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Aqueous-phase synthesis of di-(η^5-cyclopentadienyl)salicylato- and di-(η^5-cyclopentadienyl)phthalatotitanium(IV) complexes

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Abstract

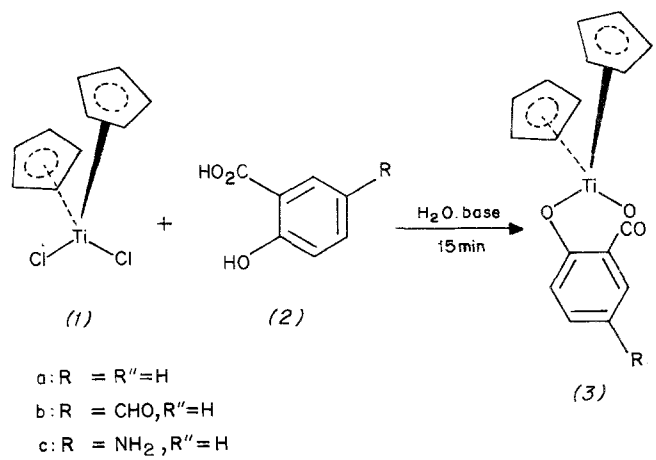
Di-(η^5-cyclopentadienyl)dichlorotitanium(IV) reacts with salicylic acid or some of its ring-substituted derivatives in aqueous medium in the presence of alkali carbonate, giving (substituted) di(η^5-cyclopentadienyl)-salicylatotitanium(IV) complexes *(3)*. Analogously, although less efficaciously, the dichlorotitanium compound reacts with phthalic acid to give the phthalato complex *(5)*, and with dipicolinic acid to yield the pyridinedicarboxylato compound *(7)*. Meticulous control of the experimental conditions is necessary to minimize hydrolytic side reactions. The product complexes *(3)* and *(5)* can be recrystallized from chloroform, in which they dissolve completely when freshly prepared; prolonged storage at ambient temperature causes reductions in solubility. I.r. and n.m.r. spectroscopic features of the product complexes are presented.

Introduction

The recent report[1] of the successful preparation of a dicyclopentadienylbisbenzoatotitanium complex in aqueous solution prompts us to communicate the results of an investigation, in our laboratories, of the aqueous-phase synthesis of dicyclopentadienyltitanium complexes comprising bidentate ligands. Dicyclopentadienyltitanium(IV) compounds have been of interest to us for some time because of their potential antineoplastic activity. The prototype titanocene complex *(1)*, di-(η^5-cyclopentadienyl)-dichlorotitanium(IV), exhibits powerful antiproliferative effects toward both liquid and solid Ehrlich ascites tumors, lymphatic and lymphocytic leukeumias and other murine tumour lines[2], and so do some of its derivatives in which the chloride ligands have been replaced by other, similarly good leaving groups[2,3]. It has been pointed out[2] that the Cl···Cl 'bite' in *(1)* and in other biomedically active metallocenes of the Cp_2ML_2 type (Cp = cyclopentadienyl, L = leaving group) is of a similar magnitude to that in *cis*-diamminedichloroplatinum(II) (cisplatin), and in light of certain similarities in the hydrolytic and aquation behavior of *(1)* and cisplatin, the mode of biological action of titanocenes has been proposed to involve crosslinking of DNA by Ti coordination with suitably spaced base units, thus mimicking cisplatin action[4]. In conformity with our prime and ultimate objective, the synthesis of water-soluble polymer-drug conjugates possessing controlled-drug release properties, we searched for titanocene complexes that would comprise leaving groups somewhat more stable towards hydrolysis than chloride and preferably would allow their formation to proceed in aqueous medium. Di-(η^5-cyclopentadienyl)-salicylatotitanium(IV) compounds were the complexes of choice, and in the following we report on their aqueous-phase preparation. Some dicarboxylatotitanium complexes are included in this investigation for comparison.

