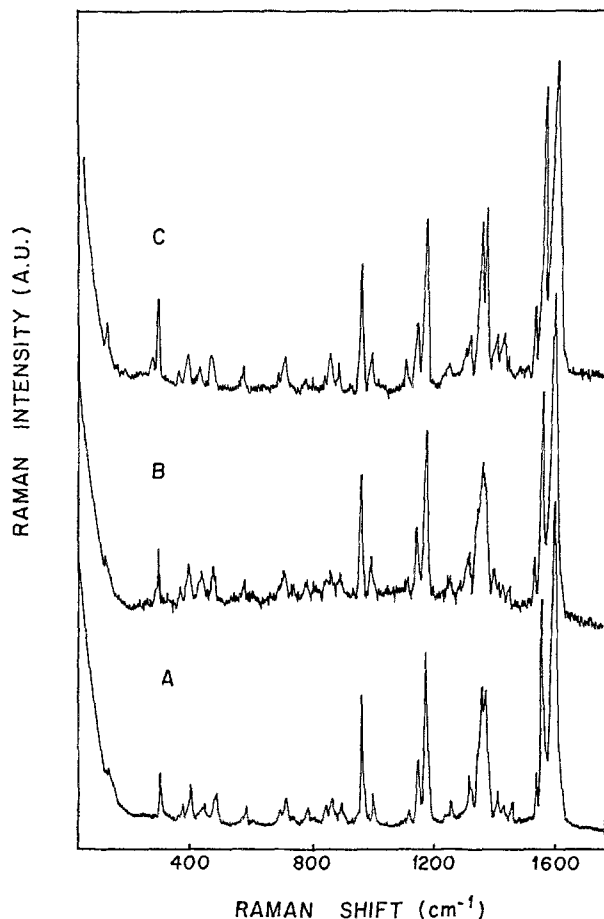
Fig. 5.   Raman spectra in the solid state of (A) rhodium(II) α-methylcinnamate, (B) the physical mixture and (C) the inclusion compound.

ally only the guest modes. The assignment of the ν(Rh—Rh) and ν(Rh—O) modes in the Raman spectrum of rhodium dicarboxylates has been the subject of a long controversy in the literature. The careful investigation by Clark *et al.* [11] was decisive and at present it is well established that ν(Rh—Rh) is expected around 290 cm^{-1}, whereas the ν(Rh—O) mode is expected around 340 cm^{-1}. It is worth mentioning that the metal–metal stretching mode is not particularly strong in the ordinary Raman spectrum of rhodium(II) dicarboxylates, but becomes very strong in the resonance Raman spectrum, excited in the UV [11]. In the present work the Raman band at ca. 333 cm^{-1}, present in the spectrum of the neat compound, included compound and physical mixture is assigned to the Rh—O symmetric stretching mode. The Raman band at ca. 317 cm^{-1}, absent from the neat compound spectrum, present in the spectrum of the included compound and as a shoulder in the case of the physical mixture, can be assigned as originating from a splitting of the 333 cm^{-1}

band. The Raman band at ca. $150\ cm^{-1}$, which shows up as a shoulder in the spectrum of the neat dicarboxylate and of the physical mixture, but more distinctively in the inclusion compound, cannot be assigned to the Rh—Rh stretching mode that is expected at much higher frequencies. On the other hand, its assignment would involve a much more detailed investigation.

It has been proposed that in rhodium(II)dicarboxylates there is an extended chain interaction between the units, resulting in extensive stacking [10], that could be a possible cause for the limited solubility. The present results suggest that in the inclusion compound, β-CD interacts mainly with the aromatic moiety of alternate cinnamate units, turning the molecule much less hydrophobic, and thus increasing its aqueous solubility.

Acknowledgements

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