Multiple Solution Species of Titanium(IV) 1,1′-Bi-2-naphtholate Elucidated by NMR and CD Spectroscopy

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The solution mixtures of (*S*)-BINOL and Ti(O^{i}Pr)$_4$, with various titanium/BINOL ratios, have been characterized by NMR and CD spectroscopies. In the presence of 1−8 metal equivalents, two main complexes (species **I** and **II**) were detected. Species **II**, identified as (BINOLate)Ti(O^{i}Pr)$_2$·Ti(O^{i}Pr)$_4$, is dominant in the conditions employed for the catalysis of enantioselective addition of alkylzinc reagents to aldehydes. NMR T_1 and DOSY results confirmed that species **I** is dimeric in solution and may be formulated as [(BINOLate)Ti-(O^{i}Pr)$_2$]$_2$. The two complexes undergo relatively fast dynamic processes at room temperature, making all naphthoate rings equivalent at NMR; spectrum decoalescence is observed at low temperature. An equilibrium process between **I** and **II**, depending on Ti(O^{i}Pr)$_4$, was ascertained and quantitatively followed by titration of BINOL with Ti(O^{i}Pr)$_4$ and variable-temperature experiments. CD spectra offered ultimate proof of titanium-chelating BINOL structures.

Introduction

Among the countless examples of metal complexes of 1,1′-bi-2-naphthol (BINOL) used as asymmetric catalysts in organic synthesis,[1] a key role is played by the family of titanium(IV) complexes. The peculiar flexibility and versatility of the BINOL ligand,[2] on one hand, and the variety of titanium coordination chemistry, on the other hand, resulted in a group of species that may be collectively indicated as "(BINOLate)TiX$_2$", employed in a sweeping range of enantioselective reactions.[1,3,4] The downside of this diversity is that the effective nature and structure of the catalytically active species is often elusive. A manifest example is offered by the catalysts obtained by mixing BINOL or a derivative R$_x$-BINOL (e.g., substituted or partially hydrogenated or fluorinated BINOL) and titanium tetraisopropoxide Ti(O^{i}Pr)$_4$ at different ratios, whose main application, among others, is the enantioselective addition of alkyl groups to aldehydes (especially with dialkylzinc reagents).[1,5,6] Numerous compounds of the type "(R$_x$-BINOLate)Ti-(O^{i}Pr)$_2$·[Ti(O^{i}Pr)$_4$]$_n$" ($n = 0-2$) have been isolated in the crystalline state and their structure determined,[3,4,7,8] showing pronounced dependence on the nature of the R$_x$-BINOL ligand and on the R$_x$-BINOL/Ti stoichiometry. Moreover, the well-known fluxionality of Ti(IV) alkoxides,[9] undergoing facile ligand addition, elimination, and exchange, frequently poses a question about

the correspondence between solid state and solution structures, thus justifying the efforts toward a separate characterization. As a matter of fact, any modern approach for understanding catalytic mechanisms has to face with a structural elucidation in the solution state, at least of homogeneous catalytic precursors and/or stable intermediates.[10]

Three different crystalline compounds have been isolated by Walsh and co-workers by mixing enantiopure BINOL (**A**, Scheme 1) and Ti(O^{i}Pr)$_4$ with 1:1, 1:2, and 1:3 proportions, respectively, [(BINOLate)Ti-(O^{i}Pr)$_2$]$_3$ (**1a**), (BINOLate)Ti(O^{i}Pr)$_2$·Ti(O^{i}Pr)$_4$ (**2a**), and (BINOLate)Ti(O^{i}Pr)$_2$· [Ti(O^{i}Pr)$_4$]$_2$ (**3a**);[4,8] they feature the trimeric, dinuclear, and trinuclear structures illustrated in Scheme 1. The solid state structure of **1a** had been previously determined by Martin and Sharpless.[11] Using racemic instead of enantiopure BINOL for preparing the 1:1 compound, a dimeric heterochiral structure like **1a$_{rac}$** was isolated in the solid state;[7] moreover, both compounds **1a** and **1a$_{rac}$** showed a dimeric character in solution, as found by a molecular weight measurement[11] and NMR evidence of the het-

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(1) (a) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503−517. (b) Pu, L. *Chem. Rev.* **1998**, *98*, 2405−2494. (c) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155−3211.
(2) (a) Noyori, R.; Takaya, H. *Chem. Scr.* **1985**, *25*, 83−89. (b) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581−1590.
(3) Boyle, T. J.; Barnes, D. L.; Heppert, J. A.; Morales, L.; Takusagawa, F. *Organometallics* **1992**, *11*, 1112−1126.
(4) Balsells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336−10348.

(5) (a) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233−6236. (b) Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585−589.
(6) For the most recent examples concerning modified BINOLs see: (a) Nakamura, Y.; Takeuchi, S.; Okumura, K.; Ohgo, Y.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3963−3969. (b) Lee, S. J.; Hu, A.; Lin, W. *J. Am. Chem. Soc.* **2002**, *124*, 12948−12949. (c) Nakamura, Y.; Takeuchi, S.; Ohgo, Y. *J. Fluorine Chem.* **2003**, *120*, 121−129. (d) Harada, T.; Hiraoka, Y.; Kusukawa, T.; Marutani, Y.; Matsui, S.; Nakatsugawa, M.; Kanda, K. *Org. Lett.* **2003**, *5*, 5059−5062. (e) Liu, G.-H.; Tang, W.-J.; Fan, Q.-H *Tetrahedron* **2003**, *59*, 8603−8611.
(7) Waltz, K. M.; Carroll, P. J.; Walsh, P. J. *Organometallics* **2004**, *23*, 127−134.
(8) Davis, T. J.; Balsells, J.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, *3*, 699−702.
(9) (a) Bradley, D. C.; Mehrotra, R. C.; Gaur, D. P. *Metal Alkoxides*; Academic Press: New York, 1978. (b) Wu, Y.-T.; Ho, Y.-C.; Lin, C.-C.; Gau, H.-M. *Inorg. Chem.* **1996**, *35*, 5948−5952. See also refs 10a,l.

