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OPTICAL ROTATORY DISPERSION STUDIES CXXIV.[1] SYNTHESIS AND CIRCULAR DICHROISM OF 3(S)^{a} - AND 3(R)^{e}-DEUTERIO-4(R)-t-BUTYLCYCLOHEXANONE AND 2(R)^{a} - AND 2(S)^{e}-DEUTERIO-4(R)-ISOPROPYLCYCLOHEXANONE.

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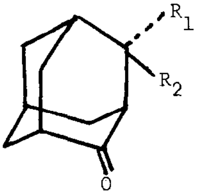
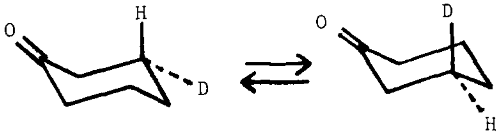
Recent refinements[2] of the octant rule[3] have stimulated interest in determining the rotational contribution of chiral deuterium in cyclic ketones.[4-6] By utilizing the recently recorded rotational contributions of β-axial (1a) and β-equatorial (1e) deuterium in the adamantanone series,[5,6] we were able to measure[1] for the first time the conformational equilibrium composition (2a ⇄ 2e) in 3-deuteriocyclohexanones. In support of further investigations in our laboratory on conformational studies associated with chiral isotopic substituents it was highly desirable to determine the hitherto unknown contribution of α-axial and α-equatorial deuterium as well as to extend the β-deuterioadamantanone studies[5,6] to simple, conformationally fixed cyclohexanones (e.g. 11,12). The present communication describes the successful completion of both aims.



1a R^1=H;R^2=D

1e R^1=D;R^2=H

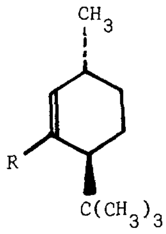


2e

2a

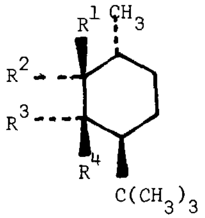
Epoxidation of the olefin 3 ($[\alpha]_D^{25}$+112.6° $CHCl_3$) derived[7] from (+)-pulegone with m-chloroperbenzoic acid followed by reduction with $LiAlD_4$ in boiling THF yielded the three isomeric cyclohexanols 5,6 and 7 (1:4:5 ratio) which could be separated by HPLC. The structure assignments are based on NMR spectral analysis and assumption of S_N2 opening of the epoxides with $LiAlD_4$.[8] The required cyclohexanol 7 (23% yield, $[\alpha]_D^{25}$+36° $CHCl_3$) was dehydrated ($POCl_3$, pyr., 0°C) to the olefin 8 ($[\alpha]_D^{25}$+102° $CHCl_3$) and then transformed with HCl gas[9] to the chloride 9. Dehydrochlorination with potassium triethylmethoxide[10] and GLC separation of the olefin mixture provided 3(S)^{a}-deuterio-4(R)-t-butyl-1-methylenecylohexane (10) and thence upon ozonolysis the desired 3(S)^{a}-deuterio-4(R)-t-butylcyclohexanone (11) of 95% isotopic (M^+ 155) and hence optical purity.[8] The epimeric 3(R)^{e}-deuterio-4(R)-t-butylcyclohexanone (12) was obtained by the same reaction sequence except that the starting olefin was 1(R)-methyl-3-deuterio-4(R)-t-butylcyclohex-2-ene (4)[11] of 60% isotopic purity and $LiAlH_4$ was substituted for $LiAlD_4$ in the reduction of the epoxide 13. Consequently, the isotopic and optical purity of the ketone 12 (d_o 40%, d_1 60%)

was only 60% and appropriate correction was made in the CD data (Fig. 1).



