Preparation of Rotaxanes by the Statistical Method

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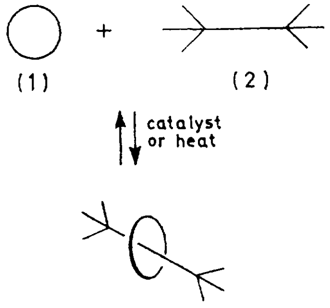
The variation in yield of rotaxane with changes in ring size has been determined for the statistical method and the resulting information has been applied to the preparation of the crystalline [2]-[1,13-di(tris-4-t-butylphenylmethoxy)tridecane]–[cyclodotriacontane]rotaxane (9).

CATENANES[1] (4) and rotaxanes[2] (3) have previously been prepared in small quantities by the statistical method, a process which has the advantage of extreme simplicity. We describe here an investigation of the factors affecting yields in the statistical method and the application of the resulting information to the preparation of a crystalline rotaxane in quantities sufficient for complete characterisation.

In our version of the statistical method an equilibrium is set up between threaded (3) and unthreaded (1) macrocycle by reversible cleavage of large end groups on a chain (2) or by thermally intruding the complete threading piece. It has been predicted[3] from rather approximate calculations, and confirmed[1] experimentally, that very low yields of threaded products will be formed in reactions of this type. The size of the macrocycle and the bulk of the blocking group appear to be the most important factors affecting yields and stability of rotaxanes and were, therefore, investigated prior to preparative work.



(1) (2)

(3) Rotaxanes

(4) Catenanes

A mixture of macrocycles (5)[2] containing all homologues from C_{14} to C_{42} was heated with 1,13-di(tris-4-t-butylphenylmethoxy)tridecane (7) in the presence of naphthalene-β-sulphonic acid, which reversibly cleaves the triaryl ether groups. After equilibrium was attained, the reaction was quenched with base and the threaded products (8) were separated by chromatography. This mixture was then treated with acid, which cleaved the ether blocking groups and released the macrocycles from the rotaxanes. G.l.c. of the released macrocycles allowed a determination of the yield of rotaxane (8) for each ring size. The values obtained, plotted in the Figure, indicate a monotonic increase in yield with ring size from C_{24} (0·0013%) to C_{33} (1·6%) with zero yield for larger ring sizes. When the chromatographic separation was performed at 0°, the thermally unstable C_{34}

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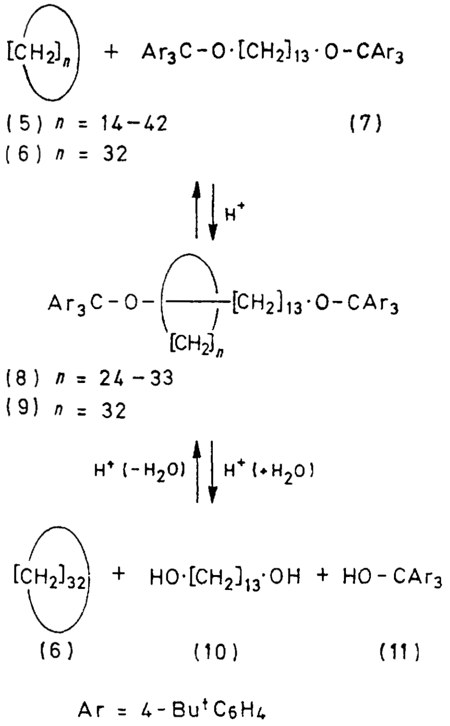
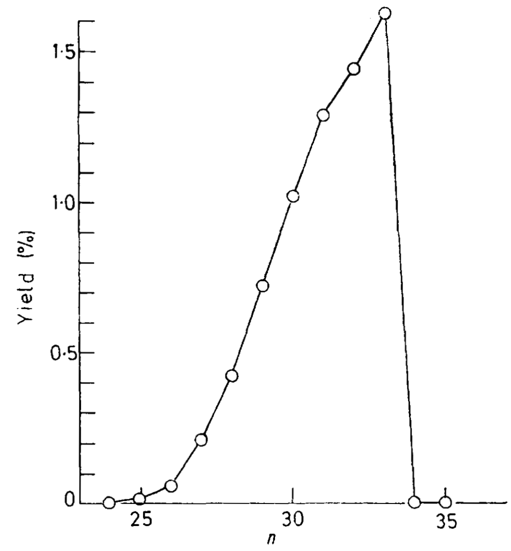
[1] E. Wasserman, *J. Amer. Chem. Soc.*, 1960, **82**, 4433.

