Synthesis of 6,21-Dioxo-5,22-diaza[10.10]paracyclophane and Its Structural Characteristics

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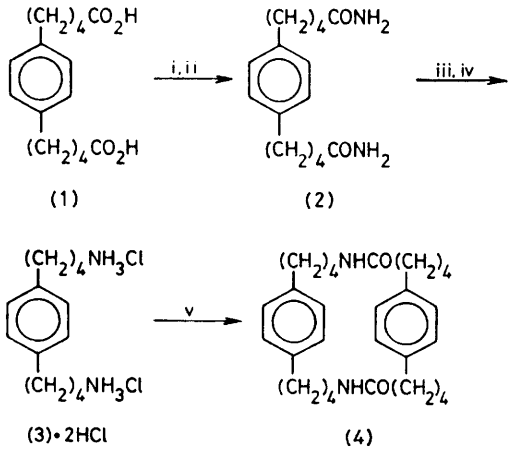
A novel paracyclophane, 6,21-dioxo-5,22-diaza[10.10]paracyclophane (4) has been synthesized by a condensation of 5,5′-*p*-phenylenebis(valeroyl chloride) (5) with 4,4′-*p*-phenylenebis(butylamine) (3) by a high dilution method. It has been characterized by means of u.v., i.r., and n.m.r. spectroscopy. The two amide bonds in compound (4) were found to assume the *s-trans*-geometry. No significant transannular interaction was observed between the two benzene rings. Upon cooling, the rotation of the benzene rings was hindered as evidenced by splitting of the n.m.r. ring proton signal into a doublet. The energy of activation for this hindered rotation was evaluated as 0.9 kcal/mol with a coalescence temperature of 30 ± 5 °C.

MACROCYCLIC compounds have received much attention from those studying structural characteristics such as conformations, restricted rotations, and transannular interactions. Functional macrocycles have also found wide application in the field of biomimetic chemistry as ionophores,[1] chirality recognition agents,[2] and enzyme models.[3] Artificial macrocycles such as [20]paracyclophanes developed by Murakami and his co-workers are especially interesting as hydrolytic enzyme models,[4] because they show significant catalytic activity in the hydrolysis of hydrophobic esters.[5] In light of the potential importance of these synthetic macrocycles, we have prepared a paracyclophane with a sizeable diameter, 6,21-dioxo-5,22-diaza[10.10]paracyclophane (4), and characterized it by means of spectroscopy. Since the arrangement of functional group(s) is of prime importance in dictating the efficiency of such a catalytic system,[6] precise information on the molecular structure is required in designing an enzyme model.

RESULTS AND DISCUSSION

Synthesis.—The macrocycle (4) was synthesized by a condensation of 4,4′-*p*-phenylenebis(butylamine) (3) with 5,5′-*p*-phenylenebis(valeroyl chloride) (5) in a 1 : 1 molar ratio (see Scheme). The high dilution method, adopted to avoid formation of polymeric compounds, was carried out by adding compound (5) slowly to compound (3) in benzene. The concentration of (3) never exceeded 2 mM, but a considerable amount (15—35%) of insoluble material was formed. Its i.r. spectrum is very close to that of the desired product and we tentatively regard it as linear polymeric amides. Compound (4) was purified by chromatography on Sephadex LH-20, in which a small peak was followed by a major peak. The latter turned out to be the desired product, while the front peak was presumed to be oligomeric amides on the basis of its elution volume relative to (4). The yield of purified compound (4) was not high (18%) but all spectral and analytical data given in the Experimental section are consistent with the assignment of structure (4).



SCHEME *Reagents*: i, $SOCl_2$; ii, NH_3, iii, NaOMe,Br_2; iv, HCl; v, *p*-$C_6H_4[(CH_2)_4{\cdot}COCl]_2$, compound (5)

Amide Bond Geometry.—An amide bond can assume either one of two conformations, *s-cis* or *s-trans*. The latter is more stable with open-chain amides as well as cyclic amides with a ring size larger than *ca.* 10.[7] On the other hand, the former conformation is assumed by cyclic amides with a small ring as typically seen in pyrrolidin-2-one and dioxopiperazines.[7,8] These two conformations are distinguished by the examination of an N–H stretching vibration band. The *s-cis* conformation gives rise to a band below 3 450 cm^{-1} while the *s-trans* shows absorption in the 3 450—3 500 cm^{-1} region.[9] Care should be taken, however, where there is an interaction of NH with π-electrons, which shifts N–H absorption to a shorter wavenumber even when the conformation is *s-trans*.[10] Data for compound (4) and 4,4′-*p*-phenylenebis(methyl butylcarbamate) (6) as well as for some reference compounds are summarized in Table 1. Compounds (4) and (6) have an absorption band at 3 450—3 455 cm^{-1}, which is completely compatible with the *s-trans*-conformation.

