Chiral and Functionalized Face-Discriminated and Side-Discriminated Macrocyclic Polyethers. Syntheses and Crystal Structures

J. P. Behr and J. M. Lehn*

Laboratoire de Chimie Organique Physique†
Institut Le Bel, Université Louis Pasteur
67000 Strasbourg, France

D. Moras and J. C. Thierry

Laboratoire de Cristallochimie‡
Institut Le Bel, Université Louis Pasteur
67000 Strasbourg, France
Received October 8, 1980

Macropolycyclic architectures are particularly well suited for the design of synthetic molecular receptors; they delineate three-dimensional cavities into which the substrates may be taken up and allow a close control of their geometrical and binding features.[1,2] The construction of such structures is greatly facilitated if suitable subunits are available which may be used as building blocks. Such subunits should (1) display strong and selective substrate binding properties and (2) possess functional groups which may be used for connection and bridging.

Many functionalized macrocyclic polyethers derived from [18]-crown-6 have been synthesized over the last years, taking advantage of the complexing properties of this cyclic structure toward cations to effect complexation[3-5] or transport[6-8] of alkali metal cations and complexation[9-13] or catalytic modification[7,11,14-16] of primary ammonium salts.

Among all these synthetic receptor molecules, the chiral tetrafunctional macrocycles **1**, based on two (*R,R*)-tartaric acid residues,[12] have been shown to give complexes of much higher stability[13] than the parent [18]-crown-6 itself. Furthermore, the ease of introduction of the side chains R into **1** has led to numerous compounds performing selective complexation[2,13] or molecular catalysis[15] on substrates bound by a primary ammonium group. This unit is therefore a particularly attractive building block, but its incorporation into macropolycyclic structures as well as the design of receptors, catalysts, and carriers based on structure **1** require independent handling of the four functional groups.

We describe here the synthesis and properties of two derivatives of **1**, containing modified functional groups, *syn*-**2** and *anti*-**2**, which possess a twofold axis of symmetry, respectively perpendicular to and in the plane of the macrocycle. With these two compounds, it becomes possible to perform reactions separately on the "top" and "bottom" (*syn*-**2** structure, "face discriminated") or on the "left" and "right" (*anti*-**2** structure, "side discriminated") of the macrocycle. The two isomers *syn*-**2** and *anti*-**2** are accessible by planned synthetic routes, which make use of suitably modified acyclic components for the ring closure step; a syn-type, "face discriminated" compound has been obtained in this way.[17]

Since large quantities of discriminated material were needed for further use, a more direct route was sought (Figure 1). Reaction of the dianhydride[18] **3** with an aromatic amine gives a mixture of the syn and anti diamide–diacid isomers which could be separated by chromatography. Compounds *syn*- and *anti*-**2a**, **-2b**, and **-2c** have been obtained by following this experimental procedure.[19] Most interestingly, however, if the reaction is performed in the presence of triethylamine, only one isomer (*syn*-**2**) is formed. Compounds *syn*-**2b**, **-2d**, and **-2e** have been prepared in this way.[20] The physicochemical properties of the two isomers differ sufficiently for allowing an easy distinction and identification; syn isomers are more polar in TLC on silica and complex cations[21] much more strongly than the corresponding anti isomers.

The initial assignment of syn or anti structure was performed by determining the crystal structures of both isomers of substance **2a**. Single crystals were grown[22] from methanol/water for the calcium complex of (*anti*-**2a**) and for a mixed strontium–calcium complex of (*syn*-**2a**). The structures were solved by standard Patterson and Fourier methods[23] and are shown in Figures 2 and 3. The following comments may be made about the structures.

(a) The complexed cation is located inside the macrocyclic cavity, as for most cation complexes of macrocyclic polyethers.[3,5] The six ring ether oxygens are in close contact with the included Ca^{2+} (2.56–2.69 Å, mean 2.61 Å) in (*anti*-**2a**) and Sr^{2+} (2.66–2.77 Å, mean 2.70 Å) in (*syn*-**2a**).

