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On the structure of the Kagan–Modena catalysts for asymmetric oxidation of sulfides

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Abstract

The reaction of Ti(O^iPr)$_4$, diisopropyl (*R*,*R*)-tartrate and *N*,*N*′-di(trifluoromethylsulfonyl)ethane-1,2-diamine in 1:2:1 ratio provided a symmetric, dinuclear complex of formula [Ti(η^2-*dipt*)(η^2-H*dipt*)(O^iPr)]$_2$ (where H_2*dipt* is diisopropyl tartrate), in which each metal bears one O^iPr ligand, a chelating tartrate diolate bridging the two metals, and a second, univalent tartrate unit in a novel binding mode, attached through alkoxy and ester carbonyl oxygens. This species appears to be stabilized through hydrogen bonding with the disulfonamide. The configuration at Ti deduced by NMR spectral information coincides with that calculated to be the most stable. In the absence of the disulfonamide, the data are consistent with an equilibrium between this complex, free tartrate and a condensation product of formula Ti_4(*dipt*)$_5$(H*dipt*)$_2$(O^iPr)$_4$ which features an η^2,η^2-tartrate linking two Ti_2(η^2-*dipt*)$_2$(η^2-H*dipt*)(O^iPr)$_2$ units. The relationship between these species and the Kagan and Modena catalysts for the asymmetric oxidation of sulfides is discussed.

1. Introduction

In 1984, the Kagan and Modena groups independently reported the asymmetric oxidation of sulfides with high enantioselectivity by ^{t}BuOOH in the presence of the stoichiometric reagents 1:2:1 Ti(O^iPr)$_4$–H_2*det*–H_2O[1] (Scheme 1) or 1:3 (or 4) Ti(O^iPr)$_4$–H_2*det*[2] (H_2*det* is diethyl tartrate in either enantiomeric form). In contrast, use of the Sharpless asymmetric epoxidation catalyst, 1:1 Ti(O^iPr)$_4$–H_2*det* or H_2*dipt* (H_2*dipt* is diisopropyl tartrate in either enantiomeric form), resulted in racemic material (with much sulfone by-product), while the Kagan system was found to not effect allylic alcohol epoxidation.[3] These differences in reagent stoichiometries and in behaviour signal very different catalyst structures. Useful turnover was obtained with catalytic amounts of the Kagan combination in the presence of molecular sieves.[4] A new, more efficient catalytic system uses isopropanol instead of water (1:4:4 Ti(O^iPr)$_4$–H_2*det*–HO^iPr) as well as molecular sieves.[5]

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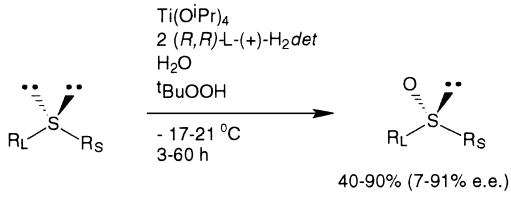


Scheme 1.

Relatively little is known of the structure of the actual catalyst(s) involved in these oxidations. In the Kagan case, IR data show the presence of coordinated and non-coordinated ester groups both before and after the addition of water, and this is unaffected by the presence of sulfide and only slightly shifted by the presence of sulfoxide, although sulfoxide inhibits sulfide oxidation.[3] Molecular weight measurements indicate a dimeric species and XANES and EXAFS data confirm a TiO_6 core throughout the reaction.[6] The observation of a non-linear dependence of product ee on tartrate ee indicates more than one tartrate near the active site.[7,8]

For the 1:2:1 Ti–tartrate–H_2O system, the Kagan group put forth a mechanistic picture (Fig. 1) to explain the origin of the enantioselectivity.[9] In spite of the fact that this picture is discordant with the optimized reaction stoichiometry and with the aforementioned relation between tartrate and product ee, no better proposal has emerged.[10]

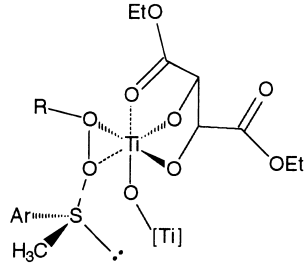


Figure 1. Proposed mechanism of enantioselective sulfide oxidation with 1:2:1 Ti(O^iPr)$_4$–H_2*det*–H_2O[10]

Based on our explorations of 1:2 Ti–tartrate mixtures, we believe that we have solved the structural mystery of this system and propose herein an analysis consistent with the accumulated data on the Kagan–Modena system and with the body of knowledge concerning the structures of Ti^{IV}–tartrate complexes.

2. Results

Unfortunately, little can be learned by direct examination by NMR of the Kagan or Modena systems. Indeed, a 1:2 Ti(O^iPr)$_4$–H_2*det* mixture revealed only a broad, unresolved mass of resonance in the OC*H* region stretching from about 4 ppm to about 5.8 ppm, overlaid with signals from free H_2*det*, HO^{i}Pr and EtOH.[11] This is probably indicative of a multitude of species arising from ligand exchanges and transesterifications (Ti(O^iPr)$_4$ is a known[13] catalyst for transesterification). The further addition of H_2O to achieve the Kagan 1:2:1 Ti(O^iPr)$_4$–H_2*det*–H_2O stoichiometry made the broad resonance even broader. An analogous result was obtained if H_2*dipt* and H_2O were used.

