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SYNTHESIS AND STEREOISOMER SEPARATION OF DIFLUORO-[2,2]PARACYCLOPHANE

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SUMMARY

Difluoro[2,2]paracylophane was synthesized by 1,6-Hofmann elimination of 2-fluoro-4-methylbenzyltrimethyl ammonium hydroxide in 34% yield. and four stereoisomers were separated by TLC and HPLC techniques.

INTRODUCTION

Since cyclophanes exhibit unusual structures, properties and applications, they have been extensively studied[1]. Many cyclophanes have been prepared for a variety of interesting studies. A number of fluorinated cyclophanes, such as octafluoro-[2], tetrafluoro-[3], monofluoro[2,2]paracyclophane[4] and 8,16-difluoro-[2,2]metacyclophane[5] are known. On the other hand, D.J. Cram and coworkers studied many disubstituted [2,2]paracyclophanes without including fluorinated paracyclophanes[6]. Therefore, in 1980 we first synthesized difluoro[2,2]paracyclophane by pyrolysis of 2-fluoro-1,4-dimethylbenzene in 12% yield[7]. As part of our continuing interest in the improved synthesis and application of cyclophane as a coating material, we present here another method of synthesis by thermolysis of 2-fluoro-4-methylbenzyltrimethyl ammonium hydroxide which gives a 34% yield, and also report the separation of four stereoisomers by TLC and HPLC techniques. ^{19}F and ^{13}C assignments of each isomer and the properties of the polyfluoroxylylene will be described in a separate paper.

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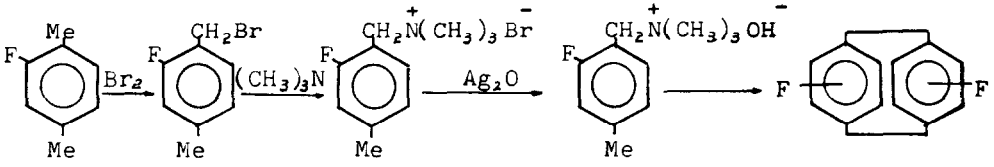
RESULTS AND DISCUSSION

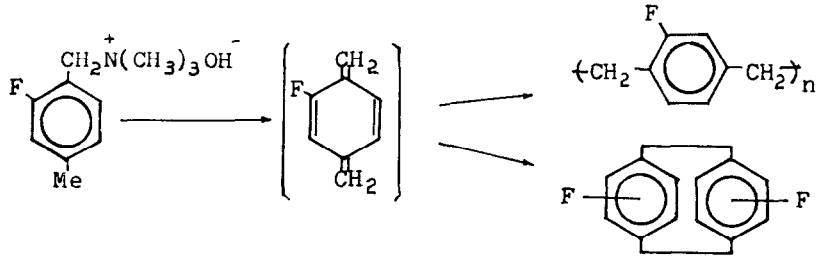
Synthesis

The synthetic procedures are shown in scheme 1.



Scheme 1.

The final step is considered to proceed through a xylylene intermediate. The xylylene subsequently either dimerizes or undergoes intermolecular polymerization(scheme 2).



Scheme 2.

The dimer, difluoro[2,2]paracyclophane,probably possesses a rigid geometry in which two distorted benzene rings lie face to face in close proximity with a strain energy close to that of [2,2]paracyclophane, 31 kcal/mole[8]. Therefore, the yields of analogous dimers are often lower than 30% when this method has been previous described in the literature. In order to prevent the polymerization,a certain amount of an inhibitor(phenothiazine) and a dilute medium are necessary. The following table shows the influence of the inhibitor and the solvent:

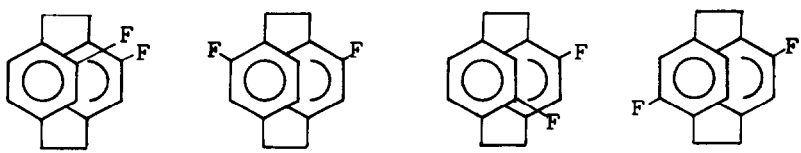
Table 1.