Scheme 1.   Structures of Solid-State Titanium(IV) BINOLate-Type Compounds
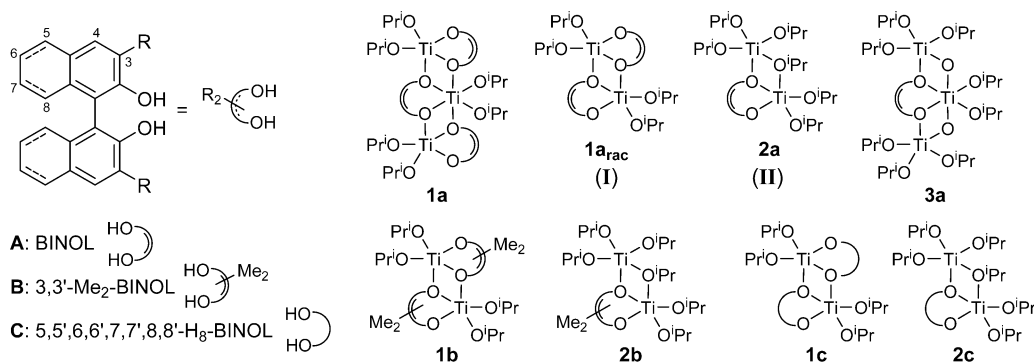
erochiral dimer.[5a,11] Compounds **2a** and **3a** also exhibited unexpected solution behavior.[4] After dissolving in CDCl$_3$, they were described to give identical ^{13}C NMR spectra, containing 20 aromatic resonances at room temperature; reported ^{1}H spectra were also identical and were attributed to a single BINOL-containing species with two nonequivalent naphthoate rings. This was taken as proof that the trinuclear structure **3a** drops one Ti(O^{i}Pr)$_4$ group upon dissolution, thus converting into the dinuclear species **2a**, where the BINOL ligand has lost the C_2 symmetry.[4]

Some of the above findings are surprisingly at odds with the results obtained for analogous complexes formed between Ti(O^{i}Pr)$_4$ and BINOL-based ligands, such as 3,3′-dimethyl BINOL (**B**, Scheme 1) and 5,5′,6,6′,7,7′,8,8′-octahydro BINOL (**C**).[3,7,12] In the solid state, **B** and **C** behave comparably to the parent BINOL (**A**). The crystals of the 1:1 compounds [(Me$_2$-BINOLate)Ti(O^{i}Pr)$_2$]$_2$ (**1b**, Scheme 1) and [(rac-H$_8$-BINOLate)Ti(O^{i}Pr)$_2$]$_2$ (**1c**) both show a dimeric structure, heterochiral for **1c**, corresponding to the parent **1a$_{rac}$**.[3,7] The crystalline 1:2 compounds (Me$_2$-BINOLate)Ti(O^{i}Pr)$_2$·Ti(O^{i}Pr)$_4$ (**2b**) and (H$_8$-BINOLate)Ti(O^{i}Pr)$_2$·Ti(O^{i}Pr)$_4$ (**2c**) feature a binuclear structure (Scheme 1)

also coincident with that of **2a**.[3,4,7] On the contrary, NMR data obtained upon dissolving **1**,**2b** and **1**,**2c** clash with those of **1**−**3a**, although the molecularity in solution is the same (dimeric for **1a**,**b** and monomeric for **2a**,**b**).[3,4]

In particular, ^{1}H and ^{13}C NMR spectra for **1**,**2b** and **1**,**2c** at 298 K showed only one set of aromatic resonances for any single species, consistent with two or four equivalent naphthoate rings and an effective C_2 (or D_2) symmetry, originated from dynamic averaging processes relatively fast on the NMR time scale;[3,7] peak decoalescence was observed for **1**,**2b** upon decreasing temperature.[3] Similarly, dissolution of **1a** led to a ^{1}H NMR spectrum consistent with a fluxional, D_2-symmetric structure;[11] instead, spectra for **2a** were assigned to a species frozen in a nonsymmetric structure.[4] Moreover, NMR data clearly indicated the existence of an equilibrium between 1:1 and 1:2 complexes, e.g., **1b**,**c**$_{1/2}$ + Ti(^{i}PrO)$_4$ ⇌ **2b**,**c**, depending on the amount of Ti(O^{i}Pr)$_4$ and on the temperature,[3,7] while no such phenomenon had been reported for **1**,**2a**. These basic differences between the titanium complexes of BINOL (**A**) and its derivatives **B** and **C**, in terms of dynamic and equilibrium processes occurring in solution, not only are intriguing from a theoretical point of view but should also reflect into practical consequences since binuclear species such as **2a** are most likely responsible for the asymmetric catalysis.[4,5a]

In an attempt to better understand the chemistry of BINOL-titanium complexes involved in the enantioselective addition of alkyl groups to aldehydes, we considered it fundamental to analyze the solution mixtures of Ti(O^{i}Pr)$_4$ and enantiopure BINOL. As a matter of fact, the reaction is usually performed by merely mixing these two compounds, in 6:1 or higher proportion (in toluene or CH$_2$Cl$_2$ or CH$_2$Cl$_2$/hexane, 10−50 mM concentration), and then adding the substrates in situ, without the need for isolating the catalytic precursor.[5] Direct NMR and CD observations of samples of BINOL/Ti(O^{i}Pr)$_4$, obtained in conditions similar to the synthetic application, immediately provided the proof of existence of multiple titanium BINOLate solution species. The comprehensive spectroscopic analysis described in the following led us to identify the two major species as 1:1 and 1:2 BINOL-titanium complexes and to uncover the occurrence of an equilibrium depending on the amount of Ti(O^{i}Pr)$_4$. The 1:2 species is prevailing at the BINOL/Ti(O^{i}Pr)$_4$ proportions employed in the asymmetric reaction. NMR and CD evidence were also collected proving the existence of the 1:1 complex as a dimer in solution.

