SYNTHESIS AND NMR STUDY OF [4,5,6,8-$^2H_4$][2.2]METACYCLOPHANE

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SUMMARY

The synthesis of [4,5,6,8-$^2H_4$][2.2]metacyclophane (**8**) was achieved starting with 2,4,5,6-tetrafluoroisophthalic acid in eight steps in 2% total yield. $^1H\{^2H\}$ and $^{13}C\{^1H\}$ NMR spectra of **8** showed that the deuterium atoms were introduced at the desired positions.

Key Words: Synthesis, Deuterium Labelling, Ni-Al Alloy, NaOD-D_2O,
[4,5,6,8-$^2H_4$][2.2]Metacyclophane, $^1H\{^2H\}$ and $^{13}C\{^1H\}$ NMR

Introduction

[2.2]Metacyclophane ([2.2]MCP) has been attracting much attention e.g. for conformational analysis and its reactivity to the reagents.[1] To the best of our knowledge, the synthesis of deuteriated [2.2]MCPs in high isotopic purity, except [8,16-$^2H_2$]MCP by Sato,[2] and their detailed NMR assignment and isotope effects have not been investigated. In the course of our study on the syntheses of deuteriated aromatic compounds, pentafluorobenzoic acid was reduced with Ni-Al alloy in 10% NaOD-D_2O at 100 °C in a period of 2 h to give [2,3,4,5,6-$^2H_5$]benzoic acid in high isotopic purity (91%) and high yield (81%).[3] Based on this finding, we envisaged that 2,4,5,6-tetrafluoroisophthalic acid (**1**) could be reductively dehalo-genated under the same

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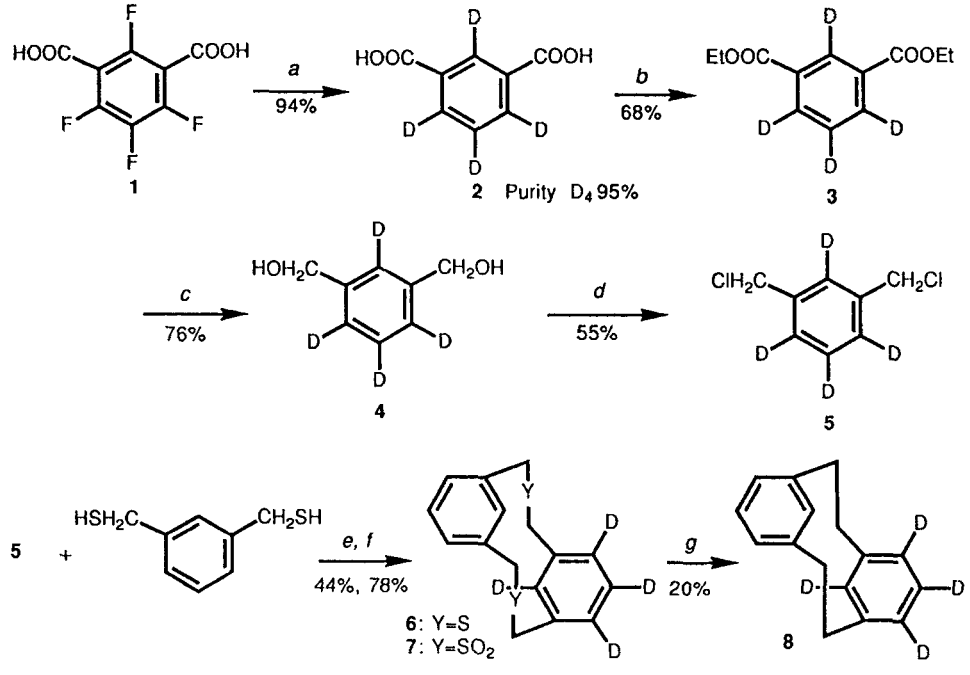
conditions, affording [2,4,5,6-$^2H_4$]-isophthalic acid (**2**), which is regarded as the key compound for the preparation to [4,5,6,8-$^2H_4$][2.2]MCP (**8**).