3 R=H

4 R=D



5 $R^1=R^3=H$

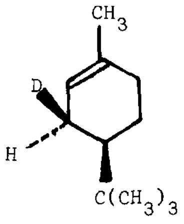
$R^2=D;R^4=OH$

6 $R^2=R^4=H$

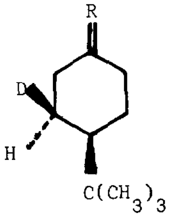
$R^1=D;R^3=OH$

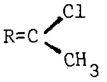
7 $R^1=R^3=H$

$R^4=D;R^2=OH$



8

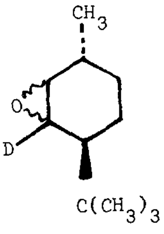




9 $R=C\begin{smallmatrix}Cl\\CH_3\end{smallmatrix}$

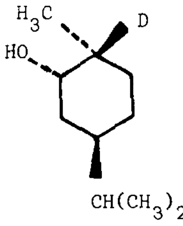
10 $R=CH_2$

11 R=O



13

The starting material for the α-equatorial and α-axial deuterated ketones was (+)-p-menthene ($[\alpha]_D^{25}$ +86.7° $CHCl_3$) which was transformed upon m-chloroperbenzoic acid oxidation and $LiAlD_4$ reduction into a 3:5:2 mixture of the three cyclohexanols 14,15 and 16 (separable by silica gel column chromatography). The structures of the two tertiary alcohols 15 and 16 are based on a comparison of the NMR spectra of the corresponding acetates 17 (NMR δ 1.55 (3H, t-C-CH_3)) and 18 (NMR δ 1.58 (s,3H, t-C-CH_3)) and of their mobilities on silica gel with those of the corresponding 1-methyl-4-t-butylcyclohexanols of established constitution.[12] Each chromatographically purified tertiary alcohol (15 and 16) was converted into the corresponding acetate (17 and 18) with acetyl chloride in N,N-dimethylaniline (90°C) and each acetate was pyrolyzed at 450°C. The resulting olefin mixture was separated in each instance by preparative GLC and the exocyclic olefins 19 and 20 upon ozonolysis afforded 2(R)^a-deuterio (21) and 2(S)^e-deuterio (22) 4(R)-isopropylcyclohexanone of >95% isotopic purity. When these two ketones were subjected prior to CD determination to GLC purification at 100°C using a 10% Carbowax column, ca. 18% reduction in isotopic purity was observed (21:M^+ 141 (31%); 22:M^+ 141 (30%)).



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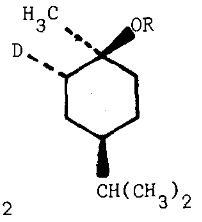
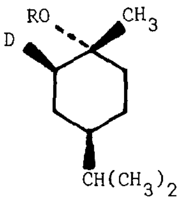


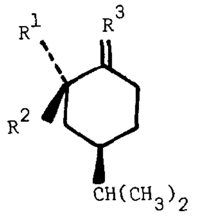
15 R=H

17 R=Ac



16 R=H

18 R=Ac



19 $R^1=D;R^2=H;R^3=CH_2$

20 $R^1=H;R^2=D;R^3=CH_2$

21 $R^1=D;R^2=H;R^3=O$

22 $R^1=H;R^2=D;R^3=O$

The CD spectra of the four deuterated cyclohexanols 11,12,21 and 22 measured at 25°C are reproduced in Fig. 1 together with their rotational strengths (corrected for 100% optical purity) at 25°C and -197°C. Contrary to the rotatory contribution of the corresponding methyl-substituted cyclohexanones,[13] the α-axial deuterated ketone 21 displayed a weaker Cotton effect as compared to the β-equatorial deuterated ketone 12. The molecular ellipticity of the latter ($[\theta]_{25^\circ C}$ 358) is in reasonable agreement with the earlier recorded values ($[\theta]_{25^\circ C}$ 300) in the adamantanone[5,6] series (1e). In qualitative agreement with earlier determined rotational contributions of α-equatorial and β-axial[14] methyl groups is the observation (Fig. 1) that the molecular ellipticities of the α-equatorial (22: $[\theta]_{25^\circ C}$-29.8) and β-axial (11: $[\theta]_{25^\circ C}$-28.4) deuterated ketones are much lower than those of 21 and 12. Finally the α-equatorial (22), α-axial (21) and β-equatorial (12) deuterium substituents all make anti-octant (dissignate)[2] contributions, which is in accordance with other recent results.[4-6] The only discrepancy is our observation (Fig. 1) of a small consignate contribution ($[\theta]_{25^\circ C}$-28.4) by a β-axial deuterium substituent in the 4-t-butylcyclohexanone series (11) as compared to the weak dissignate effect ($[\theta]_{25^\circ C}$+58) reported[6] for the

