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Synthesis, Molecular Structure (X-ray and DFT), and Solution Behavior of Titanium 4-Acyl-5-pyrazolonates. Correlations with Related Antitumor β-Diketonato Derivatives

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Previously reported structure–activity relationships have shown two features for effective antitumor activity of titanium β-diketone complexes: (a) ligand asymmetry and (b) the presence of planar substitutents on the ligand. Mono- and dinuclear derivatives, studied with diffraction and DFT methods show that (a) is consistent with different Ti–O(β-diketonato) bond lengths, which are longer than Ti–O(oxo) and Ti–O(alkoxy) ones. π–π features observed in dinuclear derivatives correlate with strong reactivity of related complexes with DNA and support DNA intercalation by such planar groups, in agreement with (b). Large variation for Ti–O bond lengths and Ti–O–C bond angles in the ethoxy moiety is associated with the titanium withdrawing effect and oxygen bonding s character; it is confirmed through exploration of the Cambridge crystallographic database. This ethoxy geometrical flexibility also suggests versatile accommodation in protein pockets and/or other biological targets. Electrospray ionization mass spectrometry (ESI-MS) spectra show formation of di- and trinuclear Ti-4-acyl-5-pyrazolonato cationic oligomers. Hydrolysis/oligomerization is also described by NMR results.

Introduction

Some titanium compounds are effective antitumor agents. For instance, budotitane[1] = $(bzac)_2Ti(OEt)_2$, bzac = benzoylacetonato, was the first metal derivative to reach clinical trials after cisplatin.[2] Biological tests were performed on more than 200 compounds, and from structure−activity relationship studies, planar substituents and ligand asymmetry established higher activity, and benzoylacetonato was the best ligand of these widely varied β-diketones.[1] This promising development was stopped because of solubility/formulation problems.[3] In addition, the antitumor activity of titanocene dichloride was in phase II clinical trials.[4,5] It has a larger spectrum of action than budotitane, probably due to its better solubility in physiological medium.[6] Recently, modified titanocenes have shown encouraging results for further studies including better performance than cisplatin in some cell lines.[7] Although many titanium compounds were analyzed by the National Cancer Institute, only derivatives containing cyclopentadienyl or β-diketone ligands progressed substantially.[8]

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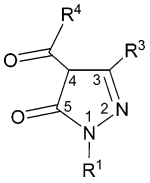
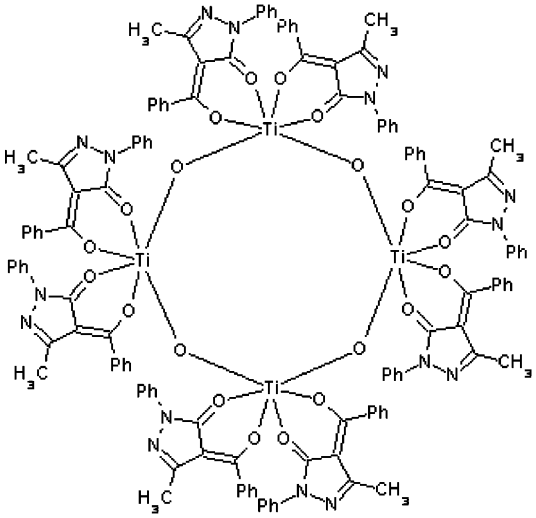
Scheme 1. 4-Acyl-5-pyrazolones, Diketo Form



Scheme 2. Tetranuclear Antitumor Complex $[(Q^{Ph})_2Ti\text{-}(\mu_2\text{-}O)]_4$



Our titanium compounds make use of 4-acyl-5-pyrazolones (HQ), a subclass of asymmetric β-diketones possessing three substitution groups, R^1, R^3, and R^4, shown in Scheme 1.

In particular, a tetranuclear derivative $[(Q^{Ph})_2Ti(\mu_2\text{-}O)]_4$ was tested in vitro and in vivo on mice bearing TA-3 mouse mammary adenocarcinoma and showed T/C values around 300%.[9] T/C is a measure of survival time increase (100% is the control for untreated tumor-bearing animals), Scheme 2.

In recent reviews,[10,11] we outlined some common features between β-diketone and cyclopentadienyl ligands that are useful in the design of titanium antitumor agents. Because titanium-ligand bonds are stronger than Ti-ethoxy and Ti−Cl (in budotitane and titanocene dichloride, respectively), they cleave later, leading to increased stability in a physiological environment, that is, avoiding hydrolysis that leads toward the inactive TiO_2 species. However, after losing the leaving groups, titanium tends to oligomerize and makes the isolation of mononuclear species in their synthesis difficult; for instance, budotitane forms a mixture of di- and trinuclear oligomers in a few minutes when dissolved in acetonitrile.[1]

Because of similar behavior, it also was difficult to isolate corresponding mononuclear Ti-4-acyl-5-pyrazolonates, but recently, after many efforts, this has been reached.[12] Additional novel compounds are reported here including the X-ray molecular structures of mononuclear, $[(Q^{nPe})_2Ti(OEt)_2]$, and dinuclear, $\{[(Q^{nPe})_2Ti(OEt)]_2(\mu\text{-}O)\}$, derivatives where the ligand Q^{nPe} differs from Q^{Ph} in having a crowded acyl moiety (R^4 = neopentyl) instead of Ph for the tetranuclear species shown above. We perform a study that includes theoretical methods to explore oligomerization both in Ti-4-acyl-5-pyrazolonato and budotitane derivatives because recently the X-ray structure of budotitane was reported.[13] This process is useful in defining the biological fate of titanium antitumor active compounds, namely, budotitane[1] and titanocene dichloride[14] oligomers.