We report here on the synthesis of the title compound in high isotopic purity and its $^1H\{^2H\}$ and $^{13}C\{^1H\}$ NMR assignment, including simulation calculation of $^1H\{^2H\}$ NMR spectra.

RESULTS AND DISCUSSION

Preparation of [4,5,6,8-$^2H_4$][2.2]metacyclophane.

The synthetic route to [4,5,6,8-$^2H_4$][2.2]MCP (**8**) starting with 2,4,5,6-tetrafluoro-isophthalic acid (**1**) is outlined in Scheme 1.



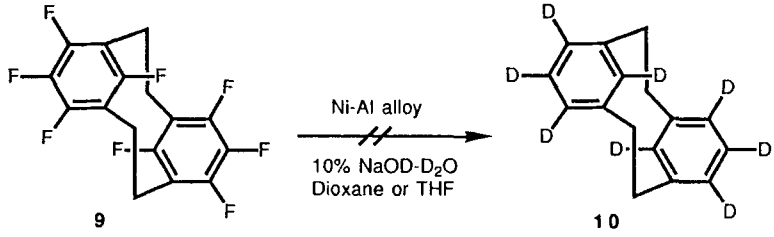
[a]Reagents and Conditions; (a) Ni-Al alloy, 10% NaOD-D_2O, 100 °C, 4 h, (b) EtOH, toluene, conc. H_2SO_4, reflux, (c) $LiAlH_4$, THF, reflux, (d) $SOCl_2$, Pyridine, Benzene, reflux, (e) KOH, EtOH, $NaBH_4$, (f) 30% H_2O_2, AcOH, (g) 500 °C, 0.75 Torr.

Scheme 1[a]

The reductive hydrodehalogenation of **1** with Ni-Al alloy in 10% NaOD-D_2O provided [2,4,5,6-$^2H_4$]isophthalic acid (**2**) in 94% yield and in 95% isotopic purity. After the [$^2H_4$] acid **2** was converted to the diethyl ester (**3**), the $LiAlH_4$-reduction of **3** afforded the corresponding bis(hydroxymethyl)benzene (**4**). The treatment of **4** with $SOCl_2$ in pyridine led to the formation of the bis(chloromethyl)benzene (**5**) in 55% yield. Cyclisation of **5** with 1,3-bis(mercaptomethyl)benzene under high-dilution conditions with ethanolic KOH in the presence of $NaBH_4$ provided the dithia[2.2]MCP (**6**) in 44% yield. Compound **6** was converted to the disulphone (**7**) upon treatment with a mixture

of 30% aqueous H_2O_2 and AcOH. The pyrolysis of **7** at 500 °C under reduced pressure (0.75 Torr) afforded the desired [4,5,6,8-$^2H_4$][2.2]MCP (**8**) in 2% total yield from **1**. The mass and ^1H NMR spectra indicated that the isotopic purity of **8** are almost coincident with that of the [$^2H_4$] acid (**2**). This shows that deuterium was neither lost nor scrambled during the above reactions.

Treating octafluoro[2.2]MCP (**9**) with Ni-Al alloy in a mixture of NaOD-D_2O and THF or dioxane in an attempted one-step synthesis of [4,5,6,8,12,13,14,16-$^2H_8$]-[2.2]MCP (**10**)[4] failed, and unchanged **9** was recovered in an almost quantitative yield (Scheme 2).



9 **10**

Scheme 2

$^1H\{^2H\}$ and $^{13}C\{^1H\}$ NMR spectra of [4,5,6,8-$^2H_4$][2.2]metacyclophane

The observed $^1H\{^2H\}$ and $^1H\{^2H\}\{16\text{-}H\}$ NMR spectra of **8** at aromatic region, which consist of AB_2M and AB_2 spin systems, respectively, are in good agreement with

Table 1 ^1H and ^{13}C chemical shifts of **8** in $CDCl_3$.