This conclusion is further supported by lanthanide-induced shifts of N–H in the n.m.r. spectrum. For the amides, in general, since a paramagnetic shift reagent interacts principally with the carbonyl oxygen,[11,12] the methylene protons adjacent to the carbonyl are subject to the largest downfield shift, followed by *N*-methylene protons which are *cis* to the carbonyl group. The *N*-methylene protons *trans* to the carbonyl group show the

smallest shift of the three kinds of protons. Thus, equimolar $Eu(fod)_3$ brings about downfield shifts of 9.2, 8.1, and 3.8 p.p.m. for acetyl methyl, *cis*-*N*-methyl, and *trans*-*N*-methyl in *N*,*N*-dimethylacetamide, respectively.[13] When $Eu(fod)_3$ was added to a solution of compound (4) in $CDCl_3$, all signals shifted downfield. The magnitude of shift was largest for the methylene adjacent to the carbonyl and *N*-methylene protons. The chemical shift of these proton signals is plotted against the $Eu(fod)_3$ concentration in Figure 1. The molar induced shifts, which were obtained by the extrapolation of the lines to an equimolar ratio of the reagent to (4), were 8.0 and 7.8 p.p.m. for CH_2CO and CH_2NH, respectively. These results indicate that the geometry around the amide bonds in (4) must be *s*-*trans*. The slope of a straight line as exemplified in Figure 1 is also a good indication for determining whether the substituent on the amide nitrogen is located *cis* or *trans* to the carbonyl.[10] If the slope for CH_2NH is close to unity relative to CH_2CO it indicates the *s*-*trans* geometry, while a smaller slope (0.6—0.8) is common for *s*-*cis* geometry. The slope for CH_2NH of (4) was 0.98, consistent with the *s*-*trans* geometry.

TABLE 1

N–H Stretching vibration in compound (4) and related compounds in chloroform

Compound	ν_{NH}/cm^{-1}	Geometry	Ref.
(1)	3 450	*s*-*trans*	This work
(6) [a]	3 455	*s*-*trans*	This work
DDPC [b]	3 436	*s*-*trans* with NH-π	9
DDCO [c]	3 453	*s*-*trans*	9
Caprolactam	3 380	*s*-*trans*	7

[a] *p*-$C_6H_4[(CH_2)_4{\cdot}NH{\cdot}CO_2Me]_2$, compound (6). [b] 2,11-Dioxo-3,10-diaza[12]paracyclophane. [c] 9,18-Dioxo-1,8-diazacyclooctadecane.

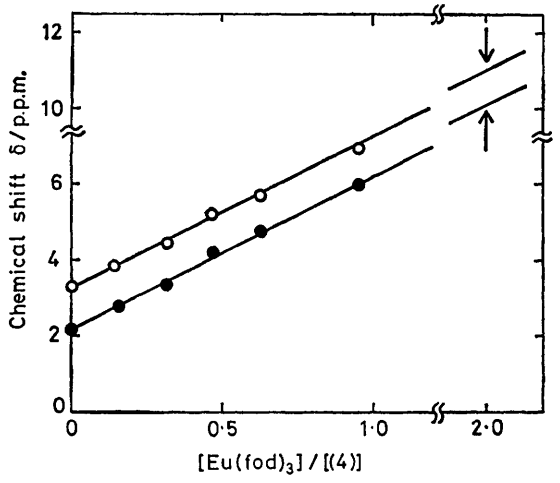


FIGURE 1 Lanthanide-induced shifts of $COCH_2$ (●) and $NHCH_2$ (○) signals in compound (4)

