

9-Fluoro-18-hydroxy-[3.3]metacyclophane: Synthesis and Estimation of a C–F⋯H–O Hydrogen Bond

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A cyclophane composed of fluorobenzene and phenol units was synthesized in order to observe the C–F⋯H–O hydrogen bond. In the crystal structure, 20% of the molecule clearly shows the intramolecular hydrogen bond and the other 80% is free from hydrogen bonding. On the other hand, a distinct low-field shift of the phenolic OH proton was observed in the ¹H NMR spectrum compared to that of the F-free analog.

Furthermore, O–H⋯F through-space coupling was observed. From the results of the crystallographic analysis, IR, and NMR spectra, the C–F⋯H–O hydrogen bond energy of this system was estimated to be 0.84–3.7 kJ·mol^{–1}.

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Introduction

The C–F⋯H–X (X = O, N) hydrogen bonds are a new type of hydrogen bond, which was first proposed by Glusker et al. in 1983.^[1] Following their work, research studies and discussions have been continued by many researchers who are still making efforts to confirm the hydrogen bonds using a variety of methods. This tendency indicates that CF⋯H–X hydrogen bonds are not widely distributed even in modern chemistry. Various methods are employed for the search, i.e., statistical methods utilizing a crystallographic database,^[2,3] crystallographic analyses, spectroscopic methods,^[4–9] and theoretical calculations.^[10–12] Howard et al. adopted fluoromethane and fluoroethene as C–F donors and concluded that the average F⋯H distance of the C(sp³)–F⋯H–O, C(sp²)–F⋯H–O hydrogen bond is 1.9 Å using ab initio calculations.^[13] They also found that examples of C–F⋯H–O and C–F⋯H–N hydrogen bonds are rare in the Cambridge Structural Database System (CCSDS) and showed that the F⋯H–X angles are dispersed (the statistically found C–F⋯H–O angles are not within the certainty

range). Therefore, they concluded that the interaction is weak. On the other hand, Caminati et al. observed the free jet millimeter wave spectra of the CH₂F₂⋯H₂O system, and concluded that the optimized distance *r*(F⋯H) = 2.20 Å and the angles ∠(F⋯H–O) and ∠(C–F⋯H) are 135 and 93°, respectively.^[14]

Our studies of the C–F⋯M⁺ interaction revealed that the C–F unit attracts all kinds of cations by a cation–dipole interaction as the main driving force.^[15] Therefore, we can deduce that C–F can be a proton acceptor because the interaction also operates in the polarized X^{δ–}–H^{δ+} (X = O, N) system.

Based on this speculation, we employed the cyclophane skeleton for investigating the C–F⋯H–O hydrogen bond. Phenol and fluorobenzene units in cyclophane **1** are fixed and close to each other (Figure 1). Its spectral features can be compared to those of the structurally analogous cyclophanes **2** and **3**. The C–F⋯H–O distance (ca. 1.9 Å) and C–F⋯H and F⋯H–O angles (ca. 99.5 and 156°) of **1** were estimated using simple molecular-model considerations. These values are close to those estimated by Howard et al. and Caminati et al. Therefore, cyclophane is thought to be an appropriate system for the observation of the C–F⋯H–O hydrogen bond. In this report, synthesis of the

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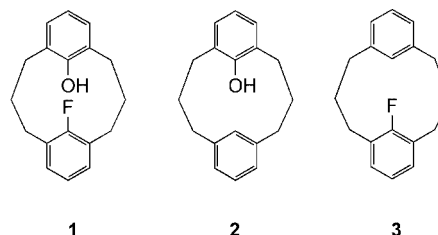
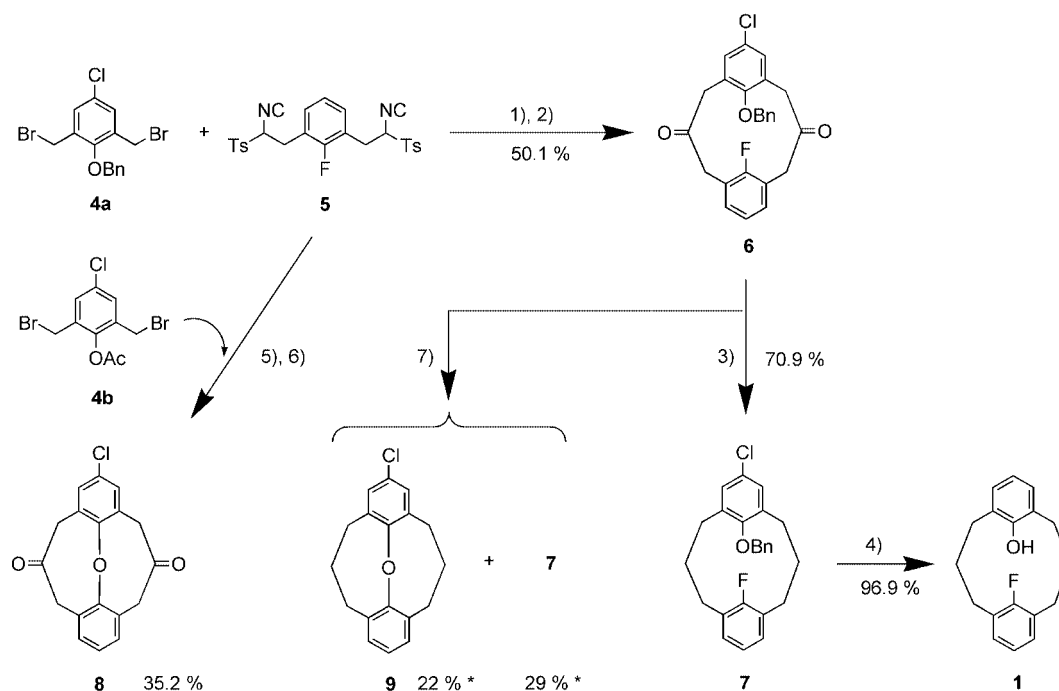


