

SYNTHESIS AND CHARACTERIZATION OF TITANOCENE POLYMER DERIVATIVES*

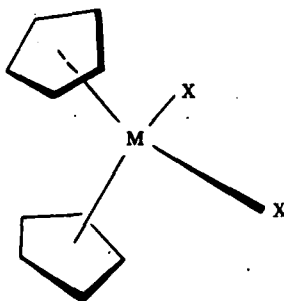
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ABSTRACT

Titanocene polymer derivatives with potential antitumor properties were synthesized by interfacial condensation. The preformed polymers used are PAA (polyacrylic acid), CPSMA (1:1 alternating copolymer of styrene and maleic anhydride) and DVEMA (1:2 copolymer of divinyl ether and maleic anhydride). The ratio of practical and theoretical titanium content is 73.6%, 92.2% and 86.2% for PAA, CPSMA and DVEMA polymer derivatives respectively. The IR spectra of the polymer derivatives possess the characteristic absorptions of titanocene. XPS (X-ray photoelectron spectroscopy) of O_{1s} and $Ti_{2p_{3/2}}$ supports the existence of Ti-O bonding.

Metallocene dihalides have been known for about 35 years and they were first reported by Wilkinson and Birmingham^[1] but their antitumor property was only known in 1979^[2]. The chemical characteristics of metallocene dihalides are their distorted tetrahedron geometry, central metal atoms M ($M=Ti, V, Nb, Mo$ and so on) and acido ligands (usually halogen) arranged in adjacent position. The other two ligands are two cyclopentadienyl rings bonded to the central atoms by metal-carbon bonding. The structure of metallocene is expressed in the following diagram.



Metallocene dihalides. $M=Ti, V, Nb, Mo$ etc. $X=$ Acido ligands.

The other two ligands are CP (cyclopentadienyl) rings.

The attachment of drugs on preformed polymers is a significant work, because inclusion of the drugs into polymers not only control the release of the drugs which directly act upon the locus of the disease but also lower the negative effects due to the drugs not passing through other organs, liver and kidney for instance. We reported the synthesis and characterization^[3] and pharmaceutical study

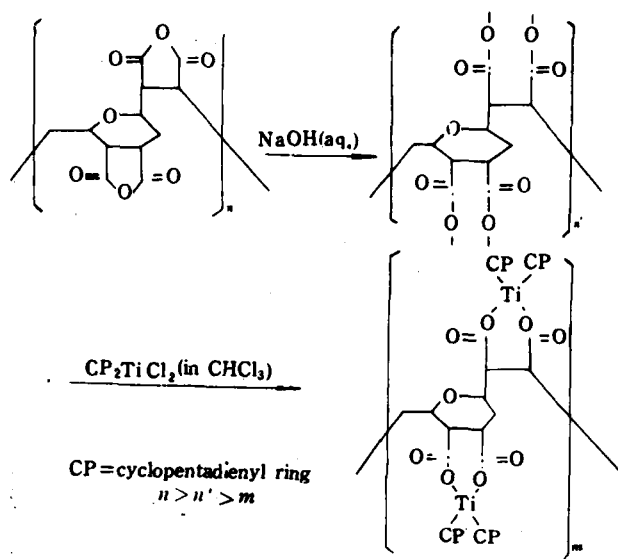
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of *cis*-platinum complex polymer derivatives from which we observed that: 1. most of the polymer derivatives possess antitumor activity, 2. polymer ligands may affect the effects of the drugs, for example, cisplatin polymer derivatives are no more the most active ones, 3. all the polymer derivatives of *cis*-platinum complexes show lower toxicity and lasting delivery compared with the *cis*-platinum complex from which the polymer derivative was obtained. These results are basically consistent with those obtained by other colleagues at home^[4].

This paper is only concerned with titanocene without involving other metallocenes. It is easy to link titanocene onto preformed polymers by interfacial condensation. The preformed polymers used are PAA, CPSMA and DVEMA. What the result will be for the last polymer derivative is being expected. The above preformed polymers were dissolved in equivalent sodium hydroxide aqueous solution and titanocene was dissolved in chloroform, when the two solutions were put together and stirred vigorously the expected yellow or orange precipitate formed after several minutes. Taking DVEMA as example, the synthetic route may be expressed as follows.



An example of synthetic route.

EXPERIMENTAL

1. Reagents and instrumentation

All reagents used are reagent grade without further purification. PAA and CPSMA used were described somewhere else^[3] and DVEMA was received. The molecular weight of DVEMA is $\bar{M} = 19000$. Titanocene was synthesized according to the literature^[5], and purified by vacuum sublimation. The dark red needle crystal with M.P. 287.0—288.5°C. was used for the interfacial condensation. IR spectra were recorded on Perkin Elmer 683 spectrometer and all the samples are KBr tablets. XPS (X-ray photoelectron spectroscopy) were performed on Kratos AEI ES-300.