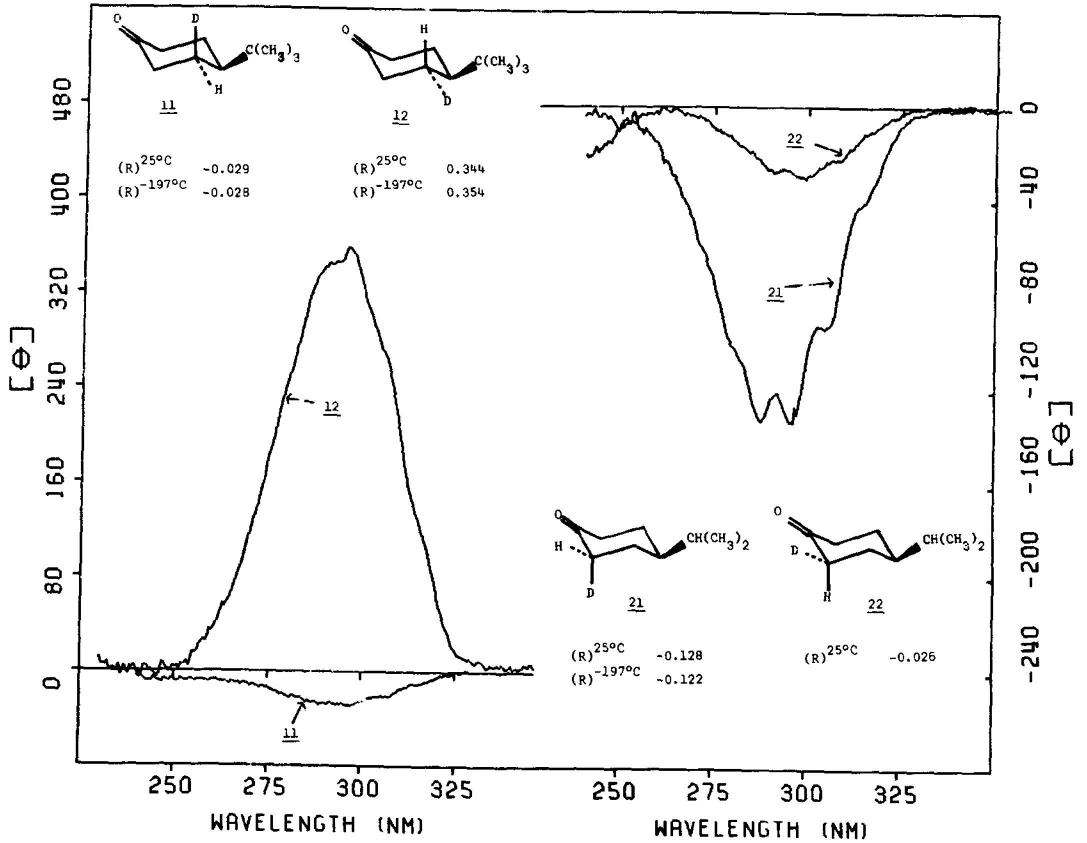


Fig. 1. Circular dichroism curves (+25°C, EPA solution) of 11,12, 21 and 22 and rotational strengths (R) at +25°C and -197°C.

corresponding adamantanone (1a). Whether this should be ascribed to experimental discrepancies or conformational differences in the two series remains to be seen. Attention is drawn to the fact, that the 18% loss in isotopic purity of 21 and 22 upon GLC purification indicates some equilibration of the α-position, which introduces a greater error in the 2-substituted 4-isopropylcyclohexanones (21,22) as compared to the 3-deuterated 4-t-butyl analogs. In spite of these quantitative uncertainties, the reference values for chiral deuterium reported herewith are of great utility[15] as will be shown in future communications from our laboratory.

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15. Substitution of the β-deuterium values based on 11 and 12 rather than 1a and 1e for the determination (ref. 1) of the 2a $\rightleftarrows$ 2e equilibrium leads only to a change of <0.35 cal/mole without, of course, affecting the qualitative conclusion that axial deuterium (2a) is favored.