(10) For recent noteworthy examples of structural studies in solution of catalytically active titanium complexes with alkoxy or aryloxy ligands, see: (a) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113−126. (b) Sasaki, C.; Nakajima, K.; Kojima, M.; Junnosuke, F. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1318−1324. (c) Seebach, D.; Plattner, D. A.; Beck, A. K. Wang, Y. M.; Hunziker, D. *Helv. Chim. Acta* **1992**, *75*, 2171−2209. (d) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, *58*, 1515−1522. (e) Tonchio, M.; Licini, G.; Modena, G.; Bortolini, G.; Moro, S.; Nugent, W. A. *J. Am. Chem. Soc.* **1999**, *121*, 6258−6268. (f) Potvin, P. G.; Fieldhouse, B. G. *Tetrahedron: Asymmetry* **1999**, *10*, 1661−1672. (g) You, J.-S.; Shao, M.-Y.; Gau, H.-M. *Organometallics* **2000**, *19*, 3368−3373. (h) Flores-Lopéz, L. Z.; Parra-Hake, M.; Somanathan, R.; Walsh, P. J. *Organometallics* **2000**, *19*, 2153-2160. (i) Sarvay, I.; Almqvist, F.; Frejd, T. *Chem. Eur. J.* **2001**, *7*, 2158−2166. (j) Hintermann, L.; Broggini, D.; Togni, A. *Helv. Chim. Acta* **2002**, *85*, 1597−1612. (k) Wu, K.-H.; Gau, H.-M. *Organometallics* **2003**, *22*, 5193−5200. (l) Pérez, Y.; del Hierro, I.; Fajardo, M.; Otero, A. *J. Organomet. Chem.* **2003**, *679*, 220−228. (m) Wu, K.-H.; Gau, H.-M. *Organometallics* **2004**, *23*, 580−588. (n) Ladipo, F. T.; Sarveswaran, V.; Kingston, J. V.; Huyck, R. A.; Bylikin, S. Y.; Carr, S. D.; Watts, R.; Parkin, S. *J. Organomet. Chem.* **2004**, *689*, 502−514. (o) Takashima, Y.; Nakayama, Y.; Hirao, T.; Yasuda, H.; Harada, A. *J. Organomet. Chem.* **2004**, *689*, 612−619. (p) Corden, J. P.; Errington, W.; Moore, P.; Partridge, M. G.; Wallbridge, M. G. H. *Dalton Trans.* **2004**, 1846−1851.

(11) Martin, C. Ph.D. Thesis, MIT, Cambridge, 1989.

(12) Other BINOL-titanium complexes, closely related to the present ones, have been investigated in the solution state: (a) Boyle, T. J.; Eilerts, N. W.; Heppert, J. A.; Takusagawa, F. *Organometallics* **1994**, *13*, 2218−2229. (b) Kitamoto, D.; Imma, H.; Nakai, T. *Tetrahedron Lett.* **1995**, *36*, 1861−1864. (c) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Inorg. Chim. Acta* **1999**, *296*, 267−272. (d) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363−2364. (e) Harada, T.; Hiraoka, Y.; Kusukawa, T.; Marutani, Y.; Matsui, S.; Nakatsugawa, M.; Kanda, K. *Org. Lett.* **2003**, *5*, 5059−5062.
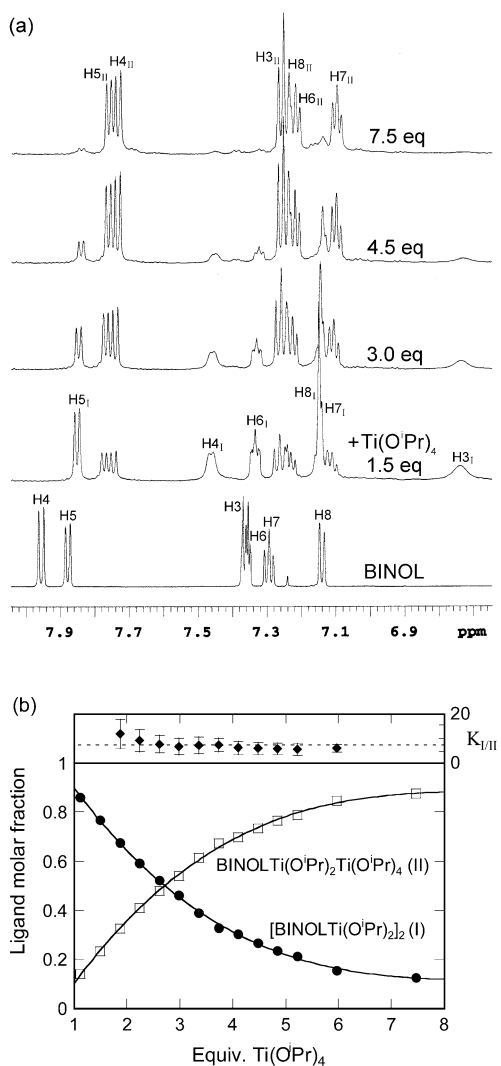
Figure 1. (a) Titration of (*S*)-BINOL (89.5 mM concentration) with Ti(O^{i}Pr)$_4$ in CDCl$_3$, followed by ^{1}H NMR (600 MHz). Assignment is shown for BINOL (lower spectrum), [(BINOLate)Ti(O^{i}Pr)$_2$]$_2$ (**I**, 1.5 equiv spectrum), and (BINOLate)Ti(O^{i}Pr)$_2$·Ti(O^{i}Pr)$_4$ (**II**, 7.5 equiv spectrum); proton numbering as in Scheme 1. (b) Plot of relative concentration of species **I** and **II** (bottom) and of equilibrium constant $K_{I/II}$ (see text, eq 1; top) calculated for each titration point.

The results of the present study not only are descriptive of the situation encountered in the enantioselective catalytic application but also definitely reconcile the solution behavior of titanium complexes of BINOL (**A**) with that of its derivatives **B** and **C**.

