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Medium-Sized Cyclophanes. VI. High-Temperature NMR Spectra of [2.2]Metacyclophane and Optical Resolution of 4,14-Disubstituted Derivatives[1)]

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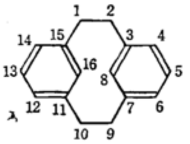
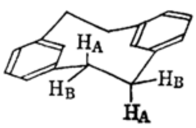
The NMR spectra of [2.2]metacyclophane have been shown to be held unchanged over a wide range of temperature, *ca.* −80 to 190°C, indicating that the ten-membered ring system undergoes no inversion and is frozen in a chair conformation. It may, then, be expected that suitably substituted derivatives of [2.2]metacyclophane would become disymmetric due to restricted inversion; such was proved to be the case by carrying out the optical resolution of the 4,14-di-substituted derivatives. The 4,14-dimethyl derivative was resolved by means of a complex formation with Newman's reagent, $[\alpha]_{578}^{26}=-3.4$ and $+4.2°$. 4,14-Dicarboxylic acid was also resolved by converting it to the quinine salt, $[\alpha]_D^{22}=+5.0°$.

Among the medium-sized ring compounds [2.2]metacyclophane (I) is one of the few examples whose molecular geometry has been completely elucidated using the X-ray technique.²⁾ The compound has been shown to exist as a step-like molecule with two slightly distorted benzene rings, which are arranged on two parallel planes. As a consequence, the distance between C_8 and C_{16} has been found to be as short as 2.689 Å in spite of deformation in both the aryl and aliphatic bonds to relieve steric overcrowding. These structural features have been shown to be well reflected in the absorption spectra of I.³⁾ By comparing the UV spectrum of I with that of 3,3′-dimethylbibenzyl, a corresponding open-chain compound, it has been noticed⁴⁾ that the absorption maximum of I at 270 mμ, devoid of any fine structure, shifts to a longer wavelength and a lower intensity, thus indicating an appreciable distortion in the aryl moiety. The absorption minimum of 3,3′-dimethyl bibenzyl occurs at 236 mμ with a low intensity ($\varepsilon=75$,) whereas I has a higher extinction ($\log\varepsilon=3.67$) at the same wavelength and the absorption minimum shifts to 260 mμ. The fact is explainable by assuming the presence of bands due to transannular interaction between the two benzene rings in this region.⁴⁾ Further, the examination of the NMR spectra of I has revealed the unusual nature of the 8,16-protons and conformational details of the ten-membered ring. In addition to an AB_2-type absorption of the peripheral aryl protons at $C_{5,13}$ and $C_{4,6,12,14}$ at δ 7.18 and 6.97 respectively, a triplet assignable to intraannular aryl protons at $C_{8,16}$ appeared at δ 4.23 ($J=1.8$ cps). The up-field shift of almost 3 ppm is due to the diamagnetic ring current effect of the diametrical benzene rings, over which the intraannular protons are extended. Methylene protons appeared as A_2B_2-type absorptions, which were analyzed as $\delta_A=2.04$ and $\delta_B=3.05$, indicating the presence of nonequivalent protons. Since the ten-membered ring in I exists in a chair conformation, it is quite natural to assign these as arising from axial (H_A) and equatorial (H_B) protons, as is shown in structure II.



I



II

The temperature dependence of NMR spectra has been proved to be a powerful tool for the detection of possible inversion in cyclic systems and has found wide application. Our interest in the conformational equilibrium of the ten-membered ring system in I led us to study the high-temperature NMR spectra of I.⁵⁾ The spectra were determined at *ca.* −80, 27, 67, 126, and 190°C; they are shown in Fig. 1. The assignments of the

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1) Part V: T. Sato, Y. Goto and K. Hata, This Bulletin, **40**, 1994 (1967).
2) C. J. Brown, *J. Chem. Soc.*, **1953**, 3278.
3) B. H. Smith, "Bridged Aromatic Compounds," Academic Press Inc., New York, N. Y. (1964), pp. 359, 407.
4) N. L. Allinger, M. A. DaRooge and R. B. Hermann, *J. Am. Chem. Soc.*, **83**, 1974 (1961).
5) The results appeared in a preliminary form, see T. Sato, S. Akabori, M. Kainosho and K. Hata, This Bulletin, **39**, 856 (1966).