Experimental Section

General Remarks. The titanium precursors 1-phenyl-3-methylpyrazolon-5-one and *tert*-butylacetyl chloride were purchased from Sigma-Aldrich (Milwaukee, WI) and used as received. 1-Phenyl-3-methyl-4-*tert*-butylacetyl-pyrazol-5-one HQ^{nPe} was prepared according to the literature.[15] All of the solvents were distilled prior to use. Light petroleum (40−60 °C) was dried by refluxing over freshly cut sodium. Methanol was dried over CaO. Dichloromethane was freshly distilled from CaH_2. Other solvents were dried and purified by standard procedures. All of the reactions were performed under a N_2 atmosphere by using standard Schlenck techniques. Samples for microanalysis were dried in vacuo to constant weight (20 °C, about 0.1 Torr). Elemental analyses (C, H, N) were performed in house with a Fisons Instruments 1108 CHNS−O Elemental Analyzer. Electrical conductivity measurements (Λ_M, reported as Ω^{-1} cm^2 mol^{-1}) of acetone, acetonitrile, and dimethylsulfoxide (DMSO) solutions of the complexes were taken with a Crison CDTM 522 conductimeter at room temperature. IR spectra were recorded from 4000 to 100 cm^{-1} with a PerkinElmer System 2000 FTIR instrument. ^{1}H NMR spectra were recorded with a VXR-300 Varian spectrometer. Melting points were determined with an IA 8100 Electrothermal instrument. Positive and negative electrospray mass spectra were obtained with a Series 1100 MSI detector HP spectrometer, using an acetonitrile mobile phase. Solutions (3 mg/mL) for electrospray ionization mass spectrometry (ESI-MS) were prepared using reagent-grade acetone or acetonitrile. For the ESI-MS data, mass and intensities were compared to those calculated using IsoPro Isotopic Abundance Simulator, version 2.1.[16] Peaks containing titanium(IV) ions are identified as the center of an isotopic cluster; abundances are given in parenthesis.

Synthesis of the Complexes. $[(Q^{nPe})_2Ti(OEt)_2]$ (1). It was prepared by adding $Ti(OEt)_4$ (0.228 g, 1 mmol) to an absolute ethanol solution (20 mL) of HQ^{nPe} (0.545 g, 2 mmol). The reaction mixture was stirred under N_2 at room temperature for 48 h, and a precipitate slowly formed, which was filtered, washed with diethyl ether (5 mL), and dried to constant weight under reduced pressure. The pale-pink residue obtained was recrystallized from 1:1 CH_2Cl_2/light petroleum (40−60 °C) and shown to be compound **1**. Yield 75%, soluble in CH_2Cl_2, $CHCl_3$, EtOH, MeOH, acetone, acetonitrile, and DMSO; Mp 152−153 °C. Anal. Calcd for $C_{36}H_{48}N_4O_6Ti$: C, 63.52; H, 7.11; N, 8.23. Found: C, 63.84; H, 7.75; N, 9.05. IR (nujol, cm^{-1}): 1603s, 1570m, 1531m ν(C=O + C=N + C=C), 468s, 396m, 359m ν(Ti−O). ^{1}H NMR ($CDCl_3$, 298 K): δ, 0.90m

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Table 1. Crystal Data and Refinement Details

compound	$[(Q^{nPe})_2Ti(OEt)_2]$ (**1**)	$\{[(Q^{nPe})_2Ti(OEt)]_2(\mu\text{-}O)\}$ (**1′**)
chemical formula	$C_{36}H_{48}N_4O_6Ti$	$C_{68}H_{86}N_8O_{11}Ti_2$
fw	680.68	1287.25
space group	$Pna2_1$	$C2/c$
a, Å	20.047(4)	25.298(3)
b, Å	11.296(2)	13.1985(14)
c, Å	16.168(3)	22.0359(19)
β, (deg)		108.744(2)
V, Å^3	3661.4(11)	6967.6(12)
Z	4	4
crystal size, mm^3	0.30 × 0.10 × 0.10	0.15 × 0.10 × 0.10
ρ_c, g/cm^3	1.235	1.227
μ, cm^{-1}	0.282	0.291
reflns [$I > 1.5\sigma(I)$]	4290	4140
refined params	435	411
R (Rw)	0.0441 (0.0904)	0.0641 (0.1591)

(18H, (C═O)$CH_2C(CH_3)_3$), 1.18m (6H, OCH_2CH_3), 2.32m (6H, C3−CH_3), 2.35m (4H, (C═O)$CH_2C(CH_3)_3$), 4.53m (4H, OCH_2-CH_3), 7.23m, 7.42m, 7.99m (10H, N1−C_6H_5). ESI-MS (MeCN) (+): m/z (%) = 295 (10) $[Na(HQ^{nPe})]^+$, 629 (60) $[Na_2K(Q^{nPe})_2]^+$, 1211 (50) $[Na_2K_2H(Q^{nPe})_4]^+$, 1235 (45) $[Ti_2(Q^{nPe})_4O_2H]^+$, 1257 (10) $[Ti_2(Q^{nPe})_4O_2Na]^+$, 1274 (10) $[Ti_2(Q^{nPe})_4O_2Na]^+$, 1820 (30) $[Ti_3(Q^{nPe})_6O_3H]^+$, 1842 (100) $[Ti_3(Q^{nPe})_6O_3Na]^+$, 1858 (15) $[Ti_3(Q^{nPe})_6O_3K]^+$.

