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Synthesis of the First Rotaxane Containing a Paracyclophane Ring

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Abstract: A rotaxane, formed in ~50% yield via the standard threading procedure, exhibits profound changes in the NMR spectrum which are attributed to magnetic anisotropy caused by aromatic rings in the trityl groups and the [2.18] paracyclophane.

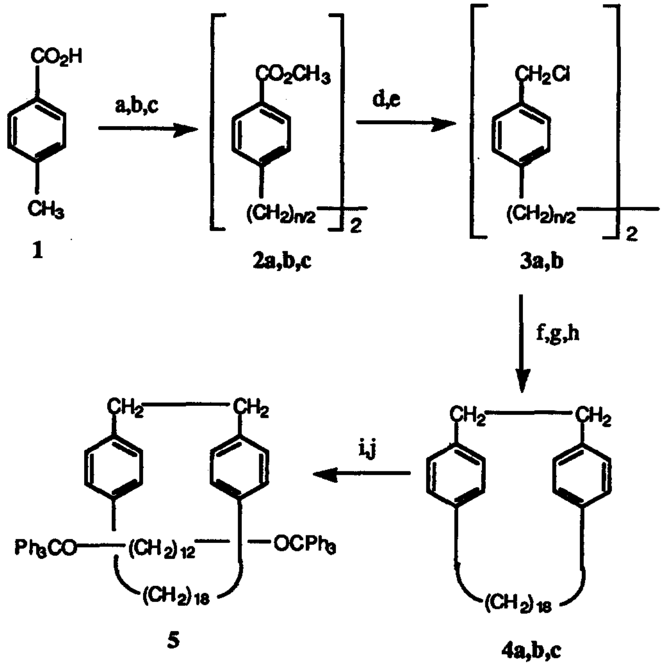
Rotaxanes are molecules in which a macrocyclic ring, playing the part of a wheel (*rota*),[1] has been penetrated by a linear molecule acting as an axle (*axis*).[1] The linear component is terminated at either end by a bulky group that prevents the ring from sliding off. Rotaxanes have been used as diagnostic tools to study the interactions between rings and chains, and as precursors to catenanes.[2] In each of the cases, the rotaxane was formed by statistical means in 1-5% yield,[3] and in cases where NMR data is available, no remarkable changes have been observed in the spectrum on rotaxane formation.[4] When a paracyclophane ring is substituted for a cycloalkane ring, the apparent similarity between the rotaxane spectrum and that of its constituents is illusory, and the synthesis is non-statistical. The 50% yield observed in this case is five times the 10% yield normally recorded for statistical threading.[5] This observation supports the idea that host-guest interactions are important in this case. Presumably steric interactions between the aromatic rings of the cyclophane moiety assist rotaxane formation by holding the macrocyclic ring open wide enough to permit facile threading by the detritylated alcohol intermediate. This type of effect has been observed by Stoddart in systems where charged intermediates and π-π stacking led to threading in 36%,[6] but an effect of this type was unanticipated in the present example. Below, the synthesis of [2]-[1,12-bis-(triphenylmethoxy)-dodecane]-2.18]paracyclophane]-rotaxane, its NMR spectrum are reported.

Based on Harrison's observation[7] that a 28-membered ring provided the optimum internal diameter (4.5 Å) for rotaxane formation, [2.18]paracyclophane was chosen. Molecular modeling studies[8] verified size of the opening, and feasibility of rotaxane formation. Tritylated 1,12-dodecanediol was chosen on the basis that the presence of aromatic rings increased the width of the cyclic component.

The tritylated diol was prepared from 1,12-dodecanediol by standard means.[9] [2.18]Paracyclophane was prepared in 12% yield based on the 1,16-hexadecane, via the appropriate 1,18-bis-(4-chloromethylphenyl)-octadecane.[10] Cyclization to the [3.18]thiaparacyclophane is achieved under infinite dilution conditions[11a] in 87% isolated yield, an improvement over previous procedures.[11b,12] Schills' conditions gave the rotaxane in 49.1% yield,[13] as formulated in the scheme.

Specifically, *p*-toluic acid is deprotonated by using two equivalents of LDA and then allowed to react with 0.5 eq of 1,16-dibromohexadecane. In contrast to the 12-carbon analog, the lithium salt of the diacid precipitates as a thick emulsion that is difficult to filter. In the presence of iodomethane in DMSO the ester forms in spite of the limited solubility of the salt. Reduction with LAH and chlorination of the alcohol with $SOCl_2$ proceed without difficulty.

Scheme

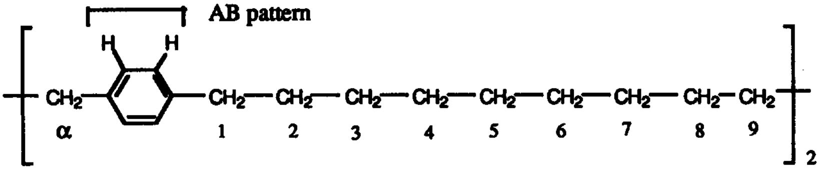


(a) 2 LDA, THF, 0°C; (b) [Br-$(CH_2)_{(n-2)/2}$—]$_2$; (c) CH_3I, DMSO, 60°C;
(d) LAH, Et_2O; (e) $SOCl_2$, cyclohexane, 60°C; (f) n = 9, Na_2S, EtOH (infinite dilution); (g) mCPBA, CH_2Cl_2;
(h) hυ, benzene; (i) [Ph_3CO—$(CH_2)_6$—]$_2$, pTSA, toluene, 100°C; (j) Et_3N.

