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CONFORMATIONAL ANALYSIS OF 2,3,5,6-TETRAKIS(METHYLENE)BICYCLO[2.2.2]OCTANES BY CIRCULAR DICHROISM.

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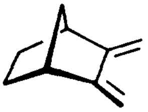
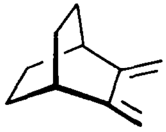
Summary. *The variable temperature CD spectra of (+)-(7R)-7-deuterio- and (+)-(7S)-7-methyl-2,3,5,6-tetrakis(methylene)bicyclo[2.2.2]octane suggest single energy minimum hypersurfaces with eclipsed bicyclic skeletons and planar dienes whereas that of (-)-(2R)-5,6,7,8-tetrakis(methylene)-2-bicyclo[2.2.2]octanol is consistent with a twisted structure.*

Theoretical calculations[1] and experimental results[2,3] indicated that the bicyclo[2.2.2]-octane skeleton possesses a broad energy minimum for twisting around the C(1)-C(4) axis. From PES[4] and ^{13}C-NMR data,[5] Klessinger et al. proposed an eclipsed structure for 1 and a twisted one for 2, whereas force field MMPI 1 calculations predicted eclipsed conformations with planar s-cis-butadiene moieties for 1-4.[6] Recently it was determined that [2.2.2]hericene (4) has virtual D_{3h}-symmetry in the crystalline state.[7] We report here the circular dichroism (CD) spectra of the optically pure tetraenes 5-7. The results suggest for 5 and 6 single energy minimum hypersurfaces with eclipsed bicyclic skeletons and planar dienes whereas a twisted structure is possible for 7.



1



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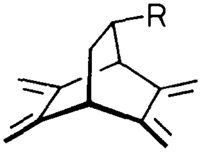
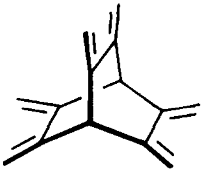


3 R = H
(+)5 R = D
(-)6 R = CH_3
(-)7 R = OH



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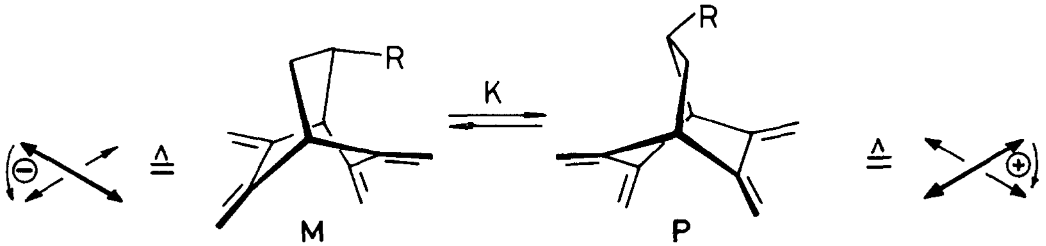
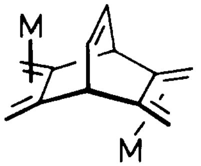
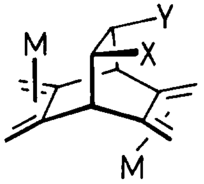


Figure 1.

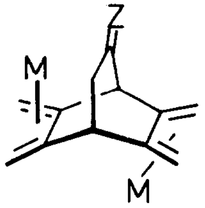
Variable temperature CD spectroscopy is a sensitive technique for detecting nearly degenerate equilibria of two conformers whose chromophores have opposite chirality.[8] This is expected to be the case for the hypothetical, rapidly equilibrating structures M $\rightleftarrows$ P (Fig. 1). Furthermore, if the twist were significant the CD spectra of M and P should possess double Cotton Effects (CE) of opposite sign around 250 nm due to exciton coupling[9] between the two dienes. If the equilibrium constant K ≠ 1, the sum of the CD spectra of M and P should also display two CE's of opposite sign. We chose substituents R = D (5) and R = CH_3 (6) in order to fullfill the following requirements: (1) the equilibrium M $\rightleftarrows$ P must be perturbed by a few cal/mol only; (2) no conformational equilibrium around the C-R bond must be introduced, and (3) polar groups must be avoided as they can lead to aggregation and solvation equilibria[10] thus making the CD spectra temperature dependent (see e.g. the variable temperature CD spectrum of (-)-7 which lacks an isochroic point, Fig. 2).



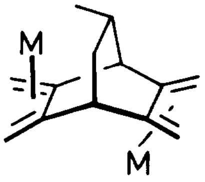
8



9 X=OH, Y= D
10 X=OMs, Y= D
11 X=H, Y= D
12 X=H, Y=OH



13 Z=O
14 Z=CH_2



15

M = $Fe(CO)_3$

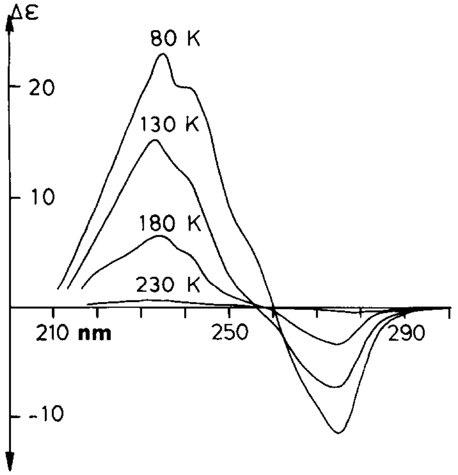


Figure 2. Variable temperature (T) CD spectra of (-)-7 in isopentane/methylcyclohexane 4:1 (IPM 41)