Figure 1. Structures of cyclophanes **1**–**3**



Scheme 1. Synthetic strategies of the cyclophane **1**: 1) Bu_4NI , $\text{CH}_2\text{Cl}_2/\text{aq. NaOH}$; 2) concd. HCl ; 3) Zn/HCl (g), diethyl ether; 4) 10% Pd/C , HCOONH_4 , MeOH ; 5) NaH , DMF ; 6) concd. HCl ; 7) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, KOH , diethylene glycol; * each yield was calculated based on the integration of signals in ^1H NMR spectrum

cyclophane, structural analysis and spectral features are discussed as one approach for investigating the $\text{C}-\text{F}\cdots\text{H}-\text{O}$ hydrogen bond.

Results and Discussion

Synthesis

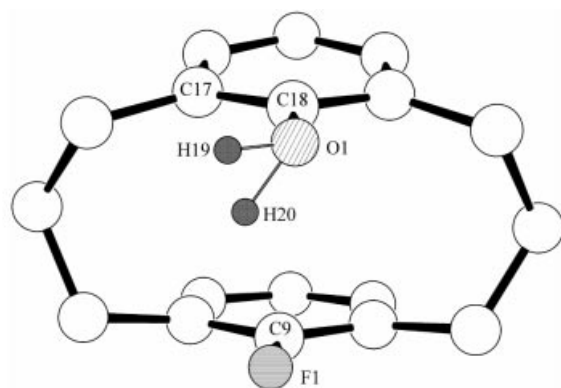
The [3.3]metacyclophane skeleton was constructed by the TosMIC method (Scheme 1).^[16] However, an unexpected ether product **8** was obtained by the initially chosen strategies employing a cyclization reaction between the acetyl-protected dibromide **4b** and TosMIC derivative **5** in DMF with NaH as the base at room temperature. This disadvantage was overcome by altering the protecting group from an acetyl to a benzyl group. The phase-transfer reaction between **4a** and **5** followed by treatment of the reaction mixture with aq. HCl afforded the diketone **6** in 50.1% yield. The Wolff–Kishner reduction of the cyclophane diketone **6** gave **7** and an ether product **9**, but the separation of each product from the mixture was difficult. Therefore, compound **6** was reduced by the modified Clemmensen reduction procedure,^[17] which gave **7** in 70.9% yield. Deprotection and dechlorination were simultaneously achieved by treating compound **7** with 10% Pd/C in the presence of ammonium formate. Cyclophane **1** was thus obtained in good yield from **7** (96.9%). The analogous reference compounds **2** and **3** were synthesized using the literature method reported by Osada et al.^[18]

Crystallographic Analysis

Crystallographic analysis of **1** at low temperature (123 K) revealed that two kinds of molecules exist in the crystal.