Results and Discussion

NMR Analysis of BINOL/Ti(O^{i}Pr)$_4$ Solution Mixtures. By mixing enantiopure (*S*)-BINOL and 2−8 equiv of Ti(O^{i}Pr)$_4$ in CDCl$_3$ (60−90 mM concentration), we recorded ^{1}H and ^{13}C NMR spectra witnessing the presence of two distinct BINOL-titanium complexes. The aliphatic region was overwhelmed by the excess of Ti-(O^{i}Pr)$_4$, yielding broad and uninformative signals at 298 K. On the contrary, the proton and carbon signals in the aromatic region could be assigned (as showed in Figures 1a and 2a) by COSY, ROESY, and HSQC (see Supporting Information, Figure S1) experiments. Two sets of aromatic signals were observed in all cases,
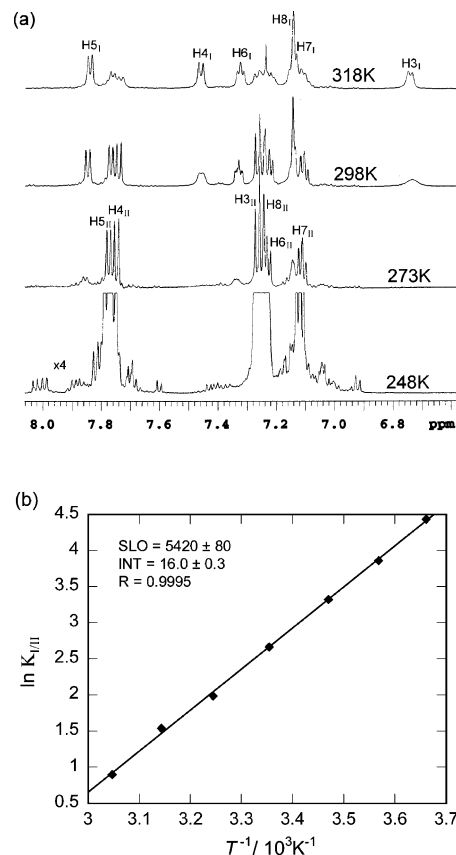
Figure 2. (a) Variable-temperature ^{1}H NMR spectra (600 MHz) of a mixture of (*S*)-BINOL (62.6 mM concentration) and Ti(O^{i}Pr)$_4$ (0.184 M) in CDCl$_3$. Assignment is shown for [(BINOLate)Ti(O^{i}Pr)$_2$]$_2$ (**I**, 318 K spectrum) and (BINOLate)-Ti(O^{i}Pr)$_2$·Ti(O^{i}Pr)$_4$ (**II**, 273 K spectrum); proton numbering as in Scheme 1. (b) Van't Hoff analysis of VT data according to the equilibrium described by constant $K_{I/II}$ (see text, eq 1).

distinct from those of BINOL in CDCl$_3$, belonging to two BINOL-titanium complexes each with equivalent naphthoate rings at 298 K; their relative proportion depended on the amount of Ti(O^{i}Pr)$_4$, on the temperature, and partially on the solvent (as noticed by using a 4.5:1 d_{12}-cyclohexane/CDCl$_3$ mixture). These data indicated the occurrence of an equilibrium, which was quantitatively followed by titrating BINOL with Ti(O^{i}Pr)$_4$ (Figure 1) and by varying the temperature (Figure 2). In the range between 0.5 and 1 equiv of Ti(O^{i}Pr)$_4$ added, complicated spectra were observed containing also the signals of free BINOL. At 298 K, a first species (**I**) is dominant up to about 3 equiv of Ti(O^{i}Pr)$_4$ added (Figure 1), while a second species (**II**) is dominant from that point on; after 8−10 equiv of Ti(O^{i}Pr)$_4$ is added, species **I** is only barely distinguishable. Using the less polar solvent mixture facilitates the complexation and especially the formation of species **II**.

Interestingly enough, all proton signals (except H8) for both species **I** and **II** are shifted to low frequencies with respect to free BINOL, while the opposite is more commonly observed as a consequence of titanium complexation by oxygen donor ligands.[10a,e,f,i] The high-frequency shift experienced by H8 is mainly the outcome of the binaphthyl dihedral angle decreasing from around 90° for free BINOL to about 55° necessary for chelating the titanium center, as found in the crystal structures

of **1a/2a**.[13] This pushes the H8 proton on one naphthoate ring closer to the second ring, in a region subjected to the deshielding effect of the aromatic ring current;[14] the conformational consequences of metal chelation on the 1,1′-binaphthyl system are also evidently manifested by CD spectra (see next section). We also notice a major discrepancy between ^{1}H NMR spectra of the two complexes **I** and **II** in terms of chemical shifts of protons H3 and H4. In species **I**, they are shifted to lower frequency by respectively 0.5 and 0.3 ppm with respect to species **II** (Figures 1a and 2a), while for other protons differences are less evident. This will be interpreted below as due to the different molecularity of the two complexes.

^{1}H NMR spectra comparable to ours for species **I** had already been reported by Martin and Sharpless upon dissolving the solid compound [(BINOLate)Ti(O^{i}Pr)$_2$]$_3$ (**1a**)[11] and also by Mikami et al. for the compound "(BINOLate)Ti(O^{i}Pr)$_2$", but with a different and possibly incorrect assignment.[12c] More interestingly, our spectrum in CDCl$_3$ at 298 K for the 1:3 BINOL/Ti(O^{i}Pr)$_4$ sample (Figure 1a, 3.0 equiv) closely resembles that obtained by Walsh and co-workers after dissolving either compound (BINOLate)Ti(O^{i}Pr)$_2$·Ti(O^{i}Pr)$_4$ (**2a**) or (BINOLate)Ti(O^{i}Pr)$_2$·[Ti(O^{i}Pr)$_4$]$_2$ (**3a**) in CDCl$_3$.[4,8] Their assignment to a single binuclear species with non-equivalent naphthoate rings was probably due to the unfortunate coexistence of the two species **I** and **II** with about 1:1 integral proportion. It is noteworthy that the occurrence of a solution equilibrium between 1:1 and 1:2 titanium-ligand complexes had been demonstrated not only for BINOL-based ligands **B** and **C**, reacting with either Ti(O^{i}Pr)$_4$[3,7] or TiCl$_4$,[12a] but also for other polydentate ligands such as Sharpless' tartrate esters[10a] and Gau's amino alcohols.[10g,k,m]