[2] I. T. Harrison, *J.C.S. Chem. Comm.*, 1972, 231. For the preparation of rotaxanes by other methods see G. Schill, C. Zürcher, and W. Vetter, *Chem. Ber.*, 1973, **106**, 228.

[3] H. L. Frisch and E. Wasserman, *J. Amer. Chem. Soc.*, 1961, **83**, 3789.

rotaxane was also detected. These results are consistent with deductions from space-filling molecular models,* which show that a macrocycle composed of less than 22 methylene groups is not likely to be threaded by another methylene chain, while macrocycles with about 34 or more methylenes allow passage of the blocking group and, thus, can give only transient rotaxanes.

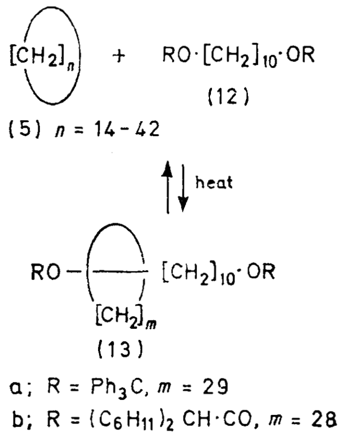




Variation in yield of the rotaxane (8) with ring size (*n*)

The preparation of rotaxanes by thermal intrusion of the complete threading piece was considered for preparative work. Our previous work[2] has shown that a rotaxane (13a) based on a 29-membered macrocycle could be selectively prepared in low yield by heating the macrocycle mixture (5) with the bistriphenylmethyl ether (12a). The triphenylmethyl group can apparently be squeezed through a 29-membered ring, but not through rings of smaller sizes; larger rings are threaded freely giving unstable rotaxanes. In a similar way, the bisdicyclohexylacetate (12b) of decane-1,10-diol formed the 28-membered rotaxane (13b) in low yield. The bistriaryl ether (7) and the macrocycle mixture (5) gave no stable rotaxane on heating to 250° in the absence of catalysts. Thus, threading by thermal means is unsuitable for the preparation of rotaxanes when the larger blocking group tris-4-t-butylphenylmethyl is used.

For preparative work the acid-catalysed cleavage of the blocking group was utilised. A mixture of cyclodotriacontane (6) and the ether (7) was heated in the presence of naphthalene-β-sulphonic acid and the crystalline rotaxane (9) was isolated by chromatography in 1% yield, sufficient for full characterisation. Unchanged starting materials (6) and (7), which could be recycled, were also obtained.



The i.r. spectrum of the rotaxane (9) was indistinguishable from that of an equimolar mixture of the components (6) and (7), as expected for a compound in which two parts are held together by mechanical linkages rather than covalent bonds. The n.m.r. spectrum of the rotaxane and the 1 : 1 mixture of the components did show an important difference. A resonance at δ 1·25 in the spectrum of the mixture due to the 64 protons of the macrocycle was shifted to 1·21 in that of the rotaxane, as a result of shielding by the phenyl groups. A molecular weight estimation of the rotaxane (9) by chromatography on Sephadex LH-20 gave a value of 1300—1600 ($C_{107}H_{168}O_2$ requires 1486).

The thermal stability of the rotaxane (9) was determined by heating small samples until decomposition occurred. At 300° for short periods no decomposition was observed. At 350° partial decomposition took place, releasing the macrocycle (6), but forming only traces of the threading piece (7). We consider that this decomposition proceeds not by extrusion of the complete

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* Constructed from Corey–Pauling (CPK) atomic models.

threading piece but by homolytic cleavage of the triaryl ether[4] blocking group with partial recombination after the macrocycle has separated from the threading chain.

Conclusive proof of the structure of threaded compounds is clearly not available from measurements of physical properties or from chemical transformations. We have, however, degraded the rotaxane (9) under mild conditions by treatment with formic acid and have characterised the resulting macrocycle (6), blocking group (11), and chain (10), which were produced in the expected relative amounts. Since the macrocycle (6) has no functional groups, it must have been bound to the rest of the molecule in some novel way. The rotaxane (9) has also been resynthesised in low yield by heating together the three components (6), (10), and (11) in the presence of an acid catalyst (copper sulphate) and a dehydrating agent (molecular sieves) followed by chromatographic separation.