In contrast, the Sharpless catalyst (1:1 Ti(O^iPr)$_4$–H_2*dipt*) displays a relatively simple, symmetrical ^{1}H NMR spectrum (Fig. 2 *a*) owing to rapid equilibration between structures **A** (Scheme 2).[14–16] The addition of extra H_2*dipt* causes a complication of the spectra (Fig. 2 *b*),[11] forming several products, but the signals remain relatively sharp as they engage in much slower exchange equilibria (the signals become

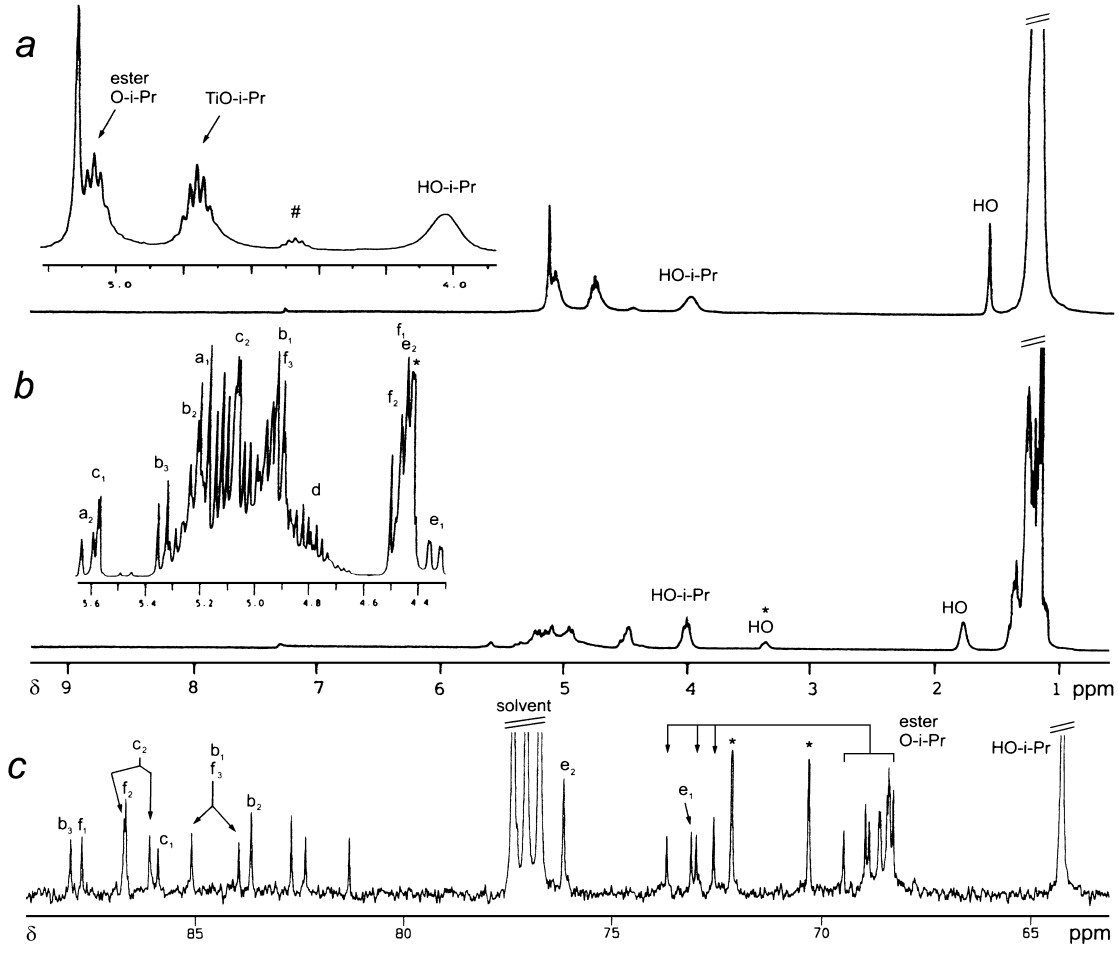
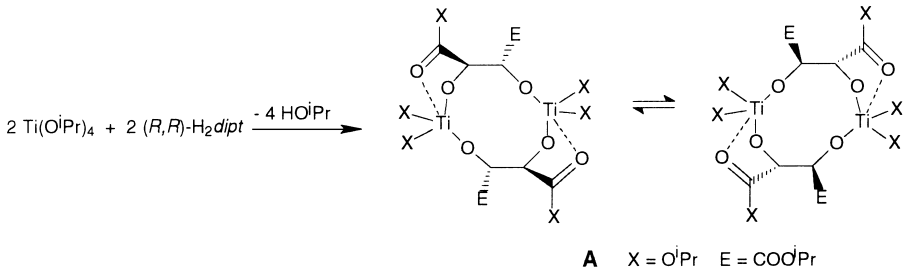


Figure 2. ^{1}H NMR spectra in $CDCl_3$ and expanded plots of the *OCH* regions from (*a*) [Ti(*dipt*)(O^iPr)$_2$]$_2$ (**A**), and (*b*) the 1:2 mixture of Ti(O^iPr)$_4$ and H_2*dipt*, with COSY-derived coupling information; then (*c*) the central region of the ^{13}C NMR spectrum of the 1:2 mixture of Ti(O^iPr)$_4$ and H_2*dipt* with HMQC-derived assignments. The heptet labelled '#' is from excess Ti(O^iPr)$_4$ and those signals labelled '*' are from unreacted H_2*dipt*. The lower case roman letter labels in spectrum *b* indicate signals analogous to similarly labelled signals in Fig. 3 *a*, while the labels in spectrum *c* denote HMQC-derived ^{1}H–^{13}C couplings to the corresponding signals in spectrum *b*

even sharper upon dilution) than is the case with the Sharpless catalyst or with H_2*det*. The only species that are readily discernible in Fig. 2 *b* are the liberated HO^iPr and, depending on the stoichiometry, the 2:2 species **A** or free tartrate. The C=O region of the ^{13}C NMR spectrum (not shown) reveals tartrate units in at least six different environments (the other regions are discussed below). The presence of more than 2 equivalents of tartrate, as in the Modena system, adds no new signals. The spectrum of Fig. 2 *b* also remains largely unaffected by EtOH, which we added (to a final 1:2:1 Ti(O^iPr)$_4$–H_2*dipt*–EtOH stoichiometry) in imitation of the putative effect of transesterification, except for a new, broad OCH_2 peak due to free EtOH. Exactly the same result was obtained if the H_2*dipt* was added after the EtOH.