(b) The short cation–carboxylate distances indicate strong electrostatic interaction with both carboxylate groups ($Ca^{2+}\cdots O^-$

†E.R.A. No. 265 of the C.N.R.S.
‡E.R.A. No. 0008 of the C.N.R.S.

(1) Lehn, J. M. *Acc. Chem. Res.* **1978**, *11*, 49–57.
(2) Lehn, J. M. *Pure Appl. Chem.* **1978**, *50*, 871–892.
(3) Pedersen, C. J.; Frensdorff, H. K. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 16–25.
(4) Lehn, J. M. *Struct. Bonding* **1973**, *16*, 1–69.
(5) *Prog. Macrocyclic Chem.* **1979**, *1*, 1.
(6) Wong, K. H.; Yagi, K.; Smid, J. *J. Membr. Biol.* **1974**, *18*, 379–397.
(7) Lehn, J. M. *Pure Appl. Chem.* **1979**, *51*, 979–997.
(8) Christensen, J. J. In "Bioenergetics and Thermodynamics: Model Systems", Braibanti, A., Ed.; D. Reidel: Boston, 1980, pp 111–126.
(9) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036.
(10) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8–14.
(11) Stoddart, J. F. *Chem. Soc. Rev.* **1979**, *8*, 85–142.
(12) Girodeau, J. M.; Lehn, J. M.; Sauvage, J. P. *Angew. Chem.* **1975**, *87*, 813–814. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 764. A chiral binaphthyl crown containing two carboxylic acid groups has been reported: Hegelson, R. C.; Timko, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 3023–3025.
(13) Behr, J. P.; Lehn, J. M.; Vierling, P. *J. Chem. Soc., Chem. Commun.* **1976**, 621–623. Vierling, P. *Thèse* de 3° Cycle, Université Louis Pasteur de Strasbourg, 1978. Behr, J. P. In "Bioenergetics and Thermodynamics: Model Systems"; Braibanti, A., Ed.; D. Reidel, Boston, 1980; pp 425–433.
(14) Chao, Y.; Weisman, G. R.; Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4948–4958.
(15) Behr, J. P.; Lehn, J. M. *J. Chem. Soc., Chem. Commun.* **1978**, 143–146. Sirlin, C.; Lehn, J. M. *Ibid.* **1978**, 949–951.
(16) Matsui, T.; Koga, K. *Chem. Pharm. Bull.* **1979**, *27*, 2295–2303.
(17) Hayward, R. C.; Lehn, J. M., unpublished results.
(18) Behr, J. P.; Girodeau, J. M.; Hayward, R. C.; Lehn, J. M.; Sauvage, J. P. *Helv. Chim. Acta* **1980**, *63*, 2096–2111.
(19) Typically, dropwise addition of aniline (0.75 g, 8 mM) in methylene chloride (3 mL) to a stirred solution of the dianhydride **3** (0.73 g, 1.8 mM) in methylene chloride (5 mL) yields the crude mixture of diacid dianilides. Chromatography (30 g silica 60H Merck for TLC, 10 × 3 cm) with elution by 150 mL of 60:19:1 $CHCl_3/CH_3OH/NH_4OH$ followed by 200 mL of 70:35:7:1 $CHCl_3/CH_3OH/H_2O/NH_4OH$ allowed the two isomers to be recovered separately as ammonium salts containing various amounts of calcium and sodium, as checked by flame emission spectroscopy. The cations were removed by passage over a strong acid Dowex 50-X8 ion-exchange resin in 8:2 CH_3OH/H_2O, yielding a total amount of 0.96 g (91%) after recrystallization. The compound eluted first on silica was later shown to be the *anti*-**2a** isomer (0.46 g from wet THF, mp 256 °C): ^1H NMR (Me_2SO) δ 3.4 (br, 2 H, OH), 3.6 (br, 16 H, OCH_2), 4.25 (s, 4 H, OCH), 6.9–7.9 (m, 10 H, phenyl-H), 9.4 (s, 2 H, NH). Anal. Calcd for $C_{28}H_{34}O_{12}N_2$ (M_r 590.6): C, 56.94; H, 5.80; N, 4.74. Found C, 57.06; H, 5.76; N, 4.75. The second material is the *syn*-**2a** isomer, as also shown later; 0.50 g from wet methanol; mp ca. 110 °C dec: ^1H NMR ($CDCl_3$) δ 3.7 (br, 16 H, OCH_2), 4.53 (s, 4 H, OCH), 6.2 (s, 6 H, OH), 7.1–7.9 (m, 10 H, phenyl H), 9.3 (s, 2 H, NH). Anal. Calcd for $C_{28}H_{34}O_{12}N_2 \cdot 2H_2O$ (M_r 626.6): C, 53.66; H, 6.11; N, 4.47. Found: C, 53.50; H, 6.10; N, 4.57.