Variable-temperature (VT) spectra in the 248−328 K range were recorded on the 1:3 BINOL/Ti(O^{i}Pr)$_4$ sample in CDCl$_3$, for which at 298 K the ligand is almost equally distributed between the two complexes; signals for species **I** were relatively increased upon heating, and vice versa, those for species **II** upon cooling (Figure 2a). Further temperature decreasing also led to spectrum decoalescence for both species. In particular, the six ^{1}H resonances for species **I**, which are well defined at 298 K, start deconvoluting into a very complex pattern already at 280 K; below 263 K, several weak signals appear which are indicative of multiple distinct naphthalene rings (Figure 2a, 248 K). On the contrary, ^{1}H resonances for species **II** (best followed for a 1:6 BINOL/Ti(O^{i}Pr)$_4$ sample, Figure 3) are almost unaffected in the 253−328 K range and start decoalescing only below 233 K; at the lower temperature limit (218 K), a complex overlapping of a dozen broad signals was found (Figure 3), which may be assigned to two different naphthalene rings. In conclusion, the simplicity of room-temperature spectra is due to relatively fast dynamic processes, which are slowed by decreasing temperature thus breaking the apparent symmetry. This finding parallels what
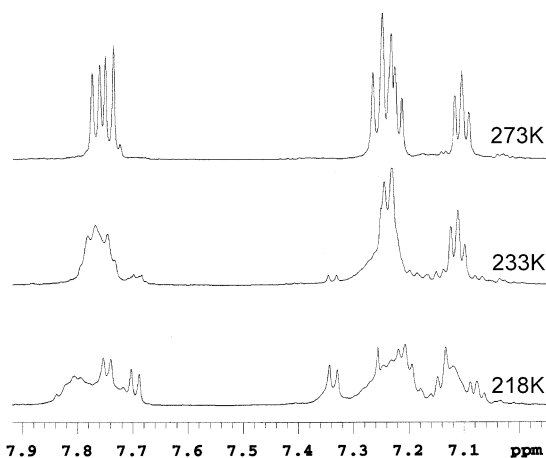
Figure 3. Variable-temperature ^{1}H NMR spectra (600 MHz) of a mixture of (*S*)-BINOL (81.1 mM concentration) and Ti(O^{i}Pr)$_4$ (0.520 M) in CDCl$_3$.

was reported for compounds **1b,c** and **2b,c**,[3,7] as discussed above, while it had been overlooked for BINOL compound **2a**; it is now established that titanium complexes of BINOL (**A**) and of its 3,3′-dimethyl and octahydro derivatives **B** and **C** exhibit similar fluxional behavior in solution, which is also in keeping with common properties of titanium complexes with alkoxy ligands.[9,10a,12a]

By comparing our titration data with the former results by Walsh and Heppert's groups outlined in the Introduction,[3,4,7] we identify species **I**, obtained at low titanium/BINOL ratios, with a 1:1 complex which may be formulated as "(BINOLate)Ti(O^{i}Pr)$_2$", and species **II** with a dinuclear 1:2 complex (BINOLate)Ti(O^{i}Pr)$_2$·Ti(O^{i}Pr)$_4$. This latter is stable with any excess of Ti(O^{i}Pr)$_4$ from 3 equiv on, while no other species (for example a trinuclear one) is apparently present in the NMR spectra. Following previous reports,[4,5a] we also conclude that the 1:2 binuclear complex (BINOLate)Ti(O^{i}Pr)$_2$·Ti(O^{i}Pr)$_4$ (**II**) should represent the main catalytic precursor formed in the standard synthetic conditions, that is, 6:1 or higher Ti(O^{i}Pr)$_4$ excess. At lower titanium/BINOL ratios non-negligible amounts of the 1:1 species **I** would be present too, which is probably less active.[4] The need for a large Ti(O^{i}Pr)$_4$ excess for increasing the rate and the enantioselectivity of the synthetic application[4,5] is therefore related to the necessity of driving the equilibrium between **I** and **II** toward the most reactive species. Gau et al. had reached a similar conclusion for catalytically active titanium-amino alcohol complexes behaving similarly to the present one,[10g,k,m] although free Ti(O^{i}Pr)$_4$ may also play some additional role.[4,10c] As already observed,[4,7] the presence of a single BINOL ligand in the catalytically active species **II** also explains the observed lack of nonlinear effects[15] upon varying the ligand enantiomeric purity.[4,5a] From a structural viewpoint, we support a structure like **2a** (Scheme 1) found in the solid state,[4,8] with two distinct Ti centers and BINOL rings made equivalent by a fast dynamic process at room temperature.

Quantitative analysis of titration and VT data required a more precise identification of species **I** too. The

(13) Representative values for the binaphthyl dihedral angles found in crystals are 54° for **2a**, 58° (on the average) for **1a**, and 56° for **1a**$_{rac}$.[4,7,8,11]

(14) Di Bari, L.; Pescitelli, G.; Pizzanelli, S.; Rosini, C.; Salvadori, P. *Stereochemical study of 1,1′-binaphthyl derivatives by means of UV/CD and NMR spectroscopies*; Abstracts, 10th International Symposium on Chiral Discrimination−ISCD'98; 1998, Aug 30−Sep 3; Vienna, Austria.

(15) (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922−2959. (b) Blackmond, D. G. *Acc. Chem. Res.* **2000**, *33*, 402−411.
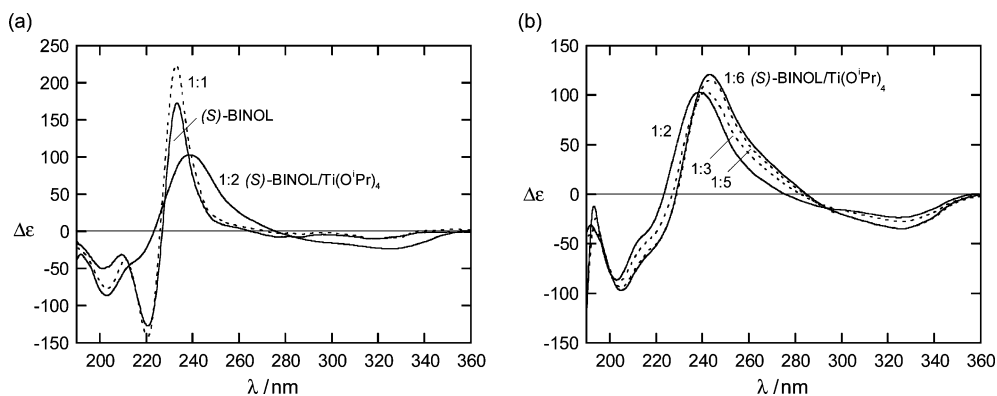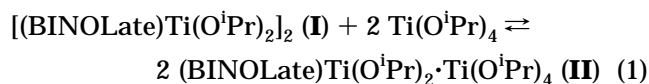
Figure 4. CD spectra of mixtures of (S)-BINOL (0.821 mM concentration) with various amounts of Ti(O^{i}Pr)$_4$ in hexane/CH$_2$Cl$_2$, 9:1. (a) Up to 2 equiv of Ti(O^{i}Pr)$_4$; (b) from 2 to 6 equiv. Spectra normalized on the total BINOL concentration; path length 0.01 cm.