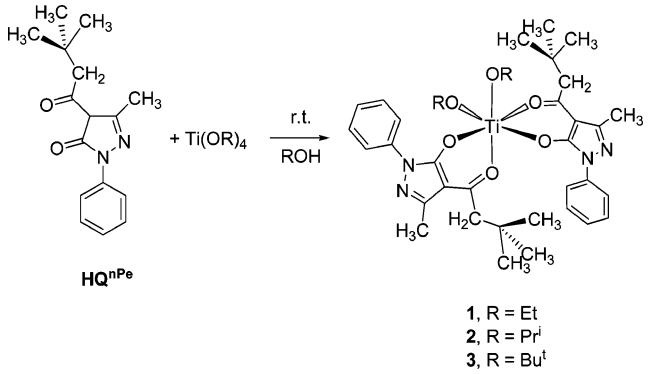
$[(Q^{nPe})_2Ti(OPr^i)_2]$ (2). It was prepared following a procedure similar to that reported for **1** by using an isopropanol solution of HQ^{nPe} (0.545 g, 2 mmol) and $Ti(OPr^i)_4$ (0.284 g, 1 mmol). Yield 77%, soluble in CH_2Cl_2, $CHCl_3$, EtOH, MeOH, acetone, acetonitrile, and DMSO. Mp 123−124 °C. Anal. Calcd for $C_{38}H_{52}N_4O_6Ti$: C, 64.40; H, 7.40; N, 7.91. Found: C, 64.15; H, 7.42; N, 7.70. IR (nujol cm^{-1}): 1624s, 1578s, 1528s ν(C═O + C═N + C═C), 469s, 398m, 364m ν(Ti−O). ^{1}H NMR ($CDCl_3$, 298 K): δ, 0.91m (18H, (C═O)$CH_2C(CH_3)_3$), 1.22m (12H, $OCH(CH_3)_2$), 2.47m (6H, C3−CH_3), 2.63m (18H, (C═O)$CH_2C(CH_3)_3$), 4.97m (2H, $OCH(CH_3)_2$), 7.27m, 7.42m, 7.98m (10H, N1−C_6H_5).). ESI-MS (MeCN) (+): m/z (%) = 295 (10) $[Na(HQ^{nPe})]^+$, 629 (60) $[Na_2K(Q^{nPe})_2]^+$, 1211 (50) $[Na_2K_2H(Q^{nPe})_4]^+$, 1235 (45) $[Ti_2(Q^{nPe})_4O_2H]^+$, 1257 (10) $[Ti_2(Q^{nPe})_4O_2Na]^+$, 1274 (10) $[Ti_2(Q^{nPe})_4O_2Na]^+$, 1820 (30) $[Ti_3(Q^{nPe})_6O_3H]^+$, 1842 (100) $[Ti_3(Q^{nPe})_6O_3Na]^+$, 1858 (15) $[Ti_3(Q^{nPe})_6O_3K]^+$.

$[(Q^{nPe})_2Ti(OBu^t)_2]$ (3). It was prepared following a procedure similar to that reported for **1** by using an isopropanol solution of HQ^{nPe} (0.545 g, 2 mmol) and $Ti(OBu^t)_4$ (0.340 g, 1 mmol). Yield 64%, soluble in CH_2Cl_2, $CHCl_3$, EtOH, MeOH, acetone, acetonitrile, and DMSO. Mp 187−188 °C. Anal. Calcd for $C_{40}H_{56}N_4O_6Ti$: C, 65.21; H, 7.66; N, 7.60. Found: C, 65.19; H, 7.77; N, 7.29. IR (nujol cm^{-1}): 1603m, 1594m, 1577m, 1531m ν(C═O + C═N + C═C), 497s, 376m ν(Ti−O). ^{1}H NMR ($CDCl_3$, 298 K): δ, 0.91m (18H, (C═O)$CH_2C(CH_3)_3$), 1.26m (18H, $OC(CH_3)_3$), 1.95m (6H, C3−CH_3), 2.41m (4H, (C═O)$CH_2C(CH_3)_3$), 7.13m, 7.69m, 8.46m (10H, N1−C_6H_5). ESI-MS (MeCN) (+): m/z (%) = 295 (10) $[Na(HQ^{nPe})]^+$, 629 (60) $[Na_2K(Q^{nPe})_2]^+$, 1211 (50) $[Na_2K_2H(Q^{nPe})_4]^+$, 1235 (45) $[Ti_2(Q^{nPe})_4O_2H]^+$, 1257 (10) $[Ti_2(Q^{nPe})_4O_2Na]^+$, 1274 (10) $[Ti_2(Q^{nPe})_4O_2Na]^+$, 1820 (30) $[Ti_3(Q^{nPe})_6O_3H]^+$, 1842 (100) $[Ti_3(Q^{nPe})_6O_3Na]^+$, 1858 (15) $[Ti_3(Q^{nPe})_6O_3K]^+$.

X-ray Crystallographic Study. Crystals of compound **1** and **1′**, a dinuclear derivative obtained by the recrystallization of **1**, were collected on a Bruker SMART diffractometer using an image plate and Mo radiation at 243 K. Crystal data are given in Table 1. Structure solutions for both crystals with all of the non-hydrogen atoms and refinement on F^2 were done with the *SHELX* system.[17] Hydrogen atoms were placed following expected models.

Theoretical Calculations. The structural features and energy parameters of the mono- and dinuclear compounds **1**, **1′**, and budotitane were analyzed with theoretical methods (DFT) using the Accelrys program *Cerius 4.6*, subroutine DMol3, on an Octane SGI computer.[18] Initial coordinates were taken from the corresponding X-ray molecular structures; hydrogen atoms were added using a DMol3 subroutine. Ti-dibenzoylacetonato derivatives were manipulated with DMol3 graphical facilities before minimization. The highest level of theory in DMol3 was used (PW91/DNP); the local density setting was the Perdew and Wang (PWC) functional[19] on all of the atoms, and DNP is a double numeric basis set with polarization functions.[20]

Scheme 3



Results and Discussion

Synthesis and Characterization of 1−3. By the interaction of the appropriate tetraalkoxytitanium(IV) with the proligand HQ^{nPe} in alcohol under a dry nitrogen atmosphere, derivatives **1**−**3** were obtained as brown powders (Scheme 3). They are mononuclear compounds that are quite stable in air for long periods (IR spectra carried out after 1 month do not show any change). Conductivity measurements in the ionizing solvents acetone, acetonitrile, or dimethylsulfoxide (DMSO) show that complexes **1**−**3** are nonelectrolytes.

The solid-state IR spectra show strong absorptions between 1500 and 1650 cm^{-1} due to C═O, C═N, and C═C of the acylpyrazolonato ligand, and the disappearance of the broad band between 2300 and 2800 cm^{-1} due to the O−H···O intramolecular system in the free neutral HQ, in accordance with deprotonation of the ligand and coordination of the monoanionic form.[15] Several new medium to strong bands between 350 and 500 cm^{-1} are due to Ti−O stretching modes.[21]

The ^{1}H NMR spectra of **1**−**3** show all of the expected resonances for the β-diketonato ligands and alkoxide groups for the proposed formulation (Scheme 3). There are several sets of resonances for each equivalent proton in rigorously anhydrous deuterated solvents, indicating the existence of cis and trans isomers (Scheme 4) in solution, as previously reported for other titanium derivatives.[12] The ^{1}H NMR spectra of **1**−**3**, carried out some hours after dissolution,

