## Stereoselective dimerization of racemic $C_3$ -symmetric Ti(IV) amine triphenolate complexes<sup>†</sup>;

Gérald Bernardinelli,<sup>*a*</sup> Thomas M. Seidel,<sup>*b*</sup> E. Peter Kündig,<sup>*b*</sup> Leonard J. Prins,<sup>*c*</sup> Andrej Kolarovic,<sup>*c*</sup> Miriam Mba,<sup>*c*</sup> Marta Pontini<sup>*c*</sup> and Giulia Licini<sup>*s*</sup>

Received 26th February 2007, Accepted 1st March 2007 First published as an Advance Article on the web 15th March 2007 DOI: 10.1039/b702958f

A novel, mononuclear Ti(IV) amine triphenolate complex obtained by reaction of Ti(OiPr)<sub>4</sub> with tris(2-hydroxy-3-phenylbenzyl)amine bearing phenyl *ortho*-substituents affords quantitatively and spontaneously the corresponding heterochiral  $\mu$ -oxo dinuclear compound whereas an analogous chiral, enantiopure complex maintains its mononuclear structure even in the presence of an excess of water.

Tripodal  $C_3$  symmetric amine triphenolate ligands 1 have attracted attention in the last years due to their ability to form complexes with a wide variety of transition metals and main group elements.<sup>1-5</sup> In particular, earlier reports on Ti(IV) complexes 2, based on NMR data and supported by X-ray crystallography, show that they are present as a racemic mixture of  $\Delta$  and  $\Lambda$  complexes, resulting from a helical wrapping of the ligand around the metal ion, with racemisation barriers of  $\Delta G^{\ddagger}$  = 65.7-74.4 kJ mol<sup>-1</sup>.<sup>3</sup> These reports also demonstrated that the stability of titanatranes 2 in solution strongly depends on the steric size of the peripheral substituents.<sup>3,4</sup> Complexes bearing small ortho substituents tend to give aggregates like µ-oxo and bis µ-oxo complexes in the presence of traces of water. In contrast, complexes bearing bulky groups like tert-butyl are highly stable and resistant to hydrolysis. The corresponding µ-oxo complex cannot be obtained by direct hydrolysis of the alkoxide, which is moisture stable, but only via evaporation to dryness of a solution of the corresponding Ti(IV)-hydroxy complex. A bent  $\mu$ -oxo bridge (155.53°) was determined in the crystal structure and it was observed that the µ-oxo bridge was not stable in solution and easily hydrolysed in the presence of traces of water.<sup>1</sup>

Here we report that a related titanatrane **2a**, bearing bulky phenyl substituents in *ortho* positions, spontaneously forms a highly stable  $\mu$ -oxo dinuclear complex in the presence of only traces of water, with rather different structural characteristics: a linear Ti–O–Ti bond with the peripheral phenyl groups intercalating and disposed in a propeller like fashion shielding the Ti–O–Ti core and with the two chiral titanatrane groups having opposite configuration ( $\Delta$  and  $\Lambda$ ). The dimerization process is highly stereoselective, since a similar chiral titanatrane **2b** in enantiopure form maintains its mononuclear structure and does not form the corresponding  $\mu$ -oxo complex, not even in the presence of large amounts of water and under much harsher reaction conditions. Therefore a stereo-self-discrimination process between two enantiomeric structures is at the origin of the  $\mu$ -oxo complex formation.

The amine triphenol ligands **1** are readily available *via* an efficient route involving reductive amination.<sup>6</sup> Reaction of **1a** with one equivalent of Ti(OiPr)<sub>4</sub> in dry CHCl<sub>3</sub> yields the corresponding mononuclear,  $C_3$  symmetric Ti(IV) complex **2a**. The <sup>1</sup>H NMR spectrum of **2a** in CDCl<sub>3</sub> shows a single set of signals for the aromatic protons and the six methylene protons appear as a single broad singlet at 3.62 ppm. This is in agreement with the formation of a  $C_3$  symmetric complex in which the two enantiomers racemise at room temperature (Scheme 1).



Scheme 1 Reagents and conditions: (i) Ti(O-*i*-Pr)<sub>4</sub> (1 equiv.), CHCl<sub>3</sub>, rt; (ii) CHCl<sub>3</sub>-H<sub>2</sub>O, rt.