EXPERIMENTAL

M.p.s were determined with a Mel-Temp apparatus. G.l.c. was performed on 93 ft × 0·03 in (int. diam.) stainless steel capillary columns without a splitter. A planimeter was used for integration. N.m.r. spectra were determined at 100 MHz for solutions in carbon tetrachloride with tetramethylsilane as internal standard. Integrations were consistent with the assignments given. T.l.c. was performed on Merck silica gel $HF_{254+366}$. All t.l.c. plates were cleaned prior to use by development with 1 : 1 hexane–acetone. When triaryl ethers were to be separated, the dry plates were exposed to 2 drops of triethylamine in an empty tank. For column chromatography Merck silica gel 60 was purified in the column by washing successively with several column volumes of acetone, dichloromethane, and pentane. For column chromatography of triaryl ethers the silica gel was suspended in water and disodium hydrogen phosphate solution was added until a pH of about 7·6 was attained. The silica gel was then filtered off without washing and the wet product was further purified in the column as before.

Macrocycle Mixture (5).—A mixture of macrocycles containing all homologues from cyclotetradecane to cyclodotetracontane was prepared as described[2] previously. Traces of n-alkanes were removed by stirring the product (120 mg) in pentane (0·6 ml) with a suspension of urea (50 mg) in saturated methanolic urea (0·6 ml) for 24 h. The upper layer was separated and evaporated, and the residue in pentane was filtered through a short column of silica gel. Evaporation of the solution left the macrocycle mixture (5) as an oil.

1,13-*Di*(*tris*-4-*t-butylphenylmethoxy*)*tridecane* (7).—A solution of toluene-*p*-sulphonic acid (1 mg) in benzene (35 ml) was dried by heating under reflux in a Soxhlet extractor containing molecular sieves (4A). To this solution was added tris-4-t-butylphenylmethanol[5] (4·82 g) and tridecane-1,13-diol (1·07 g) and heating was continued for 24 h. To the cooled solution was added triethylamine (1 ml) and the solution was filtered through a short column of basic alumina. The solvent was evaporated off *in vacuo* and the product crystallised from hexane at 0°. Recrystallisation from acetone–tetrahydrofuran containing a trace of triethylamine gave the *ether* (7) (3·25 g, 63%), m.p. 210—212° (possibly solvated) and a second crop (1·43 g) (Found: C, 86·9; H, 10·05. $C_{75}H_{104}O_2$ requires C, 86·8; H, 10·1%).

Determination of the Variation in Yield of Rotaxane with Ring Size.—The macrocycle mixture (5) (50 mg), and the bistriaryl ether (7) (100 mg; dried at 120° *in vacuo*) were heated and stirred under dry nitrogen in an oil-bath at 220° for 1 min. A solution of naphthalene-β-sulphonic acid (20 μg) in toluene (10 μl) was then added. After 3 min triethylamine (10 μl) was added and the mixture was cooled. T.l.c. in hexane on two 200 × 200 × 1·5 mm silica gel plates gave three main bands, macrocycles R_F 0·9—1·0, rotaxanes (8) R_F 0·3, and ether (7) R_F 0·1—0·25. The rotaxane and ether bands were removed and extracted with pentane–acetone. In an alternative procedure, column chromatography on silica gel was used. Elution with pentane gave the macrocycle mixture (5). Elution with hexane containing benzene (15%) gave the rotaxanes (8) and the ether (7). After evaporation of solvent from the combined solution of (8) and (7), pentane (5 ml) and boron trifluoride–ether complex (20 μl) were added and the mixture was then filtered through a 1 × 15 cm silica gel column; n-dotriacontane (internal standard) was added and most of the pentane was distilled off. The gas chromatogram (OV101; 150—250°) of the resulting macrocycle mixture was integrated and the results were compared with those from the starting material to obtain the following % yields (based on the macrocycle; ring size in parentheses): (24) 0·0013, (25) 0·015, (26) 0·068, (27) 0·21, (28) 0·42, (29) 0·72, (30) 1·02, (31) 1·29, (32) 1·44, (33) 1·62, (34—38) 0%. The C_{34} macrocycle was detected in 0·1% yield when the rotaxane separation was performed at 0°.