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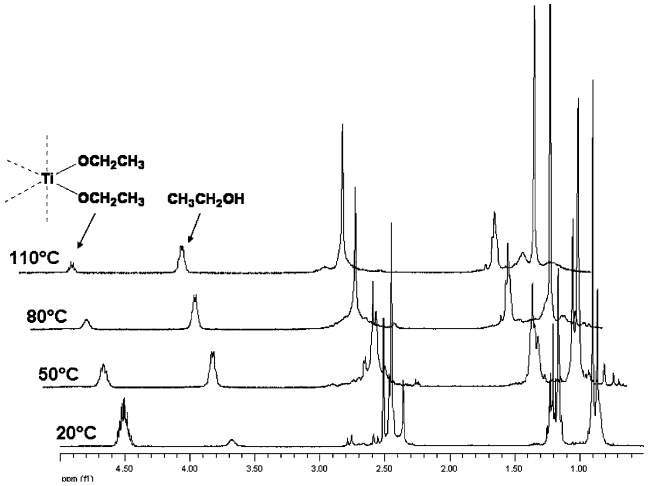

Figure 1. ^{1}H NMR spectra showing the decomposition of complex **1** in 1.1,2,2-tetrachloroethane-d_2.

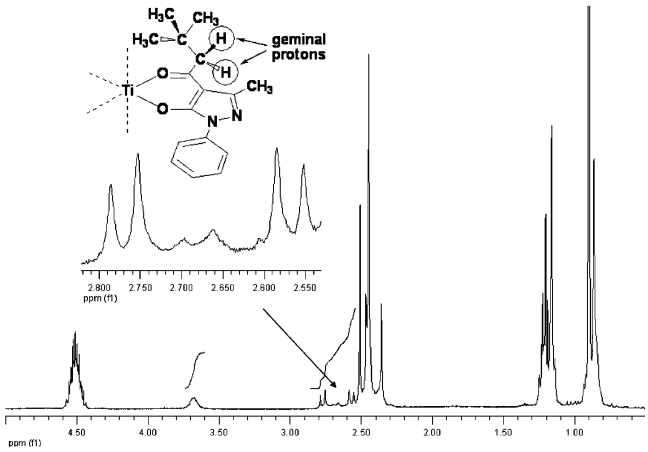

Figure 2. ^{1}H NMR spectra of complex **1** showing the details of CH_2 resonance.

show new resonances due to free alcohol ROH stemming from Ti-OR hydrolysis. Therefore, we performed a variable temperature ^{1}H NMR study to explore the influence of the temperature on the decomposition of derivative **1** in 1,1,2,2-tetrachloroethane-d_2 (bp 145 °C).

The alkyl and alkoxy region (1.0−5.0 ppm) shows changes on warming from 20 to 110 °C (Figure 1). Thus, whereas methylene resonances at 4.55 ppm, due to Ti−OCH_2CH_3 groups, decrease, that of free EtOH at 3.70 ppm increases, in accordance with the oligomerization of derivative **1** through the formation of μ-O bridges between titanium centers and the release of ethanol. The signal decrease of ethoxy groups continues and is almost complete at 110 °C, because of the formation of ethoxy-free oligomeric species, such as the tetranuclear derivative $[(Q^{Ph})_2Ti(\mu\text{-}O)]_4$ previously reported.[9]

A quartet signal is well visible at 2.65 ppm in the spectrum recorded at 20 °C and belongs to an oligomeric species arising from EtOH elimination, in accordance with its integrated area, which is twice that of the −CH_2− resonance of free ethanol at 3.45 ppm (Figure 2). This quartet is due to geminal diastereotopic protons of −CH_2− in the neopentyl

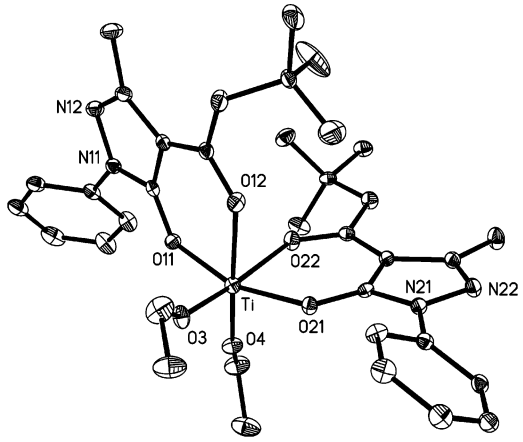

Figure 3. X-ray molecular structure of $[(Q^{nPe})_2Ti(OEt)_2]$ = **1** (hydrogen atoms omitted).

fragment of Q^{nPe} because free rotation of the neopentyl group is forbidden by steric constraints in the oligomeric species.[22]

The ^{1}H NMR spectrum of **1** in 1,1,2,2-tetrachloroethane-d_2, recorded 24 h after the variable-temperature study, shows free EtOH resonances at 3.70 ppm, together with H_2O signal at 1.70 ppm (Figure S1, deposited). In this spectrum, the −CH_2− resonances appear as broad complex signals between 2.2 and 2.8 ppm, likely as a result of full hydrolysis and complete oligomerization.

Positive electrospray mass (ESI-MS) spectra of complexes **1**−**3** indicate that, in solution, these derivatives undergo loss of the anionic pyrazolonato ligands, which immediately interact with protons, sodium, and/or potassium ions, yielding polynuclear monocharged species such as $[NaH(Q)]^+$, $[NaK(Q)]^+$, $[Na_3(Q)_2]^+$, $[Na_2K(Q)_2]^+$, $[NaK_2(Q)_2]^+$, $[Na_3H(Q)_3]^+$, $[Na_2KH(Q)_3]^+$, $[NaK_2H(Q)_3]^+$, $[Na_4H(Q)_4]^+$, $[Na_3KH(Q)_4]^+$, $[Na_2K_2H(Q)_4]^+$, $[Na_4KH_2(Q)_6]^+$, and $[Na_3K_2H_2(Q)_6]^+$. In general, protonated species are more abundant than those of Na, K, or mixed Na/K compounds. Sodium and potassium adducts are common in ESI-MS spectra[23] because the oxygen donors immediately interact and aggregate with the small quantities of sodium and potassium that are always present in solvent H_2O. The population of polynuclear species increases as trinuclear > hexanuclear > higher isomers, whereas acetonitrile derivatives containing hydrogen, sodium, and potassium are far less abundant. Compounds **1**−**3** generate similar signals because the corresponding alkoxy moieies (OEt, OPr^i, and OBu^i) are not included in the ions detected in the chamber; no signals due to monomers were found with this technique.