Results and discussion

The procedure is remarkably simple. The dichloride *(1)*, dissolved in water, was briefly treated with an aqueous solution of salicylic acid *(2a)*, or one of its derivatives *(2b–d)*, and alkali carbonate at ambient temperature (Scheme 1). Reaction was instantaneous, and the com-



(1) *(2)* *(3)*

a: R = R″=H
b: R = CHO, R″=H
c: R = NH_2, R″=H

plexes formed, which precipitated largely *(3a,b)* or partially *(3c)* from solution, were collected by filtration or by extraction with chloroform. The chloroform extracts in these operations could be washed briefly with aqueous alkali (for removal of any unreacted salicylic acids) without causing substantial solute degradation[5].

The complexes so obtained proved to be reasonably pure at this stage as judged by their i.r. and n.m.r. spectra, and recrystallization from chloroform entailed only minor additional purification. Yields were 70–90%. The reaction period, and hence the exposure time of the product complexes to the aqueous environment, is critical. Too short a reaction time (2–5 min) leaves large quantities of educts unreacted or semi-reacted, the separation of which is not always straightforward, whereas prolonged (> 20 min) contact with the water medium causes significant degradation of the complexes, manifested in the loss of Cp ligand and concomitant formation of additional Ti—O bonds. Stirring or sonication periods of 10–15 min appear to be optimal under our experimental conditions.

The freshly prepared, reddish to maroon salicylato complexes dissolved completely or almost completely in halocarbons. Prolonged storage at ambient temperature, however, resulted in diminished solubility in these solvents without noticeable other changes (e.g., the excellent solubility in dipolar aprotic solvents was not affected); this

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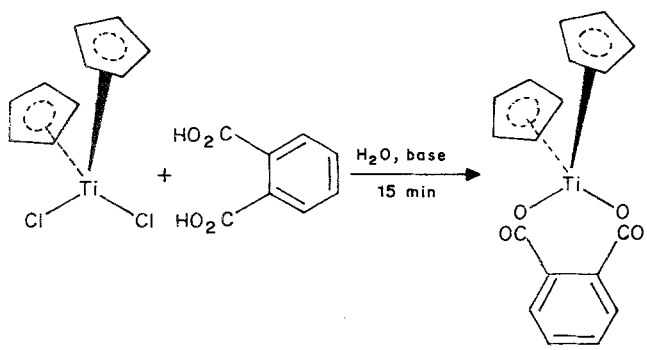
change in solubility characteristics could be appreciably delayed by low-temperature storing.

The solid-state (KBr) i.r. spectra of *(3)* display the strong out-of-plane CH deformation band of the Cp rings near 810 cm^{-1}[9,10] and show carboxylato absorption in the vicinity of 1615 [ν_2, asym ν(OCO)] and 1300 cm^{-1} [ν_1, sym ν(OCO)] (Table 1)[11] in addition to the respective benzene-aromatic ligand bands. The large separation ($\nu_2 - \nu_1$) between the two carboxylato bands in these compounds indicates a monodentate coordination mode of the carboxylato group as similarly observed with the simple dibenzoato complex[8,12]. The ^{1}H NMR spectra ($CDCl_3$) display characteristic, sharp singlets due to the Cp ring protons in the range of 6.5–6.3 ppm (Table 1) and show the expected resonance patterns of the substituted benzene rings between 8 and 7 ppm in the appropriate ratios.

For comparison with the salicylato complexes *(3a)* and *(3b)* synthesized in aqueous phase, we prepared the same compounds from dimethyltitanocene [(di(η^5-cyclopentadienyl)dimethyltitanium(IV)] and the respective free salicylic acid ligands *(2a)* and *(2b)* in deoxygenated, absolute THF by the general procedure previously elaborated for the synthesis of *(7)*[13]. Obtained under these considerably more demanding experimental conditions, the two complexes were spectroscopically pure without further recrystallization and proved identical in all aspects with the aqueous-phase products.

