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Macro Rings. II.[1] Synthesis of [2.1.1.1.1]Paracyclophane

Takahiko INAZU and Tamotsu YOSHINO
Department of Chemistry, Faculty of Science, Kyushu University, Hakozaki, Fukuoka

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A macrocyclic compound which incorporates five benzene rings and intervening methylene bridges as parts of a large ring structure, [2.1.1.1.1]paracyclophane I ($n=2$), was synthesized and then compared with a corresponding open-chain analog, X.

Because of its ability to form clathrates or charge-transfer complexes, a macrocyclic compound, I, furnished with an empty space of an appropriate size at the center of its molecule is of particular interest.

Although several attempts have been made to synthesize paracyclophane with four or five benzene rings by an intramolecular cyclization reaction, these attempts have all resulted in failure.[2,3]

As an initial step of the present investigation, [2.1.1.1.1]paracyclophane I ($n=2$) was synthesized. This may be the first example of a paracyclophane constructed with five benzene rings and intervening methylene bridges. As the result of several preliminary experiments, the Wurtz reaction was adopted for the synthesis of the paracyclophane.

The yield of a macrocyclic compound by the usual Wurtz reaction is generally poor, but the modified Wurtz reaction using sodium adduct of tetraphenylethylene has been proved to be useful for improving the yield of cyclization. It has also been verified that the improved, intramolecular Wurtz-type reaction is appreciable to a large ring formation from a compound with two distant halogen atoms in a chain molecule.

Although a chain compound of the benzylbromide type, IX, seemed to be a reactive material, an attempt to cyclize the compound IX was thwarted because of the compound's insufficient solubility in tetrahydrofuran at room temperature. This difficulty was surmounted by using the corresponding compound of the benzyl-chloride type, VIII, in place of the bromide, IX.

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[1] T. Inazu and T. Yoshino, This Bulletin, **41**, 647 (1968).

[2] J. J. Randall, *Dissertation Abstr.*, **20**, 2568 (1960).

[3] C. F. Koelsch and C. E. Bryan, *J. Am. Chem. Soc.*, **67**, 2041 (1945).