2.1. Sulfonamide-stabilized 1:2 Ti–tartrate complex

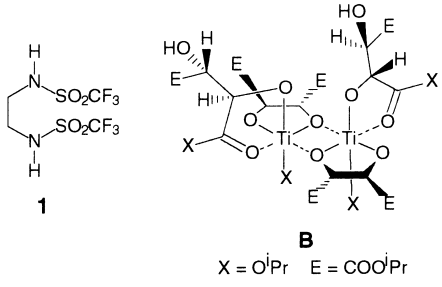
In unrelated work, we attempted to prepare Ti^{IV} complexes of the bis(triflamide) of ethylenediamine **1** (Scheme 3). This $CDCl_3$-insoluble disulfonamide did not dissolve upon addition of Ti(O^iPr)$_4$. Heat,



Scheme 2.

agitation and the presence of Et_3N were without effect.† It did dissolve, however, upon subsequent addition of H_2*dipt*. After exploring several reactant ratios, we obtained relatively clean spectra at a 1:2:1 Ti–H_2*dipt*–**1** ratio (Fig. 3) and these did not further change with the addition of more H_2*dipt* or more **1**. The same spectra were obtained whether **1** was initially present or added last. With the help of COSY and HMQC spectra, these spectra were found to be entirely consistent with the formula $[Ti(dipt)(Hdipt)(O^iPr)]_2 \cdot 2\mathbf{1}$, formed according to Eq. 1 and whose Ti-containing portion is assigned structure **B** (Scheme 3).

$$2\ Ti(O^iPr)_4 + 4\ (R,R)\text{-}H_2dipt + 2\ \mathbf{1} \rightarrow \mathbf{B}\cdot 2\mathbf{1} + 6\ HO^iPr \quad (1)$$



Scheme 3.

The justification for the structural assignment is as follows.

The ^1H NMR spectrum (Fig. 3*a*) featured two sets of signals from two asymmetric tartrate units in 1:1 ratio. One set consisted of a pair of strongly coupled OC*H* doublets (labelled b and f in Fig. 3*a*, with $\Delta\delta_H$=0.81 ppm, J=9.5 Hz) and two O*C*H peaks in the ^{13}C NMR spectrum (similarly labelled in Fig. 3*b*, with $\Delta\delta_C$=3.89 ppm) shifted downfield from the free H_2*dipt*-position to positions typical of Ti-bound diolates. By analogy with many other examples of such a signal combination,[16,17] this was assigned to a μ,η^2-*dipt*$^{2-}$-unit whose diolate moiety chelates and bridges between two metal centres, but whose ester groups are not coordinated. One difference here is that the upfield OC*H* doublet is much further upfield than usual (4.42 ppm), more upfield than even free H_2*dipt* (4.45 ppm). The significance of the upfield shift will be addressed later, but the chemical shift of the correlated O*C*H peak leaves no doubt that this grouping is ionized and Ti-bound.

† This work was initially motivated by a report that a chiral *N*,*N*′-disulfonamide promotes an enantioselective, Ti^{IV}-mediated addition of Et_2Zn to aldehydes (Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett*. **1989**, *30*, 1657). Besides, with **1**, we also found no reactions with *N*,*N*′-di(*p*-toluenesulfonyl)ethylenediamine, *N*,*N*′-di(methanesulfonyl)1,2-phenylenediamine and *N*,*N*′-di(2,4-dinitrophenyl)1,2-phenylenediamine. These results suggest that the ethylation catalyst is not necessarily a Ti^{IV} complex of ionized material.