For some systems, significant aggregation of titanium and Q is seen in acetonitrile even at 10^{-3} M, and aggregates containing Na^+, K^+, or H^+ dominate significantly over larger adducts. The most-abundant titanium-containing species for **1**−**3** are the trinuclear ions $[X(Q)_6Ti_3O_3]^+$, X = hydrogen, sodium, and potassium. Additional signals due to the dinuclear species $[X(Q^{nPe})_4Ti_2O_2]^+$ are present. The isotopic

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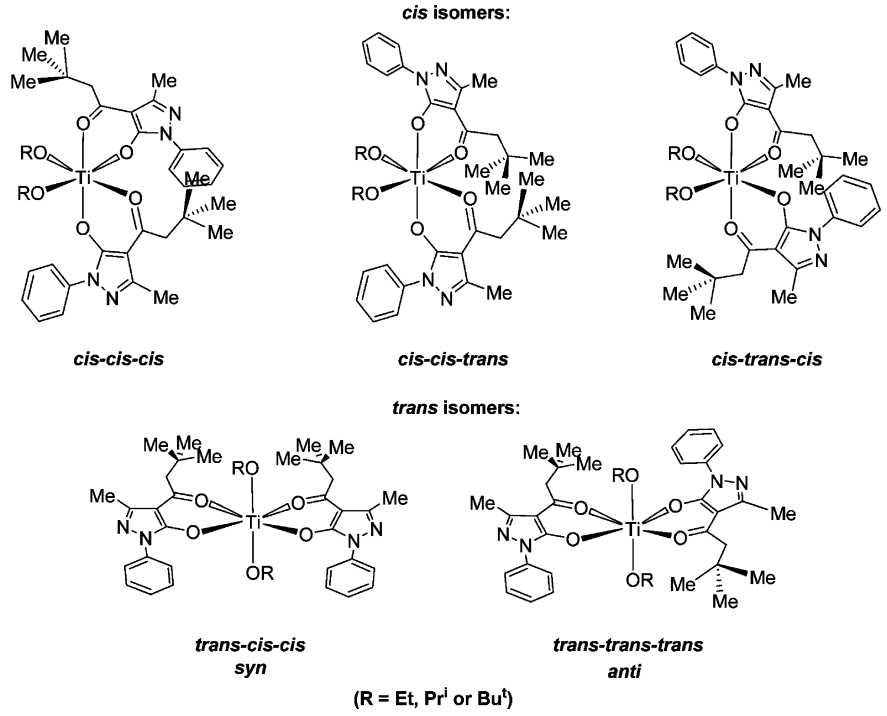
Scheme 4



distribution of these species agrees with the calculated composition. The absence of ions containing MeCN indicates that there is no binding between the solvent and titanium. Because only charged species are transferred from solution to the gas phase (droplets of solution species are likely dehydrated and ionized in the chamber), quantitative ESI-MS results do not represent the real relative distribution of the species in solution but provide useful information about ion existence. The strong association of sodium and potassium cations and protons to the Q ligands concurs with an X-ray structure of a rhodium−iodo derivative that has 4-acyl-5-pyrazolonato as a counteranion.[24] The ESI-MS spectra indicate different nuclearities, in agreement with the high number of NMR signals for the methyl group in **1**−**3**.

Structural Study. X-ray structure of [$(Q^{nPe})_2$Ti$(OEt)_2$] (1). The coordination sphere shows several sets of bond lengths. Thus, Ti−O(ethyl) bonds Ti−O3 = 1.780(3) and Ti−O4 = 1.763(3) Å are the shortest, cis to each other and trans to the longest Ti−O(acyl) bonds Ti−O12 = 2.068(3) and Ti−O22 = 2.092(3) Å. Both Ti−O(pyrazolonato) are trans to each other and of equal lengths, Ti−O21 = 1.991-(2) and Ti-O11 = 1.996(2) Å (Figure 3).

Also, the tetranuclear compound[9] [$(Q^{Ph})_2$Ti−(μ_2-O)]$_4$ (Scheme 2) has three sets of Ti−O bonds. The μ-oxo oxygens form the shortest Ti−O lengths, opposite the longest Ti−O(acyl) bonds, whereas the O(pyrazolonato) atoms are opposed to each other, forming intermediate Ti−O bond lengths; therefore, Ti−O(oxo) bonds in the oligomer correspond to Ti−O(ethyl) ones in **1**. Comparison between the Ti−O(oxo) bonds in [$(Q^{Ph})_2$Ti(μ-O)]$_4$ (from 1.77 to 1.87 Å)[9] with Ti−O(ethoxy) in **1**, (Ti−O3 = 1.780(3), and Ti−O4 = 1.763(3) Å) shows that the former can be longer. The marked differences in these three sets of Ti−O bonds suggest that the metal coordination sphere is governed by trans influence features. We have already observed that in other 4-acyl-5-pyrazolonato metal complexes the O(pyrazolonato) tends to establish shorter metal−oxygen bonds than O(acyl).[25−27] The rationale for this is that the acyl carbonyl provides a coordinative lone pair with weaker donation than the covalent O(pyrazolonato) anionic moiety. For benzoylacetonato, the pattern is less clear (Figure 7) because the O(near-Ph) and O(near-Met) donors can form either a shorter or a longer metal−oxygen length.[28] Ultimately, the ligand behavior in its titanium derivatives has been clarified from results of the recent X-ray crystal structure of budotitane.[13] Thus, in budotitane, Ti−O(ethoxy) forms the shortest bonds (1.80 and 1.81 Å); they are opposed to the O(near-Ph) groups (Ti−O(near-Ph) = 2.08 and 2.06 Å), whereas both O(near-Met) are opposed to each other with equal Ti−O(near-Met) values of 1.98 Å; the second independent molecule in the crystal of budotitane shows a similar pattern. Therefore, budotitane, [$(Q^{Ph})_2$Ti-(μ_2-O)]$_4$, and compound **1** are similarly affected by trans influence.