Threading of Cyclo-octacosane by Decane-1,10-*diyl Bisdicyclohexylacetate.*—A solution of dicyclohexylacetic acid (750 mg) in tetrahydrofuran (15 ml) and triethylamine (0·47 ml) was treated with ethyl chloroformate (0·32 ml) at 0°. After 15 min a solution of decanediol (180 mg) in tetrahydrofuran was added, followed by triethylamine (0·47 ml). After 1 h water and hexane were added, and the hexane layer was separated, washed with sodium hydrogen carbonate solution and with water, and evaporated. The crystalline residue of the *bisdicyclohexylacetate* (12b) (360 mg, 97%), which could not be recrystallised, had m.p. 52—53° (Found: C, 77·35; H, 11·2. $C_{38}H_{66}O_4$ requires C, 77·75; H, 11·35%). This diester (100 mg) and the macrocycle mixture (5) (100 mg) were heated together at 220° for 15 min. The products were separated by t.l.c. on silica gel (hexane). A band of R_F 0·4 containing the rotaxane (13b) was removed and extracted with benzene. The solvent was evaporated off, hexane (5 ml) and concentrated sulphuric acid (2 ml) were added, and the mixture was stirred for 40 min. The hexane layer was then separated and filtered through a short column of silica gel giving, after evaporation, cyclo-octacosane (*ca.* 0·5 mg), identified by g.l.c.

Cyclodotriacontanone and Cyclodotriacontane (6).—A solution of dimethyl dotriacontanedioate[6] (10·76 g) and trimethylsilyl chloride[7] (8·6 g) in dry xylene (160 ml) was added from a heated Hershberg dropping funnel during

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[4] Thermal decomposition of trityl ethers has been studied previously: J. F. Norris and R. C. Young, *J. Amer. Chem. Soc.*, 1930, **52**, 753.

[5] C. S. Marvel, J. F. Kaplan, and C. M. Himel, *J. Amer. Chem. Soc.*, 1941, **63**, 1892.

[6] S. Hünig and H. J. Buysch, *Chem. Ber.*, 1967, **100**, 4017.

[7] K. Rühlmann, *Synthesis*, 1971, 236.

11 h to a rapidly stirred suspension of sodium (2·3 g) in dry xylene (600 ml) heated under reflux in an atmosphere of nitrogen. The mixture was heated for a further 1 h, then cooled, and the solution was separated from the excess of sodium and polymer by centrifugation. The solvent was evaporated off, giving crude 2-hydroxycyclodotriacontanone as the bistrimethylsilyl enol ether. This was suspended in acetic acid (150 ml), phenol (2 g) and hydriodic acid (47%; 10 ml) were added, and the mixture was heated under reflux for 80 min.[8] Water was added and the products were extracted into benzene–ether. The organic phase was washed with water, with sodium hydrogen sulphite solution, and again with water. The solvent was evaporated off and the product in acetic acid (120 ml) and tetrahydrofuran (120 ml) was treated with zinc dust (10 g) for 1 h to reduce iodine-containing compounds. Benzene was added, the mixture was filtered, and the filtrate was washed several times with water. Evaporation left an oil which was chromatographed on silica gel (gradient elution; 100% hexane to 100% dichloromethane) yielding almost pure *cyclodotriacontanone* (3·5 g, 38%). A sample crystallised from acetone–ethanol had m.p. 59—60° (Found: C, 82·8; H, 13·55. $C_{32}H_{62}O$ requires C, 83·05; H, 13·5%).

A solution of cyclodotriacontanone (740 mg) and tosylhydrazine (320 mg) in tetrahydrofuran (2 ml) was heated under reflux for 2 h. The solvent was removed and the residue thoroughly mixed with palladium–charcoal (10%; 10 g) and hydrogenated * without solvent for 5 h in an oil-bath at 175—180°. The product was extracted with chloroform and the solution evaporated. The residue was treated with urea as described before for the removal of traces of linear alkanes, giving cyclodotriacontane (6) (484 mg, 23% from dimethyl dotriacontanedioate), m.p. 64—66°. A sample recrystallised from acetone had m.p. 67—68° (lit.,[10] 59—60°), *m/e* 448 (M^+).