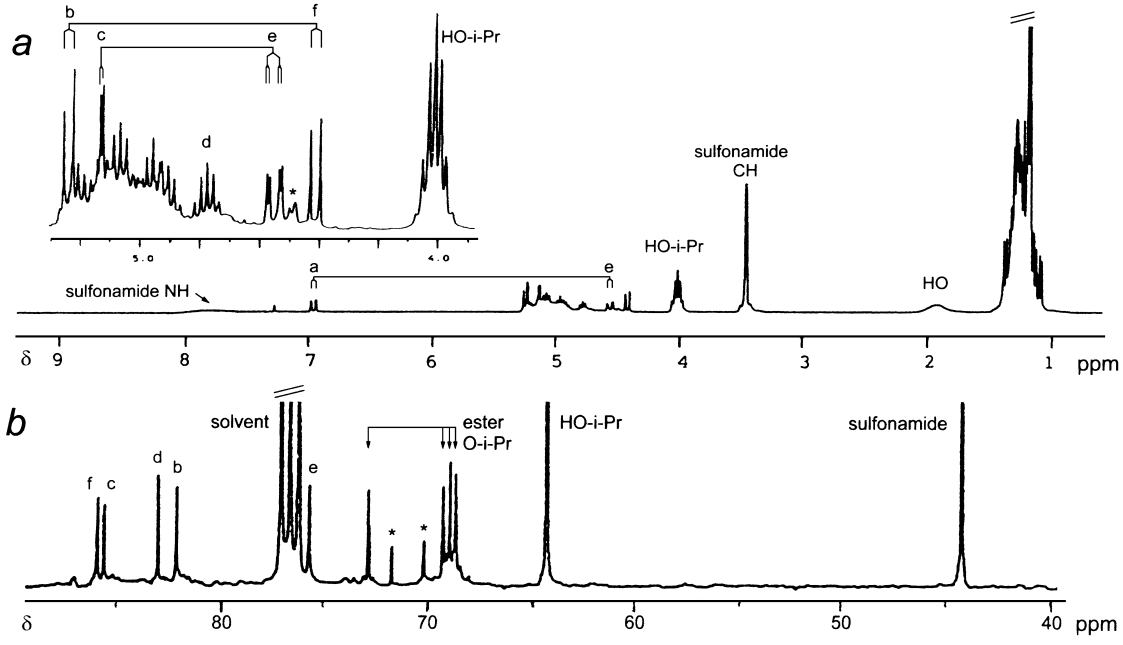


Figure 3. (*a*) ^{1}H NMR spectrum in $CDCl_3$ and expanded plot of the *OCH* region of the 1:2:1 mixture of $Ti(O^{i}Pr)_4$, H_2*dipt* and **1**, with COSY-derived coupling information; and (*b*) the central region of the ^{13}C NMR spectrum of this mixture, with HMQC-derived assignments. Those signals labelled '*' are from unreacted H_2*dipt*. The lower case roman letter labels in spectrum *b* denote HMQC-derived ^{1}H–^{13}C couplings to the corresponding signals in spectrum *a*

The second set was an AMX system attributable to a Ti–OCH_A–CH_M–OH_X fragment involving weak coupling (2.7 Hz) between a downfield H_A signal (labelled c in Fig. 3 *a*) and a H_M signal (labelled e) appearing at a position close to that of free H_2*dipt*, and strong coupling (11 Hz) between H_M and the strongly downfield-shifted OH_X signal (labelled a, at 6.85 ppm). This combination of signals from an apparently singly ionized tartrate unit (H*dipt*$^-$) is unprecedented. There is an apparent hydrogen bonding interaction between **1** and the OH groups, supported by the finding that lesser amounts of **1** resulted in less downfield positions for the OH_X signal, but the data do not indicate which group or groups in **1** are involved, nor whether the non-coordinated ester groups of **B** are also involved.

The O*C*H region of the ^{13}C spectrum included five other signals correlating to O^{i}Pr groups, one of which (labelled d in Fig. 3 *b*) was attributable to a Ti-bound O^{i}Pr but at a particularly downfield position (about 5 ppm more downfield than usual). The other four peaks were due to ester O^{i}Pr groups, one of which was about 4 ppm downfield of the other three. The *C*=O region also presented four signals, one of which was about 10 ppm downfield of the others. By analogy to previous instances,[15,16] the downfield *C*=O and ester O*C*H peaks could be attributed to a Ti-bound ester group. The coordinated ester must belong to the Ti–OCH–CHOH fragment, rather than to the chelating *dipt*$^{2-}$-unit, since [2.2.1] bicyclic strain disfavours the rare η^3 binding mode (diolate chelation+ester binding)[15,16] and because the otherwise η^1-H*dipt*$^-$-unit would not be stably bound.‡

The sulfonamide component gave rise to a very tight AB quartet (J=11 Hz) for CH_2 and to a single, weakly ^{19}F-coupled *C*H$_2$ signal, both at locations unsurprising for free **1** (which is insoluble in $CDCl_3$). The diastereotopicity is a further indication of an interaction with tartrate. There were also a very broad

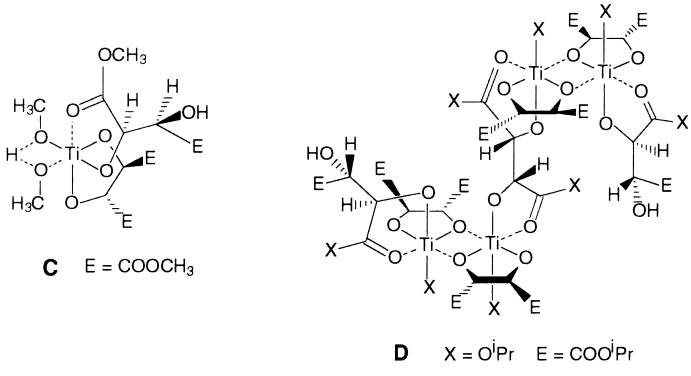
‡ That one O^{i}Pr group remains coordinated in the presence of an available tartrate OH further argues against the viability of the trihapto mode.

N*H* signal at 7.9 ppm (which sharpened considerably upon dilution of the sample) and a strongly ^{19}F-coupled *C*F_3 signal.

The unusual upfield position of one of the OC*H* doublets but not its OC*H* peak (both labelled f in Fig. 3) indicates that a shielding phenomenon is at play. A similar shielding occurred in previous cases of side-chain binding in an η^3-diolate-unit,[16,18] whence coordination of the side-chain attached to the terminal end of the diolate caused shielding of the OC*H* at the bridging end. In addition, the lone Ti–O^{i}Pr O*C*H peak (labelled d in Fig. 3 *b*) was further downfield than usual. Both of these phenomena had previously been seen with the [Ti(μ,η^2-*dipt*)(η^2-8-hydroxy-quinoline)(O^{i}Pr)]$_2$ complex[18] and the conclusions drawn in that case can be applied here. Although there are several possible ways of disposing the singly ionized tartrate unit in the present product, that depicted in **B** accounts for the observed deshielding and shielding phenomena: the Ti-bound C=O presents its deshielding zone to the *axial* O^{i}Pr attached to the same metal and its shielding zone to the bridging OC*H* on the tartrate unit that chelates the other metal. The three other possible symmetric arrangements are less satisfactory in that they do not account for either phenomenon. Moreover, the positioning of the singly ionized group in **B** minimizes interactions between its uncoordinated portion, the Ti–O^{i}Pr group and the ester group on the tartrate unit that chelates the other metal. Other arrangements are less satisfactory.

