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# Cyclophanes as Hosts for Aromatic and Aliphatic Guests*

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**Abstract.** A series of water-soluble cyclophanes, made by connecting two diarylmethane units and two bridging chains via four nitrogens, were found to provide hydrophobic cavities of definite shape and size for forming inclusion complexes with various organic compounds in aqueous solution. Some chemical modifications of these cyclophanes are described.

**Key words.** Cyclophane, aromatic guest, aliphatic guest, aqueous solution.

## 1. Introduction

Molecular recognition by host–guest complex formation is known to play a central role in biological processes, such as enzyme catalysis and inhibition, replication, immunological response, transport, drug action, etc. Since little is known about artificial reactions via a similar strategy, realization of this type of complex formation in model systems using synthetic unnatural hosts is expected to provide a novel basis for getting selectivities and efficiencies in artificial reactions.

This paper describes our studies on the design, synthesis, and properties of water-soluble cyclophanes as hosts having hydrophobic cavities of definite shape and size for forming inclusion complexes with various organic guests in aqueous solution.

## 2. Design, Synthesis, and Properties of CP44 (4) [1]

Organic compounds usually have hydrophobic moieties, and therefore, hosts capable of forming complexes with organic guests by hydrophobic interactions are extremely attractive. Earlier studies on cyclophanes such as **1** [2] and **2** [3] have suggested that they form inclusion complexes with hydrophobic guests in aqueous solution.

We intended to design novel macrocyclic compounds as hosts that have the following characteristics. The macrocyclic compounds should be soluble in water and have hydrophobic cavities inside to form host–guest inclusion complexes with organic compounds by hydrophobic interactions in aqueous solution. The hydrophobic cavities should be sufficiently rigid to show selectivity upon complexation. It is highly desirable that cavities of various sizes are available.

* This paper is dedicated to Professor D. J. Cram to celebrate his honor in receiving the 1987 Nobel Prize in Chemistry.

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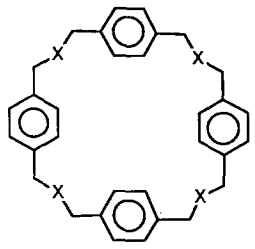
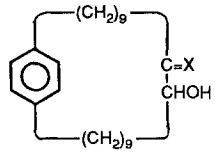
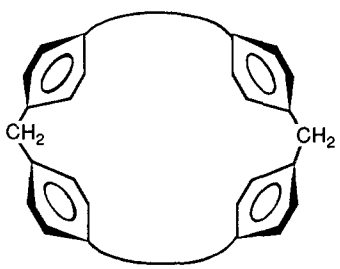


1 X = N-$CH_3$
X = $S^+CH_3$ $BF_4^-$
X = $N^+(CH_3)_2$ $BF_4^-$



2 X = N-OH
X = H, $NH_2$

Guided by CPK model studies, cyclophanes having the general structure **3** were imagined. These cyclophanes are composed of two diphenylmethane skeletons bridged by two chains. This system was chosen for the following four reasons. (i) The fixed angle of Ar—$CH_2$—Ar is expected to make the resulting cavities reasonably rigid. At the same time, face conformation [4], in which all aromatic rings are perpendicular to the macrocyclic ring, is expected to make the resulting cavities rigid and deep. (ii) Introduction of some water-soluble functional groups somewhere in these molecules is expected to make the resulting compounds soluble in water. (iii) Substitution of two diphenylmethane skeletons and two bridging chains with other units of various length is expected to give cavities of various sizes. (iv) Chemical modifications of these compounds are considered to be possible in many ways, because these compounds are totally synthetic.