(20) Dropwise addition of the dianhydride (0.81 g) in CH_2Cl_2 (10 mL) to a stirred solution of 9-aminophenanthrene (0.85 g) and triethylamine (0.50 g) in CH_2Cl_2 (10 mL) leads to a solution which contains only *syn*-**2d** (TLC); it is washed successively with aqueous molar solutions (5 mL) of HCl and NMe_4OH. The last aqueous phase is then acidified and extracted with chloroform (10 mL). The desired compound is precipitated out from this solution with heptane (60 mL) in about 90% yield. Crystallization from CH_2Cl_2/toluene gives analytically pure material: mp 170–173 °C dec; ^1H NMR ($CDCl_3$) δ 3.6 (br, 16 H, OCH_2), 4.45 (s, 4 H, OCH), 7.2–8.5 (m, 18 H, aryl H), 8.95 (s, 2 H, NH); ^{13}C NMR ($CDCl_3$) δ 69.2, 70.6, 71.1 (OCH_2), 80.2, 81.8 (OCH), 122.1, 122.3, 122.9, 126.6, 126.8, 127.3, 128.4, 128.9, 129.9, 130.7, 131.3 (aryl C), 168.7, 171.6 (CO). Anal. Calcd for $C_{44}H_{42}O_{12}N_2 \cdot H_2O$ (M_r 808.8): C, 65.33; H, 5.48; N, 3.46. Found: C, 64.97; H, 5.47; N, 3.53. Further studies on the course of this reaction are in progress; a detailed description is deferred to the final account on this work.

(21) For instance, the NH_4^+ binding constants are, respectively, 1.8×10^4 and 7.6×10^3 M^{-1} for *syn*-**2b** and *syn*-**2d**, but only 1.5×10^2 M^{-1} for *anti*-**2b** (0.1 M triethanolamine/HCl in H_2O, pH 7.0, 25 °C). Behr, J. P.; Lehn, J. M.; Vierling, P., unpublished results.

(22) They belong, respectively, to the orthorhombic space group $P2_12_12_1$, $Z = 4$, with lattice constants $a = 10.192$ (2), $b = 16.067$ (3), and $c = 19.785$ (5) Å, and to the monoclinic space group C_2, $Z = 4$, $a = 33.307$ (9), $b = 10.801$ (2), $c = 10.026$ (1) Å; $\beta = 103.21$ (3)°.

(23) A total of 2424 and 2449 independent reflections ($I > 3\sigma(I)$, $4° < 2\theta < 120°$, Cu Kα radiation), collected on a CAD4 Nonius diffractometer, were used. Hydrogen atoms were included and all nonhydrogen atoms were refined with anisotropic thermal parameters. Final least-squares refinements led to R factors of 0.081 and 0.063 for *anti*- and *syn*-**2a**, respectively.

