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SYNTHESIS OF [1.1.1.1]PARACYCLOPHANE

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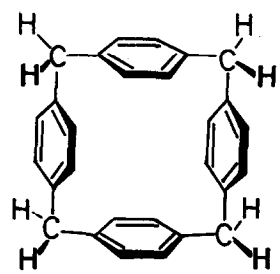
Summary: The title compound 1 has been synthesized by a route involving acyloin cyclization, pyrolytic elimination of a diacetate 5 derived from the acyloin 4, and the Diels-Alder reaction of the resultant 1,3-diene 6A with phenyl vinyl sulfoxide.

Macrocyclic cyclophanes are attracting growing interest as synthetic host molecules, because the recent X-ray analyses of several inclusion complexes[1] have confirmed molecular inclusions of guest molecules into the cavities of cyclophane hosts rather than inclusions of a channel type. The cyclophane hosts so far studied are flexible and adapt their cavities to guest molecules. We considered that rigid cavities would be more favorable for selective inclusion complex formation. In this connection we have been interested in [1$_n$]paracyclophanes (n=4-8)[2,3], because their molecular cavities are assumed to be more rigid than the existing cyclophane hosts and their perhydro derivatives resemble cyclodextrins. In particular, [1.1.1.1]paracyclophane 1 is of interest since it is expected to have a rigid, exactly square cavity surrounded by its four benzene rings fixed in a "face" conformation[4]. Although it has been mentioned in a patent literature that this strained molecule can be prepared by condensing benzyl chloride in the presence of aluminum chloride, neither its properties nor the yield has been reported[5]. Its very low solubility as described below may play an important role in its isolation and therefore the method would not be applicable to the other members of [1$_n$]paracyclophanes[6]. We wish to report here the synthesis of 1 by an indirect route in which one of the four benzene rings is created by a Diels-Alder reaction[7].



1

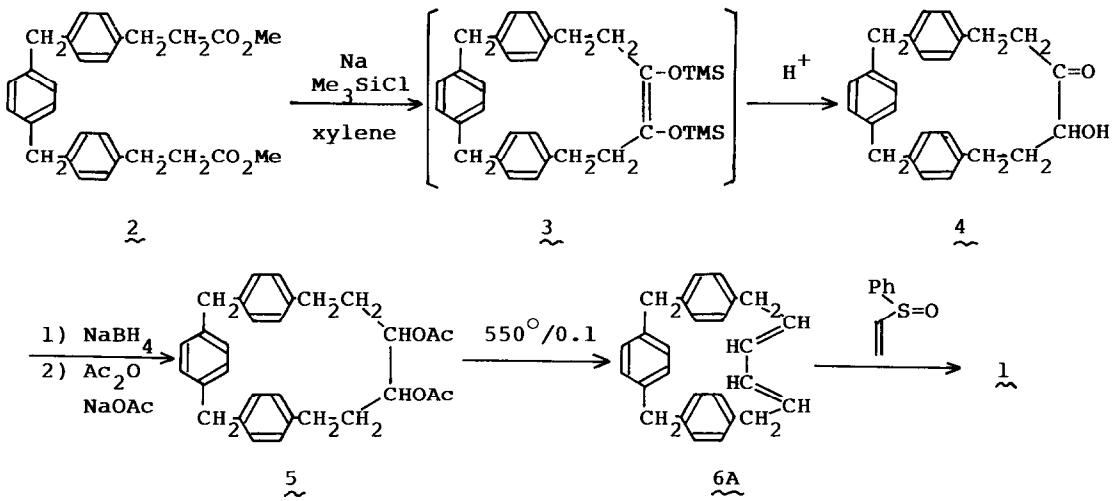
Dimethyl ester 2 was readily prepared starting from methyl 3-phenylpropionate by the Friedel-Crafts acylation with terephthaloyl chloride (78%), followed by the Wolff-Kishner reduction and esterification (86%)[8]. The acyloin cyclization of 2 was carried out by adding its xylene solution containing chlorotrimethylsilane[9] to a large excess of highly dispersed sodium[10] in refluxing xylene under high dilution conditions over a period of 13 h under argon. Since the resultant strained cyclic bis(trimethylsilyl) enediol ether 3 proved to be very unstable in the air and rapidly cleaved to the diacid of 2, the reaction mixture was, after decantation of excess of sodium, immediately hydrolyzed with hydrochloric acid in methanol. After removal of the solvents, the residue was separated by silica gel chromatography

