



Dinuclear titanium(IV) complex of *p*-*tert*-butylthiacalix[4]arene as a novel bidentate Lewis acid catalyst

Naoya Morohashi,^{a,*} Tetsutaro Hattori,^a Katsuya Yokomakura,^a Chizuko Kabuto^b and Sotaro Miyano^{a,*}

^aDepartment of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, Aramaki-Aoba 07, Aoba-ku, Sendai 980-8579, Japan

^bInstrumental Analysis Center for Chemistry, Graduate School of Science, Tohoku University, Aoba, Aoba-ku, Sendai 980-8578, Japan

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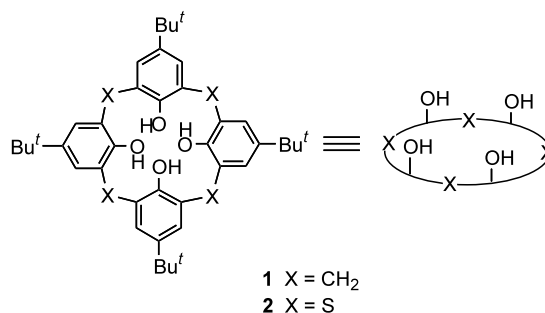
Abstract—Treatment of *p*-*tert*-butylthiacalix[4]arene (H₄L, **2**) with TiCl₄ in dichloromethane gave two novel dinuclear titanium(IV) complexes formulated as [Ti₂LCl₄]. One of the complexes was subjected to X-ray crystallographic analysis to show that the calixarene ligand (L⁴⁻) adopted a cone conformation, forcing the two metal centers to reside in close vicinity with *syn* arrangement with respect to the mean plane defined by the macrocycle (**3**). The other one was assigned to be an *anti* titanium(IV) complex (**4**) based on ¹H NMR spectroscopy. The *syn* complex showed high catalytic activity in the Mukaiyama–aldol reaction of aromatic aldehydes with silyl enol ethers, indicating the double-activation ability of the bidentate Lewis acid toward the aldehydes. © 2002 Elsevier Science Ltd. All rights reserved.

Polynuclear metal complexes have attracted much interest in the field of metal catalysis.¹ The metal centers located close in such complexes may activate substrate molecule(s) cooperatively or simultaneously, and/or migrate the substrate between the metal centers, which cannot be realized by mononuclear metal complexes. Therefore, polynuclear complexes are expected to show special catalysis or high performance in catalytic activity. Recently, we have introduced new members of calix[4]arenes, in which the four methylene bridges of calix[4]arene (e.g. **1**) are replaced by epithio (e.g. **2**), sulfinyl or sulfonyl linkages.^{2,3} They show marked ability to form metal complexes without the need to modify the upper and/or lower rim, as is the case for the conventional calix[4]arenes.⁴ This is attributed to the ligation of the sulfur-based functionalities to a metal center in cooperation with the phenoxy oxygens, as revealed by solvent extraction studies⁵ and X-ray crystallographic analyses.⁶

Keywords: calixarene; titanium complex; aldol reaction; X-ray crystallographic analysis.

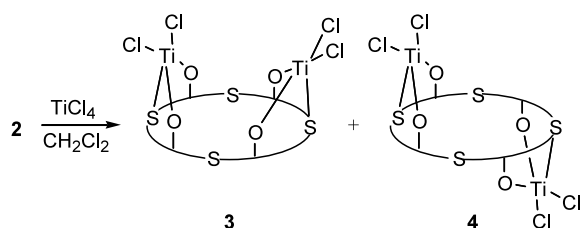
* Corresponding authors. Tel./fax: +81-22-217-7262; e-mail: miyano@orgsynth.che.tohoku.ac.jp

† Present address: Department of Materials Science and Engineering, Faculty of Engineering, Yamagata University, 3-16, Jonan, Yonezawa, Yamagata 992-8510, Japan.