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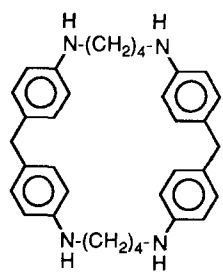

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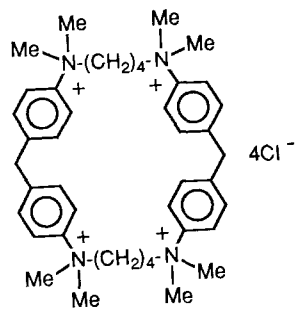

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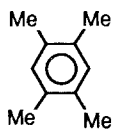
A cyclophane (**4**, abbreviated as CP44) was prepared starting from commercially available 4,4′-diaminodiphenylmethane, and its properties as a host were studied [5]. This compound (**4**) is soluble in water below pH 2. The corresponding permethylated tetra-ammonium tetra-chloride (**5**, QCP44) is soluble in water at any pH [6].

X-ray analyses of the crystalline complexes between these hosts and aromatic guests unequivocally demonstrated the formation of 1 : 1 inclusion complexes. For example, by shaking a mixture of a solution of **4** in aqueous hydrochloric acid and a solution of durene (**6**) in hexane vigorously, a crystalline complex was obtained. The structure of the complex (**7**) shows that the guest (**6**) is fully included at the center of the cavity of the host (protonated **4**). It is also shown that all benzene

rings of the host are perpendicular to the macrocyclic ring (face conformation) as expected, and that the cavity has rectangularly shaped open ends ( $\sim 3.5 \times 7.9$ Å) with a depth of 6.5 Å. The benzene ring of the guest fits well within the cavity, being nearly parallel to the inner wall, because the thickness of the aromatic ring (3.4 Å) fits well with the shorter width of the cavity open ends ( $\sim 3.5$ Å) as shown by the spacial shape of the complex (**8**). It is reasonable to assume that hydrophobic interactions play a role in this complex formation, because **6** is a nonpolar substrate, and the complex was obtained from aqueous solution.

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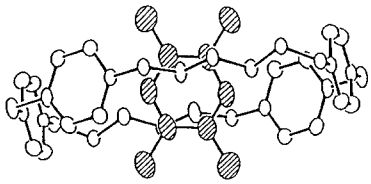

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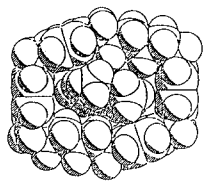


**8**

Complex formation was also observed in solution below CMC concentrations by spectroscopic methods. Figure 1 shows $^1$H NMR spectra of (a) 2,7-dihydroxynaphthalene (**9**), (b) deutated **4**, and (c) their mixture in DCl–$D_2O$ (pD 1.2). In (c), marked upfield shifts were observed for the proton signals of the guest and for the tetramethylene proton signals of the host, due to the shielding effect of the aromatic ring(s). It should be noted that each proton signal of the host and the guest shifts to a different degree, indicating that the complex is formed in a particular geometry and not in a random fashion. This feature is very important, because this phenomenon can be expected only in complexes with hosts having well-defined structures, but not with mobile systems such as micelles.

Based on the assumption that the host takes the same conformation as that in the crystalline complex with durene described above, the possible geometry of the

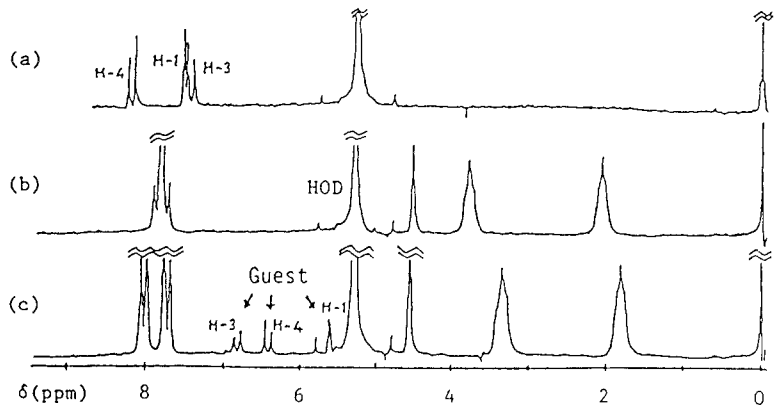
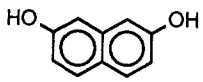



Fig. 1. $^1$H NMR spectra of (a) **9**, (b) **4**, and (c) **9** + **4** in DCl $D_2O$ (pD 1.2). [**9**] = $2.5 \times 10^{-2}$ M. [**4**] = $5.0 \times 10^{-2}$ M. TMS was used as an external reference.

