Tetrahedron Vol 33, pp 1101 to 1104 Pergamon Press 1977 Printed in Great Britain

TEMPERATURE DEPENDENT CHEMICAL SHIFT CHANGE IN 4-SUBSTITUTED[2.2.2.2]PARACYCLOPHANES[1]

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(*Received in Japan 16 October 1976; Received in UK for publication 15 November 1976*)

Abstract—Temperature dependent NMR spectra of 4-substituted tetrakis[2.2.2.2]paracyclophane (4°-PCP) were measured at low temperature. The high field shift at low temperature was remarkable for the protons *meta* and *para* to an electron withdrawing and/or bulky substituent. While the chemical shift change was very small for the aromatic protons of 4°-PCP bearing a not so bulky and electron donating substituent. From these observations it is concluded that the rotation or vibration of a benzene bearing an electron withdrawing and/or bulky substituent around C_7–C_1–C_4–C_8 axis was increasingly frozen as the temperature decreased to a more stable "lateral" (or half "lateral", the intermediary state between "face" and "lateral"[4]) conformation, in an interesting contrast to the favored face conformation of unsubstituted 4°-PCP at low temperature as well as at room temperature.

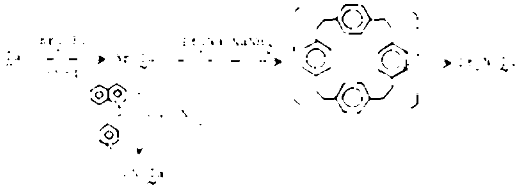
In preceding papers, the authors reported the syntheses and properties of [2.2.2]trisparacyclophane,[2] [2.2.2.2]tetrakisparacyclophane[3] and higher [2ⁿ]paracyclophanes (cyclic n-mer of *p*-xylylene),[4] where [2.2.2]trisparacyclophane or [2.2.2.2]tetrakisparacyclophane (4°-PCP) was demonstrated to have benzenes of "face" rather than "lateral" conformations[2-4] in a statistical sense[5] on the basis of NMR spectroscopy.[2]

In this article, the authors wish to report the temperature dependent NMR spectra of 4°-PCP's bearing a substituent on a benzene ring.

RESULTS AND DISCUSSIONS

Preparation of substituted 4°-PCP. Preparation of parent 4°-PCP (**Ia**) and some of its derivatives, **Ib**, **Ic**, **If** and **Ig**, was described in the preceding paper.[3] Bromo-4°-PCP (**Ie**), cyano-4°-PCP (**Ic**) and diethylamino-4°-PCP (**Ih**) were prepared according to Scheme 1.

	Ia	**Ib**	**Ic**	**Id**
X –	H	NO_2	CN	$COCH_3$
	Ie	**If**	**Ig**	**Ih**
X –	Br	OH	$OCOCH_3$	$N(C_2H_5)_2$



Scheme 1.

NMR spectra. NMR aromatic absorption of [2.2.2.2]paracyclophane, **Ia**, was singlet at room temperature, while that of a 4-substituted 4°-PCP (**Ib–h**) was spread over a moderately wide range (δ 6.22–7.42) as expected from that of simple aromatic compounds.[2,3,6] However, the observed δ values were markedly dependent on the temperature as shown in Figs. 1 and 2 for 4-nitro 4°-PCP and 4-bromo 4°-PCP respectively, as typical examples.

The observed chemical shift differences of *o*-, *m*- and *p*-protons from 31.5° to −60° are listed in Table 1. And the temperature dependence are shown in Figs. 3 and 4. As is apparent from Figs. 3 and 4, the chemical shifts of *m*- and *p*-protons were in an approximately linear relationship with the temperature and a slope of a "line" (observed temperature sensitivity) was characteristically dependent on nature of a substituent where bulkiness (nitro,