Furthermore, the sulfur-based calix[4]arenes can form not only mono- but also polynuclear metal complexes by virtue of the heterogeneous coordination sites.^{6,7} Therefore, our attention has been focused on designing polynuclear metal complexes of the sulfur-based calix[4]arenes, which should be suitable for metal catalysts.⁸ As a part of such efforts, we report, herein, the synthesis of dinuclear titanium(IV) complexes (**3,4**) of *p*-*tert*-butylthiacalix[4]arene (**2**) and the application of the former as a bidentate Lewis acid catalyst for the Mukaiyama–aldol reaction.^{9,10}

Reaction of thiacalixarene **2** with an excess of TiCl₄ in dichloromethane led to the formation of two complexes **3** and **4**, the latter being essentially insoluble in the solvent (Scheme 1).¹¹ Fortunately, diffusion of hexane



Scheme 1.

to a solution of complex **3** in dichloromethane under nitrogen gave single crystals, one of which was subjected to X-ray crystallographic analysis (Fig. 1).¹² The complex consisted of two titanium ions, a tetraanion of thiacalixarene (L^{4-}), four chlorine ions and an aqua ligand to form $[Ti_2LCl_4(H_2O)]$. Although the operation proceeded under nitrogen, the water molecule seemed to have been introduced to the complex during recrystallization, showing the high oxophilicity of complex **3** (vide infra). The L^{4-} ligand adopted a cone conformation and coordinated to each metal ion in a tridentate fashion via the two phenoxy oxygens and an epithio function. Therefore, the two titanium ions occupied *syn* positions with respect to the mean plane defined by the macrocycle. The metal centers had a distorted octahedral environment bridged by the water molecule, a C_2 symmetry axis passing through the center of the cavity of the L^{4-} ligand.

In order to gain insight into the complexation behavior, a 1H NMR titration experiment was carried out. In the absence of $TiCl_4$, the spectrum of thiacalixarene **2** in dichloromethane- d_2 showed three singlets corresponding to *tert*-butyl, aromatic and hydroxy protons (Fig. 2d). As 2 mol equiv. of $TiCl_4$ was added portionwise to the solution of thiacalixarene **2**, new signals, including those assigned to complex **3**, appeared (Fig. 2c). During the time course, complex **4** was precipitated. On reaching the molar ratio of $TiCl_4$: **2** to 2:1, all the signals of free ligand **2** disappeared and only the signals of complex **3** were observed (Fig. 2b). Further increase in the molar ratio did not cause any spectral change (Fig. 2a). These observations may indicate that complexes **3** and **4** have a stoichiometry of Ti^{4+} :**2** = 2:1. Both complexes showed the same pattern of 1H NMR peaks in THF- d_8 , that is, one singlet assigned to *tert*-butyl and two doublets to aromatic protons,¹¹ which indicates that the thiacalixarene ligand adopts a cone or 1,2-alternate

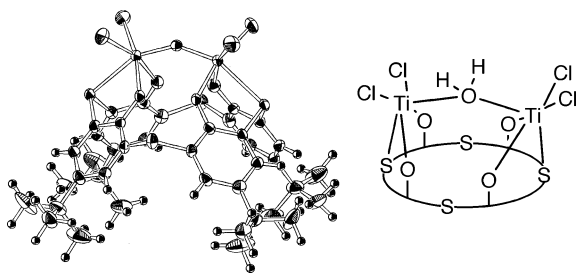


Figure 1. ORTEP drawing and schematic view of $[Ti_2LCl_4(H_2O)]$ obtained by recrystallization of complex **3**. Hydrogen atoms are omitted for clarity.

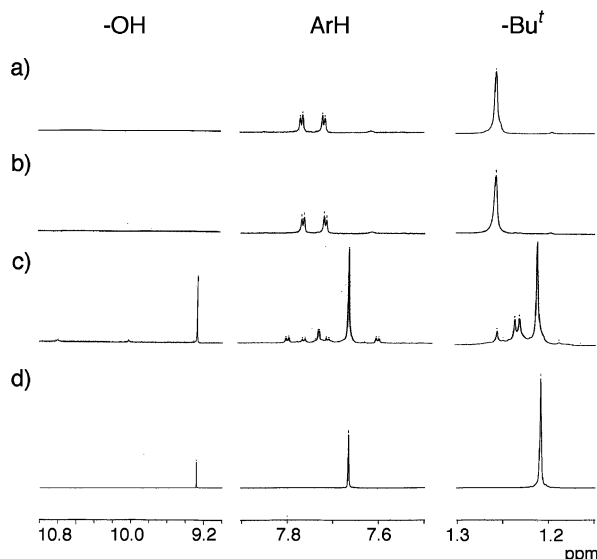
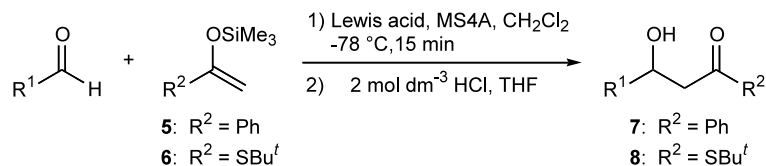