(chloroform) to afford cyclic acyloin 4 in 28.9% yield [colorless granules, mp 219.5-220.5°C, M^+ 370, IR (KBr) ν_{OH} 3380 and $\nu_{C=O}$ 1716 cm^{-1}][8]. Sodium borohydride reduction of 4 in EtOH-chloroform and subsequent acetylation (Ac_2O-NaOAc, reflux 1 h) gave diacetate 5 as a mixture of diastereomers. Recrystallization and preparative TLC (silica gel, CH_2Cl_2) gave diacetate 5A [75.0% yield, colorless prisms (hexane), mp 173.5-174°C, Rf 0.32][8] and diacetate 5B [9.8% yield, colorless plates (hexane), mp 188-189°C, Rf 0.57][8]. These isomers, 5A and 5B, were assigned as meso and dl, respectively, on the basis of their ^{1}H-NMR spectra [60 MHz, $CDCl_3$; 5A: δ 1.78 (s, CH_3CO) and 4.59 (d, J=8.4 Hz, CHOAc), 5B: δ 2.14 (s, CH_3CO) and 4.31 (d, J=9.6 Hz, CHOAc) ppm], considering the upfield shift of the acetyl protons directed inward of the macro ring in the case of the meso isomer. Preponderant formation of 5A appears to support this assignment, considering the hydride attack on the carbonyl of 4 from the less hindered side.

Flash-vacuum pyrolysis of 5A at 550°C/0.1 mmHg under nitrogen gave a mixture of dienes, which were separated by recrystallization from benzene and repeated preparative TLC (silica gel, hexane-chloroform). Three major products were isolated. 6A: colorless granules, mp 280-281°C, 38.3% yield; assigned as the desired trans,trans-diene on the basis of its IR, ^{1}H-NMR, and ^{13}C-NMR spectral data[8,11]. 6B: colorless granules, mp 185.5-186.5°C, 5.1% yield[8,12]. 6C: colorless prisms, mp 142-143°C, 28.6% yield[8,13]. They showed M^+ at 336 in the mass spectra and their fragmentation patterns resembled each other. Their UV spectra depicted in Fig. 1 as well as their ^{1}H- and ^{13}C-NMR spectra suggest that the olefinic bonds in 6C do not conjugate with each other but with benzene rings. The 1,3-diene 6A was considerably unstable and gradually decomposed on standing in the air. Furthermore, when 6A was heated to its melting point, it isomerized to 6B and 6C.

The final stage of the synthesis of 1 is to convert the diene moiety of 6A into a benzene ring. Whereas the usual method utilizing dimethyl acetylenedicarboxylate[14] gave a complex mixture of products, the use of Paquette's vinyl sulfoxide methodology[15] was found to be very expedient. Thus, the diene 6A was heated with vinyl phenyl sulfoxide in toluene at 150-170°C under argon in a sealed tube for 6 days. On cooling, the desired 1 readily crystallized out from the dark reaction mixture, which was purified by chromatography (alumina, hot toluene). Although the yield was not satisfactory (15.1%), possibly as a result of isomerization and decomposition of the strained 6A under the reaction conditions, this procedure is quite simple and the reaction can be monitored by NMR ($ArCH_2Ar$) using d_8-toluene as a solvent. Addition of pyridine[15] did not improve the yield in this case. It is interesting to note that 6C could also be transformed into 1 (10 days at 170°C, 7.5% yield), though it is not a 1,3-diene and no isomerization to 6A was detected after heating alone at 170°C for 4 h.

The structure of 1 [colorless cubic crystals of very low solubility, mp 340-341°C (sealed tube), sublimable at 250°C/0.1 mmHg] was readily established on the basis of its spectral and analytical data as follows. MS: m/e (%) 104 (10.7), 165 (18.9), 178 (17.0), 179 (36.3), 180 (12.4), 360 (M^+, 100), 361 (29.4), and 362 (4.5). ^{1}H-NMR (60 MHz, $CDCl_3$) δ 6.86 (s, 16H) and 3.51 (s, 8H) ppm. ^{13}C-NMR (22.50 MHz, $CDCl_3$) δ 141.65, 127.95, and 43.30 ppm. Anal. Found: C, 93.02; H, 6.64%. Calcd. for $C_{28}H_{24}$: C, 93.29; H, 6.71%. The UV spectrum of 1 is shown in Fig. 2. The longest wavelength band of 1 exhibits only a small bathochromic shift (4 nm) compared to 4,4'-bis(p-tolylmethyl)benzene 7. The most noticeable difference of 1 from 7 is a newly appeared shoulder at ca. 245 nm, probably arising from intramolecular charge-transfer interactions between the neighboring benzene rings.