2. Interfacial condensation

2.02g (0.01 mole) CPSMA was dissolved in 300ml water containing 0.80g (0.02 mole) NaOH. 2.50g (0.01 mole) CP₂TiCl₂ (titanocene) was dissolved in 300ml chloroform. The above two

solutions were mixed in a 1000ml three-neck flask with mechanical stirrer and a condenser. After an hour stirring, let the reaction mixture stand overnight. The precipitate was filtered by 2# sintered glass filter (better by centrifuge). The precipitate was thoroughly washed with distilled water till no chlorine ions being detected by AgNO_3 . This was washed by ethanol, followed by ether, first dried in air and then in vacuum. The yield is 95%.

Titanocene polymer derivatives of PAA, DVEMA were synthesized in the same way, the yields were 76.8% and 87.7% and the colour was pale yellow and orange respectively.

3. Estimation of titanium content in polymer derivatives

Gravimetric method was used to analyze the titanium content in polymer derivatives^[6]. Thoroughly dried polymer derivatives were burnt at 900—1000°C in a constant weighed crucible.

Titanium content was calculated from the residue TiO_2 . The result was listed in Table 1.

Table 1 Ratio of Ti_p/Ti_t

Titanocene polymer derivatives of	Ti_p/Ti_t (%)
CPSMA	92.2
PAA	73.6
DVEMA	86.2

Ti_p : practical content of titanium calculated from TiO_2 obtained from gravimetric analysis.

Ti_t : theoretical content of Ti calculated according to the carboxylic groups in the polymers completely reacted with titanocene.

4. Solubility test for the polymer derivatives of titanocene

Titanocene polymer derivatives of	CPSMA	PAA	DVEMA
Solvents			
water	X	X	X
ethanol	X	X	X
ether	X	X	X
chloroform	X	X	X
acetone	X	X	X
DMF	X	X	X
DMSO	S	X	SS
hot DMSO	S	X	S

X: insoluble; SS: slightly soluble; S: soluble.

RESULTS AND DISCUSSION

Titanium content of the polymer derivatives may be determined by the structure of the polymers used because the content does not depend upon the reaction period. The distance of the

two carboxylic groups in PAA is longer than those of other two polymers, so crosslinking might happen at the very beginning. It could be observed that once the pale yellow precipitate forms no more changes could be noticed. As a result, the later coming titanocene is more difficult to react with PAA network. So the Ti content of PAA derivative is much lower and not soluble in solvents tested. CPSMA and DVEMA polymer derivatives are soluble and have high content of titanium. These show titanocene orderly condensed with the carboxylic groups without remarkably crosslinking. This is alike to the reaction of cis-platinum complexes and CPSMA, that we discussed in other paper^[3].

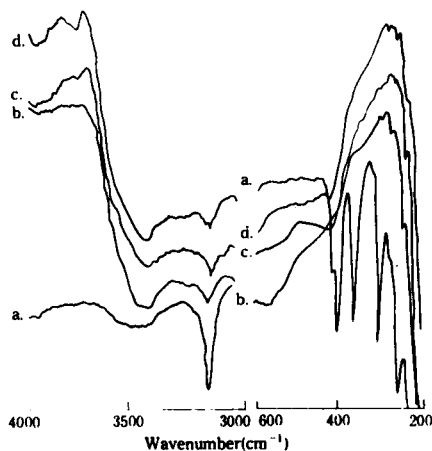


Fig.1-a IR spectra of titanocene and its polymer derivatives. 4000cm^{-1} — 3000cm^{-1} and 600cm^{-1} — 200cm regions.

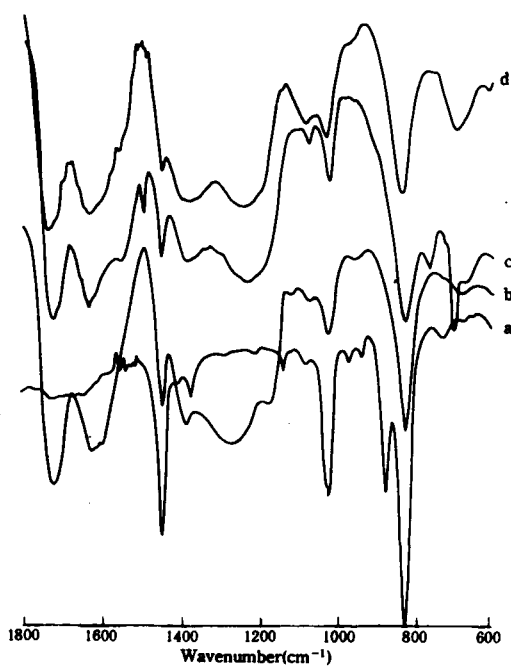


Fig.1-b IR spectra of titanocene and its polymer derivatives. 1800cm^{-1} — 600cm^{-1} region.