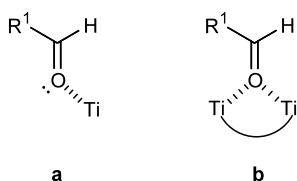
Figure 2. Partial 1H NMR spectra of thiacalixarene **2** in CD_2Cl_2 on progressive addition of $TiCl_4$. (a) $R = [TiCl_4]/[2] = 4$, (b) $R = 2$, (c) $R = 1$, (d) $R = 0$, where $[2] = 6.3 \text{ mmol dm}^{-3}$.

conformation,¹³ as long as the complexes are monomeric. Complex **4** was, therefore, assumed to adopt a 1,2-alternate conformation with an *anti* arrangement of the two titanium ions based on the titration study and the stereochemistry of complex **3**.

The highly oxophilic nature of complex **3** was attributed to simultaneous coordination of the oxygen atom of a water molecule to the two titanium centers exquisitely held by a thiacalixarene ligand, which tempted us to examine the double-activation ability of the complex toward carbonyl compounds in the Mukaiyama–aldol reaction (Table 1).¹⁴ To our pleasure, the reaction of benzaldehyde with silyl enol ether **5** in the presence of 5 mol% of complex **3** proceeded smoothly at $-78^\circ C$ to give β -hydroxy ketone **7** quantitatively in 15 min (entry 1), while a control reaction using complex **4** as a catalyst gave the product in only 2% yield (entry 2). The catalytic activity of complex **3** was clearly superior even to that of $TiCl_4$ (entry 3). These observations will indicate that complex **3** acts as a bidentate Lewis acid, which strongly enhances the reactivity of the aldehyde toward ether **5** via the double electrophilic activation of the carbonyl moiety as depicted in Fig. 3b,⁹ whereas $TiCl_4$ and complex **4** act as monodentate Lewis acid catalysts (Fig. 3a). Ether **5** was hydrolyzed in the presence of complex **3** at an elevated temperature ($0^\circ C$), which significantly reduced the product yield (entry 4). Addition of powdered molecular sieves (4 Å) (MS4A) was crucial for obtaining good results (entry 5), suggesting that the catalyst is incompatible with a trace amount of incidental water in the reaction system. Reaction of several other aromatic aldehydes was conducted under the standard conditions to give the corresponding hydroxy ketones **7** in yields depending on the substituents on the aromatic ring (entries 6–8, 10, 11 and 13). The steric bulk of the *ortho*

Table 1. Reaction of aldehydes with silyl enol ethers

Entry	Aldehyde	Silyl enol ether	Lewis acid (mol%)	Yield (%) ^a
1	Benzaldehyde	5	3 (5.0)	93
2		5	4 (5.0)	2
3		5	TiCl ₄ (10)	36
4 ^b		5	3 (5.0)	6
5 ^c		5	3 (5.0)	61
6	4-Chlorobenzaldehyde	5	3 (5.0)	85
7	4-Methylbenzaldehyde	5	3 (5.0)	88
8	2-Methylbenzaldehyde	5	3 (5.0)	57
9 ^d		5	3 (5.0)	77
10	2,6-Dimethylbenzaldehyde	5	3 (5.0)	30
11	1-Naphthaldehyde	5	3 (5.0)	50
12 ^d		5	3 (5.0)	87
13	2-Naphthaldehyde	5	3 (5.0)	91
14	Cinnamaldehyde	5	3 (5.0)	87
15	3-Phenylpropanal	5	3 (5.0)	0
16	Benzaldehyde	6	3 (5.0)	95
17	4-Chlorobenzaldehyde	6	3 (5.0)	93
18	4-Methylbenzaldehyde	6	3 (5.0)	97
19	1-Naphthaldehyde	6	3 (5.0)	95
20	2-Naphthaldehyde	6	3 (5.0)	92

^a Isolated yield.^b The reaction was conducted at 0°C for 2 h.^c MS4A was not added.^d The reaction was conducted at -78°C for 2 h.**Figure 3.** Single (a) and double (b) electrophilic activation of aldehyde by titanium Lewis acids.