One of them has an $\text{O}-\text{H}$ proton almost parallel to the benzene ring, which was observed in 80% probability. An $\text{O}-\text{H}$ of another molecule is twisted and the proton is near the F atom. In Figure 2, these protons are shown in one molecule. The dihedral angles are $\angle \text{C}(17)-\text{C}(18)-\text{O}(1)-\text{H}(19) = 1.7^\circ$ and $\angle \text{C}(17)-\text{C}(18)-\text{O}(1)-\text{H}(20) = 51.3^\circ$. The $\text{F}\cdots\text{H}(20)$ distance is 2.11 Å, which is much shorter than the sum of the van der Waals radii (2.67 Å) of the H atom (1.20 Å) and F atom (1.47 Å).^[19] On the other hand, the $\text{F}\cdots\text{H}(19)$ distance is 2.90 Å and thus, $\text{H}(19)$ apparently has no interaction with the F atom. The observed angles, $\angle \text{C}(9)-\text{F}\cdots\text{H}(20) = 105.5^\circ$ and $\angle \text{O}-\text{H}(20)\cdots\text{F} = 131.6^\circ$, and the $\text{F}\cdots\text{H}(20)$ distance are fairly near the values reported by Howard et al. and Caminati et al. The former found the potential minimum of the $\text{C}(\text{sp}^2)-\text{F}\cdots\text{H}-\text{O}$ hydrogen bond at 1.9 Å and the latter observed the angles and distances of $\angle \text{C}-\text{F}\cdots\text{H}-\text{O} = 93^\circ$, $\angle \text{O}-\text{H}\cdots\text{F} = 135^\circ$ and $r = 2.20$ Å in the $\text{CH}_2\text{F}_2-\text{H}_2\text{O}$ system. Furthermore, the $\text{O}-\text{H}(20)$ distance is 0.99 Å, while $\text{O}-\text{H}(19)$ is 0.82 Å. The two facts, formerly described as the short $\text{F}\cdots\text{H}(20)$ distance and the elongated $\text{O}-\text{H}(20)$ bond, apparently indicate the existence of a hydrogen bond between $\text{H}(20)$ and the F atom. However, the proportion of the hydrogen-bonded H atom is only 20%, and it is thus a weak interaction. According to the Boltzmann distribution law, the energy difference between $\text{O}(19)-\text{H}$ and $\text{O}(20)-\text{H}$ is only 1.6 kJ mol^{-1} , which can roughly be considered as the stabilization energy of the $\text{C}-\text{F}\cdots\text{HO}$ hydrogen bond of this system at 123 K.

Spectroscopic Investigations

Figure 2. Molecular structure of the cyclophane **1**

IR Spectra

In the IR spectra (Table 1), the ν_{OH} bands of **1** and **2** appeared as a sharp band around 3620 cm^{-1} in methylcyclohexane and CCl_4 at the concentration of $1.0 \times 10^{-1}\text{ mol dm}^{-3}$. However, in diluted solution (10^{-2} , 10^{-3} and $10^{-4}\text{ mol dm}^{-3}$), no substantial changes were observed.

Table 1. IR spectra (ν_{OH} in cm^{-1}) of **1** and **2**: (A) crystal (transmittance IR), (B) KBr pellet, (C) in methylcyclohexane ($1.0 \times 10^{-4}\text{ mol dm}^{-3}$), and (D) in CCl_4 ($1.0 \times 10^{-4}\text{ mol dm}^{-3}$)

	1	2
(A)	3610, 3560	3541, 3471
(B)	3610, 3560	3542, 3473
(C)	3620	3618
(D)	3621	3621

As seen in the crystallographic analysis, 20% of the OH proton binds to the F atom of **1**. Therefore, the IR spectra of the crystalline state are essential to detect the hydrogen bond. In the crystal lattice, the OH group is independent and no intermolecular interaction was observed (see Supporting Information; footnote on the first page of this article). Therefore, the band in the transmittance spectra of **1** should show the bands of the hydrogen-bond-free O–H and the $\text{C–F}\cdots\text{H–O}$ band. The transmittance IR spectra of the crystals of **1** and **2** were almost identical to those measured in KBr pellets. Both cyclophanes **1** and **2** have two ν_{OH} bands. In the case of **1**, a relatively broad band appears at 3560 cm^{-1} accompanied by a sharp band at 3610 cm^{-1} . Similarly, compound **2** has a relatively broad band at 3471 cm^{-1} and a sharp band at 3541 cm^{-1} . Unfortunately, crystallographic analysis of compound **2** failed, so the molecular arrangement and information about the hydrogen-bond pattern in the crystal are unknown.^[20] Further discussion seems to be difficult because assignment of those ν_{OH} bands cannot be achieved. However, we can speculate that the $\text{C–F}\cdots\text{H–O}$ hydrogen bond may have anti-hydrogen-bond character because both bands of **1** are blue-shifted ($70\text{--}90\text{ cm}^{-1}$) compared to those of **2**.^[21] The $\Delta\nu_{\text{OH}}$

is equivalent to the $\text{C–F}\cdots\text{H–O}$ hydrogen bond energy of $0.84\text{--}1.1\text{ kJ}\cdot\text{mol}^{-1}$.

