CD-Spectroscopic Investigations for the Determination of the Absolute Configuration of α -Alkylated 1,4-Cyclohexanedione Derivatives

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1,4-Cyclohexanedione Derivatives, Absolute Configuration, CD Spectra

The absolute configuration of the conformationally flexible six membered ring system 2-methyl- and 2,6-dimethyl-1,4-cyclohexanedione monoethylene acetal was determined by comparison of measured and calculated CD spectra. The rotational strengths were calculated by means of the CNDO/S-method assuming *R* at the stereogenic center. The results were compared with the predictions made by the octant rule. The enantiomerically pure material was synthesized via the corresponding SAMP- and RAMP-hydrazones.

1. Introduction

The SAMP/RAMP-hydrazone method has been used successfully to synthesize enantiomerically pure cyclohexanone and 1,4-cyclohexanedione derivatives, which are versatile chiral building blocks in the synthesis of natural compounds [1, 2]. One of the standard methods to determine the absolute configuration of these products is X-ray crystallography, but that requires single crystals of sufficient quality. There are many compounds which, in spite of all efforts, crystallize poorly or even not at all. Consequently, the structure of such compounds cannot be elucidated by this analytical method. Therefore, it is highly desirable to have methods that allow the determination of the absolute configuration in solution. The combination of experimental and theoretical CD spectroscopy provides such a procedure. Here one compares the measured CD spectrum of the compound with unknown configuration with the calculated spectrum for the compound with known absolute configuration. For the calculation we used the semiempirical CNDO/S method. We believe that this method is able to reproduce at least qualitatively the longest wave length part of the spectrum [3 - 7].

As a further test, this procedure was now used to determine the absolute configuration of the 1,4cyclohexanedione monoethylene acetal derivatives 1 and 2 (Scheme 1).

The compounds examined in the present investigation were optically active (*R*)- and (*S*)-2-methylcyclohexanedione monoethylene acetals and the C_2 -symmetric (*R*,*R*)- and (*S*,*S*)-trans-2,6-dimethylcyclohexanedione monoethylene acetals. To determine the absolute configuration at the α -carbons of these cyclohexanone derivatives we also applied the octant rule for the prediction of the sign of the Cotton effect of the n $\rightarrow \pi^*$ transition, which determines the spectrum at the longest wave length [8, 9].

2. Results and Discussion

For the monomethylated compounds **1** the ORD values at 546, 436 and 365 nm (mercurylines) are negative for the R enantiomer and positive for the S enantiomer (see Table 2). Both measurements

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Fig. 1. Measured CD-spectra of 1,4-cyclohexanedione derivatives.

were carried out in CHCl₃. The circular dichroism curve was strongly negative for the *R* enantiomer and strongly positive for the *S* enantiomer with a minimum respectively maximum at $\lambda \cong 290$ nm. The extrema for the (*R*,*R*)-2 and (*S*,*S*)-2 CD-curves appear at $\lambda \cong 295$ nm and are much more intensive then those of their monosubstituted counterparts (see Fig. 1).

Predictions of the octant rule

First, the octant rule was applied to these experimental findings. As was concluded from chemical synthesis, (R)-1 should be *R*-configurated at the α -carbon atom (see Fig. 2). In this case, the axial methyl group is not located in one of the three Cartesian planes, but in the octant where all Cartesian coordinates are negative. Its contribution to the rotational strength of the $n \rightarrow \pi^*$ transition should therefore be negative [corresponding to the octant rule: $(-) \cdot (-) \cdot (-) \equiv (-)$. The acetal substituent at carbon 4 contributes nothing to the Cotton effect because it is located in the *x*,*z*-plane. If the methyl group flips from the axial to the equatorial position, one has to locate it at the α -carbon 6. Now its contribution to the Cotton effect should be zero, because it is located in the y,z-plane. This is in perfect agreement with the experimental CD spectrum.



Fig. 2. The octant rule applied to (R)-1.

So the *R*-configuration is confirmed for (*R*)-1. In the same way, it can be concluded that (*S*)-1 has *S*-configuration at the α -carbon atom: at carbon 2 the equatorial methyl group lies in the *y*,*z*-plane and does not contribute to the Cotton effect. After flipping to the axial position, it is located at carbon 6 in the octant with -x, +y and -z, so that its contribution to the Cotton effect of the n $\rightarrow \pi^*$ transition should be positive.

The fact that the absolute values of the Cotton effects of (R,R)-2 and (S,S)-2 are still larger than in the (R)-1 and (S)-1 case is easily understood: during the flipping process one methyl group remains always axial for both molecules.

Quantum chemical calculations

To calculate the rotational strength of the $n \rightarrow \pi^*$ transition of (*R*)-1 we first optimized the geometry



Table 1. Calculated transition energies and rotational strengths. In brackets is given the corresponding value for the second transition.

Compound	Transition energy [au]	Rotational strength [au]	
(R)-1 axial (R)-1 equatorial (R,R)-2	0.119 (0.300) 0.118 (0.301) 0.119 (0.299)	-0.151 (0.401) -0.054 (0.252) -0.214 (0.485)	

Table 2. Optical rotation, enantiomeric purity and CD data of ketones 1 and 2.