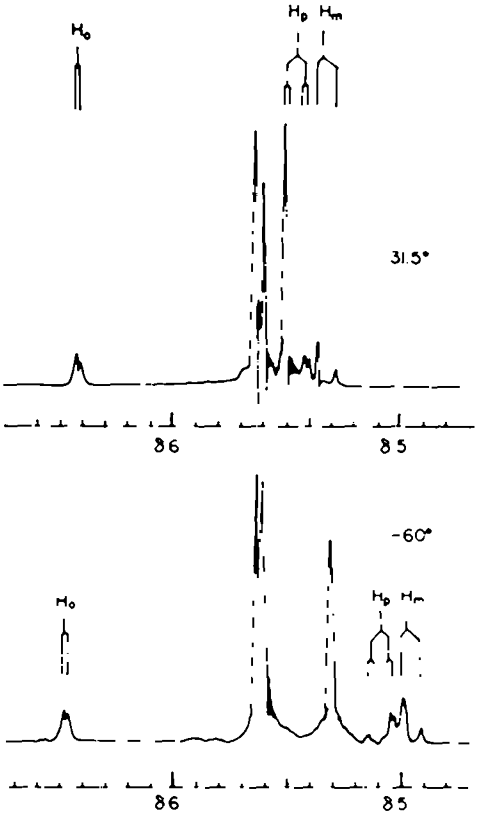


Fig. 1. Temperature dependent NMR absorptions of aromatic protons of 4-nitro[2.2.2.2]paracyclophane in CS_2 with 100 MHz. TMS as an internal standard.

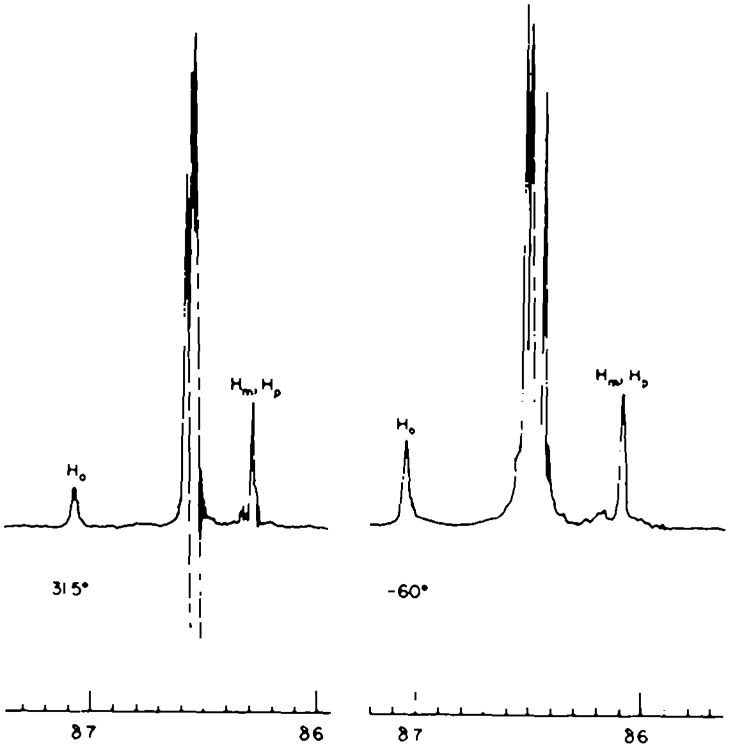


Fig. 2. Aromatic NMR absorptions of 4-bromo[2.2.2.2]paracyclophane at 31.5° (left) and −60° (right) in CS_2, with 100 MHz, TMS as an internal standard.

Table 1. Temperature dependence of chemical shift of *Tetrakis* with respect to *o*-, *m*- and *p*-protons[a]

compd	1b	1c	1d	1e	1f[b]	1g[b]	1h
$\Delta\delta_o$	0.06	0.04	0.16	0.02	0.01		
$\Delta\delta_m$	0.35	0.26	0.29	0.19	[illegible]	[illegible]	[illegible]
$\Delta\delta_p$	0.35	0.22	0.25	0.19	[illegible]	[illegible]	[illegible]

a measured in CS_2, ppm, shift difference from -60° to 31.5°
$\Delta\delta = \delta_{31.5°} - \delta_{-60°}$

b measured in $CDCl_3$

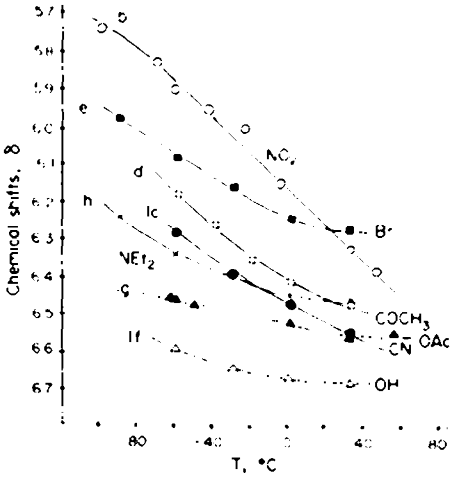


Fig. 3. Temperature dependence of the chemical shifts of *m*-protons (δ_m) of substituted *tetrakisses*.