In compound **1**, both Ti−O(ethoxy) bond lengths differ, and comparison with the literature show this is not unusual. For example, bis(μ_2-iso-propoxo)-bis(2-aminoethanolato)-tetrakis(isopropoxy)-di-titanium has three isopropoxy groups

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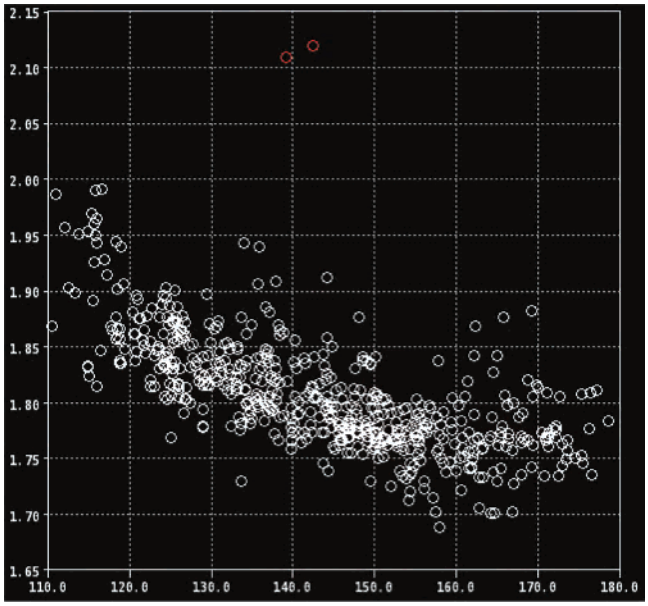

Figure 4. Ti−O bond length versus Ti−O−C bond angle for Ti−O−C(alkyl) crystal structures showing the trend: the shorter the Ti−O bond length, the wider the Ti−O−C bond angle.

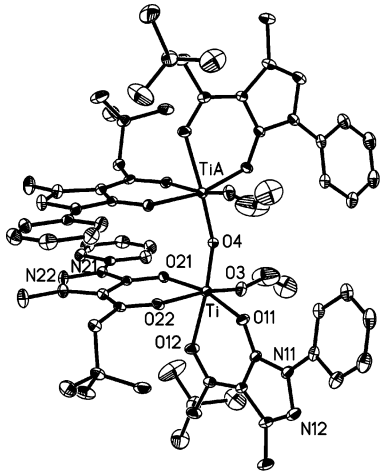

Figure 5. X-ray molecular structure of $\{[(Q^{nPe})_2Ti(OEt)]_2(\mu\text{-}O)\}$ (**1′**), hydrogen atoms omitted.

with Ti−O bonds of 1.88 Å, 1.85 Å, and 1.81 Å.[29] These bond lengths are associated with large variation of Ti−O−C angles 122, 132, and 147°, respectively, which is probably due to packing forces that bend the Ti−O−C moieties. Bond angles on ethoxy oxygens of compound **1** are also markedly different, Ti−O3−C31 = 142.6(3)° and Ti-O4−C41 = 151.0(3)°. An analysis of the CSD file for the equivalent moiety Ti−O−C(alkyl), restricted to two-coordinate oxygen and structures having R_f under 5% shows 233 hits and 571 pairs of data,[30] is shown in Figure 4. From these structural data, a trend is observed: the shorter the Ti−O bond length, the wider the Ti−O−C bond angle, with only one exception, tris(μ_2-(S)-1,1′-binaphtyl-2,2′-diolato)-tris(μ_2-5,6,7,8-tetrafluoro-1,1′-binaphthyl-2,2′-diolato)-bis(μ_2-isopropoxo)-tetraisopropoxy-hexa-titanium toluene solvate.[31] This species contains four isopropyl groups, with two following the trend and the other two not; see the upper part of Figure 4 for Ti−O lengths longer than 2.10 Å. In describing this crystal structure, the presence of O(oxo) units was unexplained.[31] The close intramolecular vicinity between O(isopropyl) and O′(ligand), O−O′ = 2.68 and 2.71 Å (shorter than the O−O van der Waals distance) shows a crowded and rigid coordination sphere; the presence of a hydrogen bond would explain the O(isopropyl)−O′(ligand) decrease. The driving force of the trend shown in Figure 4 is the marked Ti−O double-bond character due to the high electron-withdrawing effect of titanium. In other words, the oxygen s character increases for wider Ti−O−C bond angles; the limiting case for this trend is an sp hybrid for Ti−O−C equal to 180°.

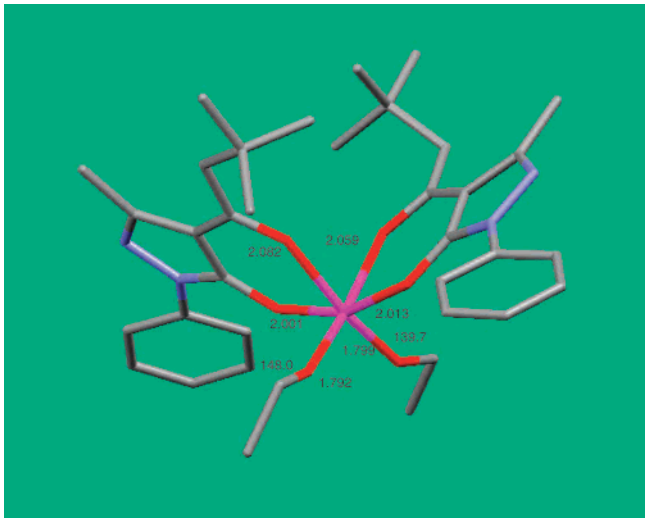

Figure 6. DFT structure of $[(Q^{nPe})_2Ti(OEt)_2]$ with hydrogen atoms omitted.