Conformation of Benzene Rings.—In paracyclophanes with a relatively small ring size, the benzene ring is distorted from planarity, a feature which is reflected in their electronic absorption spectra.[14] In relatively small [*m*,*n*]paracyclophanes, a transannular electronic interaction is observed between the two benzene rings.[15] The u.v. spectral data for compound (4) are listed in Table 2 along with those for an open-chain precursor (6) and some reference compounds. As is evident the location and extinction coefficient of the band for the present cyclophane (4) are very close to those of the compounds which show no appreciable transannular interaction. In the n.m.r. spectrum of compound (4) in $CDCl_3$ the two benzene rings appeared at almost identical chemical shifts at room temperature. This apparent coincidence is broken by the addition of $Eu(fod)_3$. As stated above the shift reagent interacts preferentially with the carbonyl oxygen, and the benzene ring located closer to the carbonyl suffers a greater paramagnetic deshielding effect. The magnitude of chemical-shift difference between the two signals is plotted as a function of $Eu(fod)_3$ concentration in Figure 2. It is concluded from these observations based on u.v. and n.m.r. spectroscopy that the benzene rings do not interact with each other to an appreciable extent but rotate freely at room temperature.

TABLE 2

Electronic spectral data of compound (4) and related compounds

Compound	$\lambda_{max.}$/nm (log $\epsilon_{max.}$)	Ref.
(4)	273 (2.67), 265.9 (2.98), 259sh	This work
(6)	273 (2.80), 265.5 (2.70), 285.5sh	This work
1,4-Dipentylbenzene	273.5 (2.69), 267.5 (2.69), 265 (2.66)	19
[7]Paracyclophane [a]	284 (2)	14
[2.2]Paracyclophane	302 (2.20), 284 (2.40)	15

[a] Hydroxymethyl derivative.

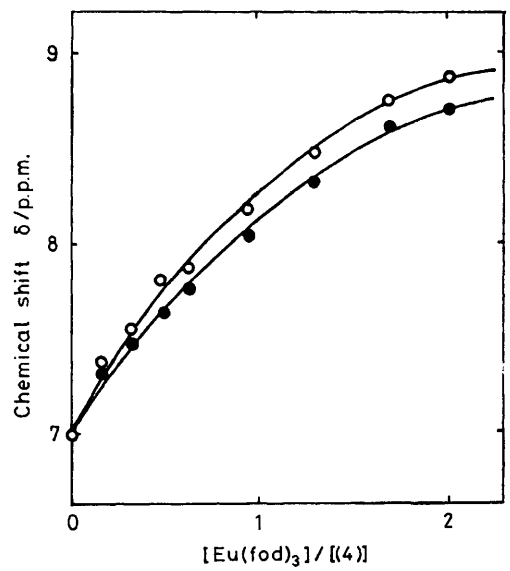


FIGURE 2 Splitting of a phenyl proton signal in compound (4) upon addition of $Eu(fod)_3$ in $CDCl_3$

Internal rotation of an aromatic ring and methylene groups in paracyclophanes is restricted at low temperature.[16-18] This is the case with the present macro-

cycle (4). When a $CDCl_3$ solution of (4) was cooled, a significant change was observed in its n.m.r. spectrum. The magnitude of change was largest for the benzene ring protons followed by the methylenes attached to the ring. The latter appeared as a triplet at room temperature. Upon cooling to −60 °C, it turned to a broad singlet, indicating that rotation of that group is hindered

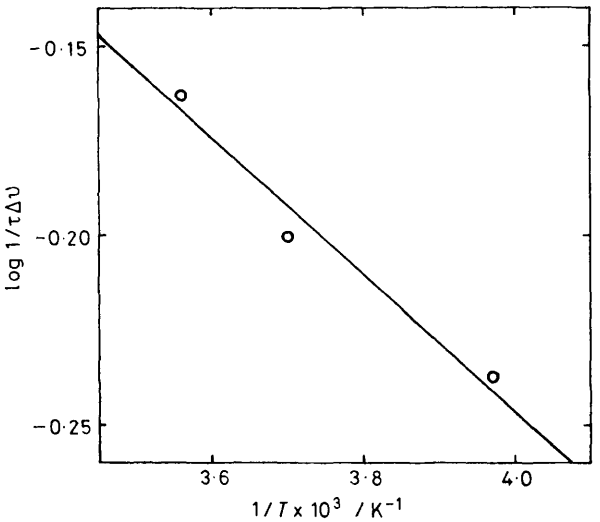
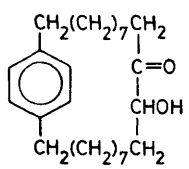