NMR Spectra

Because the IR spectra in solution did not give any information, the ^1H and ^{19}F NMR spectra were evaluated. These results are summarized in Table 2. The chemical shifts of the phenolic OH protons of **1** and **2** in CDCl_3 at the concentrations of 1.0×10^{-1} , 1.0×10^{-2} and $1.0 \times 10^{-3}\text{ mol}\cdot\text{dm}^{-3}$ were the same within the experimental errors [$\delta_{\text{OH}}(\mathbf{1}) = 4.87\text{ ppm}$; $\delta_{\text{OH}}(\mathbf{2}) = 4.61\text{ ppm}$]. On the other hand, the OH proton of **1** in $[\text{D}_{14}]\text{methylcyclohexane}$ showed concentration-dependent chemical shifts, i.e., the OH proton signal appeared at $\delta = 4.75\text{ ppm}$ ($1.0 \times 10^{-1}\text{ mol}\cdot\text{dm}^{-3}$), 4.62 ppm ($1.0 \times 10^{-2}\text{ mol}\cdot\text{dm}^{-3}$), and 4.60 ppm ($1.0 \times 10^{-3}\text{ mol}\cdot\text{dm}^{-3}$). In the case of cyclophane **2**, such chemical shifts were not observed at a concentration of 1.0×10^{-1} to $1.0 \times 10^{-3}\text{ mol}\cdot\text{dm}^{-3}$; it appears at $\delta = 4.20\text{ ppm}$ as a singlet. Although an interaction with CDCl_3 is apparent, the OH signal of **1** appears at a lower field than that of **2**, and this is the same in the noninteracting solvent, $[\text{D}_{14}]\text{methylcyclohexane}$. Therefore, the $\text{C–F}\cdots\text{H–O}$ hydrogen bond is obvious in the ^1H NMR spectra. Moreover, specific phenomena were seen in the spectrum of **1**, viz., the OH signal appeared as a doublet ($J_{\text{H,F}} = 6.0\text{ Hz}$) which shows the through-space coupling with the fluorine atom. By irradiation of the F atom, the coupling disappeared and the doublet became a singlet. Furthermore, in a donating solvent such as $[\text{D}_6]\text{DMSO}$, the signal appeared as a singlet. This is further evidence of an $\text{O–H}\cdots\text{F}$ interaction.

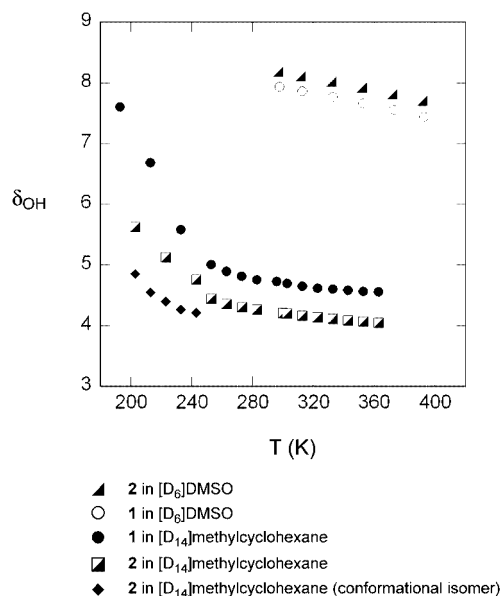
The δ_{F} values of cyclophanes **1** and **3** were compared in their ^{19}F NMR spectra (Table 2). The differences were small, but in both CDCl_3 and $[\text{D}_{14}]\text{methylcyclohexane}$, chemical shifts of the F signal of cyclophane **1** are higher than those of **3** ($1.0\text{--}1.6\text{ ppm}$). This high-field shift of the F signal reminds us of similar phenomena in the metal complexes of fluorinated cage compounds.^[22] The $\text{C–F}\cdots\text{M}^+$ attractive interaction has now been unambiguously established by this group and Plenio et al.,^[23,24] and the high-field shift of the F signal usually occurs during the $\text{C–F}\cdots\text{M}^+$ interaction. Therefore, in the $\text{C–F}\cdots\text{H}^{\delta+}\cdots\text{O}^{\delta-}$ system, the same phenomena should also be observed. Here, again, the hydrogen bond is confirmed by comparison of the ^{19}F NMR spectra of cyclophanes **1** and **3**.

