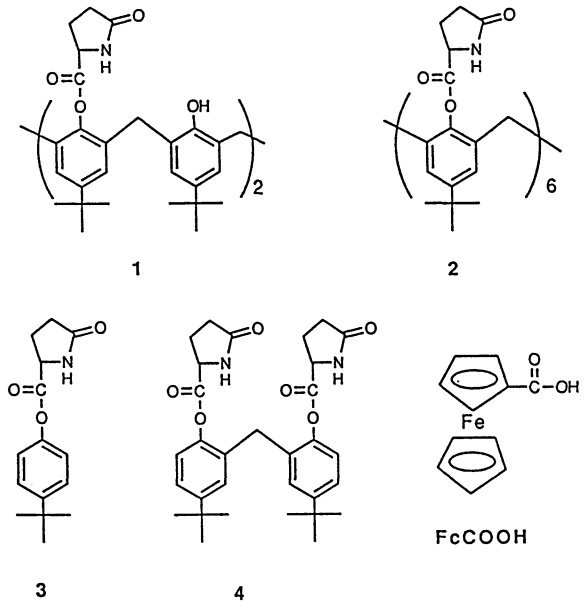
Formation of Molecular Complexes with Calixarenes as Detected by Induced Circular Dichroism

Takashi ARIMURA and Seiji SHINKAI*
Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Fukuoka 812
(Received February 2, 1991)

Calix[*n*]arenes (*n*=4 and 6) bearing (*S*)-5-oxo-2-pyrrolidinylcarbonyloxyl groups on the lower rim were synthesized. In chloroform, the hexamer bearing six (*S*)-5-oxo-2-pyrrolidinylcarbonyloxyl groups could "bind" ferrocenecarboxylic acid through hydrogen-bonding interactions, the complexation being conveniently detected by induced circular dichroism (ICD) spectroscopy (λ_{max} 445 nm). On the basis of the examination of acyclic reference compounds, the appearance of the ICD band was explained as such that one pyrrolidone unit acts as a binding site and the chiral center in the neighboring pyrrolidone unit affects the transition moments in the ferrocene π-system. The association constant for the 1 : 1 complex was estimated to be 680 M^{-1}. This is a new, convenient method for detecting the formation of molecular complexes with calixarenes in organic media.

Calixarenes are cyclic oligomers which are composed of phenol units. Because of their cavity-shaped architecture, they would be expected to be useful building-blocks in the design of novel host molecules.[1-4] Although calixarenes can include several small molecules in the solid state,[1,2] there exist only a few examples for inclusion of guest molecules in solution.[5] This is because host–guest-type complexation in organic media always competes with solvation of guests by solvent molecules. Exceptional is the aqueous system: For instance, water-soluble calixarenes can associate with organic guest molecules owing to a hydrophobic force, a driving force for association specifically operating in water.[6] Thus, the host–guest chemistry of calixarenes has been studied in aqueous solutions.[3,4,7] Only one example reported so far for complexation in organic media is the binding of *t*-butylamine to 5,11,17,23-tetraallylcalix[4]arene-25,26,27,28-tetrol.[5] However, the main driving force for this complex is supposed to be acid-base neutralization between amine and phenol.[5]

In conformity with the foregoing view, we reached a conclusion that one should adopt a new concept to effect inclusion of guest molecules in organic media. Also, some new strategies should be developed to efficiently detect host–guest interactions occurring in organic media. We noticed hydrogen-bonding interactions which have frequently been used in molecular recognition may be useful.[8-11] To detect the interactions between hosts and guests we chose induced circular dichroism (ICD) which sensitively reports the interaction with chiral centers. Thus, we synthesized calix[*n*]arenes (*n*=4 and 6) as host molecules bearing (*S*)-2-pyrrolidone units which have hydrogen-bonding sites as well as a chiral center. As guest molecules, we chose ferrocene derivatives because they have a characteristic absorption band at around 450 nm.



