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STEREOCHEMISTRY OF COMPOUNDS RELATED TO TORUS. ENANTIOMERISM

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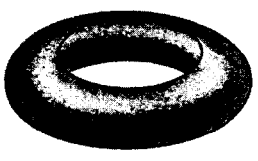
Abstract: *Optical resolution of compounds 4 and 9 were achieved. The existence of the enantiomerism is analysed in terms of the stereochemistry of compounds related to torus.*

Torus (1) is related topologically to the planar surface annulus (2)[1]. This can be illustrated by the punctured torus (3) which is a bridged annulus. Just as planar cyclic polyenes have been referred to as annulenes[2], it may be useful to consider cyclic hydrocarbons as having the torus structure. This permits us to look beyond the different conformations assumed by the cyclic hydrocarbons and concentrate on their similar topological properties. In this sense, crown ethers have also the torus structure even though they do not have a uniform meridian. Various cyclophanes[3] can be regarded as punctured toruses.



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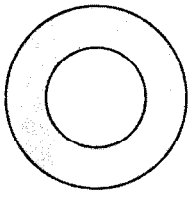

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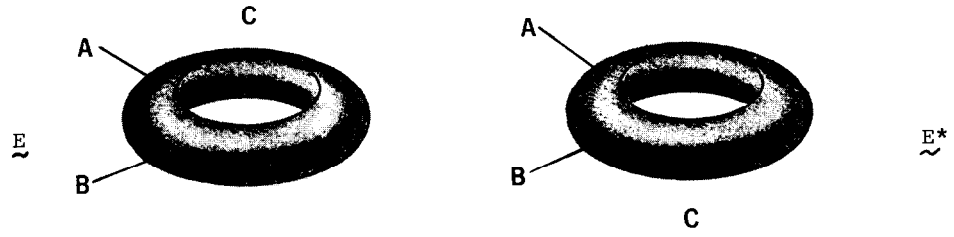
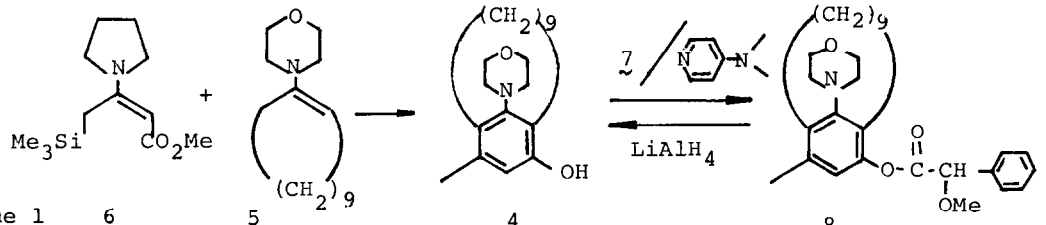
We define a plane which bisects a torus along its longitude. This plane separates the space relative to the torus into three parts: the cavity, the space above and below the plane. When two groups, A and B, are attached to a torus on the plane, the plane becomes pro-chiral[4]. If a group C is placed either above or below the plane, the two arrangements (E, E*) are enantiomeric, defined herein as torus enantiomers. Enantiomerization (E ⇌ E*) can be achieved by either of the following two processes. (1) the group C can pass through the cavity of the torus or (2) the group C can dissociate and then recombine with the torus to give either enantiomers E and E*. If either processes are pro-

hibited, optical resolution of the two enantiomers is in principle feasible[5].



We have recently synthesized the m-cyclophane compound 4 by condensation of the enamine 5 derived from cyclododecanone (scheme 1) and the silyl compound 6 under acid-catalysed conditions[6]. Examination of molecular model of 4 shows clearly that the morpholino group is too large to be accommodated inside the cavity of the hydrocarbon torus[11]. It must be placed either above or below the plane of the torus, thus satisfying the conditions for the existence of torus enantiomers. We have in fact been able to resolve the two enantiomers via the O-methyl mandelate esters according to scheme 1.



Scheme 1 6 5 4 8

When 4 was reacted with (R)-(-)-O-methylmandelic acid chloride (7) and 4-dimethylaminopyridine in THF, the ester 8 was formed in essentially quantitative yield. The ester 8 existed as a mixture of two diastereomers, α and β, clearly distinguishable by ^{1}H nmr[9]. Careful flash chromatography[8] on silica gel column using pentane, acetonitrile and ethyl acetate as eluent led to separation of the two diastereomers. Reduction of the α-diastereoisomer with lithium aluminum hydride gave the phenol (-)-4, with $[\alpha]_D^{20}$ = -30° (acetone), otherwise spectroscopically identical to the racemic compound. Similar reduction of the β-diastereomer with LAH gave (+)-4, $[\alpha]_D^{20}$ = + 26° (acetone). The two enantiomers showed mirror image relationship in their ORD curves (Figure 1).

Similar successful resolution has been achieved with the phenolic compound 9, synthesized from the corresponding enamine derived from cyclopentadecanone[10].

We believe that this successful resolution opens the door to the study of the stereochemistry of compounds related to torus. Further results will be reported in due course.