The temperature-dependent shift of the OH proton is another interesting feature in the study of the hydrogen bond. Variable-temperature ^1H NMR spectra of **1** and **2** were measured in nonpolar and polar solvents, $[\text{D}_{14}]\text{methylcyclohexane}$ and $[\text{D}_6]\text{DMSO}$. As shown in Figure 3, the OH proton spectra of **1** and **2** are strongly temperature-dependent, especially below 240 K . In the case of **2**, two kinds of OH proton signals appeared below 243 K . At this temperature, conformational changes of the trimethylene bridge (boat $\rightleftharpoons$ chair) are involved.^[25] Therefore, the two OH protons correspond to those of the conformational isomers. In the case of cyclophane **1**, conformational changes also occur below 243 K . However, only one kind of OH proton

Table 2. NMR shifts of OH and F signals ($1.0 \times 10^{-2} \text{ mol} \cdot \text{dm}^{-3}$) of the cyclophanes at 25 °C (A) in $[\text{D}_{14}]$ methylcyclohexane, and (B) in CDCl_3

	(A)	^1H , $\delta(\text{OH})$ (B)	(A)	^{19}F , $\delta(^{19}\text{F})$ (B)
1	4.60 [d, $J(\text{H}-\text{F}) = 6.6 \text{ Hz}$]	4.86 [d, $J(\text{H}-\text{F}) = 6.0 \text{ Hz}$]	-120.3 (br. s)	-119.9 (br. s)
2	4.21 (s)	4.58 (br. s)	—	—
3	—	—	-118.7 (s)	-118.9 [d, $J(\text{H}-\text{F}) = 3.5 \text{ Hz}$]

was observed. In the polar solvent ($[\text{D}_6]$ DMSO), the OH signal of **1** is shifted to a high-field region compared to that of **2** ($\Delta\delta = -0.25 \text{ ppm}$ at 298 K). This phenomenon reflects that the hydrogen bond between **1** and DMSO is inhibited by the intramolecular hydrogen bond.

Figure 3. Plots of δ_{OH} in $[\text{D}_6]$ DMSO and $[\text{D}_{14}]$ methylcyclohexane at various temperatures

The difference of chemical shift of the OH proton, $\Delta\delta$, between **1** and **2** is almost constant ($\Delta\delta \approx 0.5 \text{ ppm}$ in $[\text{D}_{14}]$ methylcyclohexane) between 273 and 363 K, and the $\Delta\delta$ value indicates the C-F $\cdots$ H-O binding energy. Schaefer represented the relationship between hydrogen-bond energy and chemical shift of *ortho*-substituted phenols.^[26] The empirical equation $\Delta\delta_{\text{OH}} = -0.4 + E$ (E is the hydrogen-bond energy in $\text{kcal} \cdot \text{mol}^{-1}$) can be applied to our cyclophane system. According to the equation, the C-F $\cdots$ H-O hydrogen bond of **1** is estimated to be $0.89 \text{ kcal} \cdot \text{mol}^{-1}$ ($3.7 \text{ kJ} \cdot \text{mol}^{-1}$) in $[\text{D}_{14}]$ methylcyclohexane and $0.65 \text{ kcal} \cdot \text{mol}^{-1}$ ($2.7 \text{ kJ} \cdot \text{mol}^{-1}$) in $[\text{D}_6]$ DMSO at 298 K.

From the results of the crystallographic analysis, IR spectra and NMR spectra, we estimated the C-F $\cdots$ H-O hydrogen bond energy of **1** to be $0.84\text{--}1.6 \text{ kJ} \cdot \text{mol}^{-1}$ in the solid state and $2.7\text{--}3.7 \text{ kJ} \cdot \text{mol}^{-1}$ in solution.

Conclusion

A [3.3]metacyclophane, which is composed of a phenol unit and a fluorobenzene unit, was synthesized. It is a simple model for the investigation of the C-F $\cdots$ H-O hydrogen bond. The cyclophane skeleton is suitable for realizing the ideal F $\cdots$ H-O distance and angles, and to obtain the entropy. Actually, evidence for the C-F $\cdots$ H-O hydrogen bond is observed from the results of the crystallographic analysis. Two kinds of OH hydrogen atoms are observed and one of them is pointing towards the fluorine atom. The H $\cdots$ F distance is shorter than the sum of the van der Waals radii of the H and F atoms, and the O-H bond is longer than that of another proton which is separated from the F atom. In the ^1H NMR spectrum, the OH proton signal of **1** appears at a lower field than that of the fluorine-free analog **2**. Furthermore, through-space coupling between the F atom and OH proton is observed. Although the IR spectra did not give a clear result, it is speculated that the C-F $\cdots$ H-O hydrogen bond has an anti-hydrogen-bond character. The C-F $\cdots$ H-O hydrogen bond energy in this system was estimated to be $0.84\text{--}3.7 \text{ kJ} \cdot \text{mol}^{-1}$ according to the results of the crystallographic analysis and the IR and NMR spectra. Although the C-F $\cdots$ H-O hydrogen bond is very rare in the crystallographic database, it is possible to observe it by this simple molecular design. A forcibly approached OH and CF unit with the appropriate distance and angle clarified this weak interaction.