Experimental

Materials. 5,11,17,23-Tetra-*t*-butylcalix[4]arene-25,26,27,28-tetrol and 5,11,17,23,29,35-hexa-*t*-butylcalix[6]arene-37,38,39,40,41,42-hexol were prepared according to Gutsche's method.[12]# (*S*)-5-Oxo-2-pyrrolidinecarbonyl chloride was prepared from (*S*)-5-oxo-2-pyrrolidinecarboxylic acid (Aldrich, 97% purity) according to the literature.[13]

25,27-Bis[(*S*)-5-oxo-2-pyrrolidinylcarbonyloxy]-5,11,17,23-tetra-*t*-butylcalix[4]arene-26,28-diol (1). Oil-dispersed NaH (152 mg; 3.8 mmol) was added to 40 ml of THF containing tetra-*t*-butylcalix[4]arenetetrol (350 mg; 0.54 mmol). The mixture was stirred for 4 h at room temperature under a nitrogen stream. (*S*)-5-Oxo-2-pyrrolidinecarbonyl chloride (0.53 g; 4.0 mmol) was added dropwise. The reaction was continued at room temperature for 15 h. After addition of a small amount of ethanol, the mixture was concentrated to dryness under reduced pressure. The residue was dissolved in dichloromethane, the solution being washed with water and dried over Na_2SO_4. After concentration to dryness, the residue was recrystallized from hexane–toluene: White powder, mp 280—284 °C, yield 57%; ^{1}H NMR ($CDCl_3$) δ=0.92 and 1.20 (18H each, s each, *t*-Bu), 2.20—2.60 (8H, m,

The nomenclature for calix[*n*]arene is a little confused now. In this paper, we named the [1$_n$]metacyclophane structure [(-CH$_2$-*m*-C$_6$H$_4$-)$_n$] "calix[*n*]arene".

CH_2CH_2 in pyrrolidone), 3.40 and 3.90 (4H each, d each (J=13 Hz), $ArCH_2Ar$), 4.28—4.32 (2H, m, CH in pyrrolidone), 6.20 (2H, broad s, NH), 6.90 and 7.15 (4H each, s each, ArH). Found: C, 74.03; H, 7.70; N, 2.94%. Calcd for $C_{54}H_{66}O_8N_2$: C, 74.45; H, 7.64; N, 3.22%. The ^{1}H NMR spectrum and elemental analysis indicate that the recovered product is 25,27-disubstituted-26,28-dihydroxy-5,11,17,23-tetra-*t*-butylcalix[4]arene. The split pattern for the $ArCH_2Ar$ protons shows that this calix[4]arene adopts a cone conformation.

37,38,39,40,41,42-Hexakis[(*S*)-5-oxo-2-pyrrolidinylcarbonyloxy]-5,11,17,23,29,35-hexa-*t*-butylcalix[6]arene (2). This compound was synthesized in a manner similar to that described for **1**: Colorless powder, mp 215—217 °C, yield 28%; ^{1}H NMR ($CDCl_3$) δ=1.20 (54H, s, *t*-Bu), 2.22—2.58 (24H, m, CH_2CH_2 in pyrrolidone), 3.80 (12H, broad s, $ArCH_2Ar$), 4.29—4.32 (6H, m, CH in pyrrolidone), 6.17 (6H, broad s, NH), 7.15 (12H, s, ArH). Found: C, 69.85; H, 6.93; N, 4.61%. Calcd for $C_{96}H_{114}O_{18}N_6$: C, 70.31; H, 7.01; N, 5.12%. The ^{1}H NMR spectrum and elemental analysis indicate that six OH groups are substituted.

***p*-*t*-Butylphenyl (*S*)-5-Oxo-2-pyrrolidinecarboxylate (3).** This compound was also synthesized from (*S*)-5-oxo-2-pyrrolidinecarbonyl chloride and *p*-*t*-butylphenol in the presence of NaH: Colorless prisms (recrystallized from acetonitrile), mp 124—127 °C, yield 60%; ^{1}H NMR ($CDCl_3$) δ=1.16 (9H, s, *t*-Bu), 2.04—2.38 (4H, m, CH_2CH_2), 4.02—4.38 (1H, m, CH), 6.12 (1H, broad s, NH), 5.73 and 7.24 (2H each, d each, (J=9 Hz), ArH). Found: C, 69.44; H, 7.70; N, 5.12%. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36%.