Finally, there remains the possibility that the H*dipt*$^-$-unit actually forms a six-membered chelate ring instead of the five-membered one depicted in **B**. This possibility cannot be eliminated directly by the spectra but models suggest that they would result in more congested assemblies, especially if one considers that the disulfonamide must have access to the uncoordinated alcohol group, whereas there is no apparent strain in the five-membered version. There are several instances in the solid state of a tartrate unit bound through such a five-membered ring, with the other end bound to a second metal,[19] but no examples of binding through six-membered rings.

In an effort to identify the most stable ligand configurations for Ti(η^2-*dipt*)(η^2-H*dipt*)(O^{i}Pr) centres, molecular mechanics (MM2) and semi-empirical (PM3-tm) calculations were performed on the hexa-coordinate, monomeric model complex Ti(η^2-*dmt*)(η^2-H*dmt*)(OMe)(HOMe) (where H_2*dmt* is dimethyl (*R*,*R*)-tartrate) and where the neutral HOMe ligand stands in for a bridging oxygen from another metal. These calculations agreed that the configuration depicted in **C** (Scheme 4) is the most stable stereoisomer, and this configuration coincides with that in **B**. This finding lends useful support to the experimental result because: (i) steric effects will largely determine the most stable stereochemistry of such centres; (ii) the neglect of π-donation from alkoxy oxygens and outer-sphere effects (i.e. of solvent and of hydrogen bonding to **1**) will little influence the steric situation at the metal and, in any case, will be similar for all stereoisomers; and (iii) at 10.7 kcal/mol (PM3-tm estimate), the energy difference between the most stable isomers was substantial.



Scheme 4.

Given the ability of compound **1** to apparently stabilize the 1:2 Ti–H_2*dipt* mixture, we also added **1** to the 1:2 Ti–H_2*det* mixture. Although **1** also dissolved in that case, and thereby apparently interacted, the spectra were no more decipherable than in the absence of **1**.

2.2. Native 1:2 Ti–tartrate complexes

Armed with the spectra of Fig. 3, one can more closely examine the 1:2 Ti(O^iPr)$_4$–H_2*dipt* mixture lacking **1**. Fig. 2*b* reveals signals very much like those analogously labelled in Fig. 3*a*, in terms of position and coupling constant, suggesting that **B** (or a stereoisomer thereof) may be present as a significant component of the 1:2 Ti(O^iPr)$_4$–H_2*dipt* mixture lacking **1**. Unfortunately, peak overlaps precluded full assignments using 2D spectra. The corresponding ^{13}C NMR spectrum (Fig. 2*c*) also reveals similarities with Fig. 3*b*: There were 11 visible ester C=O signals (not shown). Three of these were at least 9 ppm downfield of the others, indicating three Ti-bound ester groups and, therefore, five other signals from tartrates coordinated only through diolate oxygens. There were eight visible ester O*C*H signals between 68 and 70 ppm from non-coordinated ester O^{i}Pr groups. There were four signals between 72 and 74 ppm, three of which must be due to Ti-bound ester groups, as indicated by the C=O region, and correlation spectroscopy showed that the fourth (labelled e_1) was due to the non-coordinated end of an η^2-H*dipt*$^-$-unit. One O*C*H signal at 76.2 ppm is entirely analogous to that labelled e in Fig. 3*b* and is assigned to another such group. Finally, there were 12 O*C*H signals remaining, lying between 81 and 88 ppm. Assuming no overlaps in the ^{13}C NMR spectrum, the total of 14 non-ester O*C*H signals is consistent with six distinct tartrate units and at least two Ti–O^{i}Pr groups present.

Complex **B**·2**1** clearly demonstrates the viability of Ti(η^2-*dipt*)(η^2-H*dipt*)(O^iPr) centres and the tartrate-to-O^{i}Pr signal ratio of 6:≥2 observed here is consistent with the presence of three distinct Ti(η^2-*dipt*)(η^2-H*dipt*)(O^iPr) centres, albeit with one missing tartrate skeletal O*C*H or O^{i}Pr O*C*H signal, one missing non-coordinated ester O*C*H signal and one missing non-coordinated C=O signal. Other than stereoisomers of **B**, the only other conceivable, alternative assembly obeying a 1:2 Ti–tartrate stoichiometry is the hexacoordinate, monomeric species bearing two singly ionized tartrate units, Ti(η^2-H*dipt*)$_2$(O^iPr)$_2$, capable of multiple stereoisomeric forms. This hypothetical species would be entirely analogous to complexes formed by the similarly poorly basic, univalent bidentates 2,4-pentanedione and 8-hydroxyquinoline.[17] (Other possible ligand arrangements have either η^1-H*dipt*$^-$-units, which are precluded by the chelate effect, or η^3-*dipt*$^{2-}$-units which suffer [2.2.1] bicyclic strain.) However, Ti(η^2-H*dipt*)$_2$(O^iPr)$_2$ can be eliminated as a possible component since all of its isomers will display a 1:≥1 tartrate–O^{i}Pr signal ratio, inconsistent with the observed 2:1 ratio, and they will all display a 1:1 ratio of coordinated to non-coordinated ester groups, which is inconsistent with the observed 3:8 (or 9) ratio.