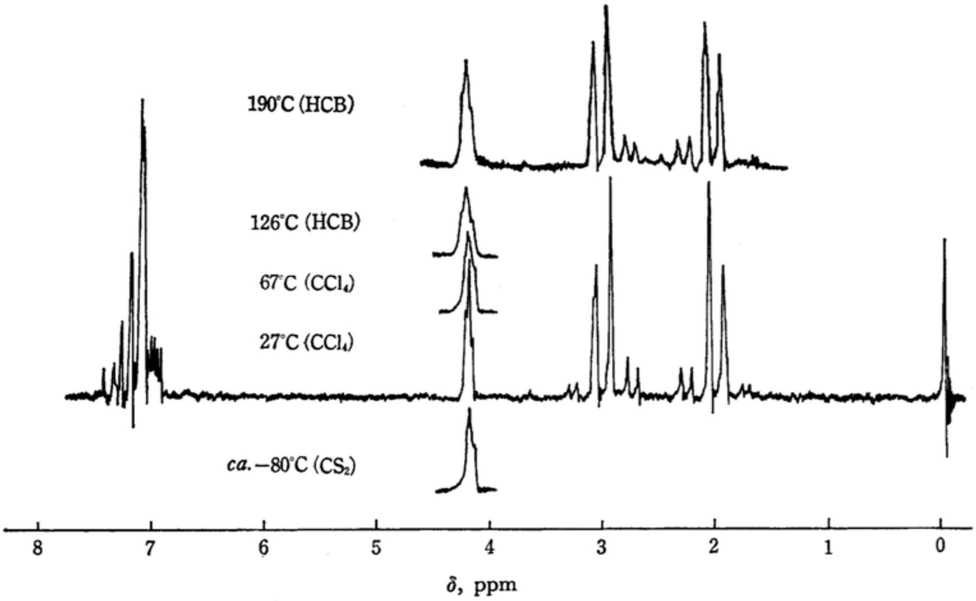

Fig. 1. NMR spectra of [2.2]metacyclophane (I) at various temperatures.

Table 1. NMR spectra data of [2.2]metacyclophane at various temperatures[a)]

Temp., °C	Solvent	AB_2		Triplet[b)] 8, 16-H	A_2B_2,[c)] 1, 2, 9, 10-H	
		5, 13-H	4, 6, 12, 14-H		Equatorial	Axial
190	HCB[d)]	431.6	418.6	270.9	193.7	135.3
126	HCB	430.4	417.4	256.6	182.2	122.6
67	CCl_4	430.2	417.1	254.5	181.7	122.7
27	CCl_4	430.8	416.0	253.8	183.3	122.7
27	HCB	431.8	418.6	254.2	182.2	122.8
27	CS_2	429.8	416.3	251.6	181·6	120.6
ca. −80	CS_2	428.4	415.2	247.4	181.2	120.0

a) The spectra were recorded on a Varian A-60 spectrometer with variable-temperature probe and expressed in cps relative to internal TMS as 0.
b) J=1.8 cps.
c) Analyzed by AB type approximation.
d) Hexachlorobutadiene.

