

Resolution and Structural Determination of Unsymmetrically 6A,6D-Disubstituted β -Cyclodextrin

Kahee Fujita,* Atsuo Matsunaga, and Taiji Imoto

Faculty of Pharmaceutical Sciences
Kyushu University 62
Maidashi, Higashi-ku, Fukuoka 812, Japan

Ken Hirotsu,* Shigehiro Kamitori, and Taiichi Higuchi

Department of Chemistry, Faculty of Science
Osaka City University, Sumiyoshi-ku, Osaka 558, Japan

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Appropriate spacial arrangement of two different functional groups is often quite important for an enzyme function. In the efforts to construct enzyme (receptor) mimics with cyclodextrins, one of the most challenging projects is attachment of two different groups on desirable positions of cyclodextrins. This was for the first time attained through double nucleophilic substitution of an unsymmetrically capped β -cyclodextrin(s) which was constituted of at least two diastereomers.¹ We report here the resolution and structural determination of a specific unsymmetrically disubstituted β -cyclodextrin which forms an inclusion complex in the crystalline state.

Isomeric mixture of 6A,6X-dideoxy-6A-(*tert*-butylthio)-6X-[(β -naphthylsulfonyl)oxyl]- β -cyclodextrin (X = B-G) was prepared by the reaction of 6-deoxy-6-(*tert*-butylthio)- β -cyclodextrin (**1**)² (1.04 g) with β -naphthalenesulfonyl chloride (1.25 g)³ in pyridine (10 mL). After usual workup,⁴ the mixture was analyzed by reversed-phase HPLC⁵ (Figure 1, inset) and preparatively separated through reversed-phase column chromatography⁶ (Figure 1) to give **2** (81 mg, 6.7%), a mixture of **3** and **4** (107 mg, 8.9%), **5** (51 mg, 4.3%), **6** (14 mg, 1.2%), and **7** (53 mg, 4.4%). The sulfonates **3** and **4** were purely isolated from the mixture by preparative reverse-phase HPLC: **3** 41 mg (3.4%), **4** 24 mg (2.0%). ¹H NMR spectra showed that they were naphthalenesulfonated (*tert*-butylthio)- β -cyclodextrins.⁷ They were converted to the corresponding 6-deoxy derivatives **8-13**⁸ by reduction with NaBH₄ in DMF. Since there is quite small structural difference between **8-13** and **1** whose structure has been determined by X-ray crystallographic study,² we expected that **8-13** would form isomorphous crystals with **1**. We also tried recrystallization of **2-7**, but we could not obtain crystals suitable for X-ray analysis. Recrystallization of **8-13** (5 mg) from boiling water (1 mL) gave orthorhombic crystals for **8-10** and **13**, monoclinic crystals for **12** and powder for **11**. Among them, only crystals of **9** were isomorphous with **1**. The following are crystallographic data of **9**: orthorhombic, *a* = 32.489 (6) Å, *b* = 15.460 (2) Å, *c* = 15.172 (2) Å, *Z* = 4, space group *P*2₁2₁2₁. Diffractometer data (3958) were measured by ω -scan with Mo K α radiation up to $2\theta = 40^\circ$ of which 2780 were regarded as observed [*I* \geq 3 σ (*I*)]. The structure was solved with the aid of

(1) Tabushi, I.; Nabeshima, T.; Kitaguchi, H.; Yamamura, K. *J. Am. Chem. Soc.* **1982**, *104*, 2017.

(2) Hirotsu, K.; Higuchi, T.; Fujita, K.; Ueda, T.; Shinoda, A.; Imoto, T.; Tabushi, I. *J. Org. Chem.* **1982**, *47*, 1143.

(3) We added the sulfonyl chloride to the pyridine solution, monitoring the formation of the products. The amount of the sulfonyl chloride was dependent on the dryness of pyridine and the cyclodextrin.