Experimental Section

General Procedure: Melting points (uncorrected): Yanaco MP-500D apparatus in Ar sealed tubes. NMR: Bruker DPX-400 (400.1 MHz for ^1H , 100.6 MHz for ^{13}C , and 376.5 MHz for ^{19}F with TMS and CFCl_3 as internal references, respectively) and JEOL GSX 270 (270 MHz for ^1H and 67.9 MHz for ^{13}C). IR: JASCO IR-700 [methylcyclohexane in NaCl cells (0.1 and 0.5 mm) at 25 °C]. FAB and EI MS: JEOL JMS-SX/SX102A. Elemental analysis: the Service Centre of the Elementary Analysis of Organic Compounds affiliated with the Faculty of Science, Kyushu University.

Crystallographic Data of 1: $\text{C}_{18}\text{H}_{19}\text{OF}$, $M_r = 270.35 \text{ g} \cdot \text{mol}^{-1}$, platelet crystal (grown from *n*-hexane), size $0.40 \times 0.20 \times 0.05 \text{ mm}$, monoclinic, space group $P2_1$ (no. 4), $a = 8.719(1) \text{ \AA}$, $b = 8.552(1) \text{ \AA}$, $c = 9.599(1) \text{ \AA}$, $V = 695.3(2) \text{ \AA}^3$, $Z = 2$, $\rho_{\text{calcd.}} = 1.291 \text{ g} \cdot \text{cm}^{-3}$, $\mu(\text{Cu-K}\alpha) = 7.01 \text{ cm}^{-1}$, $F(000) = 288.00$, $T = -150 \pm 1 \text{ }^\circ\text{C}$ using the ω -2 θ scan technique to a maximum 2θ value of 136.4° . A total

of 4177 reflections were collected. The final cycle of the full-matrix least-squares refinement was based on 1990 observed reflections [$I > 2\sigma(I)$] and 182 variable parameters and converged with unweighted and weighted agreement factors of $R = 0.067$, $R_w = 0.202$, and $GOF = 1.09$. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.22 and $-0.25 \text{ e}^- \cdot \text{\AA}^{-3}$, respectively. The ratio of two kinds of molecules in the crystal was calculated and the probability of 0.8:0.2 afforded the optimal result. CCDC-213846 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-0333; E-mail: deposit@ccdc.cam.ac.uk].

1-Benzylloxy-4-chloro-2,6-bis(hydroxymethyl)benzene: The compound was prepared by the reaction between 4-chloro-2,6-bis(hydroxymethyl)phenol and benzyl bromide with K_2CO_3 as a base in acetone (86.4%). Recrystallization from toluene/methanol gave a colorless powder; m.p. 125.2–126.9 °C. ^1H NMR ($[\text{D}_6]\text{DMSO}$): $\delta = 7.46\text{--}7.35$ (m, 5 H, ArH), 7.33 (s, 2 H, ArH), 5.27 (t, $^3J_{\text{H,H}} = 5.5 \text{ Hz}$, 2 H, OH), 4.83 (s, 2 H, CH_2), 4.52 (d, $^3J_{\text{H,H}} = 6.0 \text{ Hz}$, 4 H, CH_2) ppm. FAB-MS: $m/z = 278.1$, 280.1. $\text{C}_{15}\text{H}_{15}\text{ClO}_3$ (278.73): calcd. C 64.64, H 5.42; found C 64.72; H 5.46.

1-Benzylloxy-2,6-bis(bromomethyl)-4-chlorobenzene (4a): The compound was prepared by treatment of 1-benzylloxy-4-chloro-2,6-bis(hydroxymethyl)benzene with PBr_3 in diethyl ether (yield 86.8%). The resultant powder was recrystallized from *n*-hexane. Colorless solid, m.p. 97.3–98.5 °C. ^1H NMR (CDCl_3): $\delta = 7.53\text{--}7.39$ (m, 5 H, ArH), 7.38 (s, 2 H, ArH), 5.16 (s, 2 H, CH_2), 4.46 (s, 4 H, CH_2) ppm. FAB-MS: $m/z = 402.9$, 403.9, 404.9 [$\text{M} + \text{H}^+$]. $\text{C}_{15}\text{H}_{13}\text{Br}_2\text{ClO} \cdot 1/12\text{C}_6\text{H}_{14}$ (411.71): calcd. C 45.22, H 3.47; found C 45.08; H 3.30.