Position	δ_H[a]	δ_C[b]
1,10	2.06, 3.05	40.91
2,9	2.06, 3.06	40.81
3,7	–	138.67
4,6	–	124.96 ($^1J_{C\text{-}D}$ = 23.5 Hz)
5	–	128.29 ($^1J_{C\text{-}D}$ = 24.0 Hz)
8	–	136.14 ($^1J_{C\text{-}D}$ = 24.5 Hz)
11,15	–	138.87
12,14	7.06	125.38
13	7.27	128.79
16	4.23	136.48

a) Measured at 90 MHz. b) Measured at 125.77 MHz.

Table 2 ^1H-^1H coupling constants of **8** in $CDCl_3$.

^1H Position	12-13	13-16	12-14	12-16
J_{HH}(Hz)	7.00	0.17	1.10	1.60

simulated patterns to each other as shown in Figure 1. The ^1H chemical shifts and ^1H-^1H spin coupling constants are summarized in Tables 1 and 2.

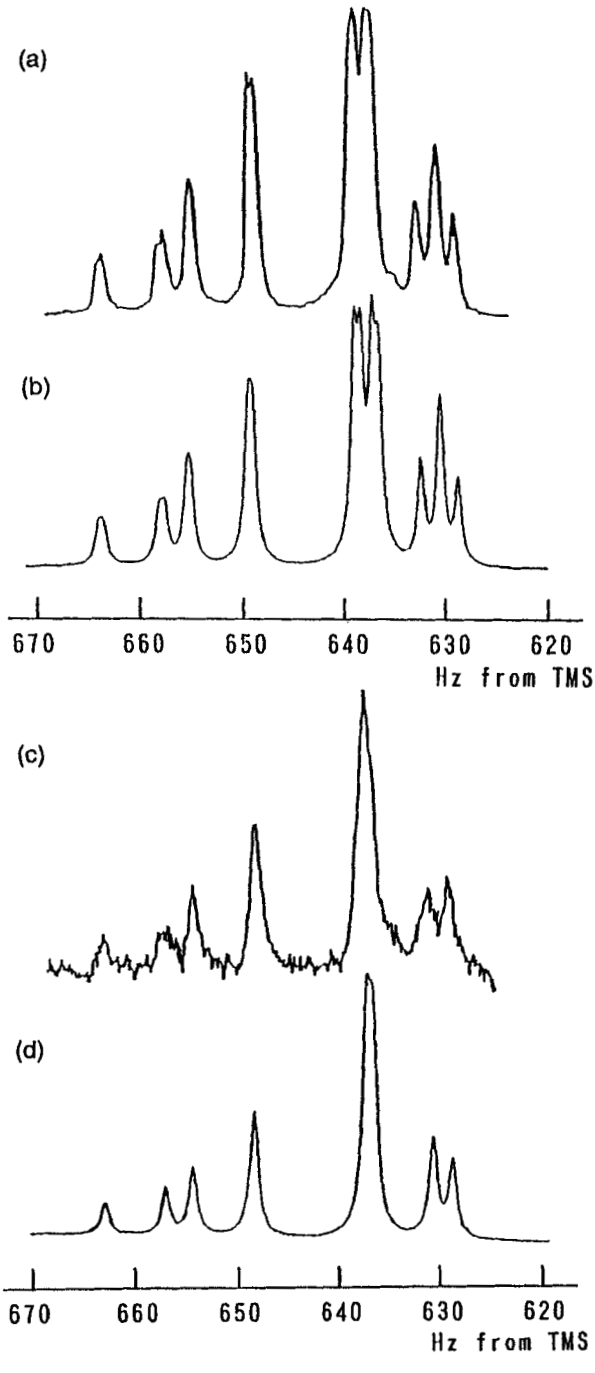


Fig. 1 Aromatic regions in 90 MHz ^{1}H NMR spectra of **8**; (a) observed {^{2}H}, (b) calculated {^{2}H}, (c) observed {^{2}H}{16-H}, (d) calculated {^{2}H}{16-H}.