The Influence of the Inhibitor and the Solvent

No.	quaternary salt(g)	inhibitor (g)	solvent (ml)	dimer (g)	polymer (g)
1	12	0.5	toluene 300	1.9	0.8
2	12	0.5	toluene 80	0.15	1,8
3	12	0.3	toluene 300	0.8	2.0
4	12	0	toluene 300	0.45	2.1
5	12	0.5	xylene 300	1.9	0.8
6	12	0	xylene 300	0.45	2.4

Separation

According to the mode of formation and the rigid structure of difluoro[2,2]paracyclophane, in which each benzene ring contains one fluorine, four stereoisomers should exist in the dimer. They are named pseudo-gem,pseudo-m-,pseudo-o-,and pseudo-p-difluoro-[2,2]paracyclophane(scheme 3).The ^{19}F nmr spectrum shows 4 peaks (proton decoupled)(Fig.1) and confirms their existence.



pseudo-gem- pseudo-m- pseudo-o- pseudo-p-

Scheme 3.

For the separation of the four isomers,thin layer chromatography has been used involving a 20*20 silica gel plates developed by benzene : petroleum ether(bp 30-60°C)= 1:4 v/v. One pure isomer was isolated, mp 215°C, MS m/e 244, chemical shift of 19F

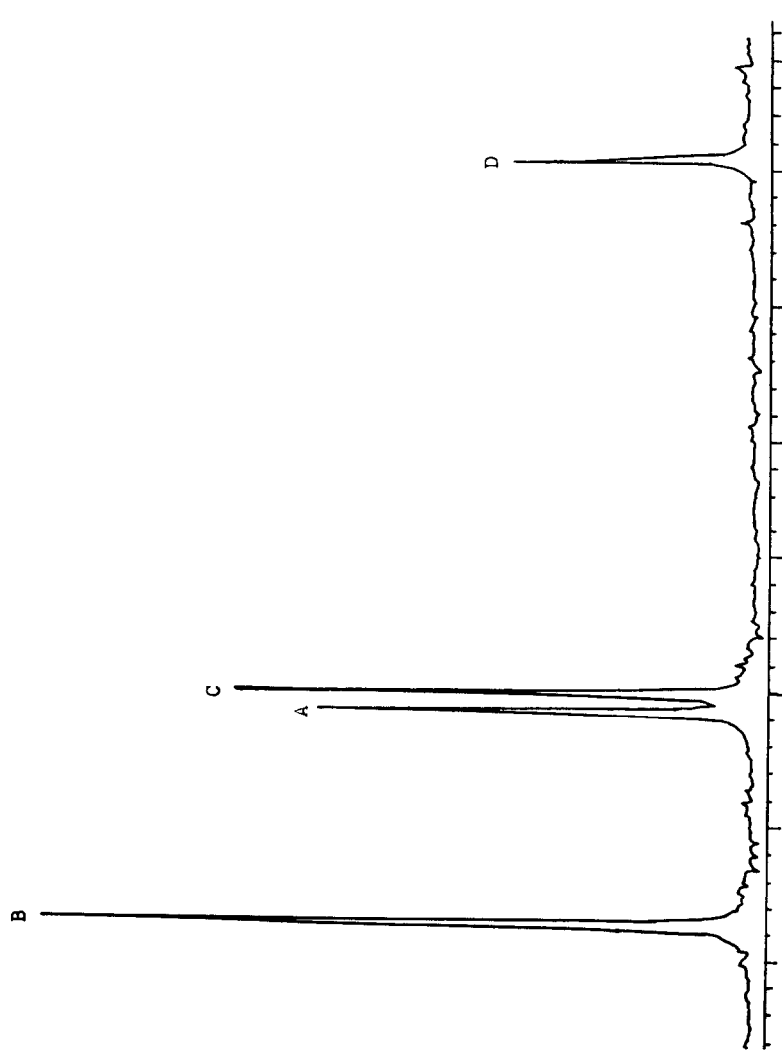


Fig. 1. ^{19}F nmr spectrum (proton-decoupled) of a mixture of stereoisomers of difluoro[2,2] paracyclophane in $CDCl_3$ on Bruker WH90 NMR spectrometer. Ref. internal C_6F_6 (-162.9 ppm).