However, upon standing in solution, complex **2a** readily transforms into a new highly symmetric species, whose <sup>1</sup>H NMR spectrum again shows a single set of signals for the ligand protons, but also reveals that the apical *i*-PrOH ligand of **2a** is released. Interestingly, the methylene protons of the new species now appear as an AB system with resonances at 4.36 and 3.28 ppm respectively, indicating that the racemisation rate of the titanatrane moiety in the new species is slower on the NMR time scale. The spontaneous formation of the new species is quantitative in a few hours and light yellow crystals precipitated out of the solution. ESI-MS

<sup>&</sup>lt;sup>a</sup>Laboratory of X-ray Crystallography, University of Geneva, 24 Quai Ernest Anserment, 1211, Geneva 4, Switzerland

<sup>&</sup>lt;sup>b</sup>Department of Organic Chemistry, University of Geneva, 30 Quai Ernest Anserment, 1211, Geneva 4, Switzerland. E-mail: Peter.Kundig@ chiorg.unige.ch; Fax: +41 223793215; Tel: +41 223796093

<sup>&</sup>lt;sup>c</sup>Dipartimento di Scienze Chimiche, via Marzolo I-35131, Padova, Italy. E-mail: giulia.licini@unipd.it; Fax: +390498275239; Tel: +390498275289 † The HTML version of this article has been enhanced with colour images. ‡ Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b702958f

experiments (1  $\mu$ M, acetonitrile, HCOOH 0,1%, as mobile phase) revealed that the new species is a dinuclear  $\mu$ -oxo complex **3**. Interestingly, **3** is stable under ESI experimental conditions being the only species detectable in the spectrum as the H<sup>+</sup> (m/z = 1233), Na<sup>+</sup> (m/z = 1255) and K<sup>+</sup> (m/z = 1271) adducts.

The synthesis of the complex in a mixture of  $CHCl_3-C_6H_6$  allowed us to obtain crystals suitable for X-ray analysis (Fig. 1). The crystal structure of  $3^7$  confirms the formation of a dinuclear Ti(IV) complex with a linear  $\mu$ -oxo bridge linking two titanatrane units of opposite stereochemistry. The  $\mu$ -oxo bridge is located on a crystallographic centre of inversion leading to a perfectly linear Ti–O–Ti bond angle. This contrasts with the bent bridge found in a corresponding  $\mu$ -oxo complex with *t*-Bu *ortho-* and *para*-substituents.<sup>1</sup> The Ti–O<sub>central</sub> distance (1.7983(7) Å) is in the range observed in other similar complexes<sup>8,9</sup> but it is shorter than the one found in complexes bearing a bent bridge (1.8251 and 1.8256 Å).<sup>1</sup> The Ti atom shows a trigonal bipyramidal geometry with Ti–N bonds of 2.327(3) Å.



Fig. 1 Top: ORTEP view of 3. Ellipsoids are represented at 40% probability level. The central O atom is located on a centre of inversion. Selected bond distances [Å] and angle [°]: Ti $-O_{central} = 1.7983(7)$ , Ti-N = 2.327(3), Ti-O-Ti = 180.0. Disordered solvent molecules are omitted for clarity. Bottom : View along the N-Ti-O-Ti-N axis.

The peripheral phenyl rings from the two ligands intercalate around the  $\mu$ -oxo bridge: each internal *ortho* proton points toward the  $\pi$ -cloud of the next ring, belonging to the other titanatrane moiety. The perpendicular distances between H<sub>ortho</sub> and the centre of the phenyl ring are 2.74 Å or 2.78 Å which suggests participation of CH– $\pi$  interactions in the stabilisation of the complex.<sup>10</sup> This structural characteristic is reflected also in solution. The <sup>1</sup>H NMR spectrum of **3** exhibits significant upfield shifts for the signals of the peripheral phenyls (*ca.* 1 ppm). Interestingly, only three sets of signals are present for the *ortho*, *meta* and *para* protons, with relative intensities in a 2 : 2 : 1 ratio, thus indicating fast rotation of the phenyl rings on the NMR time scale.