Because the ^{13}C peaks of similar origin in Fig. 2*c* and the *C*=O peaks (not shown) have approximately the same heights, the three putative Ti(η^2-*dipt*)(η^2-H*dipt*)(O^iPr) centres can be said to be in an approximate 1:1:1 ratio. These centres can, in principle, come from one or more stereoisomers of **B**, but the missing tartrate skeletal, ester and carbonyl signals suggest the presence of half an equivalent of a symmetrical tartrate unit. Indeed, the ^{13}C NMR peak count and peak height ratio can be accommodated exactly by a 1:1 mixture of **B** and a condensed form **D** (Scheme 4), a tetranuclear species built of two identical **B**-like assemblies joined by a symmetric η^2,η^2-*dipt*$^{2-}$-unit. The ^{13}C NMR data can also accommodate isomers of **B** and **D** that respect the observed symmetries, and the evidence for the assigned stereochemistries will be discussed below. Irrespective of the actual stereochemistries at the metals, such a mixture of a **B**-like dimer and a **D**-like tetranuclear condensed form also accounts for the co-presence of free H_2*dipt* at an exact 1:2 Ti–H_2*dipt* reaction stoichiometry (Eq. 2) when only Ti(tartrate)$_2$ centres (and none poorer in tartrate) are detectable.

$$6\ \mathrm{Ti(O^{\textit{i}}Pr)_4} + 12\ \mathrm{H_2}\textit{dipt} \rightarrow [\mathrm{Ti}(\textit{dipt})(\mathrm{H}\textit{dipt})(\mathrm{O^{\textit{i}}Pr})]_2\ (\mathbf{B}) + [\mathrm{Ti_2}(\textit{dipt})_2(\mathrm{H}\textit{dipt})(\mathrm{O^{\textit{i}}Pr})_2]_2(\eta^2,\eta^2\text{-}\textit{dipt})\ (\mathbf{D}) + \mathrm{H_2}\textit{dipt} + 18\ \mathrm{HO^{\textit{i}}Pr} \quad (2)$$

Unfortunately, a Signer-method measurement of the (number-average) molecular weight of the 1:2 Ti–tartrate reaction mixture cannot provide supporting evidence for Eq. 2 because, neglecting the volatile $\mathrm{HO^{\textit{i}}Pr}$, that average value would be exactly the same as the molecular weight of **B** alone.

$$2\ \mathrm{Ti_2}(\textit{dipt})_2(\mathrm{H}\textit{dipt})_2(\mathrm{O^{\textit{i}}Pr})_2\ (\mathbf{B}) \rightleftharpoons [\mathrm{Ti_2}(\textit{dipt})_2(\mathrm{H}\textit{dipt})(\mathrm{O^{\textit{i}}Pr})_2]_2(\textit{dipt})\ (\mathbf{D}) + \mathrm{H_2}\textit{dipt} \quad (3)$$

Eq. 2 suggests the possibility of an equilibrium between the reaction products (Eq. 3). Since one can reason that this putative equilibrium would be insensitive to changes in concentration, we looked for temperature dependence. The NMR spectra were quite temperature-sensitive above 300 K, but heating the samples gave inconclusive results, due to extensive signal broadening, overlaps, and migration (especially of OH peaks). Above 315 K, the signals were very broad, appearing to coalesce; the spectra resembled the case with $\mathrm{H_2}\textit{det}$, but no sharpening occurred below the solvent's upper temperature limit. The absence of kinetic control was revealed by the obtention of virtually the same spectra upon the slow addition of $\mathrm{Ti(O^{\textit{i}}Pr)_4}$ to a concentrated solution of 3 equivalents of $\mathrm{H_2}\textit{dipt}$ in $\mathrm{CDCl_3}$, which would favour the tartrate-rich component (**B**), as upon the reverse order of addition, which would favour the tartrate-poor component (**D**). The reversibility in the formation of the components was demonstrated by the treatment of a sample of a 1:3 Ti–tartrate mixture with 2 equivalents of fresh $\mathrm{Ti(O^{\textit{i}}Pr)_4}$ to produce the spectrum of the Sharpless catalyst, $[\mathrm{Ti}(\textit{dipt})(\mathrm{O^{\textit{i}}Pr})_2]_2$, in Fig. 2*a*. Another sample treated with solid **1** reproduced the spectrum of **B**·2**1** (Fig. 3*a*) containing the expected extra free tartrate. As the formation of each component is evidently reversible, then the components are in mutual equilibrium.

Sub-saturation amounts of **1**, i.e. before complete conversion to **B**·2**1**, allowed the tentative assignment of some signals. The presence of **1** caused some signals to migrate somewhat, making assignments uncertain, but it appears that the signals of Fig. 2*b* labelled c_1, b_3 and e_1 (and by extension, f_3) were present below saturation and are thus assignable to **D**. (An OH signal resembling peak a_2 was also present, but OH peaks are expected to be the most mobile, according to our experience reported in Section 2.1, and therefore the least reliably assigned.) The remaining signals labelled b_2, c_2 (and, by extension, e_2 and f_2) of Fig. 2*b* are those most similar in coupling constant and position to those in Fig. 3*a* and are therefore assignable to the free **B** component. Their ^{13}C NMR counterparts in Fig. 2*c* are also precisely the ones most closely resembling those in Fig. 3*b*.

These tentative assignments argue for the presence of free **B** as the tartrate-rich component of the 1:2 Ti–tartrate mixture but one can generalize that, just as the upfield position for the doublet labelled f in Fig. 3*a* indicated the stereochemistry drawn in **B** for the disulfonamide-stabilized material, the identification of three f-type doublets at upfield positions with the native mixture (Fig. 2*b*) indicates that same stereochemistry at each of the three metal centres in the absence of **1**. Hence, **D**, apparently formed from **B** and in exchange with it, unsurprisingly appears to have the same configuration at its metals as does **B**. Three other observations support this:

(i) That all three metal centres of the native mixture have the same stereochemistry would be consonant with a concerted and high enantioselectivity for all sulfide oxidation reaction sites.

(ii) Just as the calculations reported in Section 2.1 supported the NMR-derived assignment of configuration in **B**·2**1**, they also support the assignment of **C**-like centres in the native mixture.

