Active Cytotoxic Reagents Based on Non-metallocene Non-diketonato Well-Defined C₂-Symmetrical Titanium Complexes of Tetradeutate Bis(phenolato) Ligands

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Much research has been devoted to the identification of new cytotoxic non-platinum metal complexes,1–4 among which, Ti(IV) complexes revealed promising antitumor activity toward various cell lines.5–12 Notably, research in this area for the last two decades has been restricted to two families of complexes, the titanocene dichloride (Cp₂TiCl₂) and Budotitane ((bzac)₂Ti(OEt)₂) and their derivatives. These compounds undergo rapid hydrolysis of, first, the cis labile ligands (Cl, OR), followed by the inert ones (Cp, bzac), leading to unidentified aggregates.5,12,13 Their exact mechanism of activity is thus poorly understood, yet it is normally assumed that the ligand hydrolysis leads to formation of the active species,14,15 although some ligand inertness is apparently required.16,17 Additional studies indicated that the serum protein transferrin leads to complete ligand stripping from Cp₂TiCl₂ and transfers the Ti ion to the cell.18–21 However, an early loss of the inert ligands should abolish their influence on the interaction with the cellular target and hampers their use as a target for structure-reactivity relationship studies. Herein we report a new family of cis-bis(isoproxopxide)Ti(IV) complexes of diamine bis(phenolato) ligands, obtained as single isomers in quantitative yields, leading to appreciable in-vitro cytotoxic activity against colon and ovarian cells, where the ligand features have strong influence on reactivity which is not transferrin-dependent and apparently involves a ligand-bound active species.

As a part of our interest to develop cytotoxic well-defined Ti(IV) complexes, we focus on chelating alkoxy ligands suitable for forming strong binding to the oxophilic Ti(IV) ion. The biologically active Budotitane which includes two monoanionic diketonato ligands exhibits several cis and trans isomers, and the symmetrical analogues of the active cis isomer feature C₂-symmetry. To minimize the number of isomers and increase thermodynamic stability, yet maintain the general symmetry, we turned to dianionic diamine dialkoxy ligands, which were expected to lead to L₅Ti₂ type octahedral complexes. The diamine bis(phenolato) ligand family, easily synthesized in a single-step procedure,22 conveniently leads to the desired racemic C₂-symmetrical complexes as single isomers in quantitative yields.23–25 We thus synthesized three such complexes exhibiting ortho groups to the donor atom of varying sizes: t-Bu, Me, and H (Scheme 1). In comparison, we studied the aliphatic analogous ligand (Scheme 2), having no major steric demands.

L₁⁻²Ti(OiPr)₂ (Scheme 1) were synthesized according to known procedures by reacting H₂L₁⁻³ with one equiv of Ti(OiPr)₂ to give the Ti(IV) complexes quantitatively.23–25 'H NMR analysis has verified that the desired isomers were formed solely. Single crystals of L₅Ti(OiPr)₂ were obtained from diethylether at room temperature and the crystal structure (Figure 1) features a C₂-symmetrical octahedral complex with two cis-isopropoxide groups. L₅Ti(OiPr)₂ (Scheme 2) was synthesized by reacting H₂L₄ with 1 equiv of Ti(OiPr)₂. The resulting bis(isoproxopxide) complex crystallized from toluene at −5 °C to give yellow single crystals. The crystal structure

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Reactivity increases with longer incubation times (Figure 3, S2). In rather rapid cell penetration mechanism, and once in the cell, the active species and transport mechanism. No reactivity was observed for L4 Ti(OiPr)2 and Ti(OiPr)4, presumably due to more rapid formation of unreactive inert aggregates. To shed some light on the role of ligand hydrolysis, we studied the preparation of the C5-symmetrical analogue and Figures S1–S2 representing measurements on OVCAR-1 cells. This material is available free of charge via the Internet at http://pubs.acs.org.

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Supporting Information Available: Crystallographic data for L3 Ti(OiPr)2 and experimental procedures including Scheme S1 of the preparation of the C5-symmetrical analogue and Figures S1–S2 representing measurements on OVCAR-1 cells. This material is available free of charge via the Internet at http://pubs.acs.org.

References

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