The two titanatrane units in **3** maintain the helical conformation around the metal ion as in the monomeric complexes but, remarkably, starting from a racemic mixture of complexes,  $\Delta$  and  $\Lambda$ , exclusively the heterochiral compound ( $\Delta$ – $\Lambda$ ) is formed. No traces of the diastereomeric homochiral complexes ( $\Delta$ – $\Delta$  or  $\Lambda$ – $\Lambda$ ) are present in the <sup>1</sup>H NMR spectrum. VT NMR experiments up to 100 °C (300 MHz, toluene-d<sub>8</sub>) showed no significant modification of the spectrum nor the appearance of another diastereomeric species. The fact that even at 100 °C the methylene signals of **3** remain an AB system indicates that the new complex is much more stable towards racemisation than the mononuclear complex **2**.

In order to determine whether or not the formation of the µoxo complex 3 implies a stereo-self-discrimination process, we decided to investigate the behaviour of an analogous, enantiomerically pure complex. This requires complete control of ligand helicity in the complex. Canary and co-workers had reported that the helicity of Zn(II) and Cu(II) tripodal complexes of tris(pyridylmethyl)amino ligands can be controlled by the introduction of a single stereogenic center in one of the benzylic positions.<sup>11</sup> We speculated that this observation in 5-membered metallacycles could also hold for 6-membered metallacycles present in the enantiomerically pure Ti(IV) amine tri(phenolate) complex 2b. The synthesis of ligand (S)-1b was undertaken to confirm or refute this hypothesis. The route chosen was analogous to that published recently by one of us.12 Conversion of hydroxyarylaldehyde 4 to its benzylether and imine formation with S-(+)-2-amino-2-phenylethanol afforded (S)-5. MeLi addition gave the expected, diastereoisometrically highly enriched (S,S)-6 which was converted to the HCl salt (S)-7 of the primary amine (S)-7 via Pb(OAc)<sub>4</sub> oxidation followed by hydrolysis. Reaction of (S)-7 with two equivalents of 2-benzyloxy-3-bromomethyl-biphenyl, followed by hydrogenolysis of the benzyl groups gave ligand (S)-1b (Scheme 2).



Scheme 2 *Reagents and conditions*: (i)  $K_2CO_3$ , BnBr (1.2 equiv), CHCl<sub>3</sub>–MeOH; (ii) (*S*)-(+)-2-amino-2-phenylethanol (1.0 equiv), EtOH, MS, rt; (iii) MeLi (4 equiv.), THF, -78 °C; (iv) Pb(OAc)<sub>4</sub> (1.2 equiv.), K<sub>2</sub>CO<sub>3</sub>, MeOH; (v) AcOH–H<sub>2</sub>O; (vi) Et<sub>2</sub>O–HCl; (vii) K<sub>2</sub>CO<sub>3</sub>, 2-benzy-loxy-3-bromomethyl-biphenyl (2 equiv.), MeCN, reflux; (viii) H<sub>2</sub>, Pd/C.

Ligand (S)-1b cleanly reacts with Ti(O-*i*-Pr)<sub>4</sub> in dry CHCl<sub>3</sub> yielding the complex (S)-2b (Scheme 1). The <sup>1</sup>H NMR spectrum in CDCl<sub>3</sub> shows the quantitative formation of a single mononuclear Ti(IV) complex. Due to the loss of  $C_3$  symmetry of the system, the <sup>1</sup>H NMR spectrum of complex (S)-2b is more complicated then that of 2a, but it shows a single set of resonances for each of the diastereotopic benzylic protons. VT NMR experiments from -40 up to 60 °C gave no indication of a remote stereogenic centre is sufficient to control the helicity of the complex also for the titanatrane 2b.<sup>13</sup>

The circular dichroism spectrum of the Ti(IV) complex (*S*)-**2b** shows significantly enhanced signals compared with the spectrum of the free ligand ((*S*)-**1b**) (Fig. 2).



**Fig. 2** Circular dichroism spectra  $(CH_2Cl_2)$  for ligand (*S*)-1b and complex (*S*)-2b.

This is consistent with the presence of a propeller-like conformation for the mononuclear complex (*S*)-**2b**. Based on literature precedent and on molecular model studies,<sup>11</sup> the preferred diastereoisomer is expected to have the methyl group positioned *anti* with respect to the phenyl moiety. On the basis of the configurations present in the two heteronuclear moieties of the  $\mu$ -oxo complex **3** this should generate a  $\Delta$  (right-handed) propellerlike twist.