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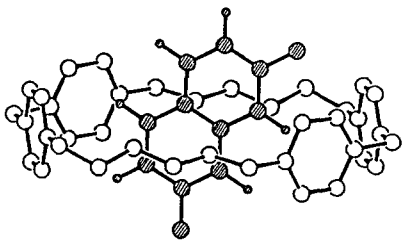


**10**

complex in solution was determined as shown in **10** by calculation employing the method of Johnson and Bovey [7]. Since the process of this calculation is now done by a computer, examinations on the possible as well as impossible structures of the complexes in solution based on NMR data can be visualized on the three dimensional computer graphic display [8]. This method may be useful for the design of hosts specific for guests having unique structures.

## 3. Chemical Modifications of CP44

Chemical modifications of **4** were made in several directions to examine the relationship between the cavity structures and complexation properties.

### 3.1. MODIFICATIONS OF THE BRIDGING CHAINS OF CP44

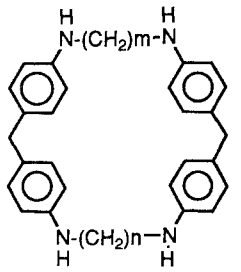
Cyclophanes (**11, 12**) having different bridging chains were synthesized to change the size and the hydrophobic area of **4**, and their complexation properties with various guests (**9, 13–21**) were examined [9].

Among these hosts, **11a** (CP33) and **11f** (CP35) did not show any evidence for complex formation with all the guests examined, probably because their cavities are too small to accommodate these guests. On the other hand, hosts (**4, 11b–e, 11g–i, 12**) formed complexes with neutral and anionic aromatic guests (**9, 13–18**), but not with aliphatic guests (**19, 20**). Complex formation with the cationic aromatic guest (**21**) was found to be negligible. Some results for hosts (**4, 11h, 12**) having cavities of different size and/or hydrophobic area are shown in Table I.

Table I. Stability constants ($K_s[M^{-1}]$) of 1:1 complexes.[a]

| Guest/host | **4**(CP44) | **11h**(CP56) | **12** |
|---|---|---|---|
| **9** | $2.8 \times 10^3$(11) | $2.6 \times 10^2$(1.0) | $4.3 \times 10^3$(17) |
| **13** | $6.3 \times 10^3$(0.15) | $4.3 \times 10^4$(1.0) | $5.0 \times 10^5$(12) |
| **14** | $2.0 \times 10^3$(2.3) | $8.7 \times 10^2$(1.0) | $1.4 \times 10^4$(16) |
| **15** | $1.5 \times 10^3$(0.39) | $3.8 \times 10^3$(1.0) | $5.3 \times 10^4$(14) |
| **16** | $1.9 \times 10^4$(6.4) | $2.9 \times 10^3$(1.0) | $3.0 \times 10^4$(10) |
| **17** | $4.4 \times 10^3$(0.041) | $1.1 \times 10^5$(1.0) | $1.4 \times 10^6$(13) |
| **18** | $1.8 \times 10^5$(5.5) | $3.3 \times 10^4$(1.0) | $3.2 \times 10^5$(9.6) |

[a] In KCl–HCl buffer (pH 1.95) at 25°C. The values in parentheses are the relative stabilities of the complexes of **4** and **12** compared with those of **11h**.