The efficient preparation of the salicylic acid derivatives *(3)* per scheme 1 encouraged us to attempt the aqueous-phase synthesis of aromatic dicarboxylatotitanium compounds. The reaction of *(1)* with phthalic acid *(4)* in the presence of alkali carbonate in water, indeed, gave the orange-yellow phthalato complex *(5)* (Scheme 2) in 50–

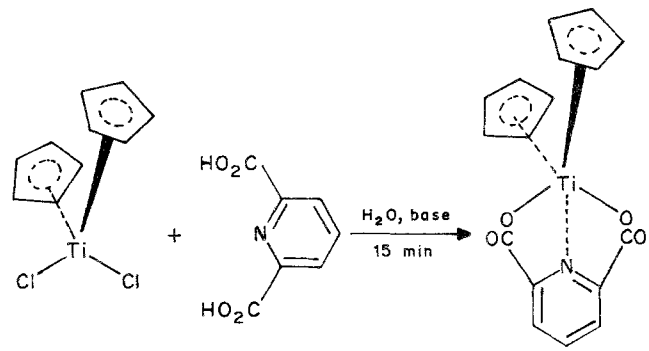


(1) *(4)* *(5)*

62% yield. However, the isolated crude complex persistently retained traces of monocyclopentadienyltitanium compounds resulting from cyclopentadiene elimination, frequently also multinuclear contaminants containing the Ti—O—Ti segment, and these impurities could not be cleanly removed by recrystallization. Accordingly, the i.r. and ^{1}H n.m.r. spectra, while displaying the aforementioned carboxylato bands[14] and the Cp proton resonance at the expected positions (Table 1), showed weak to moderately intense multi-component absorption at 720–650 cm^{-1} [$Ti(Cp)_2$—O—$Ti(Cp)_2$— and >Ti(Cp)—O—][7,15,16], overlapping weak ligand bands in this region, and gave additional weak Cp proton resonances at 6.5–6.4 ppm[16,17]. These impurity bands were absent in the n.m.r. and i.r. spectra of compound *(5)* prepared under anhydrous and anaerobic conditions from dimethyltitanocene.

Complex *(5)* initially possessed complete solubility in halocarbons; however, it turned insoluble at room temperature even more rapidly than complexes *(3)*, although recrystallization from the aprotic solvent, sulfolan, resulted in partial regeneration of halocarbon solubility without accompanying compositional changes. Whether this unusual behavior of the complexes *(3)* and *(5)* is due to solid-state isomerization (polymerization-depolymerization) or simply to a consolidation process in the solid state is an open question at this time. Interestingly, the dibenzoato complex, dicyclopentadienylbis-benzoatotitanium(IV)[8,12], when prepared in water as previously described[1] or by our similar procedure, retained its chloroform solubility over many months at ambient temperature. This compound cannot isomerize to intermolecularly coordinated species, a path open to *(3)* and *(5)*, and this might explain its structural stability relative to the bidentate-ligated complexes of the present study.

As a further example of a dicarboxylic acid ligand, dipicolinic acid (2,6-dicarboxypyridine) *(6)* was paired with *(1)* in an aqueous-phase synthesis of the yellow pentacoordinate dipicolinato compound *(7)* (Scheme 3), which had previously been obtained from dimethyltitanocene and *(6)* in anhydrous and deoxygenated THF[13]. Although *(7)* precipitated from the aqueous reactant solution in analytical (%N) purity and proved identical in elemental composition and spectroscopic features



(1) *(6)* *(7)*

(Table 1) with the product of the previous investigation[13], it tended to become insoluble in all common solvents so rapidly upon isolation that, in all but exceptional cases, controlled recrystallization proved impossible. It is apparent from these results that the synthesis of

Table 1 I.r. and ^{1}H n.m.r. spectroscopic data for some titanocene complexes.

