

Studies on *bis*(cyclopentadienyl)titanium (IV) chelates of biologically active O-hydroxynaphthoquinone and its derivatives

R K SHARMA* and S K SINDHWANI

Department of Chemistry, University of Delhi, Delhi 110007, India

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Abstract. A convenient method for the preparation of $Cp_2Ti(L)$ complexes, where Cp is cyclopentadienyl and L is the conjugate base of O-hydroxynaphthoquinone or its derivatives, has been described. The new complexes have been characterized on the basis of chemical analysis, infrared and NMR spectral studies. These studies indicate that the complex is formed in 1:1 ratio and the ligand L chelates through the oxygen of the O-hydroxy group.

Keywords. *Bis*(cyclopentadienyl)titanium (IV); chelates; O-hydroxynaphthoquinone.

1. Introduction

Studies on organotitanium compounds have been pursued with keen interest over the last few years because of their use as catalysts for polymerization (Pitzer and Gutowsky 1946; Ziegler and Martin 1956) and hydrogenation (Duoriaceva 1965; Olive and Olive 1967) of olefins and dienes, and the discovery of the cyclopentadienyl type of derivatives of titanium (IV) being potent antitumor compounds (Koepef and Koepef-Maier 1979; Koepef-Maier *et al* 1981) resulted in tremendous development in the field of titanocene derivatives.

O-hydroxynaphthoquinones are substances which have antihemorrhagic activity similar to vitamin K. O-hydroxynaphthoquinone and its derivatives have widespread applications in various biological fields. Recently it has been proposed that such metal chelates of O-hydroxynaphthoquinone and its derivatives could also have an increased antibacterial properties (Padhye *et al* 1973; Kulkarni *et al* 1981). It has been suggested that the remarkable antimicrobial activity of some of the O-hydroxynaphthoquinones (Miura 1973; Makato *et al* 1978) and its derivatives might be due to a chelate compound formed as an intermediate.

The present work describes the preparation and studies on chelates of *bis*(cyclopentadienyl)titanium (IV) with O-hydroxynaphthoquinone and its derivatives.

* For correspondence

2. Experimental

2.1 Reagents and general techniques

All the reagents used were of analytical grade. *Bis*(cyclopentadienyl)titanium (IV) dichloride, Cp_2TiCl_2 , was obtained from Fluka A G, Switzerland. Tetrahydrofuran (Baker A R) was dried over sodium metal and then boiled under reflux until it gave a blue colouration with benzophenone. It was finally dried by distillation from lithium aluminium hydride. *n*-Hexane (BDH) was dried by refluxing over sodium metal followed by distillation and triethylamine (Et_3N) was dried as reported in the literature (Vogel 1978). Titanium was determined gravimetrically as oxide and chlorine was estimated as silver chloride. Nitrogen was estimated by the standard method described by Vogel (1978).

IR spectra of the complexes were recorded as KBr pellets in the $4000\text{--}200\text{ cm}^{-1}$ region using a Perkin-Elmer 621 spectrophotometer. Proton NMR spectra were recorded at ambient temperature (20°C) at a sweep width of 900 Hz with a Perkin-Elmer R-32 spectrometer. Chemical shifts (δ , ppm) are expressed using TMS as the internal standard (1% by volume).

2.2 Preparation of ligands

2.2a *3-hydroxy-2-methyl-1,4-naphthoquinone* (i): 3-hydroxy-2-methyl-1,4-naphthoquinone (HMNQ) or phthiocol was prepared by the method of Fieser (Fieser 1940).

2.2b *2-hydroxy-1,4-naphthoquinone* (ii): 2-hydroxy-1,4-naphthoquinone monoxime (HNQM) was prepared by the method of Goldstein (Goldstein and Grandjean 1943).

2.2c *2-hydroxy-1,4-naphthoquinone monosemicarbazone* (HNQS) (iii): 1.04 g of 2-hydroxy-1,4-naphthoquinone was dissolved in a minimum amount of alcohol and an aqueous solution containing 0.67 g of semicarbazide hydrochloride, and an equal amount of anhydrous sodium acetate was added to it. The mixture was refluxed for one hour, filtered (when necessary) and cooled in ice. The semicarbazone was precipitated by adding dilute hydrochloric acid to the solution. The semicarbazone thus obtained was recrystallised from ethanol. The yield was $\approx 70\%$.