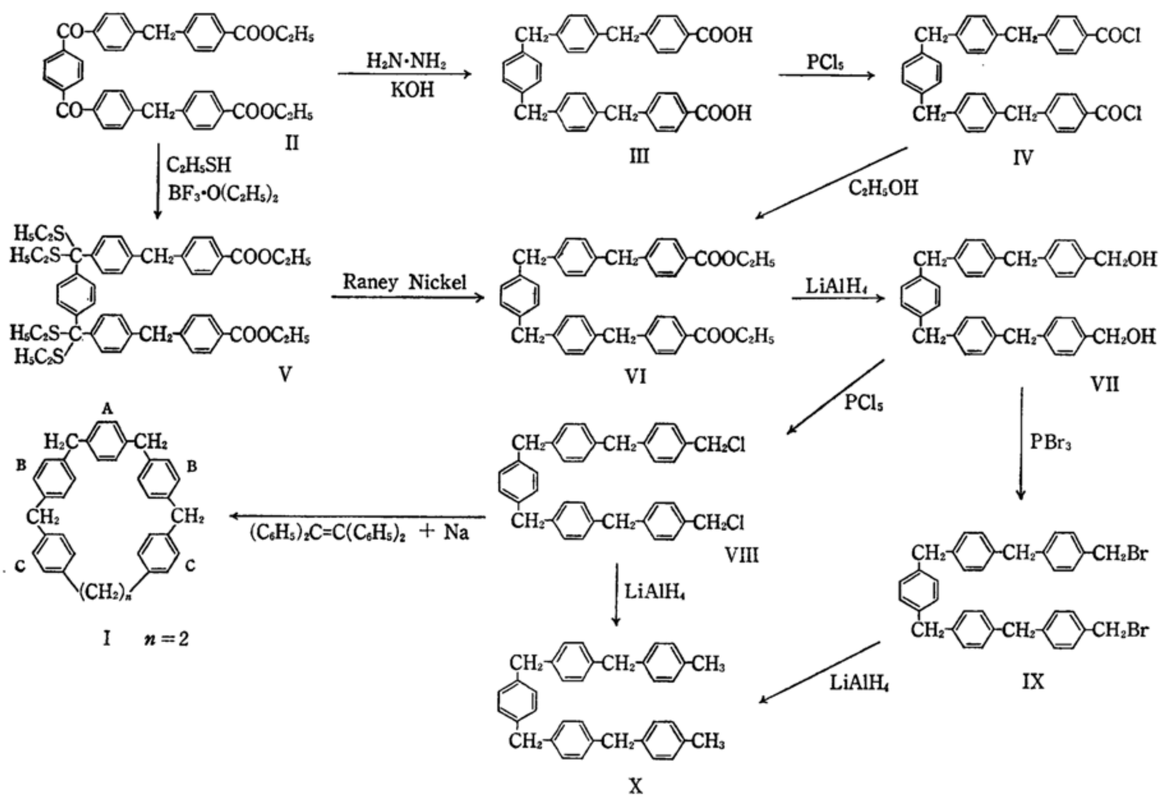

Fig. 1

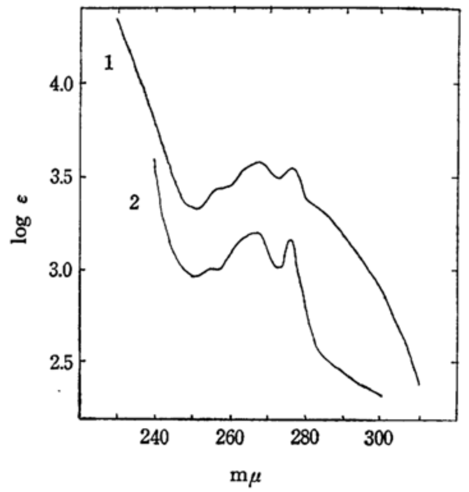

Fig. 2. Ultraviolet spectra of [2.1.1.1.1]paracyclophane I and the open chain analog X in C_2H_5OH.

Curve 1: compound I (λ_{max}: 267.5 mμ, log ε=3.58)

Curve 2: compound X (λ_{max}: 267.5 mμ, log ε=3.20)

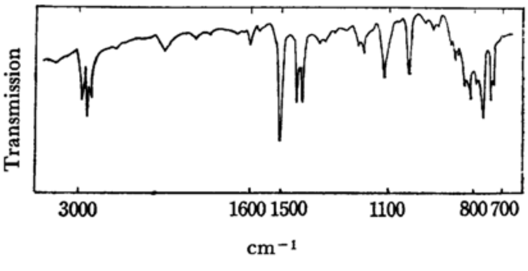

Fig. 3. Infrared spectrum of [2.1.1.1.1]paracyclophane I in KBr disk.

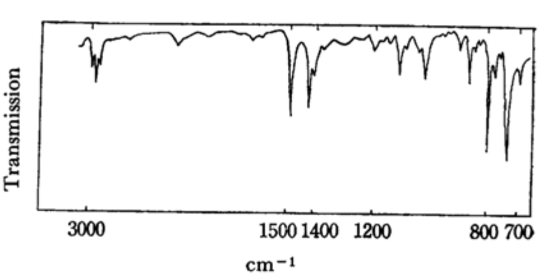

Fig. 4. Infrared spectrum of the open chain analog X in KBr disk.

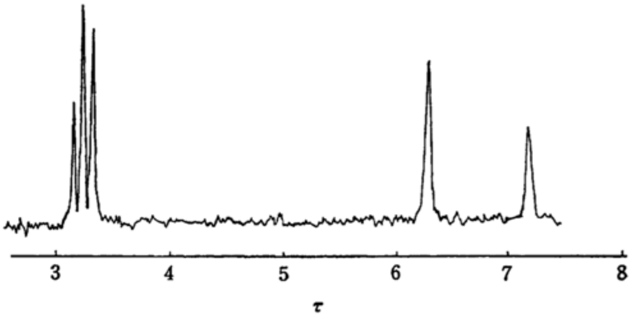

Fig. 5. The NMR spectrum of [2.1.1.1.1]paracyclophane I.

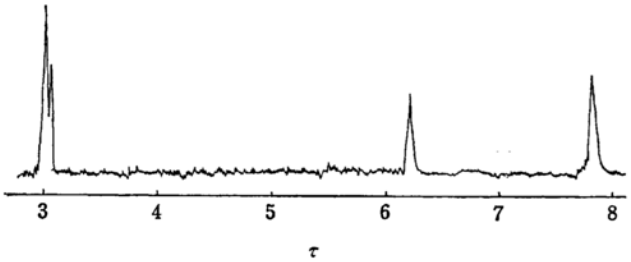

Fig. 6. The NMR spectrum of the open chain analog X.