(4) (a) Fujita, K.; Matsunaga, A.; Imoto, T. *J. Am. Chem. Soc.* **1984**, *106*, 5740. (b) Fujita, K.; Matsunaga, A.; Imoto, T. *Tetrahedron Lett.* **1984**, *25*, 5533.

(5) TSKgel LS-410 ODS SIL column, 4 \times 300 mm, 5 μ m, Toyo Soda, Japan.

(6) Lobar column LiChroprep RP8, Merck Ltd., 25 \times 310 mm.

(7) They showed similar NMR spectra although the spectra differed from one another in the chemical shifts of the *tert*-butyl groups. **1** and **5** δ 1.06; **2-4**, δ 1.18; **6**, δ 1.20.

(8) For example, **11** and **12** showed doublet absorptions at δ 1.24 (*J* = 6.0 Hz) for one methyl group, demonstrating that the sulfonation occurred on the C-6 hydroxyl. The FABMS spectrum of **12** confirmed that it was indeed the deoxy(*tert*-butylthio)- β -cyclodextrin.

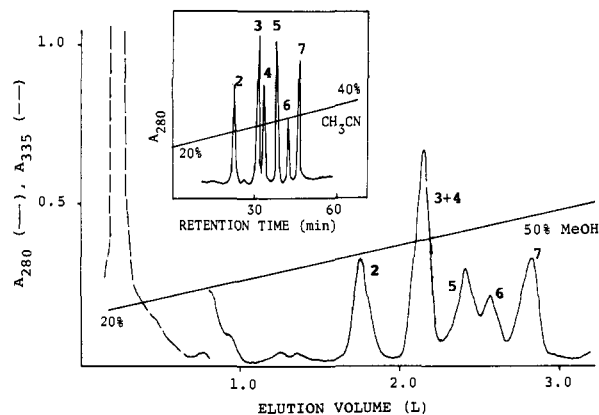


Figure 1. Reversed-phase column chromatography of the mixture obtained from the reaction of 6-deoxy-6-(*tert*-butylthio)- β -cyclodextrin with β -naphthalenesulfonyl chloride. A linear gradient elution of MeOH was applied. Inset: Reversed-phase HPLC of the same mixture. A linear gradient elution of CH₃CN was applied.

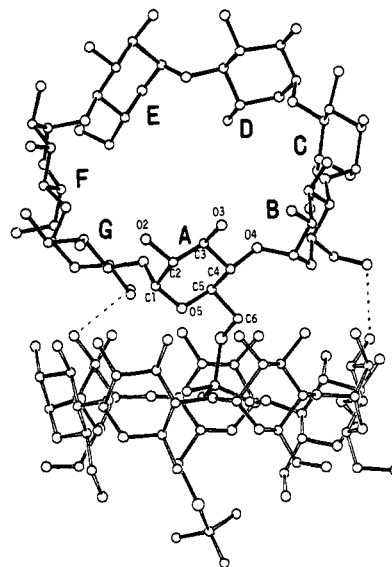


Figure 2. Drawing of 6A,6D-dideoxy-6A-(*tert*-butylthio)- β -cyclodextrin. The *tert*-butyl group is intermolecularly included in the hydrophobic cavity of the cyclodextrin. Hydrogen bondings between two molecules are shown by dotted lines.

the isomorphous complex **1**, the structure of which had been solved previously.² The coordinates of all C and O atoms from **1** (except solvent oxygen and O-6) were refined. A difference Fourier synthesis revealed the missing O-6 atoms except that at the 6D position. Block-diagonal least-squares refinement with anisotropic temperature factors for non-hydrogen atoms of **9** and isotropic water oxygen atoms converged to a standard crystallographic residual of 0.12. Figure 2 is a perspective drawing of the final X-ray model of **9** without hydrogen atoms⁹ and indicates that **9** is 6A,6D-dideoxy-6A-(*tert*-butylthio)- β -cyclodextrin and, therefore, that **3** is 6A,6D-dideoxy-6A-(*tert*-butylthio)-6D-[(β -naphthylsulfonyl)oxyl]- β -cyclodextrin. Figure 2 also shows that a *tert*-butyl group of one cyclodextrin is included in the cavity of another cyclodextrin.