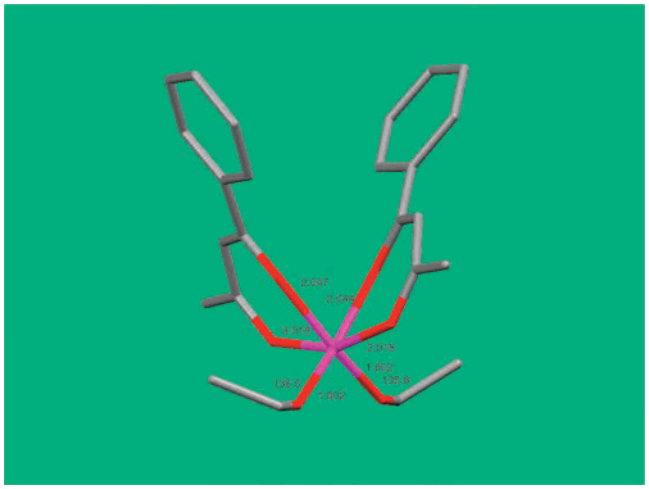

Figure 7. DFT structure of budotitane with hydrogen atoms omitted.

X-ray Structure of $\{[(Q^{nPe})_2Ti(OEt)]_2(\mu\text{-}O)\}$ (1′). These crystals appeared in the same chloroform recrystallization vessel as **1**. The asymmetric unit of this complex is half of a molecule that relates to the other half through a 2-fold axis (Figure 5). There is a bridging oxygen (O4) between both

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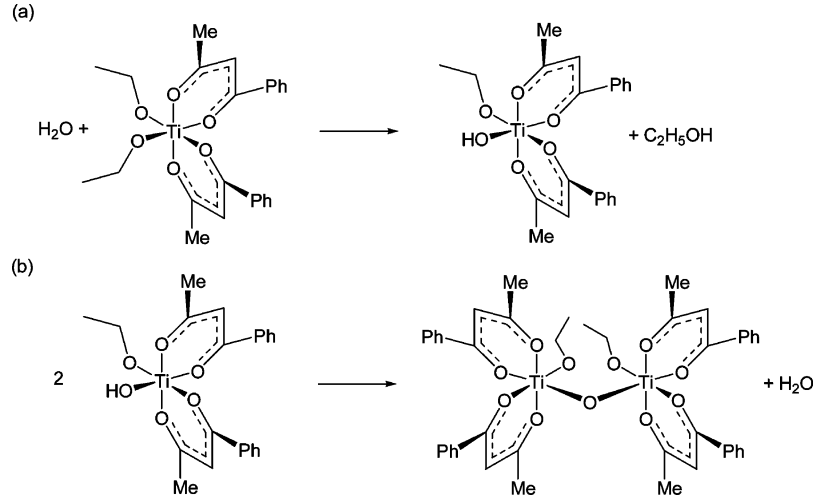
Scheme 5



[a] Hydrolysis of budotitane. [b]Two hydrolyzed molecules join, forming a dinuclear species with loss of water. The whole process consumes one molecule of water and yields two molecules of ethanol and one molecule of the dinuclear budotitane derivative.

$[(Q^{nPe})_2Ti(OEt)]$ units that lies just on the 2-fold axis. This dinuclear species displays a complex pattern of interactions. For instance, one Ph meta hydrogen atom (H21G) points to the center of the Ph ring at C111−C116, with distances between 2.84 and 3.29 Å, thus establishing an intermolecular H−π interaction, shown in Figure S2. In addition, two ligands have exact coplanarity between the pyrazolonato ring and the attached phenyl. These two planar moieties stack with a separation of 3.41 Å, establishing an intramolecular $\pi-\pi$ interaction, shown on the left side of Figure 5. In the coordination sphere, Ti−O(acyl) lengths, Ti−O12 = 2.095(2) Å and Ti−O22 = 2.091(2) Å, are again the longest bonds, whereas the O(ethoxy) and the bridging oxygen atom are trans to both O(acyl) groups and shorter, Ti−O3 = 1.747(3) and Ti−O4 = 1.797(8) Å, respectively. The Ti−O(pyrazolonato) bonds Ti−O11 = 1.992(2) and Ti−O21 = 1.985(2) Å are trans to each other and again have intermediate values as in **1** and complex[9] $[(Q^{Ph})_2Ti(\mu\text{-}O)]_4$; the Ti−O(ethoxy) bond is the shortest in the coordination sphere. It should be mentioned that the large bond-length difference between Ti−O(pyrazolonato) and Ti−O(acyl) is mainly determined by the group trans to them; the O(acyl) elongates markedly from its trans O(ethoxy) bond, whereas the O(pyrazolonato) cannot elongate from its trans O(pyrazolonato) bond. A demonstration of this feature is given by the square-planar complex bis(triphenylphosphine)-(1-phenyl-3-methyl-4-(2-thienoyl)pyrazol-5-one)-rhodium(I), where O(acyl) and O(pyrazolonato) are both trans to the PPh_3 groups; as a result, the Rh−O(pyrazolonato) and Rh−O(acyl) bond lengths are equal.[32] Nevertheless, the tendency for the O(acyl) group to establish a metal−O(acyl) bond length longer than metal−O(pyrazolonato) in this study is consistent with previous results,[25,27] and so it appears logical for O(acyl) to be displayed trans to the short Ti−O(ethoxy) groups in compound **1**. The same applies for compound **1′**, where those groups trans to O(acyl) are again the short Ti−O(oxo) and Ti−O(ethoxy) groups.

The bond angles Ti−O(bridge)−Ti = 160.94(18)° and Ti−O(ethoxy)−C31 = 157.5(6)° are of a similar order and wider than those O(oxo) centered in the oligomer $[(Q^{Ph})_2Ti(\mu\text{-}O)]_4$ (151° and 154°)[9] or those in the O(ethoxy) centered in the mononuclear species $[(Q^{nPe})_2Ti(OEt)_2]$ (**1**), 142.6(3)° and 151.0(3)°. Figure 5 shows marked displacement parameters for ethoxy atoms, which is in agreement with the ease of accommodation in its crystal pocket, a feature closely related to Figure 4.

Therefore, on the basis of the similar trans influence of our compounds compared to budotitane, we attempt to visualize structural features of budotitane oligomers, which are antitumor active,[1] using theoretical methods.

DFT Study. We tested our theoretical program DMol3 on $[(Q^{nPe})_2Ti(OEt)_2]$ (**1**) by minimizing its energy in a geometry optimization process. The resulting molecule is depicted in Figure 6 and shows excellent agreement with the corresponding X-ray structure for the three sets of Ti−O bond lengths in the coordination sphere and the Ti−O−C bond angles in the ethoxy groups.