0002-7863/81/1503-701$01.00/0

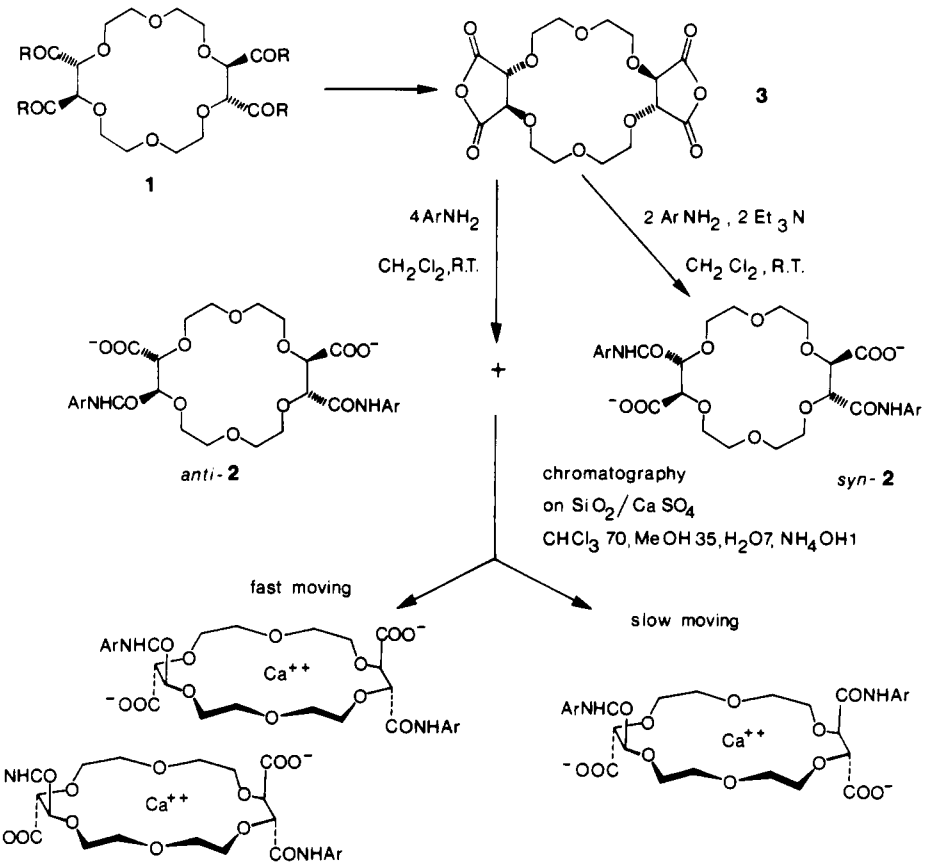

Figure 1. Pathway for the preparation of *syn*- and *anti*-**2**. **2a**, Ar = phenyl; **2b**, Ar = 4-phenylazo-1-naphthyl; **2c**, Ar = 4-iodophenyl; **2d**, Ar = 9-phenanthryl; **2e**, Ar = 1-naphthyl. The counterions of *anti*-**2** and *syn*-**2** are the ammonium cations formed in the reaction, or protons or metal cations depending on subsequent treatment.

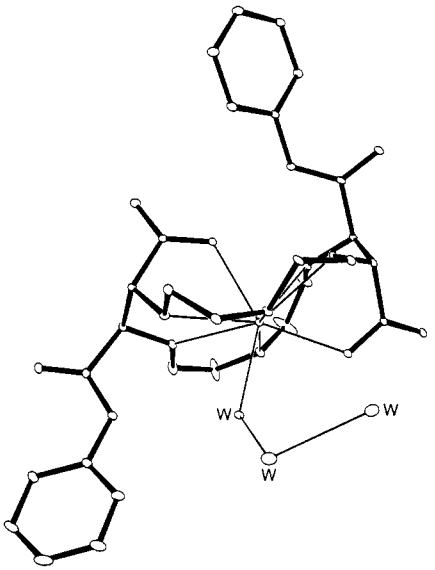

Figure 2. Structure of the (*anti*-**2a**)Ca^{2+} complex (30% probability ellipsoids). The "open" side of the macrocycle is filled with three hydrogen-bonded water molecules (W). The calcium ion is located in the center of the macrocycle.