The $^{13}C\{^1H\}$ NMR spectrum of **8** is shown in Figure 2. $^{13}C\{^1H\}$ chemical shifts and ^{13}C-^2H spin coupling constants of **8** are given in Table 1. $^{13}C\{^1H\}$ chemical shifts

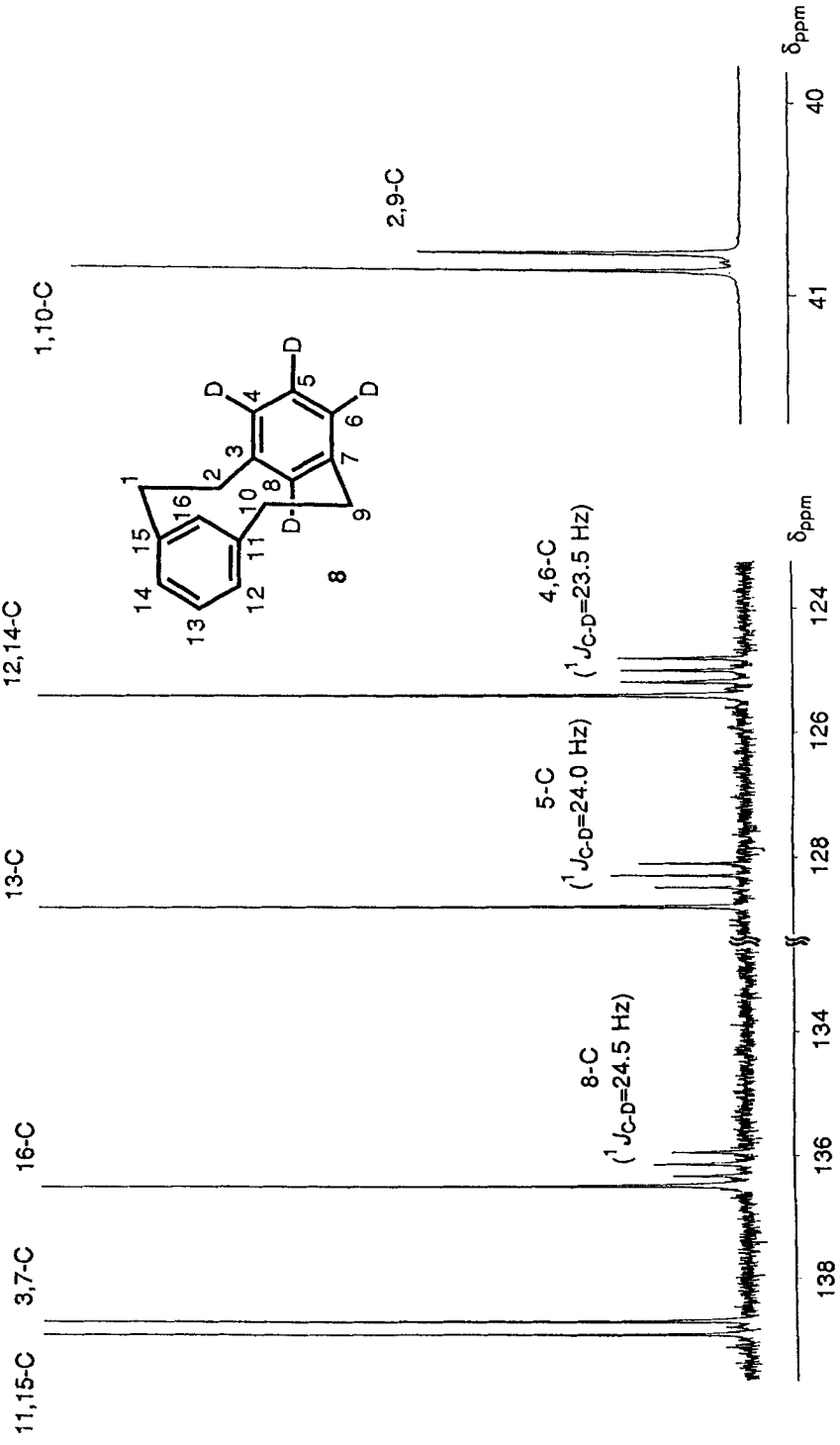


Fig. 2 125.77 MHz $^{13}C\{^1H\}$ NMR spectrum of **8**.