(iii) With an observed ratio of **B** to **D** to free $\mathrm{H_2}\textit{dipt}$ of roughly 1:1:1, the equilibrium constant governing Eq. 3 is about 1, corresponding to a free energy difference of about 0.6 kcal/mol at room temperature. Such a small difference is consonant with a ligand exchange involving similar ligating groups (i.e. in the forward direction, the free end of a metal-bound $\mathrm{H}\textit{dipt}^-$-unit replacing

the coordinated end of another) but not with a change of stereochemistry during the exchange, especially not at two metals.

3. Discussion

Regardless of the exact details of the structure of [Ti(*dipt*)(H*dipt*)(O^iPr)]$_2\cdot 2$**1**, the selective formation of a single, symmetrical isomer is in itself remarkable. Such selectivities had already been noted in the formation of ternary complexes with other, poorly basic, univalent bidentates (HL), which formed [Ti(*dipt*)(L)(O^iPr)]$_2$ complexes of similar structure.[17] Unlike those other ligands, however, there was no sign here of a $TiL_2(O^iPr)_2$ co-product. Although ligand exchanges appear to be slow on the NMR timescale at room temperature in the absence of **1**, the evidence shows that the formation of **B**$\cdot$2**1** is sufficiently reversible as to be under thermodynamic control, thus allowing the selection, upon the addition of **1**, of a single species in a unique diastereomeric form from the native 1:2 Ti–tartrate mix. The evident absence of Ti(H*dipt*)$_2$(O^iPr)$_2$ in any isomeric form under thermodynamic control attests to its relative instability, probably due to steric congestion.

3.1. Structure of the Kagan–Modena catalysts

All successful variations of the Kagan sulfide oxidation system feature at least 2 equivalents of tartrate per Ti and result in the same sulfoxide chirality with comparable selectivities — a strong indication that all variants have a similar structure.

The evidence cited earlier indicated that the Kagan 1:2:1 Ti–H_2*det*–H_2O catalyst is dimeric with two tartrates per metal. As depicted in Fig. 1, the Kagan group envisaged this species to be a singly oxo-bridged dimer with only one tartrate, an η^3-*dipt*$^{2-}$-unit, in contradiction of that evidence and of the optimized stoichiometry. Complex **B** demonstrates that the [2.2.1] bicylic strain in an η^3-*dipt*$^{2-}$-unit is incompatible with free alcohol groupings (HOR) such as in HO^iPr, and that the combination of η^2-H*dipt*$^-$ and OR^- is preferred. There are three other problems with invoking a single oxo bridge. Firstly, Ti–tartrate complexes are commonly doubly bridged with stable Ti_2O_2 cores. Secondly, oxo functions are more basic than hydroxo ones, which would rather form in the presence of free or bound alcohols. Thirdly, the presence of H_2O in the reaction mixture is not a requirement for success in asymmetric sulfide oxidation.

Because all three variants of the Kagan catalyst are prepared from H_2*det*, there is the additional possibility of having OEt bridges. Arguably, OEt groups are more basic and less sterically demanding than tartrate diolates, but we do not believe that OEt bridges form for four reasons: (i) the presence of EtOH in a 1:2 Ti(O^iPr)–H_2*dipt* mixture had apparently no influence on the spectra, whether added before or after the tartrate; (ii) OEt groups are apparently not required for successful asymmetric sulfide oxidation, as there are brief mentions of the successful use of H_2*dipt*[3,20] and dimethyl tartrate;[20] (iii) OR^- groups are more useful at terminal positions where they can contribute a significant level of π-bonding that is impossible with η^2-*dipt*$^{2-}$ or η^2-H*dipt*$^-$-units. Indeed, the crystal structure of [Ti(OEt)(μ,η^2-*det*)(*N*-phenylbenzhydroxamato)]$_2$ proves the preference, in the solid state at least, for tartrate bridges over bridging OEt groups.[21] Large Ti–O–C angles (155–160°) were measured for the OEt groups in that structure, as well as for the O^iPr groups in the complex formed from Ti(O^iPr)$_4$ and *N*,*N*′-dibenzyl tartramide[21] and for the terminal tartrate groupings of [Ti(*dipt*)(O^iPr)Br]$_4$.[19] These large angles attest to the *sp*-like, π-donating nature of terminal alkoxides. On the other hand, tartrates can more easily adopt the *sp*^{2}-like geometry of bridging groups; and (iv) finally, Ti(OEt)$_4$ can be used in Sharpless

catalysis just as well as Ti(O^iPr)$_4$ or Ti(O^tBu)$_4$, as can H_2*det*, H_2*dipt* or dimethyl tartrate;[21,22], this would be unexpected if OEt (or OMe) bridges formed in one case and not in another. What is special about OEt (and presumably OH) groups, on the other hand, is that they can engage in a bimolecular, associative mechanism for ligand interchange between complexes, presumably via transient OEt (or OH) bridges, whereas O^iPr and O^tBu groups only exchange by a unimolecular, dissociative process.[12] Such bimolecular exchanges may be at the root of the ill-resolved spectra we obtained with H_2*det* or H_2O, and for some of the broadness that the addition of EtOH brought to H_2*dipt*-containing samples.

In light of the above discussion and of our analysis of the 1:2 Ti(O^iPr)$_4$–H_2*dipt* mixture, we believe that the active Kagan–Modena systems are not single complexes but mixtures of **B**-like and **D**-like materials analogous to those elucidated for the 1:2 Ti(O^iPr)$_4$–H_2*dipt* mixture, differing only in the identities of the terminal alkoxide and ester alkyl groupings and in the relative proportions of the **B**-like and **D**-like products or transesterified versions thereof. The product distribution may also be influenced by the reaction solvent, which has some influence on the enantioselectivity.[9] Given this and the observed benefit of increasing the ratio of tartrate per Ti, which would tend to increase the ratio of **B**-like and **D**-like products, it is tempting to speculate that **B**-like assemblies are more enantioselective than **D**-like assemblies.