Compound	CH[c]	I.r. (kBr)[a] (cm^{-1})		^{1}H n.m.r. $\delta(CDCl_3)$[b] Cp ring protons
		asym ν^d_{oco}	sym ν^d_{oco}	
(1)	822			6.59
(3a)	820	1616	1320	6.39
(3b)	822	1615	1314	6.48
(3c)	818	1600	1318	6.38
(5)	815	1625	1310	6.65
(7)	828	1640	1370	6.19

[a]Principal maximum listed for multiplet absorptions. Bands are high-intensity signals throughout; [b]In ppm, rel. to Me_4Si, at 60 MHz; [c]CH out-of-plane deformation, Cp ring; [d]Partially merging with ligand fundamentals in this region.

dicyclopentadienyltitanium(IV) compounds in aqueous medium, while exceedingly convenient and certainly well suited for salicylato complexes and, possibly, other titanocenes of similar stability, has its clear limitations and cannot generally replace the clean, albeit cumbersome, anhydrous method of synthesis starting from dimethyltitanocene.

Experimental

General

M.p.s (uncorr.) were determined in sealed capillaries. I.r. spectra were taken on KBr pellets. ^{1}H n.m.r. spectra were recorded at 60 MHz (TMS internal standard). Microanalyses were performed in duplicate (results averaged) by Robertson Laboratory, Madison, N. J., and by Galbraith Laboratories, Knoxville, Tenn. Combustion catalysts were employed for analysis of the metal-containing samples to optimize combustion; despite this precaution, however, carbon values tended to be 1–2% (in exceptional cases up to 2.5%) low[18], and this included authentic Ti complexes, such as *(7)* prepared[13] from dimethyltitanocene[18]. All analytical samples were predried for 24 h at 70° C, 0.1 torr; the drying chamber containing the samples was thoroughly deoxygenated prior to application of heat. Solvents, with the exception of sulfolan (tetramethylenesulfone), were freshly distilled; those used for recrystallization of titanocenes were dried over molecular sieves, 4 A, prior to distillation. Titanocene dichloride (dicyclopentadienyldichlorotitanium(IV), *(1)* (Strem Chemicals) was recrystallized from PhMe, with dry HCl gas briefly bubbled into the filtered solution to regenerate the complex from any titanoxy-type impurities present. Dimethyltitanocene)(dicyclopentadienyldimethyltitanium)(IV), freshly prepared by a literature method[19], was used as a 0.341 M solution in PhMe (71 mg of complex per cm^3). The other reactants, salicylic acid *(2a)*, 5-formylsalicylic acid *(2b)*, 5-aminosalicylic acid *(2c)*, phthalic acid *(4)* and dipicolinic acid (2,6-dicarboxypyridine, *(6)*, all commercial products (Fluka AG, Aldrich Chemicals), were recrystallized from EtOH or EtOH–H_2O. Product complexes were routinely dried for 15–20 h at room temperature, 0.5 torr, over P_4O_{10} and were stored at − 25° C with moisture protection to retard a common aging effect resulting in reduced halocarbon solubility. All recrystallizations were performed in Schlenk-type equipment under a blanket of dry N_2. Preparative work with dimethyltitanocene was performed under dried and deoxygenated N_2 in predried glassware, and Schlenk techniques were used for product isolation.

A. Complexes (3)–(5) by aqueous-phase synthesis

Di(η^5-cyclopentadienyl)salicylatotitanium(IV) (3a)

Titanocene dichloride *(1)*, 249 mg (1.0 mmol), was rapidly dissolved in warm (60–70° C), deionized H_2O (25 ml) with a sonication aid and the filtered solution was cooled to room temperature. Separately, salicylic acid *(2a)*, (152 mg, 1.1 mmol), and anhydrous Na_2CO_3, (106 mg, 1.0 mmol), were dissolved together in H_2O (3 ml), and this solution was added rapidly, with vigorous shaking, to the solution of *(1)*. The combined mixture, from which *(3a)* soon began to settle out as a finely divided red-brown solid, was sonicated for 15 min at ambient temperature, and the product complex was directly, without filtration, extracted into $CHCl_3$ (3 × 50 cm^3). The organic solution was rapidly washed with saturated aqueous Na_2CO_3 solution (2 × 25 cm^3), briefly dried with anhydrous $MgSO_4$ and filtered. Solvent removal from the N_2-saturated solution under reduced pressure left crude *(3a)* as a reddish brown, spectroscopically (i.r. ^{1}H n.m.r.) pure solid, 250 mg (80%; 70–82% in other experiments). (Found: C, 63.0; H, 4.6. $C_{17}H_{14}O_3Ti$ *(3a)* Cald.: C, 65.0; H, 4.5%.) The compound at this point dissolved partially in PhMe and completely in $CHCl_3$ or dipolar aprotic solvents (in some of the latter with degradation). The entire work-up manipulation was performed efficiently and without any delays so as to avoid product degradation.