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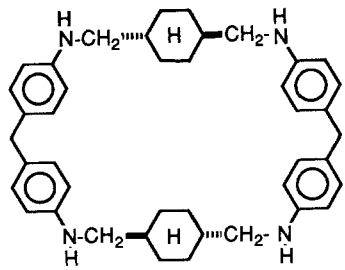
a: m=n=3 (CP33)
b: m=n=5 (CP55)
c: m=n=6 (CP66)
d: m=n=7 (CP77)
e: m=n=8 (CP88)
f: m=3, n=5 (CP35)
g: m=4, n=5 (CP45)
h: m=5, n=6 (CP56)
i: m=5, n=8 (CP58)

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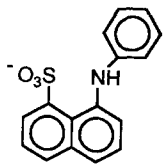


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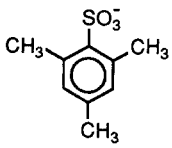


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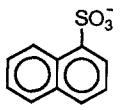


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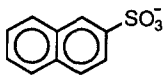


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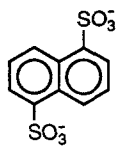


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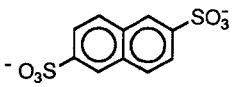


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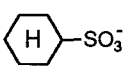


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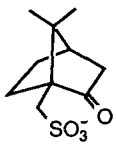


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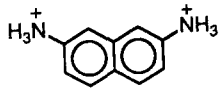


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It is shown that the increase in hydrophobic area of the cavity greatly enhances the stability of the complex. Thus, with all the guests examined, host **12** formed more stable complexes than **11h** by a factor of 10 to 17. It is also shown that the difference in cavity size also affects the stability of the complexes. For example, **4** having a smaller cavity prefers $\beta$-substituted naphthalenes (**16**, **18**) rather than $\alpha$-substituted naphthalenes (**15**, **17**), and the reverse is true for **11h** having a larger cavity.

It may be concluded that complementarity both in steric structures and electrostatic interactions between host and guest is important for strong complex formation in this type of cyclophanes.

### 3.2. CHIRAL MODIFICATIONS OF CP44

Optically active cyclophanes (**22**) having chiral centers at their bridging chains were synthesized starting from L-tartaric acid and their properties as hosts for chiral guests were examined [10]. As shown in Figure 2, $^1$H NMR spectral studies have

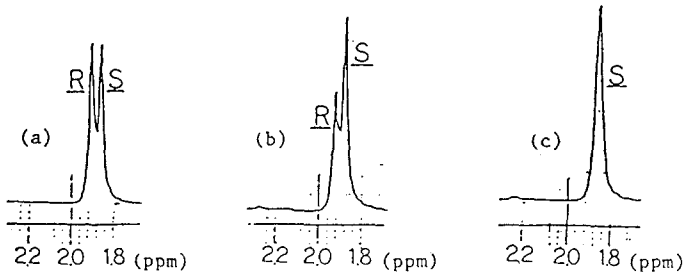
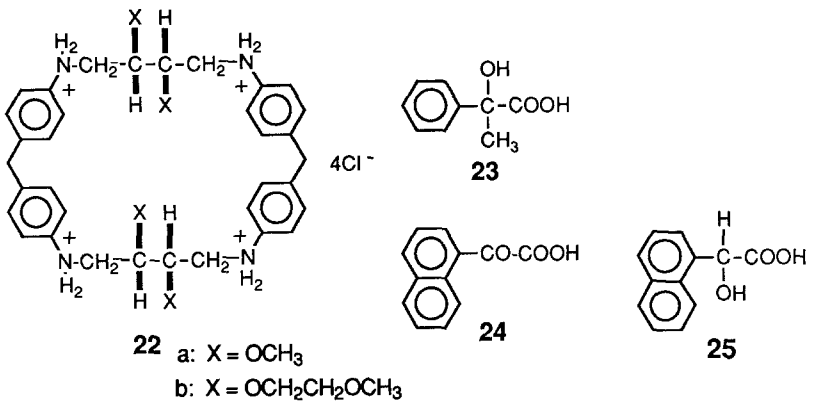