Bis[2-((*S*)-5-oxo-2-pyrrolidinylcarbonyloxy)-5-*t*-butylphenyl]methane (4). This compound was synthesized from (*S*)-5-oxo-2-pyrrolidinecarbonyl chloride and 4,4′-di-*t*-butyl-2,2′-methylenediphenol in the presence of NaH: Colorless prisms (recrystallized from hexane), mp 126—129 °C, yield 43%; ^{1}H NMR ($CDCl_3$) δ=1.25 (18H, s, *t*-Bu), 2.20—2.60 (8H, m, CH_2CH_2), 3.90 (2H, s, $ArCH_2Ar$), 4.30—4.35 (2H, m, CH), 6.15 (2H, broad s, NH), 6.76 and 7.10 (2H each, d each (J=8 Hz), ArH), 7.30 (2H, s, ArH). Found: C, 70.05; H, 7.20; H, 5.12%. Calcd for $C_{31}H_{38}N_2O_6$: C, 69.64; H, 7.16; H, 5.24%.

Results and Discussion

In O-acylation of 25,26,27,28-tetrahydroxy-5,11,17,23-tetra-*t*-butylcalix[4]arene with (*S*)-5-oxo-2-pyrrolidinecarbonyl chloride we found that only two OH groups can be substituted. The similar result was observed for O-alkylation of 25,26,27,28-tetrahydroxy-5,11,17,23-tetra-*t*-butylcalix[4]arene with 2-chloromethylpyridine.[14] In contrast, six OH groups in 37,38,39,40,41,42-hexahydroxy-5,11,17,23,29,35-hexa-*t*-butylcalix[6]arene are all substituted. The difference is attributed to the difference in the ring size: that is, the space on the narrow calix[4]arene ring readily becomes sterically-crowded by O-substitution.

When **2** was mixed with ferrocenecarboxylic acid (FcCOOH) in chloroform, a negative ICD band appeared at 445 nm (Fig. 1). This CD maximum is equal to the absorption maximum of FcCOOH. This band was weakened by the addition of methanol. In contrast, this band was not detected at all in DMSO under the same measurement conditions. These results indicate that FcCOOH "interacts" with **2** and the interaction is based on the formation of hydrogen-bonds.

To confirm the importance of the hydrogen-bonding interaction, we used ferrocene (Fc) and methyl ferrocenecarboxylate (FcCOOMe) as reference guest molecules. The ICD band for these compounds was not detected even in chloroform. Here, one can visualize that attraction between **2** and FcCOOH is ascribed to the hydrogen-bonding interaction between the COCHNHCO moiety in **2** and the COOH moiety in FcCOOH. Between two possible binding modes, (A) includes a seven-membered ring whereas (B) includes a six-membered ring (hydrogen atoms are not counted). We consider that binding mode (B) is more likely.

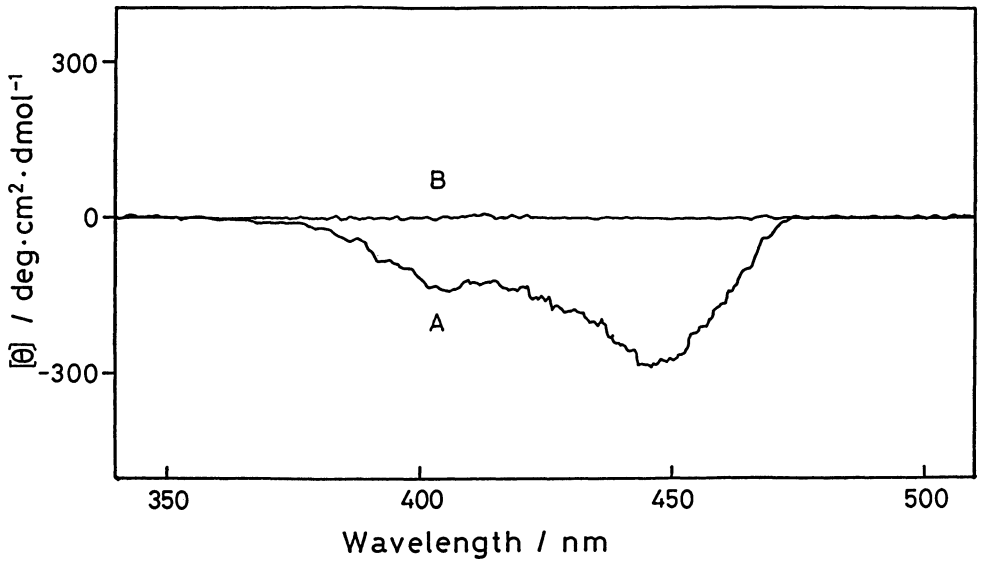
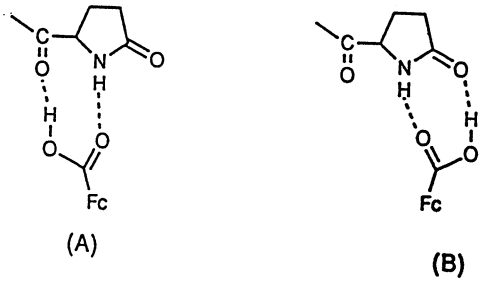


Fig. 1. ICD spectra of FcCOOH in the presence of **2**: 20 °C, [**2**]=1.00×10^{-2} M, [FcCOOH]=5.00×10^{-3} M: (A) chloroform, (B) DMSO.