Fig.1-a and Fig.1-b show the IR spectra of titanocene and its three polymer derivatives. The former includes two regions 4000cm^{-1} — 3000cm^{-1} and 600cm^{-1} — 200cm^{-1} and the later is 1800cm^{-1} — 600cm^{-1} region. These spectra clearly show that all the polymer derivatives possess the characteristic absorptions of titanocene. The absorption at $\text{ca } 3118\text{cm}^{-1}$ is the symmetric in-plane stretching of C—H of CP. 1445cm^{-1} (very strong) and 1375cm^{-1} (weak) two absorptions are symmetric and asymmetric inplane skeletal stretching of C—C in CP ring. The bands at 1030cm^{-1} (strong) and 820cm^{-1} (very strong) are CP ring's C—H asymmetric and symmetric out-of-plane deformation respectively^[7]. Małowski and Nakamoto assigned Ti—Cl stretching at 400cm^{-1} ^[8] and we can see that this band disappeared in the IR spectra of all the polymer derivatives in Fig.1-a. This clearly shows that Ti-Cl bond no more exists due to titanocene indeed condensed with the carboxylic groups in the polymers. As to the two absorptions at $\text{ca } 1625\text{cm}^{-1}$ and 1720cm^{-1} , they are the well-known C=O carbonyl stretching in —COOM (M=metal) and —COOH respectively. The carboxylic groups are the unreacted residue ones in the polymers and this show that the preformed polymers can not be converted into sodium salts when they are hydrolyzed in equivalent sodium hydroxide. Fig.2 and Fig.3 are the X-ray photoelectron spectra of $\text{Ti}_{2p_{3/2}}$ and O_{1s} in titanocene and its polymer derivatives. Because of the change of the chemical environment of titanium and oxygen after the interfacial condensation, the binding energy of the inner shell electrons of titanium and oxygen must be changed. As is known to all, oxygen is more electronegative than chlorine, so the electron density of titanium in titanocene polymer derivatives must be smaller than that of in titanocene. As a result, the electron binding energy of $\text{Ti}_{2p_{3/2}}$ in polymer derivatives of titanocene must be larger than that in titanocene. This is clearly shown in Fig.2.. It is easy to imagine that the electron density of oxygen in titanocene polymer derivatives must become larger than that in DVEMA. From the binding energy shift in Fig.3, one can easily understand why the binding energy of O_{1s} in titanocene polymer derivatives is smaller than that in DVEMA. The new bonding

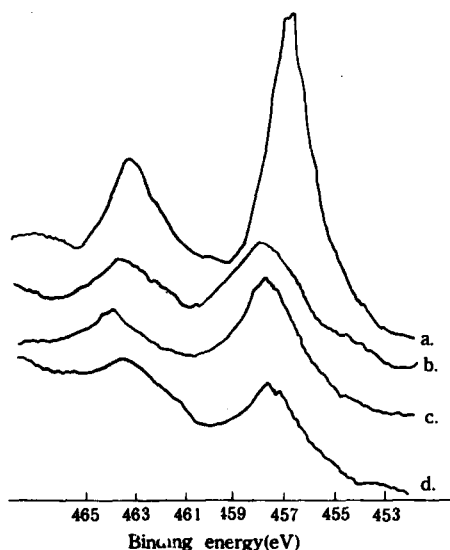


Fig.2 $\text{Ti}_{2p_{3/2}}$ XPS for titanocene and its polymer derivatives.

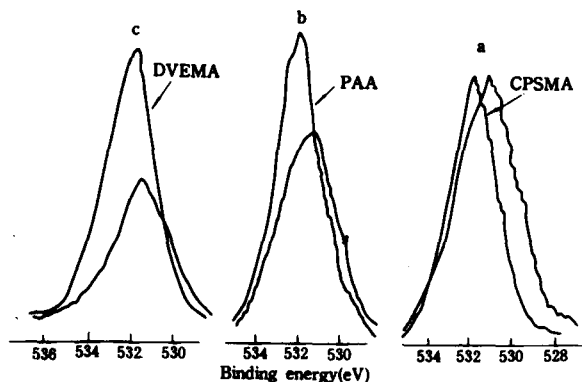


Fig.3 O_{1s} XPS for CPSMA, PAA and DVEMA and their related polymer derivatives of titanocene.

formation between Ti and oxygen can be obviously confirmed by the XPS results.

The pharmaceutical properties of these polymer derivatives will be examined.

Keywords:

Titanocene; Antitumor drug; Interfacial condensation

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