Fig. 2. $^1$H NMR spectra (C-methyl signals) of (a) racemic **23**, (b) partially resolved **23** ((*R*) : (*S*) = 3 : 5), and (c) (*S*)-**23** in DCl–$D_2O$ (pD 1.2) in the presence of **22a**. [**23**] = $2.5 \times 10^{-2}$ M. [**22a**] = $5.0 \times 10^{-2}$ M. TMS was used as an external reference.

shown that diastereomeric host–guest complexes are formed between **22a** and (*R*)- and (*S*)-atrolactic acid (**23**). It is also shown that the reduction of 1-naphthylglyoxylic acid (**24**) by complex formation with **22a** followed by treatment with sodium borohydride in acidic water afforded (*R*)-1-naphthylglycolic acid ((*R*)-**25**) in 9.7% ee.

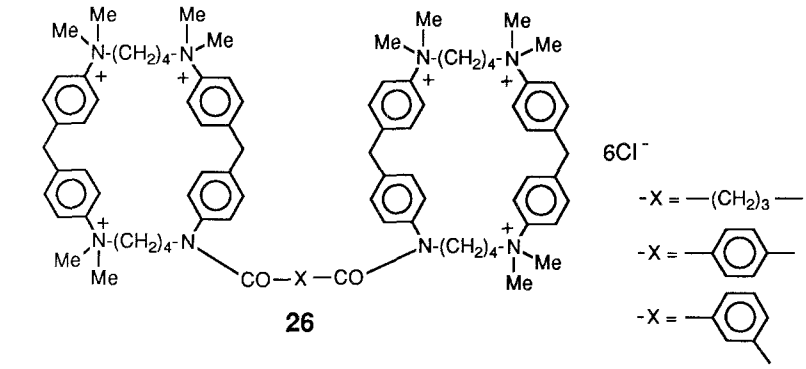



Although not very efficient at present, these results clearly show that chiral cyclophanes provide chiral cavities which can recognize and induce chirality in the bound guests.

### 3.3. BIS-CYCLOPHANES

Bis-cyclophanes (**26**) having two independent binding sites, capable of forming complexes at two sites, were synthesized by connecting two cyclophane units [11].

It is shown that these hosts form complexes with aromatic guests such as **27** at two sites simultaneously. In cases where molecules having two aromatic groups such as **28** are used as guests, examples of cooperative binding at two sites were found, when the distances between the two cavities of the host and the two aromatic groups of the guests are complementary. These hosts are of particular interest in relation to the methods for assembling and recognizing guests by multiple complexation.

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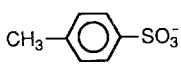


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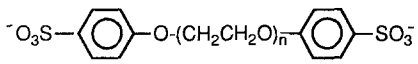
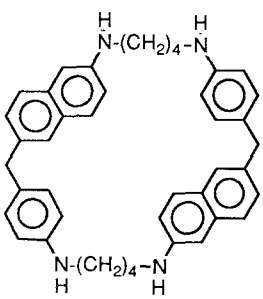



28 **a : n = 1**
**b : n = 5**

## 3.4. HOSTS FOR ALIPHATIC GUESTS

Cyclophanes such as **4** and **5**, composed of two diphenylmethane skeletons and two bridging chains are thus shown to work as hosts selectively for aromatic guests, but not for aliphatic guests.