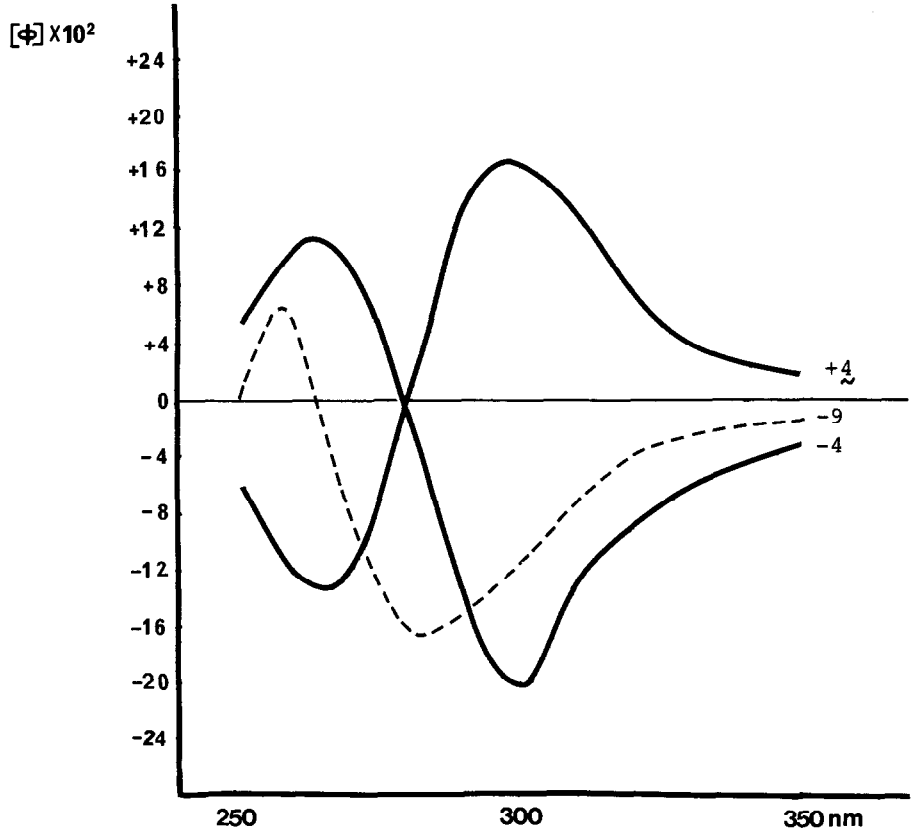
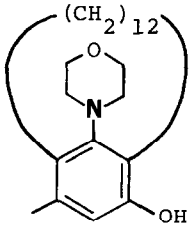


Figure 1: Optical Rotatory Dispersion Curves of Compounds 4 and 9. The ORD curve of +9 is enantiomeric to the -isomer.



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2. F. Sondheimer and R. Wolovsky, J. Amer. Chem. Soc., 84, 260 (1962).
3. See B.H. Smith, "Bridged Aromatic Compounds", Academic Press, New York, 1964.
4. K.R. Hanson, J. Amer. Chem. Soc., 88, 2731 (1966).
5. The exception is when A,B,C lie on a plane perpendicular to and bisecting the torus. The existence of this kind of enantiomerism was recognized, but optical resolution was unsuccessful. See G. Schill, Chem. Ber., 99, 2689 (1966), also G. Schill, Catenanes, Rotaxanes and Knots, Academic Press, 1971, New York, p. 60.
6. Experimental conditions: to a mixture of 5 (2.57 g, 10 mmol) and 6 (1.2 g, 5 mmol)[7] trifluoroacetic acid (1.14 g, 10 mmol) was added drop by drop at 0°C with stirring. The mixture was warmed up to room temperature and stirred for 10 minutes and then heated to 80° for 24 hrs. To the cooled reaction mixture, 300 ml ether was added. The ether solution was washed with aqueous acid (1.5N HCl), dried ($MgSO_4$), and evaporated to give 2.45 g of brown oil. Flash chromatography[8] on silica gel, eluted with petroleum ether/ethyl acetate gave 0.81 g 4, (51% yield). M.p. 174-177 ^{1}H nmr ($CDCl_3$): 6.40 (s,1H), 4.66 (s,1H), 3.70-3.86 (m,4H), 3.16-3.33 (m,4H), 2.54-3.10 (m,4H), 2.18 (s,3H), 0.68-1.5 (m,12H), 0.2-0.4 (m,2H); IR(KBr): 3290, 1590, 1110 cm^{-1}; MS: m/z = 317 (91%), 260 (37%), 249 (100%).
7. T.H. Chan and G.J. Kang, Tetrahedron Letters, 23, 3011 (1982).
8. W.C. Still, M. Khan and A. Mitra, J. Org. Chem., 43, 2923 (1978).
9. ^{1}H nmr ($CDCl_3$): α-isomer, 7.32-7.54 (m,5H), 6.52(s,1H), 4.94(s,1H), 3.68-3.73 (m,4H), 3.50 (s,3H), 3.14-3.18 (m,4H), 3.0-2.4 (m,4H), 2.18 (s,3H), 1.9-0.1 (m,14H); β-isomer, 7.32-7.54 (m,5H), 6.61 (s,1H), 4.94 (s,1H), 3.66-3.71 (m,4H), 3.46 (s,3H), 3.14-3.16 (m,4H), 3.0-2.4 (m,4H), 2.18 (s,3H), 1.9-0.1 (m,14H).
10. Compound 9: m.p. 201-204°; ^{1}H nmr ($CDCl_3$), 6.46 (s,1H), 4.44(s,1H), 3.71-3.82 (m,4H), 2.40-3.5 (m,8H), 2.21 (s,3H), 1.8-0.8 (m,20H); IR (KBr), 3300, 1585, 1100 cm^{-1}; MS, m/z = 359 (100%). For (+)-isomer, $[\alpha]_D^{20}$ = + 11° (THF); (-)-isomer, $[\alpha]_D^{20}$ = - 17° (THF).
11. X-ray structure determination of a m-cyclophane has recently been reported. F. Effenberger, K-H. Schönwälder and J.J. Stezowski, Angew. Chem. Internat. Ed., 21, 871 (1982).

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