proton signals are summarized in Table 1. Except for a small shift due to solvent effect, no significant changes in the spectral pattern were observable. It was of special note that the A_2B_2 absorption was kept surprisingly unchanged even at 190°C, indicating that the molecule is frozen in the chair conformation II, thus eliminating the possibility of interconversion between the inverted isomers. It is also noteworthy, however, that 8, 16-protons experience a small yet definite down-field shift upon going to higher temperatures. At 190°C the signal occurred at 270.9 cps down-field from TMS, whereas at room temperature it appeared at 254.2 cps, both values being determined in a hexachlorobutadiene solution. An increase in the thermal motion at higher temperatures brings about distortions of bond angle and bond length, so that the distance of 8,16-protons from the center of the opposite benzene ring increases. This molecular deformation might be responsible for the slight down-field shift of the proton signal. Recently, Griffin and his co-worker[6)] have demonstrated that the higher homolog, 2, 2-dicarbethoxy-[3.2]metacyclophane, experiences a ring inversion evidenced by the coalescence of the AB and A_2B_2 systems to two singlets above 125°C.

It is, then, to be expected that those [2.2]metacyclophane derivatives in which substituents are introduced unsymmetrically in relation to a plane of symmetry which bisects both of the benzene rings may become optically resolvable. As the

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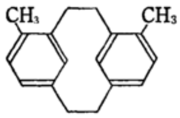
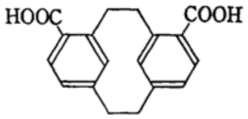
[6)] R. W. Griffin, Jr., and R. A. Coburn, *Tetrahedron Letters*, **1964**, 2571.

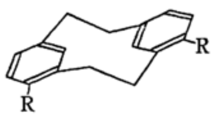
possible disymmetric molecules, two 4, 14-disubstituted derivatives III and IV, the optical antipodes of which are represented by Va and Vb, were prepared. The Wurtz dimerization reaction of 2, 4-bis(chloromethyl)toluene under high-dilution conditions using disodium tetraphenylethane as a condensing agent has been shown[5] to proceed stereospecifically to afford only the cis compound III, and not the possible trans isomer, the 4, 12-dimethyl derivative. The structural determination was achieved by the NMR spectral measurements. Dicarboxylic acid IV was obtained by the oxidation of [2.2]metacyclophane-4, 14-dicarbaldehyde, which had itself been prepared from III by bisbromination reaction with NBS, followed by the Sommelet reaction. Full accounts of the syntheses and a structural consideration based on the spectral data will be presented elsewhere.



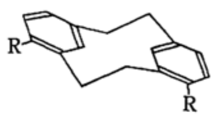
III



IV



Va



Vb

The optical resolution of compound III, which is devoid of suitable functional grouping, was achieved by using (−)-α-(2, 4, 5, 7-tetranitro-9-fluorenylideneaminooxy)propionic acid[7] as a complex-forming reagent. When kept in a refrigerator, a benzene solution of the reagent and III deposited a crystalline complex, which, by column chromatography on alumina using benzene as an eluent, was found to decompose to afford (−)-III as colorless needles, mp 54—64°C, $[\alpha]^{26}_{578}=-3.4°$. By the chromatography of the material contained in the filtrate of the complex formation, a dextrorotatory isomer, mp 58—61°C, $[\alpha]^{26}_{578}=+4.2°$, was obtained. These two isomers showed negative and positive plain ORD curves respectively, and had infrared spectra identical with those of the racemic compound. Dicarboxylic acid IV was resolved by the aid of quinine. A solution of IV and quinine in ethanol was left to stand, thus producing a crystalline salt; on recrystallization from ethanol this salt melted at 150—160°C. A benzene solution of the optically active acid, after liberation by dilute hydrochloric acid, was evaporated to give a colorless powder, mp >300°C, $[\alpha]^{22}_{D}=+5.0°$.