FIGURE 3 Arrhenius plot for the internal rotation of benzene rings in compound (4) in $CDCl_3$

to some extent at lower temperatures. The restricted rotation is better manifested for the ring protons. The ring proton signal appeared as a singlet above 30 °C but it broadened upon cooling and finally split into a doublet of equal intensity below room temperature. The energy of activation for the restricted rotation of benzene rings was evaluated by plotting log $1/\tau\cdot\Delta\nu$ against $1/T$, where $\Delta\nu$ is the chemical-shift difference between the two frozen sites and assumed to be 4.2 Hz (Figure 3). The obtained value of 0.9 kcal/mol is much smaller than those reported for paracyclophanes with a somewhat smaller ring size (*ca.* 10 kcal/mol).[17] The relative ease of internal rotation in (4) is also reflected in its coalescence temperature. The observed coalescence temperature of 30 ± 5 °C is much lower than those for common paracyclophanes.[17] The temperature effect was explored for 10-hydroxy-11-oxo[20]paracyclophane (7) for comparison. Neither proton signals showed a significant change over the entire temperature range (−50 to 50 °C), demonstrating that rotation of the benzene ring is free in (7).



(7)

From the above findings, it is concluded that the macrocycle (4) possesses a three-dimensional cavity as a CPK-model building suggests. In other words, the molecule provides an apolar cavity of sizeable diameter and depth, into which an apolar guest molecule may be incorporated through a hydrophobic interaction. Provided that the benzene rings are furnished with suitable catalytic groups such as an imidazole and/or carboxy-group, the resulting macrocycle is expected to exert a catalytic activity in some organic reactions. Flexibility of the benzene rings observed in the parent macrocycle might be advantageous in catalysis, because a good alignment of catalytic groups and the incorporated substrate in the cavity is achieved by a slight move of the benzene rings.

EXPERIMENTAL

Materials.—The lanthanide-shift reagent, tris(1,1,1,2,2,-3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium(III) ($Eu(fod)_3$) was obtained from Dojindo Lab., Kumamoto, Japan. 4,4′-*p*-Phenylenebis(valeric acid) (1) was prepared according to the literature,[19] m.p. 179—184 °C (lit.,[19] 176—180 °C).

4,4′-p-*Phenylenebis(valeroyl chloride)* (5).—A mixture of (1) (17 g, 61 mmol) and of thionyl chloride (34.5 g, 290 mmol) was refluxed in dry ether with vigorous stirring for 7 h. The insoluble material was filtered off. The solvent was removed under reduced pressure to leave low-melting solid materials (19 g, 99%), $\nu_{max.}$ (Nujol) 1 800 cm^{-1}. This was used without further purification in the following experiment.

4,4′-p-*Phenylenebis(valeramide)* (2).—To ice-cooled conc. ammonia (300 ml) was added with stirring compound (5) (19 g, 60 mmol) in small portions. The suspension was stirred at 0 °C for 2 h and then refluxed for 4 h. The solid was collected on a filter and washed with acetone. This crude product was recrystallised from DMSO (yield 8.2 g, 50%), m.p. 223—225 °C; $\nu_{max.}$ (KBr) 3 390, 3 180, 1 640, and 1 410 cm^{-1}; δ[$(CD_3)_2SO$] 1.52 [8 H, m, $(CH_2)_2\cdot CH_2CO$], 2.04 (4 H, t, *J* 7 Hz, CH_2CO), 2.48 (4 H, t, *J* 7 Hz, $PhCH_2$), 6.58 (2 H, br s, NH_2), 7.01 (4 H, s, Ph), and 7.14 (2 H, br s, NH_2) (Found: C, 69.25; H, 8.95; N, 9.8. $C_{16}H_{24}N_2O_2$ requires C, 69.53; H, 8.75; N, 10.14%).

p-*Phenylenebis(methyl δ-butylcarbamate)* (6). To a methanolic solution of compound (2) (5.52 g, 20 mmol) was added slowly sodium methoxide solution (160 ml, 12 mmol). The mixture was cooled to 0 °C and bromine (3.1 ml, 60 mmol) was added over 10 min. The reaction mixture was then heated at 70—80 °C for 5 h. The solvents were removed under reduced pressure and the residual solid was extracted extensively with acetone (20 × 50 ml). The extracts were concentrated to dryness under reduced pressure and the residue washed with water (500 ml); the crude product was recrystallised from acetone (yield 3.16 g, 47%), m.p. 126—128 °C; $\nu_{max.}$ (KBr) 3 325, 1 685, 1 520, and 1 265 cm^{-1}; δ[$(CD_3)_2SO$] 1.50 [8 H, m, $(CH_2)_2CH_2$-NH], 2.54 (4 H, t, *J* 7 Hz, $PhCH_2$), 3.02 (4 H, q, *J* 6 Hz, CH_2NH), 3.40 (2 H, m, NH), 3.53 (6 H, s, CH_3), and 7.11 (4 H, s, Ph) (Found: C, 64.55; H, 8.55; N, 8.25. $C_{18}H_{28}N_2O_4$ requires C, 64.27; H, 8.39; N, 8.33%).