2.2d *3-hydroxy-2-methyl-1,4-naphthoquinone monoxime* (HMNQM) (iv): 1 g of phthiocol was dissolved in about 20 ml of ethanol and an aqueous solution containing 1.4 g of hydroxylamine hydrochloride and an equal amount of anhydrous sodium acetate was added to it. The mixture was refluxed for 2 h and cooled in ice. The oxime was precipitated by adding water to the solution. The oxime thus obtained was recrystallised from ethanol, yield 65%.

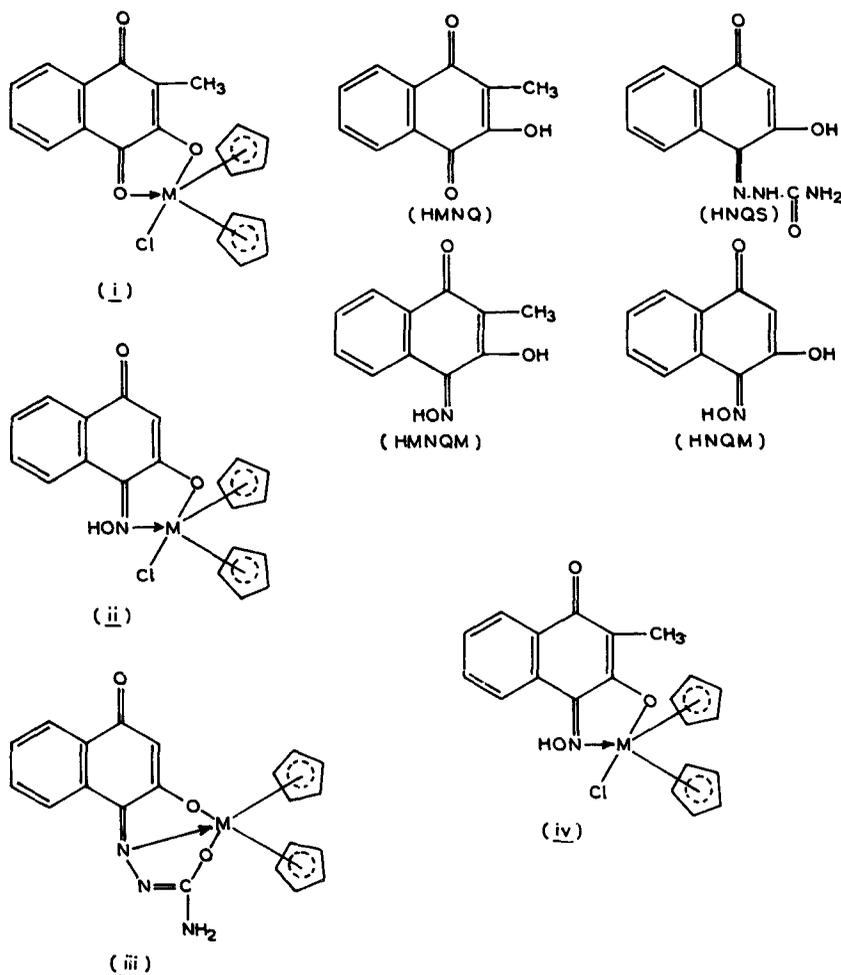
2.3 Preparation of the complexes

All the compounds were prepared in a similar manner and all operations were carried out under strictly anhydrous conditions. To a solution of *bis*(cyclopentadienyl)titanium (IV) dichloride, Cp_2TiCl_2 (5 mmol), in 50 ml dry tetrahydrofuran, a solution of

3-hydroxy-2-methyl-1,4-naphthoquinone (HMNQ), 2-hydroxy-1,4-naphthoquinone monoxime (HNQM), 2-hydroxy-1,4-naphthoquinone monosemicarbazone (HNQS) or 3-hydroxy-2-methyl-1,4-naphthoquinone monoxime (HMNQM) (5 mmol) in 50 ml tetrahydrofuran containing 6 mmol Et_3N was added. The mixture was stirred vigorously for 0.5 h and then refluxed for 4–6 h. Precipitated $\text{Et}_3\text{N}\cdot\text{HCl}$ was removed by filtration and the volume of the filtrate was reduced to one-fourth of the original under pressure. The crystals of the product were obtained by adding *n*-hexane or petroleum ether.