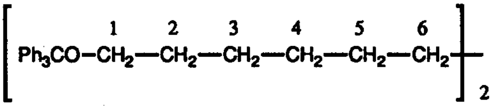
Cyclization to the [3.18]thiaparacyclophane is achieved[12] by adding a saturated solution of $Na_2S \cdot 9H_2O$ in 95% ethanol at a rate of ~1 drop per two minutes to an ethanol solution containing the dichloride at a concentration of 0.7g/L. Oxidation of the sulfide to the sulfone with mCPBA followed by photolysis in benzene yields the paracyclophane in 74% (12% based on 1,16-dibromohexadecane).[13] [2]-[1,12-*bis*-(triphenylmethoxy)-dodecane]-[2.18]paracyclophane]-rotaxane was prepared in ~50% as follows: A solution of pTSA in toluene was prepared by dissolving pTSA • H_2O (0.5 mg) in toluene (25 mL) and concentrated to 2 mL in an effort to remove all traces of water as the toluene-water azeotrope. A mixture of [2.18]paracyclophane (50 mg, 0.116 mmole) and tritylated diol (25 mg, 0.036 mmole) was dissolved in the pTSA/toluene solution and sealed under vacuum in a glass bomb. After heating the reaction mixture for 1 h at 100°C, the bomb was opened and triethylamine (2.6 µL dissolved in 0.5 mL of toluene) was added to quench the reaction. The starting materials were recovered by using column chromatography (alumina eluted with 20% toluene in pet. ether) and the rotaxane (20 mg) was obtained as a waxy solid (mp 184-185°C by using hot methanol.

Table I summarizes changes in the NMR spectra. Assignments were made possible on the basis of DQF-COSY commencing from a cross peak attributed to long range coupling between H-α and H-1. The broad signal in the range 0.8-0.9 ppm is attributed to protons on the threaded chain that fall in the shielding cone of the aromatic moieties in the paracyclophane rings, but cannot be specifically assigned at this time.

Table I. Changes in Chemical Shift as a Result of Rotaxane Formation



Assignment	[2.18]Paracyclophane (ppm)	Rotaxane (ppm)	Δδ (ppm)
H-α	2.89	4.09	+1.02
AB	6.97, 6.78	7.20, 7.14	+0.23,+0.36
H-1 (t)	2.53	3.62	+1.09
H-2 (bm)	1.54	1.43	-0.11
H-3 - H-9 (m)	1.23	1.24	+0.01



$$\left[Ph_3CO-\overset{1}{CH_2}-\overset{2}{CH_2}-\overset{3}{CH_2}-\overset{4}{CH_2}-\overset{5}{CH_2}-\overset{6}{CH_2}- \right]_2$$

Assignment	1,12-tritylated diol (ppm)	Rotaxane (ppm)	Δδ (ppm)
Trityl	7.28	7.32	+0.04
H-1 (t)	3.63	2.62	-1.01
H-2 (bm)	1.51	1.61	+0.10
H-3,4,5,6 (m)	1.27	1.20	-0.07
??		1.10	-0.17
??		0.8-0.9	-0.47 to -0.37

\+ indicates a downfield shift
\- indicates an upfield shift

Work designed to exploit the properties of paracyclophane rings confer on rotaxane - higher than expected yields and interpretable changes in the NMR spectra - is in progress. It is hoped that NMR spectra can provide data concerning the conformation of each component.

Acknowledgment

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1,n-*bis*-benzyl dimethylesters (**2c**), diols (**3a**), and dichlorides (**3b**) made during this work.

n	diester mp (yield)	diol mp (yield)	dichloride mp (yield)
6	60-61 (94.5)	90.5-91.5 (96.7)	70-72.5 (82.3)
7	62-64 (75.7)	91-92 (99.1)	71.5-73 (87.1)
8	63.5-65 (63.4)	91.5-93 (91.4)	72-75 (88.9)
10	64-66 (83.4)	92.5-94 (91.6)	77-78 (86.1)
11	66.5-68 (76.1)	93-95 (96.3)	79.5-81 (85.4)
12	67-69 (83.9)	97-98.5 (91.4)	82.5-83.5 (84.3)
13	66.5-68 (86.4)	100-102 (89.1)	83-85 (81.7)
14	68-69 (76.5)	103-105 (90.6)	84-87 (86.5)
18	71.5-72 (78.3)	106.5-108 (91.2)	91-92 (98.8)

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12. Attempts to cyclize the 1,16-*bis*-[4-chloromethylphenyl]-hexadecane by using Dutta's procedure for the 12-carbon analog failed. Less than 5% yield of the paracyclophane was obtained. No [2.18]paracyclophan-1-ene was detected in the reaction mixture.
13. All new compounds were fully characterized spectroscopically; elemental analysis of the rotaxane required eight waters of hydration even after intensive drying in vaquo. Anal. Calcd for $C_{82}H_{118}O_{10}$: C, 77.93; H, 9.41. Found: C, 77.63, H, 8.71.

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