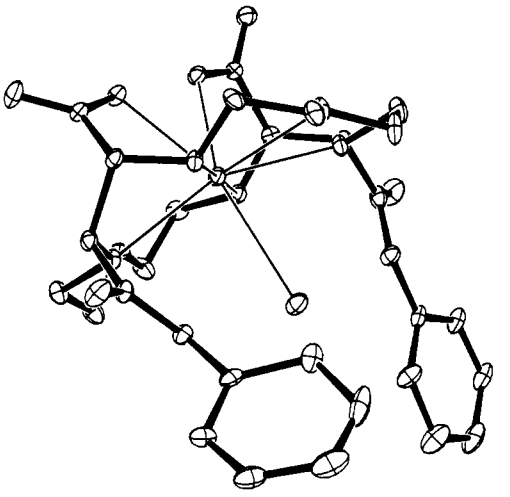

Figure 3. Structure of the (*syn*-**2a**)Sr^{2+} complex (35% probability ellipsoids). The strontium cation is coordinated to eight oxygen atoms (see text) and to a chloride anion ($Sr^{2+}\cdots Cl^{-}$ = 2.82 Å). Solvent molecules and calcium cations have been omitted.

= 2.36 Å, $Sr^{2+}\cdots O^{-}$ = 2.52 Å). Indeed, the dicarboxylate (*syn*-**2** and *anti*-**2**) and tetracarboxylate (**1**, R = O^{-}) substituted macrocycles bind cations much more strongly than the parent [18]-crown-6.[2,13,21]

(c) In both complexes, the lateral appendages X and Y are in a *diaxial relationship* [dihedral angles of 180 and 172° for (*syn*-**2a**) and 178 and 173° for (*anti*-**2a**)], a fact of great importance for further elaboration. Indeed, axial orientation of these appendages permits optimal interaction with bound species, thus allowing regulation of substrate binding (lateral recognition) as well as molecular catalysis by reaction of lateral reactive functions with bound substrates. Incorporation into macropolycyclic structures is also facilitated by diaxial orientation of the connecting functions.[24]

(d) There is a net preference for the amide groups to be aligned with the nearest ring ether oxygen (O–*CH–CO–NH torsion

(24) ^{1}H NMR studies of (*syn*-**2a**) show that this orientation is also predominant in solution, although there is a conformational change on complexation: $^3J_{H,H}$ for the *CHX–*CHY fragment decreases from 3.1 Hz to 1.8 ± 0.1 Hz upon complexation with the butylammonium cation (see also ref 18).

angles equal to 14 and 16° and 15 and 30°, respectively for the syn and anti isomer). Apart from steric considerations, this preference for an almost eclipsed O–*C–C–N conformation may result from a five-membered bent hydrogen bonding interaction;[25] thus, this fragment leads to more highly structured molecular architectures as well as to convergence of potential binding sites.

(e) The structural features provide an explanation for the marked differences between the physicochemical properties of the two isomers. For (*syn*-**2a**), the ring conformation resembles that of the cation complexes of the parent [18]-crown-6 itself;[26] the gauche and anti preferences of the CC and CO bonds, respectively,[27] are compatible with a ring conformation bringing the two carboxylate groups in close contact with the cation [see (b)]; the six ether oxygens form an almost planar hexagon (extreme deviations from 0.24 to −0.31 Å from the mean plane, from +0.20 to −0.20 Å for [18]-crown-6[26]) surrounding the complexed cation. The only conformational distorsions brought about by the tartaric acid residues involve the *C*C–OC bonds (dihedral angles of 133 and 145°) and the carbon framework ($g^+g^-g^+g^+g^-g^+$), leading to a lower pseudotwofold symmetry for the ring.