4. Conclusions

We fortuitously observed the stabilization by disulfonamide **1** of the 1:2 Ti–tartrate complex assigned structure **B**, apparently through hydrogen bonding at the non-coordinated OH ends. The native 1:2 Ti–tartrate mixture (lacking **1**) was found to fit an equilibrium mixture of **B**, **D** and free tartrate. These assignments are in keeping with all of the available published data concerning the Kagan–Modena catalysts and the body of knowledge concerning Ti–tartrate species in general. While it is tempting to seek support for the structural assignments by examining the oxidation of sulfides with **B**·2**1**, the possibility that the additive may interfere with or enhance the process denies any necessary relevance to the outcome. Irrespective of whether or not the stereochemistries at the metals have been correctly assigned, the evidence is that 1:2 Ti–tartrate mixtures contain only Ti(*dipt*)(H*dipt*)(O^iPr) centres. This renders the mechanistic picture of Fig. 1 inapplicable, but a new mechanism awaits further experimentation.

5. Experimental

5.1. General

Distilled Ti(O^iPr)$_4$, (*R*,*R*)-H_2*det* and (*R*,*R*)-H_2*dipt* stored under Ar were used. Compound **1** was a gift from Dalton Chemical Laboratories. The $CDCl_3$ was stored over activated, powdered 4 Å molecular sieves (Aldrich). NMR spectra were acquired from $CDCl_3$ solutions on Bruker 300 MHz or 400 MHz instruments. In experiments with **1**, aliquots of 18±0.5 μL of Ti(O^iPr)$_4$ were added to or treated with appropriate amounts of a 0.61 M solution of H_2*dipt* in $CDCl_3$ and/or solid **1** to achieve the required stoichiometry. In the other experiments, 180±5 μL of Ti(O^iPr)$_4$, 270±5 μL of H_2*dipt* or 220±5 μL of H_2*det*, and, optionally, 37.5±0.5 μL of EtOH or 11.5±0.5 μL of H_2O, were added in the desired order to 1.000±0.005 mL of $CDCl_3$ in a flame-dried dram vial. Then a 150±5 μL aliquot was removed and diluted with 250±5 μL of $CDCl_3$ for analysis, with a final Ti concentration of 160 μM. Alternatively, 50±5 μL aliquots of H_2*dipt*-containing mixtures were diluted with 750±5 μL of $CDCl_3$ for a final Ti

concentration of 28 μM. Liquids were delivered by syringe. Samples were prepared fresh in flame-dried NMR tubes, and analysed after a few minutes' equilibration.

5.2. *Ti(O^{i}Pr)$_4$+2 H$_2$*dipt

^{13}C NMR (free H$_2$*dipt* peaks are marked with an asterisk (*); see Fig. 3 for other assignments): δ 181.7, 181.1, 180.0, 171.2*, 170.6, 170.4, 170.3, 170.0, 169.53, 169.47, 169.2, 169.1 (C=O), 88.0, 87.7, 86.7, 86.6, 86.1, 85.9, 85.1, 84.0, 83.7, 82.7, 82.3, 81.3, 76.2, 73.7, 73.1, 73.0, 72.6, 72.1*, 70.3*, 69.5, 69.0, 68.9, 68.64, 68.60, 68.45, 68.40, 68.3, 64.3 (HO^{i}Pr), 25.3 (HO^{i}Pr), 25.1, 25.0, 24.7 (2 peaks), 24.6 (2 peaks), 21.8–21.5 (CH$_3$) ppm.

5.3. *[Ti(*dipt*)(H*dipt*)(O^{i}Pr)]$_2$·2**1***

^{1}H NMR: δ 7.9 (bs, 4H, NH), 6.85 (d, 2H, *J*=12 Hz, OH), 5.23 and 4.42 (2d, 4H, *J*=9.5 Hz, TiOCHCHOTi), 5.12 (d, 2H, *J*=2.8 Hz, TiOC*H*CHOH), 5.25–4.86 (m, 8H, COOCH), 4.54 (dd, 2H, *J*=2.7, 12 Hz, TiOCHOC*H*OH), 3.46 (ABq, 8H, *J*=11 Hz, CH$_2$), 1.39–1.08 (m, 24H, CH$_3$) ppm. ^{13}C NMR: δ 181.1, 171.2, 171.0 and 169.8 (C=O), 119.7 (q, *J*=321 Hz, CF$_3$), 86.5 (TiO*C*HCHOTi), 86.1 (TiO*C*HCHOH), 83.5 (TiO*C*HMe$_2$), 82.6 (TiOCH*C*HOTi), 76.1 (TiOCH*C*HOH), 73.2, 69.6, 69.2 and 69.0 (COO*C*H), 44.4 (CH$_2$), 25.2, 24.9, 24.8, 24.5, 21.6, 21.53, 21.49, 21.4 and 21.3 (CH$_3$) ppm.

5.4. *Molecular modelling*

MM2 and PM3(tm) geometry optimizations were performed on **C** and all its diastereomers, using the Spartan v4.1.1 suite of programs (Wavefunction Inc., 18401 Von Karman, Suite 370, Irvine CA 92715) on an SGI Indigo 4000 workstation. The PM3 heat of formation for the least energetic diastereomer (**C**) was −1659.9 kcal/mol. That for the next-most stable isomer, with the H*dipt*$^-$ carbonyl and alkoxy positions interchanged, was 10.7 kcal/mol higher in energy.

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