1:1 solid complex **1a** is trimeric in the solid state,[4,8,11] but MW measurements found a dimer in solution.[11] A hypothetical dimeric structure for species **I** would have a molecular volume V almost twice that of a monomer and only slightly larger than that of the binuclear species **II**; the estimated order is $V_{I,mon} \ll V_{II} < V_{I,dim}$. This should reflect into molecular motions such as translational and rotational ones. We therefore evaluated rotational correlation times τ_c (from ^{13}C T_1 measurements) and translational diffusion coefficients D (from DOSY experiments) for both species **I** and **II**. T_1 times for **I** were found systematically shorter by 60 ± 20 ms than those of corresponding carbons of **II** (see Supporting Information, Table S1); the average values were $T_{1,I} = 0.46 \pm 0.02$ s and $T_{1,II} = 0.52 \pm 0.02$ s, and the corresponding correlation times[16] $\tau_{c,I} = 0.72 \times 10^{-10}$ s^{-1} and $\tau_{c,II} = 0.63 \times 10^{-10}$ s^{-1}. Measured diffusion coefficients were $D_I = (4.9 \pm 0.1) \times 10^{-10}$ m^2 s^{-1} and $D_{II} = (5.5 \pm 0.1) \times 10^{-10}$ m^2 s^{-1}. Both sets of values demonstrate that **I**, as a solute, possesses a slightly larger molecular size than **II**;[17] therefore, it should have a dimeric structure, which may be paralleled with the solid state ones **1a$_{rac}$** and **1b,c**. A further spectroscopic evidence of the presence of two BINOL ligands in the solution species **I** comes from simple consideration of ^{1}H chemical shifts. The relative shielding of binaphthyl protons 3 and 4 with respect to the monomeric species **II** (Figures 1a and 2a), as noticed above, is probably the

consequence of the ring current shift exerted by the second binaphthalene moiety.[12c,e,18]

With the above assignment in mind, we could analyze titration and VT experiments quantitatively, according to the following equilibrium:

$$[(\text{BINOLate})\text{Ti}(\text{O}^i\text{Pr})_2]_2 \ (\mathbf{I}) + 2\ \text{Ti}(\text{O}^i\text{Pr})_4 \rightleftarrows$$
$$2\ (\text{BINOLate})\text{Ti}(\text{O}^i\text{Pr})_2\cdot\text{Ti}(\text{O}^i\text{Pr})_4 \ (\mathbf{II}) \quad (1)$$

The concentration of the three species was easily extracted from ^{1}H spectra.[19] The data from two independent titrations (BINOL concentration 72.3 and 89.5 mM in CDCl$_3$) were both well fitted (Figure 1b) by the single equilibrium above (eq 1), leading to calculated equilibrium constant $K_{I/II} = \{[\mathbf{II}]^2\}/\{[\mathbf{I}]\cdot[\text{Ti}(\text{O}^i\text{Pr})_4]^2\} = 8.0 \pm 0.9$ and 7.2 ± 1.8 M^{-1} at 298 K. A more precise value was afforded by Van't Hoff analysis of VT data (Figure 2b), which led to $K_{I/II} = 9.1 \pm 0.5$ M^{-1} at 298 K, $\Delta H^0 = -44.9 \pm 0.4$ kJ·mol^{-1} (-10.7 ± 0.1 kcal·mol^{-1}), and $\Delta S^0 = -134 \pm 3$ J·mol^{-1} deg^{-1} (-32.0 ± 0.6 eu). These values compare well with those found by Heppert and co-workers for the corresponding equilibrium involving the 3,3'-dimethyl analogues **1b/2b**.[3]

CD Spectra of BINOL/Ti(O^{i}Pr)$_4$ Complexes. 1,1'-Binaphthyl derivatives have pronounced CD spectra extremely sensitive to geometrical changes, especially in the dihedral angle between the naphthalene planes.[20] Thus, we followed the evolution of CD spectra of (S)-BINOL solutions in 9:1 hexane/CH$_2$Cl$_2$ (0.8−1 mM concentration) titrated with Ti(O^{i}Pr)$_4$ (Figure 4). (S)-BINOL shows the characteristic intense positive cou-

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(16) Calculated in the extreme narrowing limit: $T_{1dd}^{-1} = (4/3)\cdot E_{CH}r_{CH}^{-6}\tau_c$, with $E_{CH} = (\mu_0/4\pi)^2(\hbar\gamma_C\gamma_H)^2 S_C(S_C + 1)$, where S and γ are the nucleus spin and magnetogyric ratio; the average value $r_{CH} = 1.10$ Å was used. T_{1dd} is the dipole−dipole longitudinal relaxation time, estimated from total T_1 and ^{13}C−^{1}H NOE: NOE $= 1 + (\gamma_H/2\gamma_C) T_{1dd}^{-1}/T_1^{-1}$. Experimental NOEs varied between 2 and 2.7 (±0.2) for species **I** and 2.0−2.4 (±0.2) for species **II**, with a similar average value of 2.3 (see Supporting Information, Table S1).