The assigned **3** will serve as a 6A,6D-authentic specimens for structural determination of 6A,6D-unsymmetrically bifunctionalized β -cyclodextrins (artificial enzymes or receptors) and also will give unique enzyme (or receptor) mimics having a hydrophobic group (*tert*-butyl) on the 6A-carbon and a functional group, which is derived from the (naphthylsulfonyl)oxyl moiety, on the 6D-carbon.

(9) Johnson, C. Report ORNL-3794; USAEC: Oak Ridge National Laboratory, Oak Ridge, TN, 1965.

Acknowledgment. We are indebted to Japan Maise Products Co. Ltd. for generous gift of β -cyclodextrin and to the crystallographic Research Center, Institute for Protein Research, Osaka University, for computer calculation. This work was supported in part by the Scientific Culture of Japan (56540281 and 59212039).

Supplementary Material Available: Tables for atomic coordinates, bond distances and angles, and observed and calculated structure factors for **9** (12 pages). Ordering information is given on any current masthead page.

Very Twisted η^4 -*trans*-Diene Complexes^{1,2}

Allen D. Hunter, Peter Legzdins,* and Charles R. Nurse

Department of Chemistry
The University of British Columbia
Vancouver, British Columbia, Canada V6T 1Y6

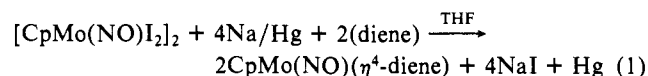
Frederick W. B. Einstein* and Anthony C. Willis

Department of Chemistry, Simon Fraser University
Burnaby, British Columbia, Canada V5A 1S6

Received August 13, 1984

Numerous, monomeric transition-metal complexes containing acyclic conjugated dienes have been synthesized since the first report of $(\eta^4\text{-C}_4\text{H}_6)\text{Fe}(\text{CO})_3$ in 1930,³ and many of these have found applications in organic synthesis.⁴ In the vast majority of these compounds, the diene ligand is attached to the metal center in a planar η^4 -*s-cis* manner.⁵ Indeed, the only examples to date of η^4 -*s-trans* diene coordination to a single metal⁶ occur in $\text{Cp}_2\text{M}(\eta^4\text{-diene})$ complexes ($\text{Cp} = \eta^5\text{-C}_5\text{H}_5$; $\text{M} = \text{Zr}, \text{Hf}$).¹⁰ We now wish to report the preparation and characterization of three $\text{CpMo}(\text{NO})(\eta^4\text{-diene})$ compounds (**1**) which, in addition to being rare examples of (diene)nitrosyl complexes,¹¹ possess a novel type of diene-metal linkage.

The new molybdenum complexes **1** may be conveniently synthesized, albeit in low yields, by the general reaction



where diene = 2-methylbutadiene (**a**), 2,3-dimethylbutadiene (**b**), or 2,5-dimethyl-2,4-hexadiene (**c**). In a typical experiment, a red

solution of $[\text{CpMo}(\text{NO})\text{I}_2]_2$ (2.00 g, 2.25 mmol) in THF (50 mL) containing the diene (2 mL, a 10- to 20-fold excess) was added to a sodium amalgam (0.23 g, 10 mmol of Na in 5 mL of Hg), and the mixture was stirred at room temperature. The supernatant solution immediately became yellow-brown in color. After 15 min, the final mixture was filtered through alumina (3 \times 6 cm, Woelm neutral, activity 1), and the filtrate was taken to dryness in vacuo. Crystallization of the resulting orange residue from hexanes at -10°C afforded ~ 0.15 g ($\sim 10\%$ yield) of the appropriate diene complex (**1a-c**) as yellow, somewhat air-sensitive crystals.¹³

