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THE ABSOLUTE CONFIGURATION OF CIS, TRANS- 1,5-CYCLOOCTADIENE. DETERMINATION OF ENANTIOMERIC PURITY WITHOUT KNOWLEDGE OF THE MAXIMUM OPTICAL ROTATION AND WITHOUT THE AID OF AN AUXILIARY OPTICALLY ACTIVE SUBSTANCE.

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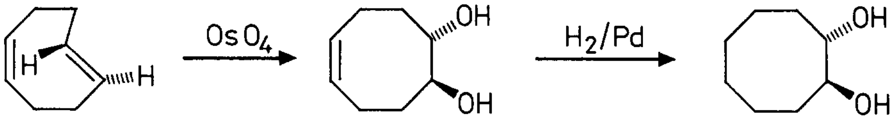
(-)-cis,trans-1,5-cyclooctadiene (1), prepared by resolution of the racemic diene (1), was transformed into (+)-trans-1,2-cyclooctanediol (3) according to scheme I.



R-(-)-1 (1S, 2S)-(+)-2 (1S, 2S)-(+)-3

Scheme I

Dropwise addition of 1,2 mmole OsO_4 in 8 ml ether to 1.1 mmole of 91.3 % enantiomerically pure (-)-1 in 8 ml ether + 0.5 ml pyridine under agitation at -70°C, warming to r.t., collecting the brown precipitate, refluxing it for 2 1/2 hr with 1.7 g Na_2SO_3 in EtOH/H_2O, workup by ether/H_2O partitioning and Kugelrohr distillation gave 43 mg (+)-2, colorless oil, b.p. 90°C/0.01 mm, 99 % pure by g.l.c., CH satisfactory; ^{1}H.m.r. (CCl_4): δ = 1.2-2.5 (m, 8H, CH_2), 3.28 (s, 2H, OH), 3.53 (broadened A_2 part of an A_2X_2 system, 2H, α to OH), 5.54 (quasi t 8 cps wide, 2H, olefinic); $[\alpha]^{30}_{546}$ = +34.7°, $[\alpha]^{30}_{578}$ = +31.7° (c 0.49, ethanol). Catalytic hydrogenation of 30 mg (+)-2 (10 % Pd/C, ethanol, r.t., 1 at.) resulted in rapid uptake of 1 mol of H_2 to give after Kugelrohr distillation 22 mg (+)-3, which by g.l.c. and ^{1}H.m.r. proved to be 99 % pure, identical to authenic racemic material and free from the cis isomer (2), $[\alpha]^{27}_{546}$ = +17.7°, $[\alpha]^{27}_{578}$ = +15.4° (c 1.33, ethanol). Taking into account the 91.3 % enantiomeric purity of the starting (-)-1, $[\alpha]^{27}_{578}$ = +16.9° is thus calculated for enantiomerically pure (+)-3 which compares well with the values reported by Cope and Mehta (+17.21°, ethanol) (3) and Corey and Shulman (4). Since the absolute configuration of (+)-3 has been established as (1S,2S) by Cope and Mehta (3), this transformation, together with the assumption that OsO_4 attacks the unhindered side of the trans double bond of 1, shows the absolute configuration of (-)-1 to be R.

The enantiomeric purity of 1 was determined as follows.

A general method to determine the enantiomeric purity of a substance whose maximum optical rotation (i.e. the optical rotation of an optically pure sample) is not known is to convert it irreversibly into dimers of any kind (e.g. an alcohol into a diester by esterification with a dicarboxylic acid, or an amino acid into a dipeptide, and so on) in which the configurations of the monomers are retained (5). The dimers formed from d+l will then be diastereomeric to those formed from d+d and l+l and the enantiomeric purity can be obtained from the relative amounts of the diastereomeric dimers formed: If a denotes the ratio of d+l dimer(s) to (d+d) + (l+l) dimer(s) obtained from racemic material and b_o, b_c and b_1 the analogous ratios from the optically active material under investigation, extrapolated to zero conversion, after 100 c%, and after 100% conversion to dimers, respectively, then it can easily be shown that the following expressions hold (6):

$$\%\ \text{enantiomeric purity} = 100\sqrt{\frac{a - b_o}{a + b_o}}$$

and, for the limiting case of enantiomeric purities near 100%,

$$\underset{(\rightarrow\ 100)}{\%\ \text{enantiomeric purity}} = 100\left(1 - \frac{b_o}{a}\right) = 100\,\frac{1-(1-c)^{a}-\frac{c}{2}b_c}{1-(1-c)^{a}+\frac{c}{2}b_c} = 100\,(1-b_1)$$

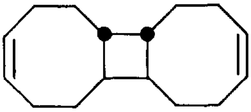
The merits of this method are that 1.) it does not require any auxiliary optically active material (it is therefore independent from the enantiomeric purity of such a material)- in fact, it does not even require a measurement of optical rotation- and 2.) may - as in the case under investigation here - allow the precise determination of even a very small enantiomeric impurity.