4,4′-p-*Phenylenebis(butylamine)* (3). A suspension of compound (6) (3.10 g, 9.2 mmol) in conc. HCl (80 ml) was heated at 110—120 °C for 29 h under a nitrogen atmosphere.

The insoluble material was filtered off and washed with water (20 ml). The filtrate and washings were combined and the solvent removed under reduced pressure to leave light yellow solids, m.p. 250—260 °C (decomp.); $\nu_{max.}$ (KBr) 3 000, 2 930, 1 600, and 1 505 cm^{-1}; $\delta(CF_3CO_2H)$ 1.81 [8 H, m, $(CH_2)_2CH_2NH_3^+$], 2.70 (4 H, m, $PhCH_2$), 3.26 (4 H, m, $CH_2NH_3^+$), 6.80 (6 H, br, NH_3^+), and 7.16 (4 H, s, Ph) (Found: C, 51.9; H, 8.45; N, 8.25. $C_{14}H_{26}Cl_2N_2 \cdot 2H_2O$ requires C, 51.06; H, 9.18; N, 8.51%).

The free base was obtained in the following way. Compound (3)·2HCl was redissolved in water (100 ml) and the insoluble material was filtered off. The filtrate was adjusted to pH 12 with 1% aqueous NaOH and a small amount of insoluble material was filtered off. The final filtrate was extracted with benzene (*ca.* 300 ml) until the aqueous layer became ninhydrin-negative. The extracts were dried over Na_2SO_4 and the solvent evaporated off to give a viscous liquid, which solidified with time (yield 1.32 g, 65%), m.p. 97—104 °C; $\nu_{max.}$ (KBr) 3 340, 2 920, 1 560, 1 430, and 810 cm^{-1}. The n.m.r. spectrum in CF_3CO_2H was identical with that of compound (3)·2HCl.

6,21-*Dioxo*-5,22-*diaza*[10.10]*paracyclophane* (4).—A mixture of compound (3) (0.49 g, 2.2 mmol) and triethylamine (0.90 g, 8.9 mmol) was dissolved in dry benzene (1 200 ml) and the resulting solution was refluxed with vigorous stirring under a nitrogen atmosphere. To this was added dropwise a solution of compound (5) (0.70 g, 2.2 mmol) in dry benzene (500 ml) during 34 h. The insoluble material was filtered off and the solvent was removed under reduced pressure to leave a viscous oil. This was triturated with acetone to give the crude product (0.35 g), m.p. 210—225 °C. It was further purified by chromatography on Sephadex LH-20 (1.8 × 71 cm) with chloroform as an eluant. Following the elution of a small peak of material with 80 ml of eluant, the product was eluted with 100—115 ml of eluant (yield 0.18 g, 18%), m.p. 227—230 °C. The best quality product was obtained by recrystallisation from acetone–chloroform (5 : 1 v/v) as colourless needles, m.p. 230—231 °C; $\nu_{max.}$ (KBr) 3 280, 2 920, 1 630, 1 545, and 810 cm^{-1}; $\delta(CDCl_3)$ 1.63 [16 H, m, $(CH_2)_2CH_2CO$ and $(CH_2)_2CH_2NH$], 2.16 (4 H, m, CH_2CO), 2.58 (8 H, m, $PhCH_2$), 3.26 (4 H, m, CH_2NH), 5.90 (2 H, br s, NH), and 7.05 (8 H, s, Ph) (Found: C, 77.7; H, 9.35; N, 5.75%; M^+, 462.3246. $C_{30}H_{42}N_2O_2$ requires C, 77.88; H, 9.15; N, 6.05%; *M*, 462.3246).

Apparatus.—U.v. spectra were taken on a Hitachi 323 spectrophotometer. I.r. spectra were determined on a Hitachi 285 spectrometer or a Jasco IRA-1 for routine work. Mass spectra were recorded with a Jeol JMS-01 SG mass spectrometer. N.m.r. spectra were taken on a Jeol JNM-MH-100 spectrometer. The temperature in the probe cavity was determined on the basis of the chemical shift of the hydroxy-proton of methanol.

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