Table 1. Absorption and ICD Spectra of Ferrocene Derivatives[a)]

Guest	Solvent	λ_{max} in absorption spectrum	$\lambda_{max}(\theta)$ in ICD spectrum			
		nm	Host=1	2	3	4
Fc	$CHCl_3$	440	nd	nd	nd	nd
Fc	DMSO	440	nd	nd	nd	nd
FcCOOH	$CHCl_3$	445	nd	445(−260)	nd	445(−20)
FcCOOH	DMSO	443	nd	nd	nd	nd
FcCOOMe	$CHCl_3$	446	nd	nd	nd	nd
FcCOOMe	DMSO	446	nd	nd	nd	nd

a) 20 °C, chloroform: [1]=[2]=1.00×10^{-2} M, [3]=8.00×10^{-2} M, [4]=4.00×10^{-2} M, [ferrocene derivative]=5.00×10^{-3} M. Nd denotes that the ICD band is not detected.



Here, we discuss how the interaction between **2** and FcCOOH becomes CD-active. Compound **1**, having two pyrrolidone units at 1,3-position, should interact with FcCOOH through the hydrogen-bonds in chloroform. Actually, however, the perceptible ICD band was not recognized. The difference suggests that two neighboring pyrrolidone units would be essential for the ICD-activity. To estimate this hypothesis, we synthesized acyclic analogs **3** and **4**. As summarized in Table 1, the ICD band of FcCOOH did not appear in the presence of monomeric **3**. In the presence of dimeric **4**, on the other hand, the weak but perceptible ICD band appeared at 445 nm. This supports the view that two neighboring pyrrolidone units act cooperatively to make the bound FcCOOH CD-active; conceivably, one pyrrolidone unit acts as a binding site and the chiral center in the neighboring pyrrolidone unit affects the transition moments in the ferrocene π-system. With this cooperative action of two neighboring units the ICD-activity is observed for the **2**·FcCOOH complex.

We determined the stoichiometry for complexation between **2** and FcCOOH on the basis of a continuous variation plot (Fig. 2). It is seen from Fig. 2 that **2** and FcCOOH form a 1 : 1 complex. Why do they form a 1 : 1 complex although **2** has six pyrrolidone units on the lower rim? The result implies that the binding of FcCOOH to one pyrrolidone unit strongly suppresses the binding to other remaining pyrrolidone units. Previously, Aoyama et al.[15] synthesized lipophilic calix[6]arenes bearing amide groups on the lower rim. These compounds provide a polar (DMF-like) microenvironment composed of the amide linkages. Possibly, the lower rim in **2** has such a polar microenvironment.

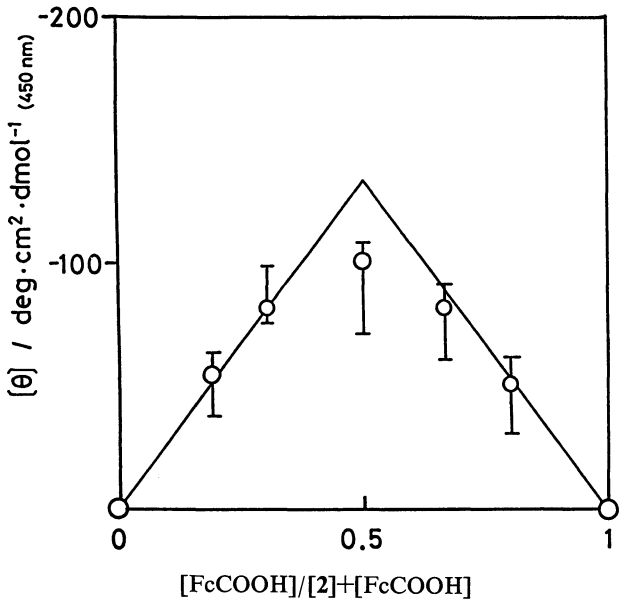


Fig. 2. Continuous variation plot for complexation of **2** and FcCOOH: 20 °C, chloroform, [2]+[FcCOOH]=5.00×10^{-3} M.