[2]-[1,13-*Di(tris-4-t-butylphenylmethoxy)tridecane*]-[*Cyclodotriacontane*]*rotaxane* [11] (9).—A mixture of cyclodotriacontane (6) (420 mg), the ether (7) (420 mg), and naphthalene-β-sulphonic acid (0·35 mg) was heated and stirred under nitrogen for 2 min in an oil-bath preheated to 220°. The bath was allowed to cool to 100° during 15 min and triethylamine (3 μl) was added. The products were dissolved in pentane and chromatographed on silica gel (50 g). Elution with pentane gave cyclodotriacontane (400 mg, 95% recovery). Elution with hexane containing acetone (10%) gave a mixture of the ether (7), rotaxane (9), and smaller amounts of other compounds. This mixture was dissolved in heptane and applied to five 200 × 200 × 1·5 mm silica gel t.l.c. plates, which were developed twice with pentane. The u.v.-absorbing band just above that due to the ether (7) was removed and extracted with hexane containing acetone (20%). Evaporation of the extract gave the pure *rotaxane* (9) as a white solid (15 mg, 1·1% based on cyclodotriacontane), which separated from acetone at 0° as small white prisms (11 mg), m.p. 150—151°, unchanged by further recrystallisation (Found: C, 86·6; H, 11·4. $C_{107}H_{1}$ O_2 requires C, 86·45; H, 11·4%), δ 1·21 (s, cyclodotriacontane), 1·28 (s, Bu^t), 2·98 (t, OCH_2), and 7·19 (s, ArH). The resonance due to $[CH_2]_{11}$ of the threading chain was not resolved from the resonances at 1·21 and 1·28. An equimolar mixture of cyclodotriacontane and the ether (7) had δ 1·25 (s, cyclodotriacontane), 1·28 (s, Bu^t), 2·97 (t, OCH_2), and 7·20 (s, ArH). The i.r. spectra (KBr) of the rotaxane (9) and the mixture of cyclodotriacontane and ether (7) were identical (17 peaks and 3 inflections) but were not highly characteristic owing to the presence of a large proportion of methyl groups and methylene chains. The molecular weight of the rotaxane (9) was estimated to be 1300—1600 ($C_{107}H_{168}O_2$ requires 1486) by chromatography on Sephadex LH-20 with ether (7) and tris-4-t-butylphenylmethanol (11) as standards [elution with chloroform containing triethylamine (0·5%)].

Thermal Decomposition of the Rotaxane (9).—Samples (*ca.* 0·1 mg) of the rotaxane (9) under nitrogen in thin-wall m.p. capillaries were heated for 30 s in a Wood's metal bath. At 300° no significant decomposition occurred. At 350° partial decomposition gave cyclodotriacontane (6) (separated by t.l.c. and identified by g.l.c.), traces of the ether (7) (t.l.c. identification), and other, unidentified compounds.

Degradation of the Rotaxane (9).—A solution of the rotaxane (9) (4 mg) in dichloromethane (0·2 ml) was added to a mixture of formic acid (10 μl), water (20 μl), and acetone (0·4 ml). After 24 h, the solvents were evaporated off. G.l.c. of the residue indicated the presence of tridecane-1,13-diol (10), tris-4-t-butylphenylmethanol (11), and dotriacontane (6) in the same ratio (±10%) as from treatment of an equimolar mixture of dotriacontane and the ether (7) with acid. The products of the rotaxane degradation were separated by t.l.c. on silica gel and recrystallised in 0·5 ml stoppered tubes. The tubes were inverted and centrifuged, forcing out all mother liquors around the stopper and leaving the crystals in the tube. Washing of the crystals was not required. The products were tris-4-t-butylphenylmethanol, m.p. 220—222° (possibly solvated) (from acetone–hexane), cyclodotriacontane, m.p. 67—68° (from acetone), and tridecane-1,13-diol, m.p. 77° (from acetone–hexane), all identical (mixed m.p.) with authentic samples.

Synthesis of the Rotaxane (9) *from Cyclodotriacontane* (6), *Tris-4-t-butylphenylmethanol* (11), *and Tridecane*-1,13-*diol* (10).—A mixture of cyclodotriacontane (110 mg), tris-4-t-butylphenylmethanol (110 mg), tridecane-1,13-diol (24 mg), anhydrous copper sulphate (100 mg), and molecular sieves (4A) (100 mg) was heated and stirred in an oil-bath at 180° for 30 min. The mixture was cooled to 100° and triethylamine (50 μl) was added. The products were separated by chromatography as in the previous preparation of the rotaxane (9). The resulting rotaxane (*ca.* 1 mg) had the same R_F value (t.l.c.) as an authentic sample and was degraded by formic acid to cyclodotriacontane (6), tris-4-t-butylphenylmethanol (11), and tridecane-1,13-diol (10), identified by g.l.c. and t.l.c.

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* This method of vigorous hydrogenation was found to give higher yields than the process using sodium borohydride.[9] Hydrogenation could also be achieved with smaller ratios of catalyst to substrate in butane-1,3-diol at 130°.

[8] W. Reusch and R. LeMahieu, *J. Amer. Chem. Soc.*, 1964, **86**, 3068.

[9] L. Caglioti and P. Grasselli, *Chem. and Ind.*, 1964, 153.

[10] L. Ruzicka, M. Hürbin, and M. Furter, *Helv. Chim. Acta*, 1934, **17**, 78.

[11] For nomenclature of rotaxanes see G. Schill, 'Catenanes, Rotaxanes and Knots,' Academic Press, New York, 1971, p. 7.