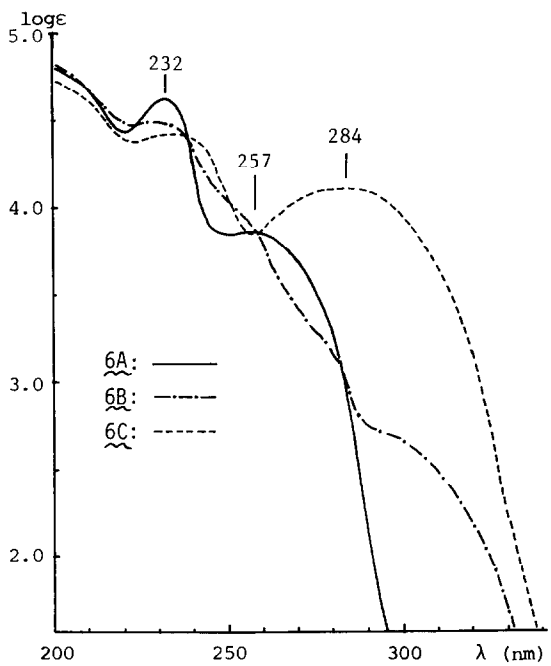


Fig. 1. UV spectra of 6A-C in cyclohexane.

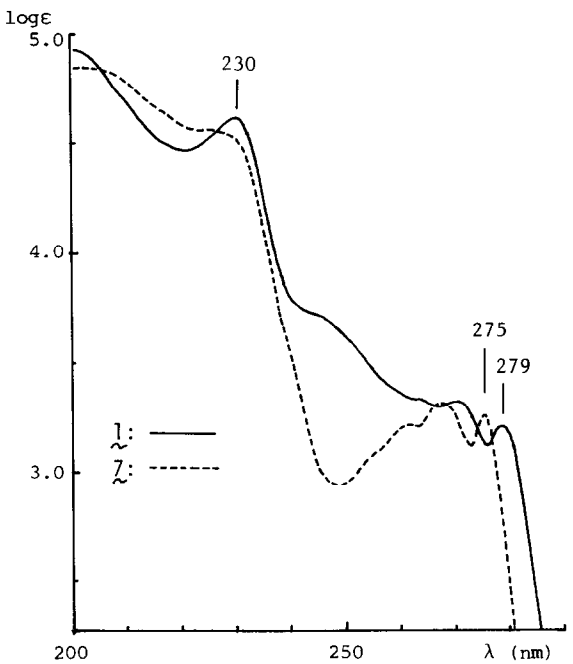


Fig. 2. UV spectra of 1 and 7 in cyclohexane.

This route should allow the synthesis of the other members of [1n]paracyclophanes and, with appropriate dienophiles, their suitably functionalized derivatives which can be utilized as enzyme models. Further synthetic studies are now in progress.

References and Notes

1) For examples, see K. Odashima, A. Itai, Y. Iitaka and K. Koga, J. Am. Chem. Soc., 102, 2504 (1980); S. J. Abbott, A. G. M. Barrett, C. R. A. Godfrey, S. B. Kalindjian, G. W. Simpson, and D. J. Williams, J. Chem. Soc., Chem. Comm., 1982, 796.

2) Tetrathia[1.1.1.1]- and pentathia[1.1.1.1.1]paracyclophanes have recently been isolated from poly(p-phenylene sulfide): M. L. Kaplan and W. D. Reents, Jr., Tetrahedron Lett., 23 373 (1982).

3) As preliminary studies [2.1.1.1.1][a] and [2.1.1.1]paracyclophanes[b] have been synthesized.
a) T. Inazu and T. Yoshino, Bull. Chem. Soc. Jpn., 40, 2213 (1967), ibid., 41, 652 (1968).
b) T. Kawato, T. Inazu, and T. Yoshino, ibid., 44, 200 (1971).

4) The "face" conformation has been shown to be favored even in the more flexible [2.2.2.2]-paracyclophane. See I. Tabushi, H. Yamada, and Y. Kuroda, J. Org. Chem., 40, 1946 (1975).