This suggests that when FcCOOH is bound to **2** through the hydrogen-bonding interaction, the ferrocene moiety is trapped in the cavity through the dipole-dipole interaction. In this binding model the lower rim is wholly occupied by the first FcCOOH, so that the binding of the second FcCOOH becomes sterically difficult. To prove this association mode, we measured the ^{1}H NMR spectrum of the **2**·FcCOOH complex ($CDCl_3$, 25 °C, [2]=5.00×10^{-2} M, ## [FcCOOH]=7.50×10^{-3} M). FcCOOH in the absence of **2** gave three peaks at 4.25 (5H), 4.45 (2H), and 4.48 (2H) ppm, which were assigned to the cyclopentadiene ring protons without COOH, C<u>H</u>(CHCCOOH), and C<u>H</u>(CCOOH) protons in the cyclopentadiene ring with COOH, respectively. In the presence of **2** the C<u>H</u>(CHCOOH) protons specially shifted to 4.81 ppm whereas the chemical shifts for other protons were scarcely affected. This result means that these protons are placed in the plane of the benzene

1 M=1 mol dm^{-3}.

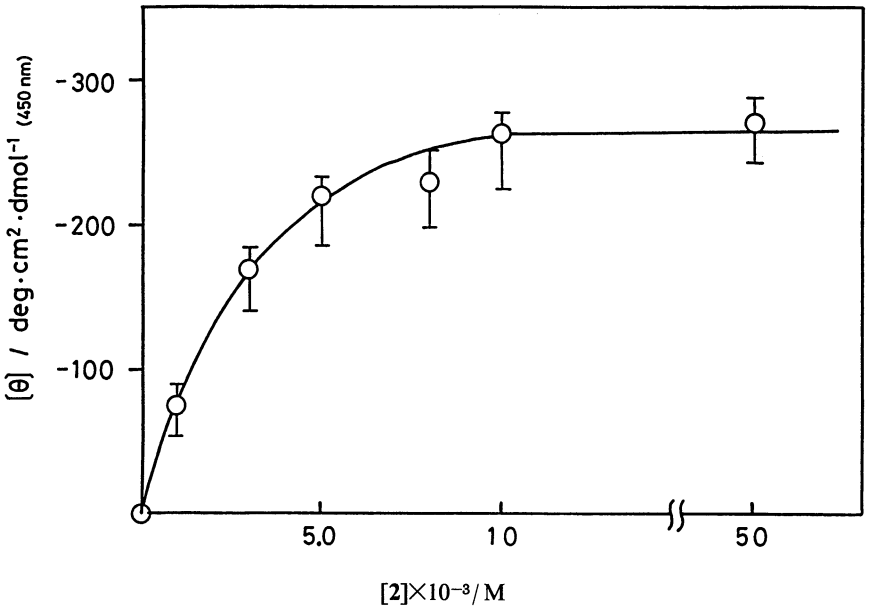


Fig. 3. Plot of θ vs. [2] in chloroform at 20 °C: [FcCOOH]=5.00×10^{-3} M.

rings in **2**; that is, the part of the ferrocene moiety is trapped in the lower rim of the calix[4]arene ring.

We measured θ as a function of [2] (Fig. 3). The plot showed a typical saturation curve. By the analysis of this plot by the Benesi–Hildebrand equation for a 1 : 1 complex, we estimated the association constant to be 680 M^{-1} (correlation coefficient 0.997). This value is comparable with those for complexes formed through two-to-three hydrogen bonds.[16]

Since the complexation between **2** and FcCOOH is based on the hydrogen-bonding interaction, FcCOOH should be substituted by other additives bearing a carboxyl group. This process is similar to the action of "competitive inhibition" in enzyme chemistry. We used trifluoroacetic acid (pK_a in water 0.23), benzoic acid (pK_a in water 4.19), adamantane-1-carboxylic acid (pK_a in water 4.50), and acetic acid (pK_a in water 4.76) as "inhibitors". To a chloroform solution containing **2** (1.00×10^{-3} M) and FcCOOH (2.00×10^{-2} M) was injected a chloroform solution containing concentrated "inhibitors". The final concentration of "inhibitors" was adjusted to 2.00×10^{-2} M. On the addition of adamantane-1-carboxylic acid and acetic acid, the ICD band on the basis of the **2**–FcCOOH interaction was scarcely affected. On the addition of trifluoroacetic acid, in contrast, the ICD band disappeared completely. Benzoic acid moderately competed with FcCOOH, the CD band being decreased with increasing benzoic acid concentration. These results support the view that the association on the basis of hydrogen-bonding interaction is primarily governed by the "acidity" of protons.