Complex (*S*)-**2b** turned out to be stable towards reaction with water. We were unable to detect a  $\mu$ -oxo complex even after the addition of water (10 equiv.) and heating to 60 °C. Extensive heating resulted in partial decomposition. ESI-MS experiments (1  $\mu$ M, acetonitrile, HCOOH 0.1% as mobile phase) did not show the presence of any  $\mu$ -oxo species in solution, even after long reaction times. The behaviour of the enantiopure complex (*S*)-**2b** confirms that the formation of the  $\mu$ -oxo dimer **3** is driven by a chiral self-discrimination process of two enantiomeric moieties. This completely selective stereo-self-discrimination between enantiomeric propeller shaped units could have interesting applications in supramolecular chemistry<sup>14,15</sup> or in asymmetric catalysis with amplification of chirality.<sup>16</sup>

We acknowledge with thanks the sponsorship of this project by MIUR, FIRB-2003 CAMERE-RBNE03JCR5 project, the University of Padova, CP0A054893 and Assegni di ricerca di Ateneo 2006 (M.M. and M.P. fellowships), Givaudan S.A., Vernier (T.S. fellowship) and the Swiss State Secretariat for Education and Research (E.P.K, SER C02.0029/COSTD24). The project was carried out in the framework of COST, Action D24 'Sustainable Chemical Processes: Stereoselective Transition Metal-Catalysed Reactions' (WG D24/0005/2001).

## Notes and references

- 1 V. Ugrinova, G. A. Ellis and S. N. Brown, *Chem. Commun.*, 2004, 468–469.
- 2 Y. Kim and J. G. Verkade, Organometallics, 2002, 21, 2395–2399; S. D. Bull, M. G. Davidson, A. L. Johnson, D. Robinson and M. F. Mahon, Chem. Commun., 2003, 1750–1751; K. C. Fortner, J. P. Bigi and S. N. Brown, Inorg. Chem., 2005, 44, 2803–2814; S. A. Cortes, M. A. Muñoz Hernández, H. Nakai, I. Castro-Rodriguez, K. Meyer, A. R. Fout, D. L. Miller, J. C. Huffman and D. J. Mindiola, Inorg. Chem. Commun., 2005, 8, 903–907.
- 3 M. Kol, M. Shamis, I. Goldberg, Z. Goldschmidt, S. Alfi and E. Hayut-Salant, *Inorg. Chem. Commun.*, 2001, **4**, 177–179.
- 4 M. Mba, L. J. Prins and G. Licini, Org. Lett., 2007, 9, 21-24.
- R. J. Motekaitis, A. E. Martell, S. A. Koch, J. W. Hwang, D. A. Quarless and M. J. Welch, *Inorg. Chem.*, 1998, **37**, 5902–5911; N. V. Timosheva, A. Chandrasekaran, R. O. Day and R. R. Holmes, *Organometallics*, 2001, **20**, 2331–2337; Y. J. Kim, P. N. Kapoor and J. G. Verkade, *Inorg. Chem.*, 2002, **41**, 4834–4838; S. Groysman, S. Segal, I. Goldberg, M. Kol and Z. Goldschmidt, *Inorg. Chem. Commun.*, 2004, **7**, 938–941; S. Groysman, I. Goldberg, M. Kol, E. Genizi and Z. Goldschmidt, *Adv. Synth. Catal.*, 2005, **347**, 409–415; S. Groysman, I. Goldberg, Z. Goldschmidt and M. Kol, *Inorg. Chem.*, 2005, **44**, 5073–5080; C. Redshaw, M. A. Rowan, D. M. Homden, S. H. Dale, M. R. J. Elsegood, S. Matsui and S. Matsuura, S., *Chem. Commun.*, 2006, 3329–3331.
- 6 L. J. Prins, M. Mba, A. Kolarović and G. Licini, *Tetrahedron Lett.*, 2006, 47, 2735–2738.
- 7 *Crystal data for* **3**: {O[(TiN(C<sub>13</sub>H<sub>10</sub>O)<sub>3</sub>]<sub>2</sub>}(C<sub>6</sub>H<sub>6</sub>)<sub>2</sub>(CHCl<sub>3</sub>)<sub>0.79</sub>, M = 1483.4, monoclinic, space group  $P2_1/n$ , a = 13.2828(8), b = 15.6644(7), c = 18.5844(12) Å,  $\beta = 105.269(7)^{\circ}$ , V = 3730.3(4) Å<sup>3</sup>, Z = 2, T = 200 K,  $\mu = 0.36$  mm<sup>-1</sup>,  $D_c = 1.32$  g cm<sup>-3</sup>,  $\lambda$ (MoK $\alpha$ ) = 0.71073 Å, 27925 measured reflections, 7259 unique ( $R_{int} = 0.084$ ) from which 3203 with  $|F_o| > 4\sigma$  ( $F_o$ ). The structure was solved by direct methods (SIR-97) and refined by full matrix least-squares (XTAL 3.2) on *F*. R = 0.044, wR = 0.042, GOF = 1.33(2). CCDC reference number 629066. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b702958f.
- 8 M. M. Olmstead, P. P. Power and M. Viggiano, J. Am. Chem. Soc., 1983, **105**, 2927–2928; N. Kuhn, T. Kratz, D. Blaser and R. Boese, *Inorg. Chim. Acta*, 1995, **238**, 179–181; A. Kayal, A. F. Ducruet and S. N Lee, *Inorg. Chem.*, 2000, **39**, 3696–3704; T. C. H. Lam, E. Y. Y. Chan, W.-L. Mak, S. M. L. Lo, I. D. Williams, W.-T. Wong and W.-H. Leung, *Inorg. Chem.*, 2003, **42**, 1842–1847.
- 9 M. L. N. Rao, H. Houjou and K. Hiratani, *Chem. Commun.*, 2002, 420–421; W. Levason, M. C. Popham, G. Reid and M. Webster, *Dalton Trans.*, 2003, 291–294; E. F. DiMauro, A. Mamai and M. C. Kozlowski, *Organometallics*, 2003, **22**, 850–855.
- 10 M. Nishio, M. Hirota and Y. Umezawa, *The CH*/ $\pi$  *interaction*, Wiley-VCH, New York, 1998.
- 11 J. W. Canary, C. S. Allen, J. M. Castagnetto and Y. J. Wang, Y., J. Am. Chem. Soc., 1995, 117, 8484–8485; Z. Dai, X. Zhu and J. W. Canary, Chirality, 2005, 17, 227–235.
- 12 G. Bernardinelli, D. Fernandez, R. Gosmini, P. Meier, P., A. Ripa, P. Schüpfer, B. Treptow and E. P. Kündig, *Chirality*, 2000, **12**, 529–539; E. P. Kündig, C. Botuha, G. Lemercier, P. Romanens, L. Saudan and S. Thibault, *Helv. Chim. Acta*, 2004, **87**, 561–579.
- 13 During the preparation of this manuscript, an analogous enantiopure triphenolamine bearing *ortho* and *para t*-Bu groups has been published. A similar synthetic sequence was used. In analogy with what we observe with ligand 1b the corresponding Ti(IV) complex forms a single diastereomeric species, both in solution and in the crystal structure. P.