5) M. Armand and F. Jeanne, Eur. Pat. Appl. 20,210 (1980), Chem. Abstr., 95, 9378y (1981). We have not received as yet any response to our inquiry about the properties of their sample of 1.

6) Although tetradecamethyl[1.1.1.1]metaparametaparacyclophane[a] and dodecamethyl[1.1.1.1]-metacyclophane[b] have been prepared by the Friedel-Crafts reaction, the cyclization to much more strained and conformationally unfavorable 1 would be very difficult and formation of many byproducts may also be produced via dealkylation-alkylation processes. Consequently, the Friedel-Crafts method would not be applicable, if the product solubility were not as low as to make separation feasible.
a) F. Bottino, S. Caccamese, and R. Passerini, Ann. Chim. (Rome), 58, 947 (1968).
b) F. Bottino, G. Montaudo, and P. Maravigna, ibid., 57, 972 (1967).

7) Recently Hart and Takeshita have reported their attempts to convert the fourfold benzyne adduct of octamethyl[1.1.1.1](2,5)furanophane to octamethyl[1.1.1.1]naphthalenophane. See H. Hart and Y. Takeshita, J. Org. Chem., 47, 4370 (1982).

8) All the new compounds reported herein gave satisfactory elemental analyses.

9) U. Schräpler and K. Rühlmann, Chem. Ber., 97, 1383 (1964); K. Rühlmann, Synthesis, 236 (1971). For mechanism, see J. J. Bloomfield, D. C. Owsley, C. Ainsworth and R. E. Robertson, J. Org. Chem., 40, 393 (1975).

10) Molten sodium was dispersed in the presence of aluminum laurate. The use of large excess of sodium (sixfold excess) was found to to be very advantageous. Using 20% excess of sodium and adding 3 over a period of 32 h, 4 was obtained in only 7.5% yield.

11) 6A: IR (KBr) 989 (s, trans) cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 6.99 (s, 4H, Ar), 6.88 (AA'BB', 8H, Ar) 5.56 (m, 4H, CH=CH), 3.70 (s, 4H, CH_2), and 3.06 (d, J=6.5, 4H, CH_2) ppm, ^{13}C-NMR ($CDCl_3$) δ 141.0, 140.9, 140.2 (Ar), 132.2, 130.5 (CH=CH), 127.8 (Ar), 42.1 (Ar_2CH_2), and 37.8 ppm.

12) 6B: IR (KBr) 987 (m) cm^{-1}, ^{1}H-NMR δ 6.98 (s, 4H, Ar), 6.86 (s, 4H, Ar), 6.73 (AA'BB', 4H, Ar), 5.4-6.2 (m, 4H, CH=CH), 3.73 (s, 4H, CH_2), and 3.1-3.4 (m, 4H, CH_2) ppm, ^{13}C-NMR δ 141.4, 141.1, 141.0, 140.7, 138.7, 137.5 (Ar), 133.7, 131.8, 128.4, 126.2 (CH=CH), 128.7, 128.2, 127.8, and 127.4 (Ar), 42.1, 41.6 ($ArCH_2$), 36.0 ($ArCH_2$), and 32.0 (=CH-CH_2) ppm.

13) 6C: IR (KBr) 994 (m) cm^{-1}, ^{1}H-NMR δ 6.99 (s, 4H, Ar), 6.88 (s, 4H, Ar), 6.80 (s, 4H, Ar), 5.6-6.8 (m, 4H, CH=CH), 3.78 (s, $ArCH_2$), 3.73 (s, $ArCH_2$), and 2.0-2.7 (m, 4H, CH_2) ppm, ^{13}C-NMR δ 142.2, 141.0, 140.3, 140.0, 139.2, 135.1, 128.6, 128.5, 128.3, 128.2, 127.8, 127.1 (Ar), 135.5, 130.6 (CH=CH), 42.5, 42.0 ($ArCH_2$), 34.2, and 33.7 (=CH-CH_2) ppm.

14) L. F. Fieser and K. L. Williamson, "Organic Experiments" 3rd Ed. D. C. Heath and Company, 1975, p. 169; L. F. Fieser and M. J. Haddadin, J. Am. Chem. Soc., 86, 2392 (1964).

15) L. A. Paquette, R. E. Moerck, B. Harirchian, and P. D. Magnus, J. Am. Chem. Soc., 100, 1597 (1978).

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