Single-crystal X-ray crystallographic analysis of **1c**¹⁴ revealed it to possess a type of "three-legged piano stool" molecular structure (Figure 1)¹⁵ with normal Cp-Mo and Mo-NO geometries.¹⁶ The most chemically interesting feature of the structure involves the diene-Mo linkage in which the diene carbons adopt a transoidal, nonplanar arrangement with a torsion angle of $124.8(4)^\circ$ (Figure 1b). The central atoms are slightly closer to the metal center (Mo-C ~ 2.22 Å) than are the terminal carbons (Mo-C ~ 2.38 Å). Furthermore, the carbon-carbon bond lengths in the diene fragment are all similar (1.401-1.418 (4) Å) and classically intermediate to those expected for C-C and C=C bonds.¹⁷ This structural feature of **1c** stands in marked contrast to that found for $\text{Cp}_2\text{Zr}(\eta^4\text{-PhCH=CH-CH=CHPh})$ ¹⁸ (the only other structurally well-characterized monometallic η^4 -*trans*-diene complex) in which the analogous carbon-carbon bond distances exhibit the short (~ 1.40 Å)-long (~ 1.48 Å)-short (~ 1.40 Å) alternation characteristic of a diene. In molecular orbital terms,¹⁹ the unprecedented type of interaction between the dienes and the central molybdenum atoms in complexes **1** may thus be viewed as resulting from increased back-donation of electron density into the π_3^* MO's of the *trans*-diene ligands, a view supported by preliminary theoretical investigations.²⁰

The spectroscopic properties of all three complexes **1**¹³ indicate that they retain this twisted η^4 -*trans*-diene-Mo configuration in solution.²¹ In this connection, it may be noted that the ¹H NMR spectrum of **1c** in CDCl_3 displays a coupling constant for the meso hydrogens of the diene ligand (i.e., $^3J_{\text{HH}} = 12$ Hz) that is more in accord with those previously reported^{10,22} for the *cis*-diene

(12) Seddon, D.; Kita, W. G.; Bray, J.; McCleverty, J. A. *Inorg. Synth.* **1976**, *16*, 24.

(13) For **1c**. Anal. Calcd for $\text{C}_{13}\text{H}_{19}\text{NOMo}$: C, 51.83; H, 6.36; N, 4.65. Found: C, 51.95; H, 6.44; N, 4.66. IR (CH_2Cl_2) ν_{NO} 1584 (s) cm^{-1} ; ¹H NMR (CDCl_3) δ 5.30 (s, 5 H, C_5H_5), 3.34 (d, 1 H, CH, $J = 12$ Hz), 2.71 (d, 1 H, CH, $J = 12$ Hz), 2.09 (s, 3 H, CH_3), 1.93 (s, 3 H, CH_3), 1.72 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3); low-resolution mass spectrum (probe 50°C), m/z 303 (P^+ , ⁹⁸Mo). Analogous data for **1a** and **1b** are presented in the supplementary material.

(14) X-ray diffraction data for $(\eta^5\text{-C}_5\text{H}_5)\text{Mo}(\text{NO})(\eta^4\text{-C}_8\text{H}_{14})$: monoclinic; space group $\text{P}2_1/c$; $a = 12.153(2)$ Å, $b = 9.275(1)$ Å, $c = 12.909(4)$ Å; $\beta = 117.31(2)^\circ$; $V = 1292.9$ Å³; $Z = 4$; absorption coefficient = 9.69 cm^{-1} ; diffractometer, Enraf-Nonius CAD4F; radiation, Mo $K\alpha$, graphite monochromator ($\lambda(K\alpha_1) = 0.70930$ Å); scan range = $0^\circ \leq 2\theta \leq 50^\circ$; reflections = 1862 with $I_0 \geq 3\sigma I_0$; $R = 0.021$, $R_w = 0.024$; error in observation of unit weight = 1.61 e. All atoms, including H atoms, were refined.