Axe, S. D. Bull, M. G. Davidson, C. J. Gilfillan, M. D. Jones, D. E. J. E. Robinson, L. E. Turner and W. L. Mitchell, *Org. Lett.*, 2007, 9, 223–226.

- 14 J.-M. Lehn, Supramolecular Chemistry, VCH, Weinheim, 1995; J. W. Steed and J. L. Atwood, Supramolecular Chemistry, Wiley, Chichester, 2000.
- 15 M. Albrecht, Chem.-Eur. J., 2000, 6, 3485–3489; A. Rammal, F. Brisach and M. Henry, J. Am. Chem. Soc., 2001, 123, 5612–5613; M. Albrecht,

S. Mirtschin, M. de Groot, I. Janser, J. Runsink, G. Raabe, M. Kogej and C. A. Schalley, *J. Am. Chem. Soc.*, 2005, **127**, 10371–10387; K. Matsumoto, Y. Sawada, B. Saito, K. Sakai and T. Katsuki, *Angew. Chem., Int. Ed.*, 2005, **44**, 4935–4939 and references therein.

16 C. Girard and H. B. Kagan, Angew. Chem., Int. Ed., 1998, 37, 2923–2959; amplification of asymmetric induction is discussed in, E. L. Eliel, S. H. Wilen and L. N. Mander, Stereochemistry of Organic Compounds, Wiley, New York, 1994, ch. 12.5.