(f) In contrast, the structure of (*anti*-**2a**) shows a strained, sigmoidal conformation for the macrocyclic ring. The electrostatic interaction of the complexed cation with the two anti carboxylate groups imposes two eclipsed CC-bond conformations (dihedral angles of 1 and 14°), and the six ether oxygen atoms are displaced from their mean plane by distances ranging from −0.86 to +0.55 Å. This may explain why the complexes of the anti isomers are ca. 100 times less stable than those of the syn isomers.[21] Furthermore, the carboxylate group above the ring in Figure 2 is shielded from its environment by the aromatic group located in front of it, a feature which may be related to the lower polarity of this isomer in the chromatographic separation. This view is strengthened by the structural study of a dimeric form as schematically depicted in Figure 1, which has been isolated for (*anti*-**2c**)Ca^{2+} after chromatography. Although the diffraction data were of poor quality, it appears that in the structure arrived at, a second molecule lies in a pseudocentrosymmetric way at the open side of the macrocycle (replacing the water molecules shown in Figure 2), thus shielding the polar sides of both macrocycles in an organic shell.

Both the *syn*-**2** and *anti*-**2** macrocycles possess attractive features. The syn species are synthesized selectively and have very interesting conformational and complexing properties; developments into the *macropolycyclic dimension* are being pursued. The laterally discriminated anti system may allow placing a complexed substrate in an electrostatic field between charged sites, a feature of much interest for developing "*charge-relay*"-*type catalytic systems*.

(25) H···O distances with the calculated hydrogen position range from 2.20 to 2.26 Å.
(26) Dunitz, J. D.; Dobler, M.; Seiler, P.; Phizackerley, R. P. *Acta Crystallogr., Sect. B* **1974**, *B30*, 2733–2738.
(27) Dale, J. *Tetrahedron* **1974**, *30*, 1683–1694.

Di-μ-oxo-(η^1:η^5-1,2,3,4-tetramethyl-5-methylene-1,3-cyclopentadiene-bis[(η-pentamethylcyclopentadienyl)titanium], (μ-O)$_2$[μ-[η^1:η^5-$C_5(CH_2)(CH_3)_4$]][Ti[η^5-$C_5(CH_3)_5$]]$_2$, a Complex Containing a Bridging Tetramethylmethylenecyclopentadienyl Ligand

Frank Bottomley,* Ivan J. B. Lin, and Peter S. White

Department of Chemistry, University of of New Brunswick Fredericton, *New Brunswick, Canada E3B 6E2*

Received August 13, 1980

We wish to report the preparation and structure of (η-O)$_2$-[μ-[η^1:η^5-$C_5(CH_2)(CH_3)_4$]][Ti[η^5-$C_5(CH_3)_5$]]$_2$ (I), the first structurally characterized complex containing a bridging [η^1:η^5-$C_5(CH_2)(CH_3)_4$] ligand. It has been previously suggested

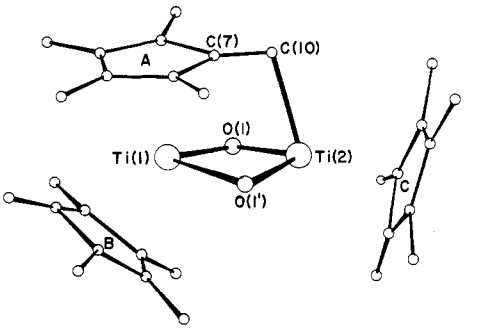

Figure 1. Structure of I. Hydrogen atoms have been omitted for clarity. There is a crystallographic mirror plane through atoms C(7), C(10), Ti(1), and Ti(2) and bisecting each of the three rings.

that monomeric complexes containing the [η^1:η^5-$C_5(CH_2)(CH_3)_4$] ligand occurred as reactive intermediates in the chemistry of [η^5-$C_5(CH_3)_5$]$_2$Ti, in particular during the perdeuteration of this complex.[1,2] Structural evidence is, however, lacking, and no dimeric species were involved. In complexes of the parent C_5H_5 ligand, (η^1:η^5-C_5H_4) is known to bridge two Ti atoms.[3] The synthesis of I followed from our continuing investigation of the use of N_2O as a controlled source of oxygen atom oxidation for transition-metal complexes.[4,5]