Obviously these are the first examples which demonstrate that suitably substituted [2.2]metacyclophane derivatives become disymmetric due to the restricted inversion of the ten-membered ring system. After the completion of the present studies, two papers along similar lines have appeared. Lüttringhaus and his co-worker[8] have achieved a partial resolution of a cyclotriveratrylene derivative, the molecular disymmetry of which is due to a restricted inversion of the 9-membered ring, by passing its benzene solution through a column of cellulose-2 1/2-acetate, thus obtaining optical isomers with $[\alpha]^{22}_{405}=+7.5$ and $-5°$ As a new optically resolvable [mn]paracyclophane due to the restricted rotation of the aromatic rings, disymmetric tetramethyl[2.2]paracyclophane has been resolved into optical antipodes, $[\alpha]^{27}_{D}=-3.2$ and $+4.2°$, with the aid of Newman's reagent.[9]

Experimental

Physical Measurements. The measurements of NMR spectra at various temperatures were carried out using a Varian A-60 spectrometer equipped with a V-6040 variable temperature controller. Calibrations at high and low temperatures were performed by using ethylene glycol and methanol respectively; this method permitted an accuracy of ±1°C at higher temperatures. ORD curves were recorded with a Nihon Bunko ORD/UV-5 spectrometer. The optical rotations were measured by using a Carl Zeiss LEP A-2 or an Applied Electric Lab. Model MP-1T polarimeter.

Materials. 4, 14-Dimethyl[2.2]metacyclophane (III) was prepared[5] as colorless needles, mp 68—69°C, by the dimerization reaction of 2, 4-bis(chloromethyl)-toluene under high-dilution conditions realized by the slow addition (68 hr) of the latter compound to disodium tetraphenylethane in THF at −60 to −70°C. [2.2]-Metacyclophane-4, 14-dicarboxylic acid (IV), mp >300°C, was obtained either by the direct oxidation of III with potassium permanganate or *via* [2.2]metacyclophane-4, 14-dicarbaldehyde, which had itself been prepared from III by dibromination with NBS, followed by treatment with 2-nitropropane and sodium ethoxide in DMSO.[10]

Optical Resolution. a) A solution of 300 mg (1.0 mmol) of III and 300 mg (0.67 mmol) of (−)-α-(2, 4, 5, 7-tetranitro-9-fluorenylideneaminooxy)propionic acid in 2 m*l* of benzene was kept in a refrigerator for 4 days. Orange-red crystals of the complex were collected by filtration; a benzene solution of these was then submitted to column chromatography on alumina, using benzene as an eluent. There were thus obtained 49 mg of colorless needles which had a mp of 54—64°C and an $[\alpha]^{26}_{578}$ value of $-3.4°$(*c* 1.8, ethanol).

Similar treatment of the filtrate from the complex formation furnished 80 mg of colorless needles, mp 58—61°C, which showed $[\alpha]^{26}_{578}=+4.2°$ (*c* 3.3, ethanol).

The two compounds showed negative and positive

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[7] M. S. Newman and W. B. Lutz, *J. Am. Chem. Soc.*, **78**, 2469 (1956).

[8] A. Luttringhaus and K. C. Peters, *Angew. Chem. internat. Edit.*, **5**, 593 (1966).

[9] D. T. Longone and M. T. Reetz, *Chem. Commn.*, **1967**, 46.

[10] B. H. Klanderman, *J. Org. Chem.*, **31**, 2618 (1966).

plain ORD curves respectively and had IR spectra identical with those of the racemic compound.

b) A solution of 330 mg (1.1 mmol) of IV and 730 mg (2.3 mmol) of quinine, which had been liberated from the hydrochloride, in 9 m*l* of hot ethanol was left to stand at room temperature for one day. Filtration then afforded 280 mg of a crystalline salt, which was recrystallized from ethanol, mp 150—160°C. Dicarboxylic acid was freed from the salt by shaking it with 20 m*l* of benzene and 10 m*l* of dilute hydrochloric acid. By the evaporation of the benzene solution, there were obtained 45 mg of a colorless powder, mp >300°C, with $[\alpha]_D^{22}=+5°$ (*c* 1.8, ethanol). It had IR spectra identical with those of the racemic compound.

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