1-Fluoro-2,6-bis[2-isocyano-2-(4-tolylsulfonyl)ethyl]benzene (5): The compound was synthesized by reaction between 2,6-bis(bromomethyl)-1-fluorobenzene and TosMIC (yield 62.8%) according to the literature method.^[16] Recrystallization from CH_2Cl_2 /diethyl ether gave colorless fine crystals, m.p. 112 °C (dec.). ^1H NMR (CDCl_3): $\delta = 7.91$, 7.45 (AB q, $^3J_{\text{H,H}} = 8.4 \text{ Hz}$, 8 H, ArH), 7.28–7.13 (m, 3 H, ArH), 4.68 (dd, $^3J_{\text{H,H}} = 10.8 \text{ Hz}$, 2 H, CH), 3.73–3.04 (m, 4 H, CH_2), 2.50 (s, 6 H, CH_3) ppm. FAB-MS: no molecular peak was found. $\text{C}_{26}\text{H}_{23}\text{FN}_2\text{S}_2\text{O}_4$ (510.60): calcd. C 61.16, H 4.54, N 5.49; found C 60.88, H 4.63; N 5.52.

9-Benzylloxy-6-chloro-18-fluoro[3.3]metacyclophane-2,11-dione (6): A mixture of CH_2Cl_2 (1.3 L), 40% aq. NaOH (50 mL), and $n\text{Bu}_4\text{NI}$ (1.69 g, 4.58 mmol) was heated under reflux with vigorous stirring. To this mixture, a solution of **4a** (4.05 g, 10.0 mmol) and **5** (5.62 g, 11.0 mmol) in CH_2Cl_2 (250 mL) was added dropwise over a period of 6 h. Additional heating and stirring were continued for 5 h. After cooling, the organic phase was separated and washed with brine. The solution was concentrated to ca. 300 mL, conc. HCl (30 mL) was added and the mixture was stirred at room temperature for 40 min. The organic phase was separated, washed with water and dried with MgSO_4 . The solvent was removed under reduced pressure and a small amount of acetone was added. After several hours, the precipitated colorless prisms were collected (yield 2.12 g, 50.1%), m.p. 138.4–138.8 °C. ^1H NMR (CDCl_3): $\delta = 7.53\text{--}7.32$ (m, 3 H, ArH), 7.24 (s, 2 H, ArH), 7.12 (dd, $^3J_{\text{H,H}} = 7.0 \text{ Hz}$, 2 H, ArH), 7.05–7.03 (m, 2 H, ArH), 6.84 (t, $^3J_{\text{H,H}} = 7.5 \text{ Hz}$, 1 H, ArH), 4.32 (s, 2 H, CH_2), 3.80–3.15 (m, 8 H, CH_2) ppm. FAB-MS: $m/z = 423$ [$\text{M} + \text{H}^+$]. $\text{C}_{25}\text{H}_{20}\text{ClFO}_3$ (422.88): calcd. C 71.01, H 4.77; found C 71.03; H 4.78.

9-Benzylloxy-6-chloro-18-fluoro[3.3]metacyclophane (7): Dry HCl gas was bubbled into dry ether (80 mL) at -10 °C for 1 h, and compound **6** (1.48 g, 3.5 mmol) was added. The resultant suspension was cooled to -20 °C and activated Zn powder (2.0 g) was added in small portions. After the addition, the temperature was raised to -5 °C and the mixture stirred for 2 h. The resultant mixture was poured onto crushed ice (40 g) and the organic phase was separated. The aqueous phase was extracted twice with ether, and all the diethyl ether solutions were combined. They were washed with aq. NaHCO_3 and dried with MgSO_4 , the solvent was removed and the resultant powder was recrystallized from *n*-hexane. Colorless prisms (yield 980 mg, 70.9%), m.p. 102.1–102.6 °C. ^1H NMR (CDCl_3): $\delta = 7.53\text{--}7.31$ (m, 5 H, ArH), 6.73 (m, 1 H, ArH), 6.63 (dd, $^3J_{\text{H,H}} = 7.0 \text{ Hz}$, 2 H, ArH), 6.52 (s, 2 H, ArH), 4.65 (s, 2 H, CH_2), 3.10–3.02 (m, 4 H, CH_2), 2.52–2.33 (m, 6 H, CH_2), 1.85–1.75 (m, 2 H, CH_2) ppm. FAB-MS: $m/z = 394$ [M^+]. $\text{C}_{25}\text{H}_{24}\text{ClFO}$ (394.91): calcd. C 76.03, H 6.13; found C 75.99, H 6.10.