of **8** were assigned by considering C-H COSY spectrum of perprotio form of **8**. It should be noted that a 6.5 ppm high field shift of 16-C of **8** as compared to 2-C of *m*-xylene[5] was observed. The assignment of the two unequivalent peaks in alkyl part could be made on the basis of the height of the two peaks and the high field shift of 2-C and 9-C, caused by the isotope effect. The peaks of 2-C and 9-C, broadened by the small coupling with 4-^{2}H, 6-^{2}H, and 8-^{2}H were observed at 0.1 ppm higher field position than those of 1-C and 10-C. The carbon peaks of the aromatic region were assigned by considering their abundance and the relativity to 8-^{2}H. The signals of 4-C, 5-C, 6-C, and 8-C showed triplets, and were observed at 0.35-0.50 ppm higher field position, as compared to those of 12-C, 13-C, 14-C, and 16-C. The signals of 3-C and 7-C appeared at 0.20 ppm higher field than those of 11-C and 15-C. The above results indicated that the isotope shifts were almost identical with substituted benzenes.

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EXPERIMENTAL

General.

All melting points were determined on a Yanagimoto micro-apparatus and are uncorrected. Mass spectra were recorded on a Nippon Denshi JMS-OISG-2 mass spectrometer at 75 eV using a direct inlet system. ^{13}C NMR spectrum was taken on a JEOL GSX-500 NMR spectrometer at 125.77 MHz. ^{1}H NMR spectra were obtained on a JEOL GSX-500 and a Hitachi R-90 H FT-NMR spectrometers in $CDCl_3$ with Me_4Si as an internal reference. In the simulation calculation of ^{1}H{^{2}H} NMR spectra a programme developed for the personal computers, NEC-9801 and Apple Computer Macintosh was used. Column chromatography was performed on silica gel (Wako gel C-300).

Materials.

D_2O (99.9 atom %D) was obtained from Division of Merck Frosst Canada Inc. and 40% NaOD-D_2O (99.5 atom %D) from Merck & Co. Inc. The preparation of the fluorophane (**9**) has already been reported [4]

[2,4,5,6-$^2H_4$]Isophthalic acid (2). -To a vigorously stirred mixture of 239 mg (1 mmol) of **1** and 10 ml of 10% NaOD-D_2O was gradually added 300 mg of Ni-Al alloy. This operation was carried out in a glove box under a nitrogen stream. Then the reaction apparatus was taken out from the box and the solution stirred at 100 °C for 4 h. After cooling to room temperature, insoluble materials were filtered off using a celite filter aid and washed with a small portion of water. The filtrate and the washing were acidified with conc. HCl to pH 1 and the precipitates were collected by filtration and recrystallised from water to afford **2** (160 mg, 94%) as colourless prisms, m.p. 355-362 °C (lit.,[6] m.p. 347-349 °C as for $^2H_0$ form).

[2,4,5,6-$^2H_4$]Diethyl isophthalate (3). -A mixture of 2.8 g (16 mmol) of **2**, 20 ml of toluene, 25 ml of ethanol, and 0.9 ml of conc. H_2SO_4 was heated under reflux for

21 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and to the residue was added ice-water. The whole mixture was extracted with CH_2Cl_2 and the extracts were dried over $MgSO_4$. The removal of the solvents gave the oily product, which was distilled under reduced pressure to afford **3** (2.52 g, 68%) as a colourless liquid, b.p. 105 °C/ 1.5 Torr (lit.,[7] b.p. 170-170.5 °C/ 2.4 Torr as for $^2H_0$ form).