(17) A semiquantitative prediction of τ_c and D's is possible by evaluating the radius r of a sphere with equivalent molecular volume V (estimated by molecular modeling) and applying Stokes and Stokes−Einstein equations: $\tau^{-1} = 3k_B T/4\pi\eta r^3$, $D = k_B T/6\pi\eta r$ (where η is the solvent viscosity, 0.56 cP for chloroform at 298 K). Starting from available X-ray structures,[3,4] molecular models were built for a 1:1 monomer (BINOLate)Ti(O^{i}Pr)$_2$ (**I,mon**), a 1:1 dimer [(BINOLate)Ti(O^{i}Pr)$_2$]$_2$ (**I,dim**), and the 1:2 binuclear compound (BINOLate)Ti(O^{i}Pr)$_2\cdot$Ti(O^{i}Pr)$_4$ (**II**). Estimated values for the three models are $\tau_{I,mon} = 0.60 \times 10^{-10}$, $\tau_{I,dim} = 1.2 \times 10^{-10}$, and $\tau_{II} = 1.0 \times 10^{-10}$ s^{-1}; $D_{I,mon} = 8.2 \times 10^{-10}$, $D_{I,dim} = 6.6 \times 10^{-10}$, and $D_{II} = 7.0 \times 10^{-10}$ m^2 s^{-1}. Apart from a systematic overestimation due to the approximations used, it is clear that the two last values for each set (**I,dim** and **II**) are in good agreement, relatively speaking, with the experimental ones for species **I** and **II** (see text).

(18) In the X-ray structures of **1a$_{rac}$**, **1b**, and **1c**,[3,7] two nonattached naphthalene planes lie almost parallel to each other, and the substituted benzene rings face each other at a distance of about 4 Å. Therefore, the corresponding H$_3$ and H$_4$ protons are positioned in a region subjected to strong diamagnetic anisotropy (shielding effect).

(19) The integrals of the doublet at 7.84 ppm (H$_5$ proton for **I**) and the two doublets at 7.76−7.78 ppm (H$_4$ and H$_5$ protons for **II**), which are well isolated from the remaining peaks (Figures 1a and 2a), were used. Free Ti(O^{i}Pr)$_4$ concentration was calculated as the difference from the total quantity, since titanium-containing species other than **I** and **II** are negligible.

(20) (a) Mason, S. F.; Seal, R. H.; Roberts, D. R. *Tetrahedron* **1974**, *30*, 1671−1682. (b) Di Bari, L.; Pescitelli, G.; Salvadori, P. *J. Am. Chem. Soc.* **1999**, *121*, 7998−8004. (c) Di Bari, L.; Pescitelli, G.; Marchetti, F.; Salvadori, P. *J. Am. Chem. Soc.* **2000**, *122*, 6395−6398. (d) Rosini, C.; Superchi, S.; Peerlings, H. W. I.; Meijer, E. W. *Eur. J. Org. Chem.* **2000**, 61−71. (e) Di Bari, L.; Pescitelli, G.; Reginato, G.; Salvadori, P. *Chirality* **2001**, *13*, 548−555. (f) Di Bari, L.; Lelli, M.; Pintacuda, G.; Pescitelli, G.; Marchetti, F.; Salvadori, P. *J. Am. Chem. Soc.* **2003**, *125*, 5549−5558.

plet, due to the exciton coupling between long-axes polarized ^1B_b transitions,[20,21] with a positive maximum at 233.6 nm and a negative minimum at 220.8 nm (couplet amplitude $\Delta\Delta\epsilon = +300$), plus a further negative band at 201.8 nm allied to the higher energy ^1B_a transition (Figure 4a). The lower energy ^1L_a and ^1L_b transitions, both polarized approximately along the naphthalene short axis, give weak features between 270 and 330 nm.[21]

While the CD of the 1:1 BINOL/Ti(O^{i}Pr)$_4$ sample is still dominated by the spectrum of free BINOL,[22] the effects of Ti(O^{i}Pr)$_4$ addition become striking after the addition of 2 equiv (spectrum "1:2" in Figure 4a,b). The ^1B_b couplet is heavily broadened and reduced in intensity, merging with the ^1B_a band into a complex feature with a positive maximum at 238.8 nm, a negative minimum at 203.1 nm, and a shoulder at 216 nm. The low-energy transitions are emphasized resulting in a very broad band between 275 and 355 nm with a negative minimum at 324.5 nm. When more Ti(O^{i}Pr)$_4$ is added, the overall appearance is maintained, but all bands progressively increase and shift to the red (Figure 4b); no additional evolution is observed after 5−6 equiv of Ti(O^{i}Pr)$_4$ is added (spectrum "1:6" in Figure 4b). By comparison with NMR results,[22] the CD spectrum obtained at 1:2 BINOL/Ti(O^{i}Pr)$_4$ ratio should be mostly due to [(BINOLate)Ti(O^{i}Pr)$_2$]$_2$ (**I**) (no trace of free BINOL is apparently left), while the stationary one at 1:6 ratio is dominated by (BINOLate)Ti(O^{i}Pr)$_2\cdot$Ti(O^{i}Pr)$_4$ (**II**). The differences between CD spectra of free BINOL and its titanium complexes are the consequences of both geometric and electronic variations.[23] In particular, the wavelength splitting[24] of the main couplet increases from 11.2 nm for (*S*)-BINOL to 16.2 nm for the CD of species **II** (and to a slightly smaller value for **I**);[25] this is mainly due to the decreasing of the binaphthyl dihedral angle[20b,c,e,f] consequent to the chelation (see above). Thus, CD offers a final spectroscopic proof that the major species obtained by adding excess Ti(O^{i}Pr)$_4$ to BINOL both have chelate structures and confirms what was already demonstrated by Walsh et al. by chemical means:[4] chelated BINOL-titanium complexes

are chiefly responsible for the observed catalytic activity, while open BINOL forms should not participate.

Low-temperature CD spectra were measured for species **II** (1:6 BINOL/Ti(O^{i}Pr)$_4$ in hexane/CH$_2$Cl$_2$, 9:1) to be compared with VT NMR spectra. Cooling to the low-temperature limit (183 K) had no appreciable effect on the CD spectrum (data not shown). This confirms that the variation observed below 233 K in the NMR spectra is actually due to signal decoalescence consequent to slowed dynamics and not to a structural rearrangement.