The association constant for FcCOOH (K_{FcCOOH}) is defined by Eq. 1. The substitution with benzoic acid (BA) occurring on the lower rim is expressed by Eq. 2. This gives Eq. 3 for the equilibrium constant (K_e). Thus, the association constant for BA (K_{BA}) is expressed, assuming the 1 : 1 substitution between FcCOOH and BA, by Eq. 4.

$$K_{FcCOOH}=\frac{[2\cdot FcCOOH]}{[2][FcCOOH]}, \quad (1)$$

$$2\cdot FcCOOH+BA \rightleftarrows 2\cdot BA+FcCOOH, \quad (2)$$

$$K_e=\frac{[2\cdot BA][FcCOOH]}{[2\cdot FcCOOH][BA]}, \quad (3)$$

$$K_{BA}=K_{FcCOOH}\cdot K_e. \quad (4)$$

We obtained K_e=0.22 from Eq. 3. This allows the estimation of K_{BA}=150 M^{-1}.

In conclusion, the present paper demonstrated the guest complexation through hydrogen-bonding interactions occurring in organic media. In the past, it was difficult to detect the formation of molecular complexes with calixarenes in organic media. In fact, NMR spectroscopy was the sole method.[5] It is shown here that CD spectroscopy serves as an efficent and convenient technique to detect how the guest interacts with the host calixarenes. We plan to extend this concept to chiral recognition of guest molecules.

This work was supported by the Grant-in-Aid from the Ministry of Education, Science and Culture.

References

1) C. D. Gutsche, *Acc. Chem. Res.*, **16**, 161 (1983).
2) C. D. Gutsche, "Calixarenes," Royal Society of Chemistry, Cambridge (1989).
3) S. Shinkai, *Pure Appl. Chem.*, **58**, 1523 (1986).
4) T. Arimura, S. Shinkai , and T. Matsuda, *Yuki Gosei Kagaku-Kyokaishi*, **47**, 523 (1989).

5) Bauer and Gutsche reported inclusion of *t*-butylamine in calix[4]arenes, but the driving force for inclusion is supposed to be a combination of proton transfer plus electrostatic attraction: L. J. Bauer and C. D. Gutsche, *J. Am. Chem. Soc.*, **107**, 6063 (1985).

6) C. Tanford, "The Hydrophobic Effect," Wiley Intersci., New York (1973).

7) S. Shinkai, *Bioorg. Chem. Front.*, **1**, 161 (1990).

8) J. Rebek, Jr., *Angew. Chem., Int Ed. Engl.*, **29**, 245 (1990).

9) S. Goswami and A. D. Hamilton, *J. Am. Chem. Soc.*, **111**, 3425 (1989), and references cited therein.

10) Y. Aoyama, Y. Tanaka, and S. Sugahara, *J. Am. Chem. Soc.*, **111**, 5397 (1989), and references cited therein.

11) K. Kano, K. Yoshiyasu, and S. Hashimoto, *J. Chem. Soc., Chem. Commun.*, **1988**, 801.

12) C. D. Gutsche and M. Iqbal, *Org. Synth.*, **68**, 234, 238, 243 (1989).

13) S. Wilk, T. C. Friedmann, and T. B. Kline, *Biochem. Biophys. Res. Commun.*, **130**, 662 (1985).

14) S. Shinkai, T. Otsuka, K. Araki, and T. Matsuda, *Bull. Chem. Soc. Jpn.*, **62**, 4055 (1989).

15) Y. Aoyama, Y. Nonaka, Y. Tanaka, H. Toi, and H. Ogoshi, *J. Chem. Soc., Perkin Trans. 2*, **1989**, 1025.

16) A. D. Hamilton and D. V. Engen, *J. Am. Chem. Soc.*, **109**, 5035 (1987).