(15) Thermal ellipsoids enclose 50% probabilities. H atoms are shown as spheres with arbitrarily small radii. Davies, E. K. "CHEMGRAF Users' Guide"; Chemical Crystallography Laboratory; University of Oxford, England, 1983.

(16) (a) Malito, J. T.; Shakir, R.; Atwood, J. L. *J. Chem. Soc., Dalton Trans.* **1980**, 1253 and references therein. (b) Reinsner, M. G.; Bernal, I.; Brunner, H.; Doppelberger, J. *J. Chem. Soc., Dalton Trans.* **1978**, 1664. (c) McCleverty, J. A.; Murray, A. J. *Transition Met. Chem. (Weinheim, Ger.)* **1979**, *4*, 273.

(17) Pauling, L. "The Nature of the Chemical Bond", 3rd ed.; Cornell University Press: Ithaca, NY, 1960; pp 232-239.

(18) Kai, Y.; Kanehisa, N.; Miki, K.; Kasai, N.; Mashima, K.; Nagasuna, K.; Yasuda, H.; Nakamura, A. *J. Chem. Soc., Chem. Commun.* **1982**, 191.

(19) Tatsumi, K.; Yasuda, H.; Nakamura, A. *Isr. J. Chem.* **1983**, *23*, 145.

(20) Bursten, B. E.; Gatter, M. G., personal communication.

(21) The ¹H NMR spectrum of **1a** in CDCl_3 at 30°C also reveals that the compound exists as a 3:1 mixture of isomers which presumably differ in the orientation of the 2-methyl substituent with respect to the Cp group. For purely steric reasons, the major isomer probably has the methyl group directed away from the Cp ring.

(22) Yasuda, H.; Kajihara, Y.; Mashima, K.; Nagasuna, K.; Lee, K.; Nakamura, A. *Organometallics*, **1982**, *1*, 388.

(1) Organometallic Nitrosyl Chemistry 24. For part 23, see: Legzdins, P.; Rettig, S. J.; Sánchez, L.; Bursten, B. E.; Gatter, M. G. *J. Am. Chem. Soc.*, in press.

(2) Taken in part from: Nurse, C. R. Ph.D. Dissertation, The University of British Columbia, Vancouver, Canada, 1983.

(3) Reihlen, H.; Grühl, A.; von Hessling, G.; Pfrengle, O. *Liebigs Ann. Chem.* **1930**, *482*, 161.

(4) Davies, S. G. "Organotransition Metal Chemistry: Applications to Organic Synthesis"; Pergamon Press: Oxford, England, 1982.

(5) See, for example: (a) Erker, G.; Engel, K.; Krüger, C.; Müller, G. *Organometallics* **1984**, *3*, 128. (b) Chinn, J. W., Jr.; Hall, M. B. *Organometallics* **1984**, *3*, 284 and references therein.

(6) Transoidal 1,3-butadiene is known to function as a bridging ligand between two metal centers in $[\text{CpMn}(\text{CO})_2]_2(\mu_2\text{-}\eta^4\text{-C}_4\text{H}_6)$,⁷ $[\text{Mn}(\text{CO})_4]_2(\mu_2\text{-}\eta^4\text{-C}_4\text{H}_6)$,⁸ and $\text{Os}_3(\text{CO})_{10}(\mu_2\text{-}\eta^4\text{-C}_4\text{H}_6)$.⁹

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(10) (a) Czisch, P.; Erker, G.; Korth, H.-G.; Sustmann, R. *Organometallics* **1984**, *3*, 945 and references therein. (b) Yasuda, H.; Nagasuna, K.; Akita, M.; Lee, K.; Nakamura, A. *Organometallics* **1984**, *3*, 1470 and references therein.

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