When N_2O reacted with a toluene solution of Cp*$_2$Ti[1] (Cp* = [η^5-$C_5(CH_3)_5$]) at 0 °C, there was a color change from orange to green-yellow and an immediate evolution of N_2. On reduction of the volume of the solution, precipitation of light green crystals, together with a small amount of an unknown brown, hexane-soluble material, occurred. The moderately air-stable green crystals had the apparent stoichiometry "Cp*$_3$Ti$_2$O$_2$" but showed an ^{1}H NMR spectrum in the ring methyl region very similar to that of $C_{10}(CH_3)_9CH_2TiH$ (see Figure 1 of ref 1), indicating the presence of a cyclopentadienyl ring other than [η^5-$C_5(CH_3)_5$]. The structural analysis showed that the green compound has formula I, and the reaction can therefore be represented by

$$2Cp^*_2Ti + 2N_2O \rightarrow \underset{\mathbf{I}}{(\eta\text{-}O)_2[\eta^1\text{:}\eta^5\text{-}C_5(CH_2)(CH_3)_4][Ti[\eta^5\text{-}C_5(CH_3)_5]]_2} + 2N_2 + C_5(CH_3)_5H$$

The complex (see Figure 1) has several very unusual structural features.[6,7] It is clear that one methyl group of a $C_5(CH_3)_5$ ring attached to one titanium has become a methylene bridge to the second titanium. The Ti(2)–CH_2 distance, 2.176 (6) Å, is similar to the 2.19 (2) Å found in (η^5-C_5H_5)$_2$Ti-μ-(η^1:η^5-C_5H_4)-Ti(η^5-C_5H_5)[3] and the 2.15 (1) and 2.09 (1) Å in [(C_2H_5O)($C_6H_5CH_2$)$_2$Ti]$_2$(η-C_2H_5O)$_2$.[8] The CH_2–ring A distance [C(7)–C(10) in Figure 1] of 1.473 (9) Å is barely significantly different from the average CH_3–ring distance in the three rings, 1.501 (6) Å. The C–C ring distances in ring A do not differ significantly from those in ring B or C. These two facts coupled with the Ti(2)–C(7) distance of 2.872 (6) Å and the C(7)–C(10)–Ti(2) angle of 102.1 (4)° indicate that the Ti(2)–CH_2 bond

(1) Bercaw, J. E.; Marvich, R. H.; Bell, L. G.; Brintzinger, H. H. *J. Am. Chem. Soc.* **1972**, *94*, 1219–38.
(2) Bercaw, J. E. *J. Am. Chem. Soc.* **1974**, *96*, 5087–95.
(3) Pez, G. P. *J. Am. Chem. Soc.* **1976**, *98*, 8072–8.
(4) Bottomley, F.; White, P. S. *J. Chem. Soc., Chem. Commun.*, in press.
(5) Bottomley, F.; Lin, I. J. B.; Mukaida, M. *J. Am. Chem. Soc.* **1980**, *102*, 5238–42.
(6) The structure was determined by X-ray crystallography. Crystal data: $C_{30}H_{44}O_2Ti_2$, M = 532.5; orthorhombic, *Pnma*; a = 10.650 (5), b = 15.283 (3), c = 17.064 (8) Å; R = 0.041, R_w = 0.060 for 1120 observed reflections out of 1904 measured. Hydrogen atoms were refined isotropically, all other atoms anisotropically. Full details will be published elsewhere.
(7) We have considered the possibility that there is an additional hydrogen atom in the structure. However, attempts to place a hydrogen at various likely positions on the Ti, O, or C(7) atoms gave unrefinable structures. Also, the diamagnetism of the complex is not compatible with the presence of a hydrogen atom.
(8) Stoeckli-Evans, H. *Helv. Chim. Acta* **1975**, *58*, 373.

0002-7863/81/1503-703$01.00/0