3. Results and discussion

HMNQ, HNQM, HNQS and HMNQM react with *bis*(cyclopentadienyl)titanium (IV) dichloride (Cp_2TiCl_2) in 1:1 molar ratios giving derivatives of titanium (IV) of types (i), (ii), (iii) and (iv), respectively.



All the compounds crystallised as yellow to yellowish brown products. The oxime and semicarbazone complexes are soluble in dimethylsulphoxide, N,N-dimethylformamide, partially soluble in chloroform and acetone and are insoluble in alcohol and water. The solubility of phthiocol derivatives is very poor in all these solvents. Table 1 describes the analytical and physical data of the complexes.

The assignment of the characteristic IR frequencies of the complexes is listed in table 2. Absorption bands, indicating the presence of cyclopentadienyl group (Lippincott and Nalson 1953; Fritz 1964) are located at approximately 3100 cm^{-1} [$\gamma(\text{C-H})$], 1435 cm^{-1} [$\gamma(\text{C-C})$], 1025 cm^{-1} [$\gamma(-\text{CH})$] and 810 cm^{-1} [$\gamma(-\text{CH})$]. Persistence of the bands of the cyclopentadienyl ring in the complexes indicates that these groups remain π -bonded to the metal and retain their aromatic character. Apart from this, an additional band near 440 cm^{-1} can be assigned to $\text{Ti-C}_5\text{H}_5$ vibrations (Nesmeyanov 1968; Coutts and Wailes 1975).

A medium intensity band at $\approx 1280\text{ cm}^{-1}$ is observed in the spectra of all the ligands due to phenolic $\gamma(\text{C-O})$ vibration. In the complexes this band is shifted slightly to the higher wave number and appears at around 1310 cm^{-1} indicating the bonding of ligand to the metal through oxygen (Khera *et al* 1983, 1984; Sharma *et al* 1984).

Table 1. Analytical and physical data.

Compound	Decomp. temp. ($^{\circ}\text{C}$)	Elemental analysis: Found (calc.) %				
		C	H	N	Cl	M
HMNQ	173-73	68.20 (70.21)	5.23 (4.26)	—	—	—
$\text{Cp}_2\text{Ti}(\text{HMNQ})\text{Cl}$ (i)	153	64.50 (62.94)	5.20 (4.50)	—	9.20 (8.87)	11.42 (11.96)
HNQM	180	65.80 (63.49)	3.86 (3.70)	7.04 (7.41)	—	—
$\text{Cp}_2\text{Ti}(\text{HNQM})\text{Cl}$ (ii)	170	63.20 (59.79)	4.92 (4.24)	3.08 (3.49)	8.62 (8.84)	11.60 (11.93)
HNQS	147	56.48 (57.14)	4.40 (3.90)	17.96 (18.18)	—	—
$\text{Cp}_2\text{Ti}(\text{HNQS})$ (iii)	96	63.18 (61.93)	5.12 (4.67)	10.02 (10.32)	—	11.62 (11.77)
HMNQM	200-1	65.86 (64.71)	5.04 (4.90)	6.60 (6.86)	—	—
$\text{Cp}_2\text{Ti}(\text{HMNQM})\text{Cl}$ (iv)	74	62.30 (60.52)	5.16 (4.80)	3.18 (3.36)	8.34 (8.53)	11.28 (11.50)

Table 2. Characteristic IR bands and ^1H NMR data.

Complex	IR (cm^{-1})		^1H NMR (δ , ppm)	
	$\gamma(\text{C=O})$	$\gamma(\text{C-O})$	C_5H_5	Aromatic ring protons
$\text{Cp}_2\text{Ti}(\text{HMNQ})\text{Cl}$	1670	1300	6.20(s)	6.70-7.80
$\text{Cp}_2\text{Ti}(\text{HNQM})\text{Cl}$	1660	1300	6.20(s)	6.70-7.80
$\text{Cp}_2\text{Ti}(\text{HNQS})$	1670	1295	6.20(s)	6.70-7.80
$\text{Cp}_2\text{Ti}(\text{HMNQM})\text{Cl}$	1665	1300	6.15(s)	6.70-7.80

This fact is further supported by the disappearance of the broad $\nu(\text{OH})$ vibrations in the $3300\text{--}3150\text{ cm}^{-1}$ region in the complexes.