In agreement with crystal structures of other metal-4-acyl-5-pyrazolonates,[24−26] there is more phenyl−pyrazole coplanarity in Figure 6 than in its crystal structure (where related torsion angles are −34.9 and −40.6° instead of close to 0°), which is ascribed to packing forces in **1**.

Good agreement is obtained between our calculated budotitane structure (Figure 7) and its corresponding X-ray structure[13] as well. Interestingly, the two calculated Ti−O(ethoxy)−C bond angles are more similar (about 136°) than in the crystal (127 and 153°), which is again consistent with the trend of Figure 4 because the isolated calculated molecule has no packing constraints.

Next, we analyze stereoisomers of a dinuclear budotitane derivative resulting from hydrolysis, as in Scheme 5.

Because an asymmetric ligand such as bzac offers several arrangement options, we used the symmetrical ligand dibenzoylacetonato to simplify DFT calculations. Two different arrangements are explored, one having stacked units closely related to $\{[(Q^{nPe})_2Ti(OEt)]_2(\mu\text{-}O)\}$ (**1′**) above and one

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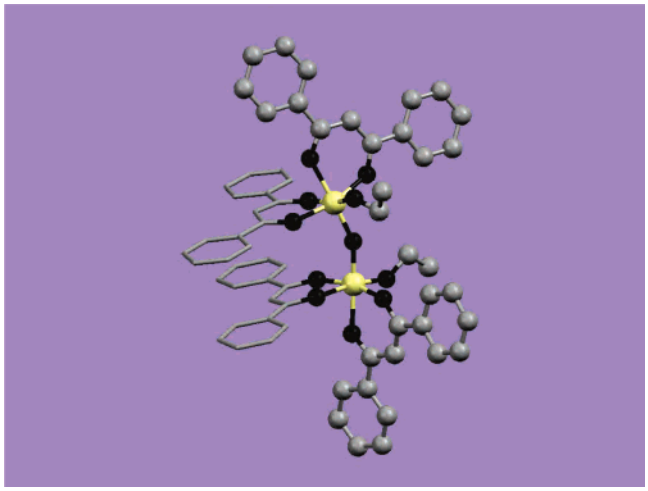

Figure 8. DFT stacked dinuclear budotitane derivative with hydrogen atoms omitted; the stacked moieties are stick style.

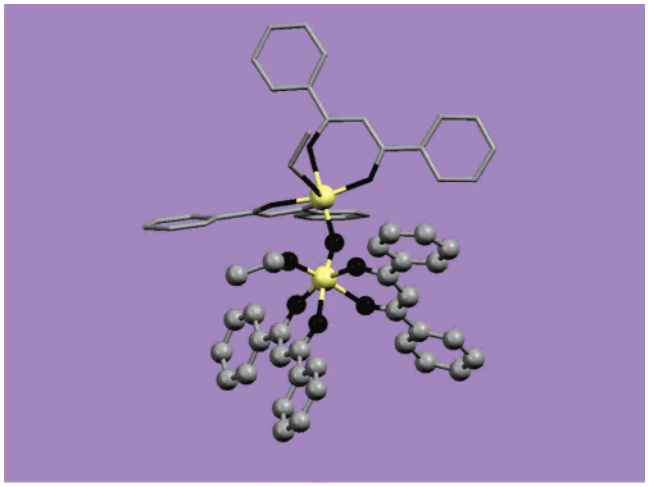

Figure 9. DFT nonstacked dinuclear budotitane derivative with hydrogen atoms omitted. Stick-style atoms belong to a previous mononuclear unit.

lacking this interaction. Their respective minimized geometries are shown in Figures 8 and 9; the stacked arrangement is energetically favored (−4.0 kcal/mol).

It is relevant that when aromatic substituents of budotitane are replaced by alkyl groups, the antitumor activity totally disappears.[1] In addition, di-aqua complexes, arising from hydrolysis of ethoxy groups, strongly bind to DNA,[33] and, thus, intercalation of planar groups on DNA appears to be highly feasible.

Conclusions

Titanium complexes of classical β-diketones (acetylacetonato derivatives) and 4-acyl-5-pyrazolones show similar chemical and antitumor behavior. They are strongly affected by trans influence, establishing longer Ti−O(ligand) bonds than Ti−O(oxo) and Ti−O(alkoxy) ones. Mono-, di-, and tetranuclear Ti-4-acyl-5-pyrazolonato crystals are consistent with a unique stereoisomeric form, and IR spectra in the mononuclear solid show several Ti−O stretching bands, in agreement with several Ti−O bond lengths in the crystal. Existence of other stereoisomers in solution is ascertained by NMR spectra that show their interconversion. Alkoxy groups bound to titanium are strongly affected by packing effects in the solid, and so large ranges of Ti−O bond lengths and Ti−O−C bond angles are available because the related energy changes are minimal.[34] This flexibility might aid in reactivity with biological molecules, for example, the interaction of titanium with the protein transferrin has been shown for titanocene dichloride.[35]

Evidence for $\pi-\pi$ stacking interaction in the crystal structure of dinuclear compound **1′** and the calculated structure of a dinuclear budotitane derivative are provided in this study. Because titanium complexes of classical β-diketones and 4-acyl-5-pyrazolones tend to hydrolyze and form oligomers that have antitumor activity, they are probably carriers of planar groups to the biological target. Structure−activity studies for budotitane confirm the need of planar groups in the diketonato ligand and the strong interaction of di-aqua derivatives of budotitane with DNA.[33] Evidence for intercalation of titanium derivatives with DNA is therefore supported.

Acknowledgment. The authors would like to thank Cristian Opazo at Vassar College SCIVIS lab, Consiglio Nazionale delle Ricerche C.N.R.-Rome, Università di Camerino, CARIMA, and Vassar College Research Committee.

Supporting Information Available: CIF files for compounds **1** and **1′**, Figure S1 (^{1}H NMR spectrum of **1**, recorded 24 h after the variable-temperature study, showing complete complex oligomerization) and Figure S2 (Intermolecular H−π interaction for dinuclear titanium derivative, **1′**). This material is available free of charge via the Internet at http://pubs.acs.org.

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