18-Fluoro-9-hydroxy[3.3]metacyclophane (1): A mixture of the cyclophane **7** (197 mg, 0.50 mmol) and ammonium formate (221 mg, 3.5 mmol) in MeOH (60 mL) was stirred at room temperature under N_2 ; 10% Pd/C (100 mg) was added to the mixture, which was then stirred at room temperature for 5 h. The mixture was filtered through Celite and the solvent was removed. The resultant mixture was extracted with diethyl ether and the solution was washed with brine and dried with MgSO_4 . After removal of the solvent, compound **1a** was obtained as a white powder, which was recrystallized from *n*-hexane. Colorless prisms (yield 131 mg, 96.9%), m.p. 84.5–84.8 °C. ^1H NMR (CDCl_3): $\delta = 6.63\text{--}6.53$ (m, 5 H, ArH), 6.39 (t, $^3J_{\text{H,H}} = 7.0 \text{ Hz}$, 1 H, ArH), 4.87 (d, $^3J_{\text{H,H}} = 6.0 \text{ Hz}$, 1 H, CH_2), 3.09–2.99 (m, 4 H, CH_2), 2.65–2.54 (m, 4 H, CH_2), 2.42–2.35 (m, 2 H, CH_2), 1.92–1.81 (m, 2 H, CH_2) ppm. FAB-MS: $m/z = 270$ [M^+]. $\text{C}_{18}\text{H}_{19}\text{FO}$ (270.34): calcd. C 79.97, H 7.08; found C 79.91, H 7.08.

1-Acetoxy-2,6-bis(bromomethyl)-4-chlorobenzene (4b): A mixture of 2,6-bis(bromomethyl)-4-chlorophenol (6.29 g, 20 mmol), acetic anhydride (2.4 mL, 25 mmol), and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.1 mL, 0.8 mmol) in dry diethyl ether (20 mL) was stirred at room temperature for 10 h. The mixture was added to water (20 mL) and the resultant white powder was collected by filtration and washed with water to give the pure compound (yield 6.10 g, 85.6%). Recrystallization from *n*-hexane gave colorless needles, m.p. 143.3–144.2 °C. ^1H NMR (CDCl_3): $\delta = 7.39$ (s, 2 H, ArH), 4.31 (s, 4 H, CH_2), 2.15 (s, 3 H, CH_3) ppm. FAB-MS: $m/z = 354.9$, 356.9, 358.9 [$\text{M} + \text{H}^+$]. $\text{C}_{10}\text{H}_9\text{Br}_2\text{ClO}_2$ (356.44): calcd. C 33.70, H 2.55; found C 33.80, H 2.50.

Compound 8: A solution of **4b** (3.56 g, 10 mmol) and **5** (5.11 g, 10 mmol) in dry DMF (500 mL) was added to a stirred mixture of NaH (60% in mineral oil, 1.20 g, 30 mmol) and dry DMF (700 mL) at room temperature over a period of 10 h. Additional stirring was continued for 10 h and then the mixture was quenched with MeOH. The solvent was removed under reduced pressure and MeOH was added. After several hours, pale-yellow crystals precipitated. The crystals were collected by filtration and dissolved in CH_2Cl_2 (300 mL). Concentrated HCl (20 mL) was added to the solution, which was stirred at room temperature for 30 min. The organic phase was separated, washed with water and dried with MgSO_4 . The solvent was removed and a small amount of acetone was added to the residue. Colorless prisms that precipitated after several hours were collected (yield 1.10 g, 35.2%), m.p. 259.7–260.1 °C. ^1H NMR (CDCl_3): $\delta = 7.17\text{--}7.13$ (m, 5 H, ArH), 3.72–3.56

(m, 8 H, CH₂) ppm. FAB-MS: m/z = 313 [M + H⁺]. C₁₈H₁₃ClO₃ (312.75): calcd. C 69.13, H 4.19; found C 69.15, H 4.20.

Compound 9: A mixture of **8** (665 mg, 2.13 mmol), 80% hydrazine hydrate (3.4 mL, 53 mmol), diethylene glycol (30 mL), and KOH (1.57 g, 23.8 mmol) was heated at 120 °C for 2 h, and then the temperature was raised to 180 °C. The water generated during the reaction was removed by a Dean–Stark condenser. Additional heating was continued for 2 h, then the mixture was cooled, poured into water and extracted twice with CH₂Cl₂. The organic phase was washed with water and brine, then dried with MgSO₄. The solvent was removed and the residue was recrystallized from MeOH. Colorless needles (421 mg, 69.4%). M.p. 112.3–112.7 °C. ¹H NMR (CDCl₃): δ = 6.97–6.89 (m, 5 H, ArH), 3.21–3.13 (m, 2 H, CH₂), 2.81–2.70 (m, 2 H, CH₂), 2.39–2.32 (m, 1 H, CH₂), 1.76–1.55 (m, 1 H, CH₂) ppm. FAB-MS: m/z = 284 [M⁺]. C₁₈H₁₇ClO (284.78): calcd. C 75.92, H 6.02; found C 75.84, H 6.05.

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