substituent significantly affected the reactivity of the aldehyde (compare entry 8 with 1, entry 10 with 8 and entry 11 with 13), while the electronic effect of the *para* substituent is negligible (compare entry 6 with 7). Molecular model inspections suggested that the benzene ring of benzaldehyde, when the aldehyde coordinates to complex **3**, will be oriented perpendicular to the carbonyl plane to avoid the steric repulsion between itself and the chlorine atoms. As a result, the *ortho* substituent resides on a side of the carbonyl plane, which will prevent enol ether **5** from attacking the carbonyl group. An aldol adduct was also obtained by the reaction of 3-phenylpropanal (cinnamaldehyde) (entry 14), while 3-phenylpropanal was left intact after treatment with ether **5** under the standard conditions (entry 15). Reaction of the aromatic aldehydes with silyl enol ether **6** derived from a thioester proceeded smoothly to afford the corresponding hydroxy thioesters **8** in excellent yields (entries 16–20).

In conclusion, we have shown here that *p-tert*-butylthiacalix[4]arene can be used as an efficient scaffold for the construction of a dinuclear titanium(IV) complex, in which two metal centers are located so closely as to activate aldehydes doubly as a bidentate Lewis acid. Further studies on the synthesis and catalytic application of polynuclear metal complexes based on *p-tert*-butylthiacalix[4]arene and its analogues are in progress.

Acknowledgements

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 - Synthesis of complex **3**: To a solution of thiacalixarene **2** (288 mg, 399 μmol) in dichloromethane (100 cm^3) was added TiCl_4 ($d=1.73 \text{ g cm}^{-3}$; 175 mm^3 , 1.60 mmol) and the mixture was stirred for 1 h to form a red precipitate. After the precipitate was filtered off, hexane (210 cm^3) was added to the filtrate. The resulting solid was collected by filtration and dried in vacuo to give complex **3** (132 mg, 35%) as an orange powder; $^1\text{H NMR}$ (400 MHz, $\text{THF-}d_8$) δ 1.21 (36 H, s, $\text{Bu}'\times 3$), 7.60 (4H, d, $J=2.4 \text{ Hz}$, ArH) and 7.64 (4H, d, $J=2.4 \text{ Hz}$, ArH). Synthesis of complex **4**: To a solution of thiacalixarene **2** (144 mg, 200 μmol) in dichloromethane–benzene (3:1, 80 cm^3) was added TiCl_4 (1.0 mol dm^{-3} in dichloromethane; 800 μl , 800 μmol) and the mixture was stirred for 1 h. The precipitated solid was collected by filtration and dried in vacuo to give complex **4** (96.7 mg, 51%) as a red powder; $^1\text{H NMR}$ (400 MHz, $\text{THF-}d_8$) δ 1.27 (36H, s, $\text{Bu}'\times 3$), 7.38 (4H, d, $J=2.8 \text{ Hz}$, ArH) and 7.52 (4H, d, $J=2.8 \text{ Hz}$, ArH).
 - Crystal data for $[\text{Ti}_2\text{LCl}_4(\text{H}_2\text{O})]\cdot\text{H}_2\text{O}\cdot 2\text{CH}_2\text{Cl}_2$: $\text{C}_{44}\text{H}_{52}\text{Cl}_8\text{O}_6\text{S}_4\text{Ti}_2$, $M=1160.48$, monoclinic, $a=10.594(2)$, $b=20.055(4)$, $c=14.491(3) \text{ \AA}$, $\beta=110.427(3)^\circ$, $V=2885(1) \text{ \AA}^3$, Mo-K α radiation ($\lambda=0.71069 \text{ \AA}$), space group $P2_1/m$ (no. 11), $Z=2$, $D_{\text{calc}}=1.336 \text{ g/cm}^3$, $T=223 \text{ K}$, $\mu(\text{Mo-K}\alpha)=8.30 \text{ cm}^{-1}$, data collection using a Rigaku/MSC mercury CCD diffractometer, number of measured reflections = 27307 ($2\theta < 55^\circ$), independent reflections = 6705 ($R_{\text{int}}=0.033$), final $R=0.051$, $R_w=0.061$ for 3747 observed reflections ($I_{\text{O}} > 5\sigma(I_{\text{O}})$), GOF = 1.83. Selected bond distances (\AA): Ti–O $_{\text{phenoxy}}$, 2.040 and 2.042; Ti–S, 2.639; Ti–Cl, 2.251 and 2.256; Ti–O $_{\text{aqua}}$, 1.813.
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