In repeat experiments, the sonicated reaction mixture was rapidly filtered, and the residue was immediately taken up in $CHCl_3$, followed by washing, drying and solvent removal from the halocarbon solution as above. This procedure gave essentially the same results; crude yields: 75–85%.

Recrystallization of crude *(3a)* from $CHCl_3$ gave red to dark-red material with identical spectroscopic properties; the compound, while undergoing some darkening at temperatures exceeding 200° C, did not melt below 310° C. (Found: C, 62.9; H, 4.4%.) In these recrystallizations, hexane was added to the filtered, warm solutions to cause turbidity, and the mixtures were kept at − 25° C for product separation. Both the first and the ultimate fractions occasionally contained impure material and were disregarded.

Di(η^5-cyclopentadienyl)-5-formylsalicylatotitanium(IV) (3b)

The solutions of *(1)* (1.0 mmol) in H_2O (25 ml) and of *(2b)* (1.1 mmol) and Na_2CO_3 (1.0 mmol) in H_2O (3 cm^3) were combined and sonicated for 15 min at room temperature. The formylsalicylato complex *(3b)* precipitated almost quantitatively during this treatment, generally in an analytically pure state. However, as a precautionary measure, the compound was routinely extracted from the reaction mixture into $CHCl_3$ (3 × 35 cm^3) without prior filtration, and the combined extracts, after a single washing with saturated Na_2CO_3 solution, drying ($MgSO_4$) and filtration, were freed from solvent as described for the preceding experiment. This left crude *(3b)* as a red solid, 302 mg (88%; 75–90% in other experiments), completely soluble in chlorocarbons and dipolar aprotic solvents. The compound generally was spectroscopically pure at this stage. (Found: C, 62.1; H, 4.3. $C_8H_{14}O_4Ti$ *(3b)* Calcd.: C, 63.2; H, 4.1%.) Recrystallization from $CHCl_3$, with hexane added to the routinely filtered, warm solution, gave deep-red *(3b)* as the major center fraction, infusible up to 310° C. (Found: C, 62.3; H, 4.3%.)

Di(η^5-cyclopentadienyl)-5-aminosalicylatotitanium(IV) (3c)

The complex was prepared from *(1)* (1.0 mmol), *(2c)* (1.1 mmol) and Na_2CO_3 (1.0 mmol) in H_2O as in the preceding experiments. However, stirring (10 min), the milder agitation method, was preferred over sonicating in order to prevent significant hydrolytic degradation of this more sensitive complex. The product complex, possessing

enhanced solubility in H_2O relative to *(3a)* and *(3b)*, remained largely in solution and required a total of 200–250 ml of $CHCl_3$ for exhaustive extraction. In this operation a small, dark interphase of oily consistency was observed to form between the water and organic layers in the separating funnel, and care was taken to avoid draining this oily phase into the $CHCl_3$ layer during phase separation. The combined extracts were washed with two 30 ml portions of the alkali carbonate solution. Particularly speedy manipulation and moisture removal was required in the overall isolation step. The crude *(3c)*, 267 mg (81%; 74–83% in repeat experiments), obtained upon solvent removal as a reddish-black solid, soluble in $CHCl_3$ and dipolar aprotic solvents, was almost spectroscopically pure at this stage. (Found: C, 60.0; H, 4.5; N, 4.0. $C_{17}H_{15}NO_3Ti$ *(3c)* Calcd.: C, 62.0; H, 4.6; N, 4.25%.) Careful recrystallization from $CHCl_3$ gave pure complex as (red-tinted) black microcrystals infusible up to 310° C. (Found: C, 59.6; H, 4.4; N, 4.1%.)