1,3-[2,4,5,6-$^2H_4$]Bis(hydroxymethyl)benzene (4). -To a suspension of 7.60 g of $LiAlH_4$ in 40 ml of THF was added dropwise a mixture of 2.62 g (11.6 mmol) of **3** in 10 ml of THF at room temperature under a nitrogen stream, and the mixture was heated under reflux for 3 h. After cooling to room temperature, to the reaction mixture was added aqueous saturated NaF and the continuous liquid-liquid extraction of the whole mixture was carried out with ether for 2 days. The extract was dried over $MgSO_4$ and the solvent was evaporated. Recrystallization of the residue from CH_2Cl_2 afforded **4** (1.25 g, 76%) as colourless needles, m.p. 57 °C (lit.,[7] m.p. 57 °C as for $^2H_0$ form).

1,3-[2,4,5,6-$^2H_4$]Bis(choloromethyl)benzene (5). -A mixture of 1.42 g (10 mmol) of **4**, 14.3 ml of $SOCl_2$, 50 ml of benzene, and 1 ml of pyridine was heated under reflux for 24 h. After cooling to room temperature, the solvents were removed and the residue was extracted with CH_2Cl_2. The extracts were washed with water, dried over $MgSO_4$, and evaporated to leave a residue which, on distillation at 94 °C under reduced pressure (3 Torr), gave **5** (979 mg, 55%) as a colourless liquid, (lit.,[8] b.p. 250-255 °C as for $^2H_0$ form).

2,11-[5,6,7,9-$^2H_4$]Dithia[3.3]metacyclophane (6). -A solution of 2.03 g (11.4 mmol) of **5** and 1.62 g (11.4 mmol) of 1,3-bis(mercaptomethyl)benzene was added dropwise from a Hershberg funnel with stirring in a period of 1 day to a refluxing solution of 1.6 g (28.5 mmol) of KOH and 860 mg (22.8 mmol) of $NaBH_4$ in 3 l of EtOH. After the addition was completed, the content was concentrated to dryness. To the residue was added 1 l of water and the mixture was extracted with CH_2Cl_2. The extract was washed with 10% aqueous HCl and dried over $MgSO_4$, and concentracted *in vacuo*. The residue was chlomatographed using a mixture of hexane and AcOEt (*v*/*v*=100:1) as an eluent and the solvents were removed *in vacuo*. Recrystallization from hexane afforded **6** (1.38 g, 44%) as colourless needles, m.p. 120-121 °C (lit.,[9] m.p. 120-121 °C as for $^2H_0$ form).

2,11-[5,6,7,9-$^2H_4$]Dithia[3.3]metacyclophane-2,2,11,11-tetraoxide (7). -A mixture of 505 mg (1.83 mmol) of **6** in 3.7 ml of 30% aqueous H_2O_2 and 10 ml of AcOH was refluxed for 1 day. After cooling to room temperature, the reaction mixture was poured into 5% aqueous NaOH and the precipitates formed were collected by filtration and washed with water. Recrystallization from hexane afforded **7** (485 mg, 78%) as colourless needles, m.p. >260 °C (lit.,[9] m.p. >260 °C as for $^2H_0$ from).

[4,5,6,8-$^2H_4$][2.2]Metacyclophane (8). -Pyrolysis of 500 mg (1.47 mmol) of **7** was performed at 500 °C under reduced pressure (0.75 Torr) in an apparatus consisting of a horizontal tube (15 mm in diameter) passing through a tube furnace (20-cm long). The pyrolysate was dissolved into CH_2Cl_2 and the solvent was removed to leave a residue which was chromatographed with hexane as an eluent. The solvents

were removed *in vacuo* and the residue was recrystallised from hexane to afford **8** (62 mg, 20%) as colourless needles, m.p. 131.5 °C (lit.,[10] m.p. 131.5 °C as for $^2H_0$ form).

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