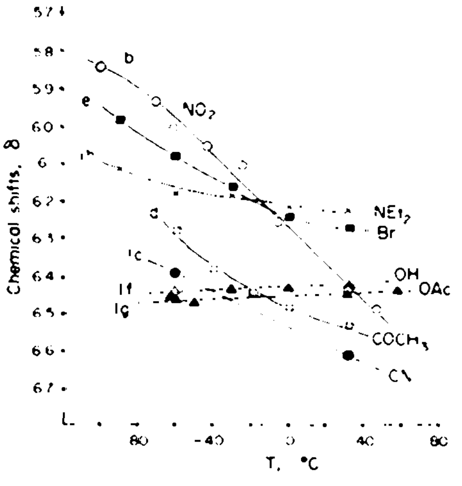


Fig. 4. Temperature dependence of the chemical shifts of *p*-protons (δ_p) of substituted *tetrakisses*.

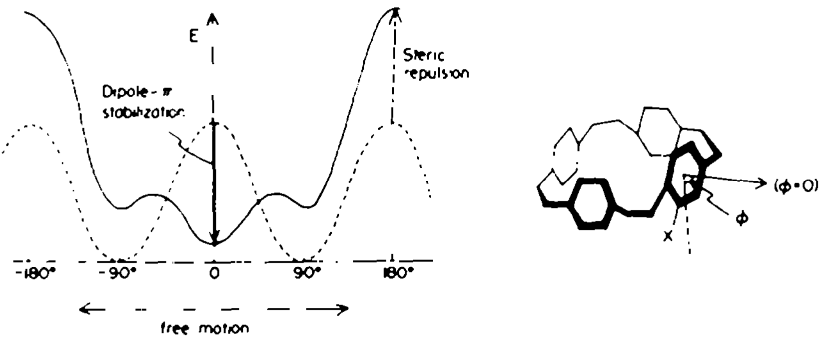


Fig. 5. Assumed potential curve of substituted [2.2.2.2]paracyclophane (dotted line: unsubstituted paracyclophane).

N,N-diethylamino or acetyl) and/or electron withdrawing property (nitro, acetyl, cyano) seem to shift absorption of *m*- and *p*-protons effectively to the higher field at lower temperature.

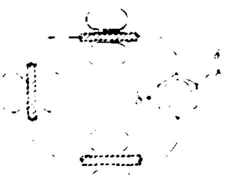
The second point to note is that the observed magnitude (and sign in the case of hydroxyl or acetoxyl, although small in magnitude) of the shifts were not the same for *o*-, *m*- and *p*-protons of benzene bearing a substituent. In the case of 4-nitro[2.2.2.2]paracyclophane, for example, δ_0 was less affected by temperature change (Fig. 1), $\Delta\delta$ $(\delta_{46^\circ} - \delta_{-100^\circ}) = -0.07$ ppm, while δ_m and δ_p showed remarkable upfield shifts ($\Delta\delta = +0.64$ ppm for both) from +46° to −100°. Similar situation was observed for other 4-substituted 4°-PCP. To an interesting contrast, the observed chemical shift of parent 4°-PCP, in which the "face" conformation is favored,[2-4] was little affected by temperature change and only the high-field shift of −0.02 ppm was observed from 31.5° to −70°.

Conformation change in the paracyclophane. These interesting findings seem to be correlated with the conformation change of a 4-substituted 4°-PCP at different temperature.[7] A bulky substituent may energetically destabilize the "face" relative to the "lateral" conformation of benzene bearing the substituent due to the steric repulsion between a substituent and the protons of other benzenes, leading to lateral, face, face, face conformation (which will be called as the (face³·lateral) conformation). In this (face³·lateral) conformation, a substituent turns to the outside of macrocyclic molecule (Fig. 5), which results remarkable upfield shifts of the *m*- and *p*-protons because of the enhanced transannular shielding by the other "face" benzenes.

An electron withdrawing substituent may stabilize the X-"lateral" (face³ X-lateral) conformation probably because of dipole-π interaction shown in **III**, and as the temperature decreases population of **II** increases. As is apparent from Figs. 3 and 4, protons *m*- or *p*- to a (bulky or electron-withdrawing) substituent are still shifting to a higher field even at −80° or below, suggesting that the energy difference between the *face* and *lateral* conformation is small.

For a substituent not bulky, not electron-withdrawing (**If**, **Id**), the temperature dependence of chemical shift was as small as for unsubstituted [2.2.2.2]paracyclophane.