Di(η^5-cyclopentadienyl)phthalatotitanium(IV) (5)

The preparation of the phthalato complex from *(1)* (1.0 mmol), *(4)* (1.1 mmol) and Na_2CO_3 (1.0 mmol) in H_2O, with concentrations the same as in the synthesis of *(3a)*, was accomplished by stirring the combined solutions for 10 min (yellowish complex partly precipitated), extracting the entire reaction mixture with $CHCl_3$ ($2 \times 30\,cm^3$), drying the combined extracts and removing the solvent under the conditions previously described. The crude, orange-yellow *(5)*, 198 mg (58%; 50–62% in repeat experiments), completely soluble in halocarbons and dipolar aprotic solvents at this stage, was slightly contaminated by hydrolysis products (weak- to medium-intensity impurity i.r. absorption at 720–650 cm^{-1}, ^1H n.m.r. signals at 6.5–6.4 ppm). (Found: C, 60.3; H, 3.9. $C_{18}H_{14}O_4Ti$ *(5)* Calcd.: C, 63.2; H, 4.1%.) A slightly purer product, showing the aforementioned i.r. and n.m.r. impurity bands in reduced intensity, was obtained if the yellowish precipitate formed during the stirring period was rapidly filtered off, immediately redissolved in $CHCl_3$ (50 ml) and the solution treated as above. Yields, however, were even lower (50–55%).

Recrystallization of crude *(5)* from $CHCl_3$, only the center fractions being utilized, gave yellow microcrystals, which were infusible up to 310° C (but darkened above 200° C) and showed essentially the same spectroscopic features as the crude complex, except that the impurity bands appeared in reduced intensities. (Found: C, 61.9; H, 4.2%).

Di(η^5-cyclopentadienyl)dipicolinatotitanium(IV) (7)

Complex *(1)* was allowed to react with *(6)* and Na_2CO_3 in H_2O in the same concentrations as used in the syntheses of the salicylato complexes. The combined solutions were stirred for 10 min. The fine yellow precipitate of *(7)*, collected by centrifugation, washed with H_2O and Et_2O and briefly freeze-dried at −35° C, at this stage was partially soluble in chlorocarbons but turned almost completely insoluble after further drying over P_4O_{10} at room temperature. (In two out of a total of 16 repeat experiments the crude products showed good $CHCl_3$ solubility and retained this feature for several weeks.) The yield was 152 mg (44%; 35–50% in other experiments). (Found: N, 4.0. $C_{17}H_{13}NO_4Ti$ *(7)* Calcd.: N, 4.1%.) Successful recrystallization from $CHCl_3$ was achieved only in a single experiment; this gave $CHCl_3$-soluble *(7)* possessing precisely the same spectroscopic properties as the crude complex.

Complexes (3a), (3b) and (5) from dimethyltitanocene

To the stirred solution or suspension of *(2a)*, *(2b)*, or *(4)* (1.0 mmol), in abs. THF (20–30 cm^3) [PhMe, 70 cm^3, for *(4)*], cooled to 0° C, was added dimethyltitanocene as a 0.341 M solution in PhMe, (3.0 cm^3, 1.02 mmol). The mixture was stirred for 40 min at 0° C and for 5 h at ambient temperature. The vol. of the filtered solution was reduced to 7–8 cm^3 and, upon the addition of abs. pentane (20–50 ml), was left at −20° C. The product complexes *(3a)*, *(3b)*, or *(5)*, which had crystallized from solution, were separated by filtration, washed with pentane and dried. Yields: 40–60%. The complexes were of acceptable analytical (Found *(3a)*: C, 62.6; H, 4.6; for *(3b)*: C, 62.3; H, 4.2; for *(5)*: C, 61.7; H, 4.1) and spectroscopic (i.r., n.m.r.) purity, and no further enhancement in purity resulted from recrystallization.

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