Conclusions

Solution mixtures between enantiopure BINOL and Ti(O^{i}Pr)$_4$ were investigated, by NMR and CD spectroscopies, in conditions descriptive of those employed for catalyzing the enantioselective additon of alkylzinc reagents to aldehydes.

This kind of direct approach allowed us to confirm the binuclear complex (BINOLate)Ti(O^{i}Pr)$_2\cdot$Ti(O^{i}Pr)$_4$ (**II**), obtained at high titanium-to-BINOL ratios, as chiefly responsible for the observed catalytic activity, as previously indicated.[4,5a,7] In fact, this is largely the dominant species in the presence of 6−10 equiv of Ti(O^{i}Pr)$_4$, which is required to obtain high degrees of enantioselection.[5] We clarified that the necessity for excess titanium is due to the existence of an equilibrium between **II** and a 1:1 species **I**, formulated as **I** + 2Ti-(O^{i}Pr)$_4$ ⇌ 2 **II** with $K_{eq} = 9.1$ in chloroform, which needs to be driven toward the most active catalytic precursor **II**.

NMR and CD data afforded direct and conclusive spectroscopic proof that (1) complexes **I** and **II** present titanium-chelating BINOLate moieties, as observed for most BINOLate-titanium complexes;[3,4,7,12] (2) **I** is dimeric in solution, thus existing as [(BINOLate)Ti(O^{i}Pr)$_2$]$_2$, coinciding with what was found by dissolving the solid compound [(BINOLate)Ti(O^{i}Pr)$_2$]$_3$;[11] and (3) the two complexes undergo relatively fast dynamic processes in solution, rendering all naphthoate rings NMR-equivalent at room temperature.

Beyond the catalytic interest, these observations have other significant and more general implications. In fact, it is demonstrated that BINOL/Ti(O^{i}Pr)$_4$ complexes share common solution behavior not only with the corresponding systems for BINOL-based ligands (3,3′-Me$_2$-BINOL and H$_8$-BINOL)[3,7] but also with other titanium complexes having diverse anions (BINOL/TiCl$_4$)[12a] and even different ligands (tartrate esters).[10a] This is true in terms of the nature and structure of solution species, as well as of their dynamic and equilibrium processes, despite the well-known heterogeneity observed in the chemistry of titanium alkoxides.[9] It is especially noteworthy how the properties of closely analogous titanium complexes of BINOL derivatives, which crystallize in different manners,[3,4] are de facto reconciled in the solution state, thus witnessing once again the necessity for independent structural characterization in solution.

Experimental Section

All manipulations, including NMR and CD sample preparation, were carried out under an inert atmosphere. BINOL

(21) Hanazaki, I.; Akimoto, H. *J. Am. Chem. Soc.* **1972**, *94*, 4102−4106.

(22) The different concentration and solvent used must be kept in mind when comparing NMR and CD spectra.

(23) For example, the hyperchromic effect on $^1L_a/^1L_b$ bands, passing from BINOL to its titanium complexes, should have a mainly electronic origin, since a similar feature is obtained by dissolving BINOL in a 0.1 M NaOH water solution.

(24) The wavelength difference between the low- and high-energy (positive and negative) couplet components, which may differ from the apparent couplet amplitude.[20b] It was extracted by deconvoluting experimental spectra by means of the Fourier self-deconvolution (FSD) method (Kauppinen, J. K.; Moffatt, D. J.; Mantsch, H. H.; Cameron, D. G. *Appl. Spectrosc.* **1981**, *35*, 271−276), checking self-consistency upon varying the estimated bandwidth. The FSD routine is integrated in Jasco Spectra Analysis Software, v. 1.51.

(25) A minor discrepancy between CD of species **I** and **II** is apparent especially in terms of a wavelength shift (5.4 nm in the couplet crossover point, Figure 4b). Rather than due to geometrical rearrangements of the BINOL moiety, this is probably more associated with the dimeric nature of **I**. In addition to the two strong intrabinaphthylic exciton couplings (i.e., between attached naphthalenes), three further interbinaphthylic couplings are possible for **I** between nonattached naphthalene rings (lying at 6.5−8.5 Å from each other in the crystal structures of **1a$_{rac}$** and **1b**).[3,7] These further coupling mechanisms are weaker than the major one, but their effect may be non-negligible due to short interchromophoric distances, and their contribution to the overall spectrum becomes appreciable.[20e,f]

solutions were prepared by weighing the desired amount into septum-capped vials (CD samples, 0.8–1 mM concentration) or NMR tubes (NMR samples, 60–90 mM concentration), followed by solvent addition via syringe and stirring to complete dissolution. BINOL-titanium samples were prepared by adding the appropriate amount of $Ti(O^iPr)_4$ via calibrated microsyringe to BINOL solutions, followed by stirring for a few minutes. All solvents, including deuterated ones, were refluxed over calcium hydride and distilled before use. (*S*)-1,1′-Bi(2-naphthol) (ee > 99%) was purchased from Fluka. Titanium(IV) isopropoxide (99.999% purity) was purchased from Aldrich and distilled prior to use. NMR spectra were recorded with a Varian INOVA 600 spectrometer operating at 14.1 T. COSY, ROESY (mixing time 0.2 s), and HSQC spectra were acquired with standard pulse sequences. Longitudinal relaxation times (T_1) were measured by an inversion–recovery sequence. Dipole–dipole relaxation times (T_{1dd}) were calculated starting from T_1's and experimental C–H NOEs. ^{1}H DOSY experiments were performed with the DgcsteSL pulse sequence,[26] using gradient pulses having 2 ms width and 1.17–46.8 G·cm^{-1} strength. CD spectra were measured with a Jasco J715 spectropolarimeter, using a 0.01 cm cell, with the following conditions: speed 10 nm/min, response 2 s, bandwidth 1.0 nm.

Supporting Information Available: HSQC spectrum, ^{13}C assignment, T_1's, and C–H NOEs for (*S*)-BINOL/$Ti(O^iPr)_4$ (1:3) in CDCl$_3$ (species **I** and **II**). This material is available free of charge via the Internet at http://pubs.acs.org.

OM049709V

(26) Johnson, C. S., Jr. *Prog. Nucl. Magn. Reson. Spectrosc.* **1999**, *34*, 203–256.