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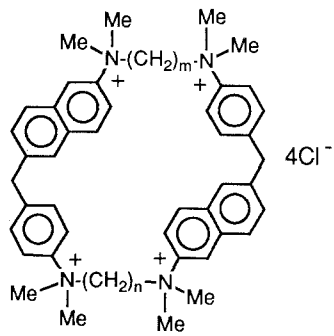


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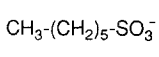


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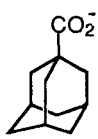


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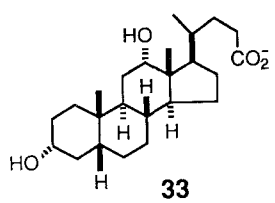


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To get hosts capable of binding aliphatic guests, novel cyclophanes (**29**, **30**) having naphthylphenylmethane skeletons instead of diphenylmethane skeletons were designed based on CPK model studies [12]. In their most expanded conformations, these hosts are expected to provide wider cavities of about 5.4 Å in their shorter width of their open ends.

Although these hosts do not show any evidence for complex formation with smaller aliphatic guests such as **19** and **31**, they form reasonably stable complexes ($K_s$ values of $10^2 \sim 10^4(M^{-1})$) with more bulky aliphatic guests such as **20**, **32**, and **33**. It is also shown that these hosts form complexes with aromatic guests.

## 4. Conclusion

Water-soluble cyclophanes made by connecting two diarylmethane skeletons and two bridging chains via four nitrogens are shown to provide cavities of definite shape and size and constitute a group of artificial hosts that form 1 : 1 inclusion complexes with various organic guests in water. For complexation to occur in particular geometries with remarkable selectivities, the importance of the fit in steric structure and charge between the host and the guest has been recognized.

Since these hosts are totally synthetic, design for selective and efficient artificial systems via host–guest complex formation is open as one of the most challenging and exciting fields in synthetic organic chemistry.

## References

1. K. Odashima and K. Koga: in 'Cyclophanes', Vol. 2, ed. by P. M. Keehn and S. M. Rosenfeld, Academic Press, New York, 1983, Chapter 11.
2. I. Tabushi and K. Yamamura: *Top. Curr. Chem.* **113**, 145 (1983).
3. Y. Murakami: *Top. Curr. Chem.* **115**, 107 (1983).
4. (a) D. J. Cram and M. F. Antar: *J. Am. Chem. Soc.* **80**, 3103 (1958); (b) I. Tabushi, H. Yamada, and Y. Kuroda: *J. Org. Chem.* **40**, 1946 (1975).
5. (a) K. Odashima, A. Itai, Y. Iitaka, and K. Koga: *J. Am. Chem. Soc.* **102**, 2504 (1980); (b) K. Odashima, A. Itai, Y. Iitaka, and K. Koga: *J. Org. Chem.* **50**, 4478 (1985).
6. (a) A. Miwa, K. Odashima, and K. Koga: unpublished data; (b) J. Winkler, E. Coutouli-Argyropoulou, R. Leppkers, and R. Breslow: *J. Am. Chem. Soc.* **105**, 7198 (1983).
7. K. Odashima, A. Itai, Y. Iitaka, Y. Arata, and K. Koga: *Tetrahedron Lett.* **21**, 4347 (1980).
8. A. Itai, M. Sakamoto, Y. Iitaka, K. Odashima, and K. Koga: unpublished data.
9. (a) T. Soga, K. Odashima, and K. Koga: *Tetrahedron Lett.* **21**, 4351 (1980); (b) K. Odashima, T. Soga, and K. Koga: *Ibid.* **22**, 5311 (1981).
10. (a) I. Takahashi, K. Odashima, and K. Koga: *Tetrahedron Lett.* **25**, 973 (1984); (b) I. Takahashi, K. Odashima, and K. Koga: *Chem. Pharm. Bull.* **33**, 3571 (1985).
11. C. F. Lai, K. Odashima, and K. Koga: *Tetrahedron Lett.* **26**, 5179 (1985).
12. (a) H. Kawakami, O. Yoshino, K. Odashima, and K. Koga: *Chem. Pharm. Bull.* **33**, 5610 (1985); (b) H. Kawakami, K. Odashima, and K. Koga: unpublished data.