II



III

EXPERIMENTAL

Materials. Compounds **Ia**, **Ib**, **Id**, **If** and **Ig** were prepared according to the methods described.[3]

4-bromo[2.2.2.2]*paracyclophane* (**Ie**). Br_2 (0.21 ml) was dissolved in 30 ml CCl_4. To a stirred suspension of 0.1 g Fe powder in 10 ml CCl_4, Br_2-soln (3 ml) was added at once. Then 27 ml of the Br_2 soln was added dropwise to the stirred mixture. After the addition was over, the mixture was stirred at room temp. for 1 day and then washed with $NaHSO_3$ aq, dil HCl, water and NaCl aq and dried over Na_2SO_4. Distillation off the solvent gave 2.05 g of a white solid, the part of which (1.04 g) was chromatographed on silica gel. First elution with 5% dichloromethane-petroleum ether gave an isomeric mixture of dibromo[2.2.2.2]paracyclophane (390 mg, 0.68 mmole, 37%) as a white solid, IR (KBr): 3000, 2900, 2840, 1597, 1505, 1485, 1430, 1035, 803 cm^{-1}.

Further elution gave 538 mg (1.09 mmole, 60%) of **Ie** as white crystals, **Ie** was recrystallized from EtOAc and then from benzene; m.p. 124.5–125.5°; IR (KBr): 2995, 2915, 2830, 1510, 1435, 1040, 812, 580 cm^{-1}. (Found: C, 77.30; H, 6.17. Calc. for $C_{32}H_{31}Br$: C, 75.57; H, 6.31%).

4-N,N-*Diethylamino*[2.2.2.2]*paracyclophane* (**Ib**). A mixture of diethylamine (20 ml) and sodium amide (2 g) was refluxed with stirring for 20 min. To the stirred mixture was added a soln of the crude bromo-4°-PCP (480 ng) dissolved in diethylamine (20 ml). The mixture was refluxed for 3 hr and sodium amide (1 g) was added. After the mixture was refluxed for an additional 1 hr, water was added and the mixture was extracted with ether. The ether extract was washed with NaCl aq and dried over Na_2SO_4. After distilling off the solvent, a residue was obtained, which was chromatographed on silica gel. Elution with 50% benzene-petroleum ether gave **Ib** (206 mg; 0.42 mmole, 50% yields based on **Ia** used) as white crystals; m.p. 118.5–119° (from EtOAc); IR (KBr): 2995, 2905, 2830, 1510, 1437, 1412, 1377, 1242, 810, 588 cm^{-1}. (Found: C, 88.46; H, 8.48. Calc. for $C_{36}H_{41}N$: C, 88.66; H, 8.47%). Further elution with benzene-petroleum ether (2/1) gave 85 mg of an additional compound which was tentatively assigned as the impure **Ib** (0.152 mmole, 18% based on **Ia**); IR (KBr): 3000, 2970, 2925, 2850, 1510, 1495, 1435, 1412, 1245, 815, 805 cm^{-1}.

4-*Cyano*[2.2.2.2]*paracyclophane* (**Ic**). A part of the crude bromo-4°-PCP (530 mg), cuprous cyanide (134 mg), quinoline (15 ml) and pyridine (2 ml) were mixed and the mixture was heated at 220° for 8 hr under the N_2. Then to the cooled mixture ether was added and the ether layer was washed twice with 28% aqueous ammonia, twice with dil HCl, $NaHCO_3$ aq and then sat NaCl aq. The ether layer was dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel to give **Ic** (89 mg; 0.20 mmole, 22% yield based on **Ia** used) as an oily material from the elute with benzene-petroleum ether (1/1). Crude **Ic** was re-chromatographed on silica gel with benzene to give pure **Ic** as white crystals; m.p. 118.5–120°, mass spectrum, *m/e* (relative intensity) 441 (M^+, 28), 207 (28), 193 (14), 149 (12), 117 (12), 105 (23), 104 (100); IR (KBr): 3000, 2925, 2850, 2110, 1508, 1435, 815 cm^{-1}.

NMR measurement. Variable temp NMR spectra were measured by using Varian HA100 and Jeol NMR 60H. Temp was determined by the NMR chemical shift difference between hydroxyl and Me protons of MeOH.

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[4] I. Tabushi, H. Yamada and Y. Kuroda, *J. Org. Chem*. **40**, 1946 (1975).

[5] In [2.2.2.2]paracyclophane, for example, each benzene actually rotates around C_2–C_3–C_6–C_7 axis at room temp., but the "face" conformation seems to have higher population than "lateral" conformation statistically.

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