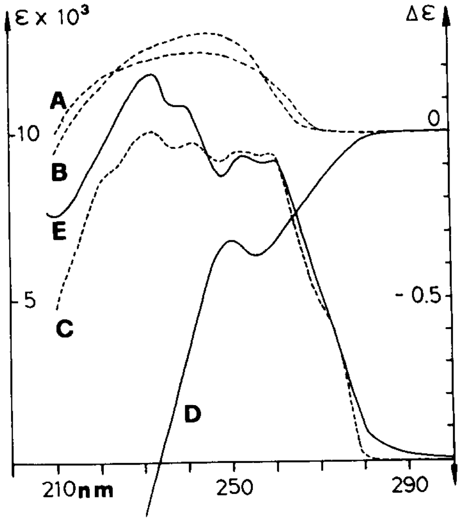


Figure 3. CD spectra of (+)-5 in (A) ether/isopentane/ethanol 5:5:2 (EPE 552) and (B) in IPM 41; they do not vary with T. UV absorption spectrum (C) of 3 and (E) of 6 in isooctane. (D): CD spectrum of (+)-6 in EPE 552, same in IPM 41; they do not vary with T.

Oxidative deuteroboration ($NaBD_4/BF_3\cdot Et_2O$) of **8**[11] gave alcohol (±)-**9** whose optical resolution was accomplished using Gerlach's technique[12] (HPLC separation of the camphanates). Treatment of (+)-**9** ($[\alpha]_D^{25}$ + 25 °, c = 2, $CHCl_3$)[13] with methanesulfonyl chloride (pyridine, 20 °C, 30 min) yielded (+)-**10** (79%, m.p. 123-4 °C; $[\alpha]_D^{25}$ + 38 °, c = 2, $CHCl_3$). Reduction ($NaBH_4$, THF) furnished (-)-**11** (36%, m.p. 98-99 °C; $[\alpha]_D^{25}$-2.5 °, c = 2, $CDCl_3$). Oxidation with $(CH_3)_3NO$ afforded (+)-**5** (67%, m.p. 99-99.5 °C; $[\alpha]_D^{25}$ + 6.5 °, c = 1, hexane). Oxidative hydroboration of **8** gave alcohol (±)-**12**. After Gerlach's optical resolution[12], (-)-**12**[13] was oxidized into ketone (+)-**13** (64%, m.p. 160-1 °C; $[\alpha]_D^{25}$ + 312 °, c = 2, $CHCl_3$).[16] Methylenation (Zn, CH_2Br_2, $TiCl_4$, THF)[17] gave (-)-**14** (58%, m.p. 127-8 °C; $[\alpha]_D^{25}$ - 57 °, c = 2, $CHCl_3$). Catalytical hydrogenation (PtO_2, $CH_3COOCH_2CH_3$, H_2 4 atm, 20 h) yielded (-)-**15** (94%, m.p. 54-5 °C, $[\alpha]_D^{25}$ - 35 °, c = 1, $CHCl_3$). Oxidation (Me_3NO, acetone) afforded tetraene (+)-**6** (49%, oil; $[\alpha]_D^{25}$ + 7 °, c = 1, hexane). Tetraenol (-)-**7** (68%, m.p. 86-7 °C, $[\alpha]_D^{25}$ - 5 °, c = 1, $CHCl_3$) was obtained by $(CH_3)_3NO$ oxidation of a camphanate of (-)-**12** followed by saponification.[16,18]

The CD spectra of tetraenes (+)-**5**[19] and (+)-**6** (Fig. 3) were determined to be both solvent and temperature (80 - 300 K) independent. As possible explanations of this result the following hypotheses must be considered. (1) The equilibrium $\underline{M} \rightleftharpoons \underline{P}$ is strongly shifted towards one of the twisted species and consequently K does not vary in a detectable fashion under our conditions. If true, one would expect a typical exciton coupling CD spectra, as in the case of (-)-**7** (see Fig. 2)[20] which has a twisted structure (probably due to hydrogen bridging between hydroxy and diene moieties,[21] as shown by ^1H-NMR measurements[13b]); (2) the deuterium and methyl substituents do not lift the degeneracy of $\underline{M} \rightleftharpoons \underline{P}$; (3) the tetraenes (+)-**5** and (+)-**6** (and thus **3**) have eclipsed or nearly eclipsed conformations and belong to single energy minimum hypersurfaces. We favor this third interpretation, rejecting the first because the CD spectra of (+)-**5** and (+)-**6** do not show typical exciton Cotton Effects,[20] and the second because while possible for (+)-**5** it is a difficult explanation for (+)-**6** which exhibited an identical spectrum in two different solvents. The third explanation is also consistent with MMPI1 calculations on **3**[6] as well as X-ray data on **4**[7]. The Van der Waals repulsions between the methylene groups are apparently insufficient to make the butadiene units deviate from planarity. However, a substituent at C-7 different than D and CH_3 (e.g. OH, see (-)-**7** Fig. 2) can induce a significant twist of the 2,3,5,6-tetrakis(methylene)bicyclo[2.2.2]octane system. The CD properties of further derivatives of **3** are under study in our laboratory.

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