nmr -118.1 ppm. The other three isomers were not isolated until HPLC was used.The conditions are as follows:

HPLC : Waters, model 510

Column : Whatman Partisil M9, 50cm

Detector : UV 254nm

Mobile phase : pentane:ethyl acetate = 1.4 : 1.0

Each fraction was collected manually, and the isomer identified by ^{19}F nmr

Retention time(min.)	^{19}F nmr(ppm)
38.9	-113.9*
39.6	-112.3*
42.7	-114.0
46.5	-118.1**

* The pure fraction A,B is from 4 times separation under the same HPLC condition.

** This fraction is the same as that from TLC.

EXPERIMENTAL

^{19}F nmr spectra were recorded on a Bruker WH-90 84.66MHZ in $CDCl_3$, C_6F_6 as internal standard. Mass spectrum were determined on a Finnigan quadrupole instrument at 70ev.

The starting material 2-fluoro-1,4-dimethylbenzene was provided by our own laboratory, from nitration of xylene, followed by reduction, diazotization and decomposition of the diazonium tetrafluoroborate salt. Pure 2-fluoro-1,4-dimethylbenzene is a colorless liquid bp 145-147°C.containing 15.27% fluorine(calcd.C_8H_9F 15.32%).

Preparation of 2-fluoro-4-methylbenzyl bromide--- To 63g (0.5 mol) of 2-fluoro-1,4-dimethylbenzene was added dropwise 80g (0.5 mol) of dry bromine over two hours over a 130-50°C oil-bath When the color of bromine disappeared, the reaction mixture was cooled and air bubbled through it to remove HBr until no white fumes passed off. The mixture was distilled to recover the unre-

acted starting material(26g). The residue was distilled under reduced pressure to give two fractions at 97-100°C and 110-115°C /15mmHg. The first one is 55g of 2-fluoro-4-methylbenzyl bromide (yield 86%).and the last one is 9g of 2-fluoro-@@-dibromoxylene.

Anal. Calcd. for C_8H_8BrF: Br, 39.41% Found Br, 39.93%

Preparation of 2-fluoro-4-methylbenzyltrimethylammonium bromide --- To a saturated ether solution of trimethylamine made from 35ml of 33% aqueous trimethylamine and 33g of sodium hydroxide was addded 20g(0.1mol) of 2-fluoro-4-methylbenzyl bromide with stirring to give a white precipitate. Stirring was continued for a further 2 hours and the mixture allowed to stand overnight.The filtered solid was washed 3-4 times with ether and dried under vacuum. 22g of a white hygroscopic salt was obtained mp 178-182°C, yield 85%.

Anal. Calcd. for $C_{11}H_{17}BrFN$: N 5.32% Found: N 4.98%

Preparation of difluoro[2,2]paracyclophane ___ The quaternary hydroxide was prepared by mixing 12g(0.046mol) of the quaternary bromide 12g(0.046 mol) of freshly prepared silver oxide and 40ml of boiled water, stirring at 40-50°C for 1.5 hr..The filtered alkali solution was added in portions to a solution of 0.5g of phenothazine in 300ml of toluene over a 135°C bath. The water separated gradually by azeotropic distillation from a oil-water separator over a period of 2 hr. When the removal of water had been approximately completed, trimethylamine began to evolve and some polymers precipitated. After additional heating with stirring for 2 hr. the reaction mixture was allowed to cool and an insoluble solid was separated. by filteration. The solid was then extracted with toluene in a Soxhlet extrator. The combined toluene layers were evaporated to dryness, giving 2.1g of crude product. Recrystallization from ethanol gave 1.9g of difluoro-[2,2]paracyclophane, mp 211-213°C, yield 34%.M.S m/e 244, ^{19}F nmr(^1H decoupled)-112.3, -113.9, -114.0, -118.1 ppm.

Anal. Calcd. for $C_{16}H_{14}F_2$: C 78.71% H 5.76% F 15.56%
Found C 78.28% H 5.87% F 15.65%

A little solid(mp 68°C) was also obtained from the mother ethanol. It was not studied in detail.

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