The synthetic route is outlined in Fig. 1. A keto ester, II,[1] was converted to another ester, VI, either by the desulfurization of a thioketal, V, with Raney nickel, or by the Wolff-Kishner reduction to an acid, III, followed by esterification *via* acid chloride, IV. The ester VI was reduced with lithium aluminum hydride, and the resulting carbinol, VII, was treated with phosphorus tribromide or phosphorus pentachloride to give, respectively, a bromide, IX, or a chloride, VIII. This bromide and this chloride were each then reduced with lithium aluminum hydride to a compound, X. This compound was synthesized as a reference compound which served as a chain analog of the cyclophane, I, for a comparison of their spectra.

With the aid of a modified high-dilution technique, [2.1.1.1.1]paracyclophane, I, was obtained as colorless crystals by the intramolecular condensation of the chloride VIII with the sodium adduct of tetraphenylethylene in tetrahydrofuran at room temperature under a nitrogen atmosphere; this was done according to the method of Müller and Röscheisen.[4]

The close resemblance of the ultraviolet spectrum of the compound I to that of a corresponding chain compound, X, reveals that benzene rings of the compound I are probably planar, unlike the distorted non-planar rings in [2.2]paracyclophane.[5] This fact was anticipated from our having been able to assemble a molecular model of the macrocyclic compound, I, without any strain.

The NMR spectrum of the compound I was in accord with that assumed tentatively for the cyclic structure: $\tau=7.13$ singlet (ethylene protons), $\tau=6.26$ singlet (methylene protons), and three singlets (benzene ring protons) at $\tau=3.13$, 3.20, and 3.29. Each of the peaks for protons of the benzene ring and methylene and ethylene groups was a singlet; this suggests that the conformation of the cyclic compound, I, may be flexible, without any rigid fixation, in a solution at room temperature. In the NMR spectra, the peak for methylene protons in the cyclic compound, I, was found to shift upfield by 0.14 ppm from that for the methylene protons of diphenylmethane. Peaks for benzene the rings A, B, and C in the cyclic compound, I, were also found to shift upfield by 0.17, 0.24, and 0.33 ppm respectively from those for benzene protons in diphenylmethane. These upfield shift is attributable to the fact that protons of the cyclophane I may be a little more shielded by transannularly-situated benzene rings than are protons of diphenylmethane.

Although no marked difference was observed between the IR spectra of the compound, I, and that of the chain analog, X, the results of the molecular-weight determination excluded the possibility of the compound I being a polymer. The cyclic structure of the compound I being different from that of the chain compound, X; this

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[4] E. Müller and Röscheisen, *Chem. Ber.*, **90**, 543 (1957).

[5] D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, **73**, 5691 (1951).

fact was confirmed by the NMR spectrum, as has been described above.

Experimental

All melting points are uncorrected. The ultraviolet spectra were measured on a Hitachi EPS-3T spectrophotometer. The infrared spectra were measured on a Hitachi EPI-S2 spectrophotometer. The NMR spectra were recorded on a Varian Associates A-60 model, using tetramethyl silane as the internal standard and carbon tetrachloride as the solvent.

***p*-Bis[*p*-(*p*-carboxybenzyl)benzyl]benzene (III).** A mixture of 20 g of a keto ester, II, 80 m*l* of 80% hydrazine hydrate, 60 g of potassium hydroxide, and 240 m*l* of ethylene glycol was refluxed for 17.5 hr. After cooling, the mixture was neutralized with concentrated hydrochloric acid to give 17.2 g (almost a theoretical yield) of a white powder, mp above 290°C. Found: C, 81.51; H, 5.82%. Calcd for $C_{36}H_{34}O_4\cdot \frac{1}{4}H_2O$: C, 81.41; H, 5.80%.

***p*-Bis[*p*-(*p*-chloroformylbenzyl)benzyl]benzene (IV).** A mixture of 24.5 g of the acid, III, and 70 g of phosphorus pentachloride in 200 m*l* of chloroform was refluxed for 3 hr; after the solvent and phosphoryl chloride had been removed by distillation under reduced pressure, pale pink crystals were obtained in an almost theoretical yield.