Racemic 1 on standing changes into a mixture of three dimers, 4-6 (7). (-)-1, prepared by thorough resolution of racemic 1 (crystallisation of the mono Pt complex to constant rotation and m.p.) (1), gives the same three dimers; their proportions, however, are very different. Table I shows the results (average values in case of RS-1, representative runs in case of R-(-)-1).

T(°C)	chirality of 1	% relative yield 4	5	6	conversion[a)] c	ratio 4/5 a	b_c	calculated % enantiomeric purity
	RS	64.57	6.56	28.87	b)	9.84	-	0
25	R-(-)	0.58	69.2	30.2	0.03	-	0.00842	99.90
	"	0.47	73.1	26.4	0.059	-	0.00646	99.92
	RS	59.42	9.18	31.4	b)	6.47	-	0
70	R-(-)	0.63	69.3	30.1	0.044	-	0.00906	99.84
	"	0.57	70.3	29.1	0.078	-	0.00813	99.85

Table I.) Dimerization of racemic (RS)-1 and of R-(-)-1 (10% in dimethylformamide)

a.) 100% conversion → $c \equiv 1$ b.) relative yield independent from c



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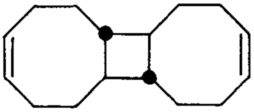

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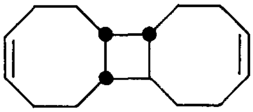

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Clearly - both from the relative yields and from the structures - 4 is a d+l dimer, 5 a (d+d) + (l+l) dimer and 6 is formed from both (d+l) and (d+d) + (l+l). The ratios of 4 to 5 therefore have to be considered. (6 can be omitted from the considerations in this specific case as it happens to be formed in virtually equal proportion both from d+l and from d+d and l+l (7) and thus cancels out from the equations.). With the assumptions that the small amount of 4 in the dimer mixture formed from (-)-1 is exclusively a d+l product i.e. exclusively due to the enantiomeric impurity, and, conversely, that the 5 formed from racemic 1 is formed exclusively from d+d and l+l - the latter assumption has been verified by kinetic measurements (7) - one calculates the values for a, b_c, and "% enantiomeric purity" given in Table I.

The optical rotation of enantiomerically 100% pure (-)-1 was calculated from the rotations of two different samples of (-)-1, 98.4 and 99.9% enantiomerically pure. It was found as $[\alpha]_{546}^{20}$: - 140.3°, $[\alpha]_{578}^{20}$: - 122.9°, $[\alpha]_{D}^{20}$ (calculated) : -117.4° (c 0.49, CH_2Cl_2) from one sample and -145.4°, -127.7°, -122.2°, respectively, (c 0.45, CH_2Cl_2) from the other. Like values were obtained from enantiomerically less pure samples. These values are at variance with the value $[\alpha]_{D}^{0}$ = -152° reported by Cope (1). A possible explanation for our lower values would be partial dimerization and polymerization - the dimers from (-)-1 show positive rotation (7) - and/or other impurities. This explanation however is ruled out by the fact that our (-)-1 (prepared neat by cold NH_3/H_2O decomposition of its pure crystalline Ag complex followed by rapid cold workup and rapid Kugelrohr distillation at 32°/11 mm using a chilled receiver bulb) had its rotation measured immediately after preparation and subsequently was found to be virtually free from dimers, cis,cis-1,5-cyclooctadiene, polymers and other impurities by g.l.c. using n-$C_{16}H_{34}$ as a weighed added standard. The reason for the discrepancy therefore remains unclear; it should be noted, however, that values comparable to ours, $[\alpha]_{D}^{25}$ = +121.3°, -120.5°, had been found by Cope for (-)-1 obtained by Hoffmann degradation of enantiomerically ca. 100% pure cyclooct-(4)-enyl trimethyl ammonium salt (8); this might mean that the Hoffmann degradation really had proceeded with ca.100% conservation of the absolute configuration.

References and notes

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6.) All that is required are the second order kinetic expressions for the formation of the dimers and the expressions for enantiomeric purity and for conversion in terms of the concentrations of d and of l.

7.) Full details and implications of this dimerization reaction will be treated in a forthcoming paper; J. Leitich, manuscript in preparation.

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