Com- pound	Optical rotation (c in CHCl ₃)	ee [%]	Sign*	λ_{\max} . [nm]
(<i>R</i>)-1	$[\alpha]_{546}^{26^{\circ}\text{C}} = -1.3 \ (c = 1.11)$	92 ^a	_	290
(<i>S</i>)-1	$\begin{split} & [\alpha]_{456}^{26^\circ C} = -12.8 \ (c = 1.11) \\ & [\alpha]_{365}^{26^\circ C} = -60.7 \ (c = 1.11) \\ & [\alpha]_{546}^{26^\circ C} = +1.1 \ (c = 1.08) \\ & [\alpha]_{436}^{26^\circ C} = +13.4 \ (c = 1.08) \\ & [\alpha]_{366}^{26^\circ C} = +60.4 \ (c = 1.09) \end{split}$	91 ^a	+	290
(R,R)-2	$[\alpha]_D^{26^{\circ}C} = -93.0 \ (c = 1.20)$	94 ^b	-	295
(<i>S</i> , <i>S</i>)- 2	$[\alpha]_D^{26^{\circ}C} = +93.2 \ (c = 1.13)$	86 ^b	+	295

* Sign of the Cotton effect; ^a determined by Pirkle shift NMR; ^b determined by GC on chiral stationary phases (de \geq 96%, determined by ¹³C NMR).

with the methyl group in the axial and in the equatorial position using the AM1 method [10]. The molecule with the equatorial methyl group is lower in energy than the molecule with the methyl group in axial position (≈ 0.84 kcal/mol), as expected. The energy of (*R*,*R*)-2 was also optimized with the AM1 method. For the three optimized structures



CNDO/S-calculations using the programs DZDO and MCD3SP, [11], taking into account only single excitations from the 13 highest occupied into the 13 lowest unoccupied molecular orbitals, were performed.

The transition energies and the rotational strengths for the longest wave length transitions are collected in Table 1. From an investigation of the CI coefficients it follows that the first excited state is an $n \rightarrow \pi^*$ state. The results agree, at least qualitatively, with the experimental findings and the predictions of the octant rule. The next transition occurs at much higher energy (see Table 1) and does not influence the peak at the longest wave length.

3. Experimental section

The 1,4-cyclohexanedione derivatives **1** and **2** were synthesized starting from commercially available 1,4-cyclohexanedione monoethylene acetal **3** following the protocol outlined in Scheme 2. In the first step the free ketone function of **3** was converted into SAMP-hydrazone (*S*)-**4**, which was then metalated with LDA and alkylated with MeI to give compound (*S*,*R*)-**5**. Cleavage of the hydrazone with saturated aqueous oxalic acid [12] gave the desired α -monoalkylated ketone (*R*)-**1** with an enantiomeric excess of *ee* = 92 % (see Table 2).

The ketone (R,R)-2 was synthesized by a second metalation of monoalkylated hydrazone (S,R)-5 carried out with LiTMP and further alkylation with MeI to form hydrazone (S,R,R)-6. Cleavage of (S,R,R)-6 with saturated aqueous oxalic acid [12] gave the desired $\alpha\alpha'$ bis-alkylated ketone (R,R)-2 with an enantiomeric excess of ee = 94 %. The other enantiomers (S)-1 and (S,S)-2 were synthesized following the same protocol as outlined in Scheme 2 using (R)-1-amino-2-methoxymethylpyrrolidine (RAMP) instead of (S)-1-amino-2-methoxymethylpyrrolidine (SAMP) as the chiral auxiliary for the ketone **3**. The enantiomeric excesses of the monomethylated ketones **1** were determined by Pirkle shift NMR [13]. The *ee*'s of the bismethylated ketones **2** were determined by GC on chiral stationary phases (chiral column: Chirasil dex 25m, Chrompack). These results are collected in Table 2.

Measurements

All measurements were performed in spectrograde or purified solvents. The ORD spectra were measured on a Perkin Elmer polarimeter. For the CD measurements a solution of the ketone was prepared at a concentration of 0.200 mmol / 5 ml acetonitrile. CD spectra were collected on an AVIV (Lakewood, NJ, USA) 62 DS spectrometer $(\lambda < 260 \text{ nm})$ and a JASCO (Japan Spectroscopic Co., Ltd., Tokyo, Japan) J-600 ($\lambda > 260 \text{ nm}$), both calibrated according to Chen and Yang [14]. The spectral bandwidth / path length of the optical cells used were 2 nm / 20 mm ($\lambda < 260 \text{ nm}$) and 1 nm / 20 mm ($\lambda > 260 \text{ nm}$) for the monoalkylated compounds and 2 nm / 5 mm ($\lambda < 260 \text{ nm}$) and 1 nm / 5 mm ($\lambda > 260 \text{ nm}$) for the bisalkylated compounds. The AM1 calculations were performed on an IBM 43P/150 computer, using the program SPARTAN 5.1 (Wavefunction, Inc. ; Irvine, CA 92612 USA).

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