***p*-Bis[*p*-(*p*-ethoxycarbonylbenzyl)benzyl]benzene (VI).** To a solution prepared by dissolving the acid chloride, IV, derived from 24.5 g of the acid, III, in 100 m*l* of chloroform, 100 m*l* of ethanol was added, little by little under cooling, and the mixture was refluxed for 30 min. The removal of the chloroform by distillation gave 20.3 g (74.5%) of colorless crystals, which were confirmed to be identical with a smaple prepared from the compound II *via* a thioketal, V, by a comparison of their infrared spectra and melting points.

***p*-Bis[*p*-(*p*-hydroxymethylbenzyl)benzyl]benzene (VII).** A solution of 7.8 g of the ester VI in 200 m*l* of tetrahydrofuran was added, at room temperature, to a mixture of 1.9 g of lithium aluminum hydride in 100 m*l* of tetrahydrofuran placed in a flask fitted with a reflux condenser, after which the mixture was refluxed for 1¾ hr with stirring. After being cooled and treated with hydrochloric acid, the mixture was distilled under diminished pressure to remove the solvent. The residue gave 6.4 g (96% yield) of a white powder, which was recrystallized from tetrahydrofuran to give a white crystalline powder, mp 203—205°C. Found: C, 86.53; H, 7.04%. Calcd for $C_{36}H_{34}O_2$: C, 86.71; H, 6.87%.

***p*-Bis[*p*-(*p*-chloromethylbenzyl)benzyl]benzene (VIII).** A mixture of 6.4 g of the diol, VII, 25 g of phosphorus pentachloride, and 150 m*l* of chloroform was refluxed for 3 hr, and then distilled under diminished pressure to remove the chloroform and phosphoryl chloride. The residue gave a white crystalline mass, which was recrystallized from tetrahydrofuran to give 5.05 g (73.5% yield) of colorless crystals, mp 182.5—183°C. Found: C, 80.47; H, 6.02%. Calcd for $C_{36}H_{32}Cl_2$: C, 80.74; H, 6.02%.

***p*-Bis[*p*-(*p*-bromomethylbenzyl)benzyl]benzene (IX).** A mixture of 1.0 g of the diol VII and 12 m*l* of phosphorus tribromide was refluxed for 3.5 hr and then, after the addition of 50 m*l* of chloroform, refluxed for an additional 5 hr. After cooling, the whole was poured onto crushed ice. The evaporation of the chloroform gave 1.3 g (almost a theoretical yield) of a white crystalline powder, mp 191°C (dec.). Found: C, 69.38; H, 5.36%. Calcd for $C_{36}H_{32}Br_2$: C, 69.24; H, 5.17%.

***p*-Bis[*p*-(*p*-methylbenzyl)benzyl]benzene (X).** A suspension of 500 mg of the bromide, IX, in 100 m*l* of tetrahydrofuran was stirred, drop by drop, into a mixture of lithium aluminum hydride in 40 m*l* of tetrahydrofuran at room temperature; after stirring for an additional 1.5 hr, the mixture was refluxed for 2 hr. After cooling, the mixture was treated with water and then with dilute hydrochloric acid. The removal of the tetrahydrofuran under reduced pressure gave a pale yellow powder, which was recrystallized from an ethanol-benzene mixture to give 240 mg (65% yield) of a white crystalline powder, mp 153°C. Found: C, 91.86; H, 7.41%. Calcd for $C_{36}H_{34}$: C, 92.66; H, 7.34%.

[2.1.1.1.1]Paracyclophane (I). Into a dark-violet solution of an adduct of sodium and 1.8 g of tetraphenylethylene in 100 m*l* of tetrahydrofuran, there was stirred a solution of 2.0 g of the chloride, VIII, in 400 m*l* of tetrahydrofuran; the addition was made *via* a modified Hershberg dropping funnel6) at room temperature, under a nitrogen atmosphere, and over a period of 14.5 hr. After being left standing for several hours, the mixture was distilled to remove the tetrahydrofuran; then water and ethanol were added to give 3.5 g of a pale yellow powder, which was collected by filtration and then subjected to fractional crystallization from a benzene-ethanol mixture to give 87 mg of colorless crystals, mp 257°C. Found: C, 92.73; H, 6.96%; mol wt, 495 (Rast). Calcd for $C_{36}H_{32}$: C, 93.06; H, 6.94%; mol wt, 464.62.

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6) E. B. Hershberg, "Organic Syntheses," Coll. Vol. II, p. 129 (1943).