A strong band is observed at $\approx 1680\text{ cm}^{-1}$ in the IR spectra of free phthiocol which is characteristic of $\nu(\text{C}=\text{O})$ vibrations. Coordination of oxygen to the metal atom would be expected to reduce the density of the carbonyl linkage and thus lower the $\nu(\text{C}=\text{O})$ frequency (Bellamy 1975). In the complexes this band is observed as a doublet between $1680\text{--}1630\text{ cm}^{-1}$. This shift of the $\nu(\text{C}=\text{O})$ band to lower wave numbers indicates the coordination of one of the carbonyl oxygens to the metal.

A medium intensity band at 1620 cm^{-1} due to $\nu(\text{C}=\text{N})$ in the oxime and semicarbazone is shifted to lower frequencies ($\approx 1575\text{ cm}^{-1}$) in the complexes, indicating that the $\text{C}=\text{N}$ bond order decreases and the nitrogen atom coordinates to the metal (Khera *et al* 1983, 1984; Sharma *et al* 1984). The band around 3400 cm^{-1} in the oxime ligand due to the asymmetric stretching vibration of the terminal $-\text{NH}_2$ group is not affected on complexation and this indicates that the terminal $-\text{NH}_2$ group does not participate in the coordination by this ligand (Ghosh *et al* 1981; Sankhla *et al* 1983).

The appearance of a band at $\approx 350\text{--}375\text{ cm}^{-1}$ in the phthiocol and oxime complexes due to $\nu(\text{M}-\text{Cl})$ vibrations confirms the presence of coordinated chlorine (Kaushik *et al* 1978). However, this band is absent in the semicarbazone complexes which indicates the replacement of both the chlorines by a single semicarbazone group. The bands appearing at $500\text{--}460\text{ cm}^{-1}$ in all the complexes may be assigned to $\nu(\text{M}-\text{O})$ and $\nu(\text{M}-\text{N})$ vibrations respectively (Khera *et al* 1983, 1984; Sharma *et al* 1984).

The $^1\text{H NMR}$ spectra of oxime and semicarbazone complexes have been recorded in deuterated DMSO. The single sharp resonance due to the C_5H_5 group occurs at $\delta 6.2$ ppm. The resonance signals due to the aromatic protons in both kinds of complexes are observed as multiplets in the range $\delta 6.70\text{--}7.80$. This shows considerable downfield shift as compared to the corresponding signals in the case of oxime and semicarbazone (observed at about $\delta 6.50\text{--}7.40$) and supports the coordination of nitrogen of oxime and semicarbazone ligand to the metal. Further, the appearance of the $-\text{NH}_2$ protons signals at 4.9 ppm in the semicarbazone complex indicate that the terminal $-\text{NH}_2$ group of the semicarbazone does not take part in the complexation.

The disappearance of the phenolic $-\text{OH}$ protons(s) signal(s) in the complexes indicates its deprotonation and its taking part in bond formation to the metal through the oxygen. However, the resonance signals due to the $-\text{OH}$ group of oxime ($\text{N}-\text{OH}$) are retained in the complex showing that the oxygen of the $-\text{NOH}$ group remains intact in the complexation. The semicarbazone ligand shows an $-\text{NH}$ resonance signal at 9.8 ppm which disappears upon complexation. Further, no enolic OH resonance signal is observed in its complexes. This supports the enolisation of ligand and its deprotonation after complexation which, in turn, confirms the participation of the enolic oxygen of the semicarbazone in bond formation.

Studies show that 3-hydroxy-2-methyl-1,4-naphthoquinone (HMNQ) or phthiocol, 2-hydroxy-1,4-naphthoquinone monoxime (HNQM) and 3-hydroxy-2-methyl-1,4-naphthoquinone monoxime (HMNQM) act as monofunctional bidentate ligands. Coordinations occurs through one phenolic oxygen and one carbonyl oxygen in phthiocol, while in the case of HNQM and HMNQM the coordination sites are the phenolic oxygen and nitrogen of the oxime group. The 2-hydroxy-1,4-naphthoquinone monosemicarbazone acts as a tridentate ligand with the coordination sites being the phenolic oxygen, the enolic oxygen and the nitrogen of the semicarbazone group.

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