Determination of the Absolute Configuration of Bis(tetrahydropyran-2-yl)methane by Comparison of Measured and Calculated CD-spectra

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The absolute configuration of bis(tetrahydropyran-2-yl)methane (**1**) was determined by comparison of measured and calculated CD spectra.

The theoretical CD spectra were obtained by means of the CNDO/2S method. The five presumably lowest local minima on the energy hypersurface of the title compound were used to describe the conformer equilibrium mixture. The geometries of these conformers were calculated employing the MM3 force field, the semiempirical AM1 method and one-determinant *ab initio* calculations employing the 6-31G* basis set. Boltzmann factors were then obtained using relative energies calculated with three different basis sets and including correlation- and zero point vibrational energy. Based on the sign of the observed and calculated longest wavelength Cotton effect we assign an absolute configuration to the compound which is in keeping with the chirality expected from the assumed reaction mechanism.

The results of force field and *ab initio* calculations converge to the point that the conformer equilibrium is dominated (85 - 96%) by one single conformer which is energetically separated from the other conformers by about 2 - 3 kcal/mol. This result agrees with previous experimental data.

1. Introduction

The absolute configuration of a molecule can frequently be deduced from the mode of its synthesis. However, such an assignment might be ambiguous. Standard X-ray structure determination of the absolute configuration yields the most reliable results but requires single crystals. Thus, this method might not be applied to such compounds which, inspite of all effects, crystallize poorly or even not at all like the title compound **1**.

It is well known that the absolute configuration can also be elucidated by comparison of experimentally determined and calculated CD spectra [1 - 4]. However, since the CD spectrum of a compound also depends on the molecular conformation prediction of the absolute configuration of a molecule in solution requires knowledge of its conformational equilibrium. Therefore, theoretical prediction of the absolute configuration of a flexible molecule also involves a computational study of its equilibrium mixture.

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Synthesis of enantiomerically pure bis(tetrahydropyran-2-yl)methane was published recently [5]. Based on the assumed reaction mechanism the authors concluded that the absolute configuration of the product was *R,R* (Figure 1). The authors further studied the conformer equilibrium of **1**. Experimental data and computational results revealed that one conformer of the title compound strongly dominates in the conformer equilibrium. The temperature dependence of the NMR spectra led to the conclusion that the major component amounts to 85% at 27°C and more than 90% at –30°C, respectively.

In this paper we present the results of further investigations carried out in order to show that the assignment of the absolute configuration in [5] was correct.

A computational study of the equilibrium mixture requires reliable relative energies of the different conformers. We therefore applied not only the MM3 forcefield [6 - 8] and the semiempirical AM1 method [9] but also performed *ab initio* calculations to locate stationary points on the molecule's hypersurface. In these calculations the geometries were optimized at the Hartree-Fock (HF) level. To obtain more reliable final relative energies we included

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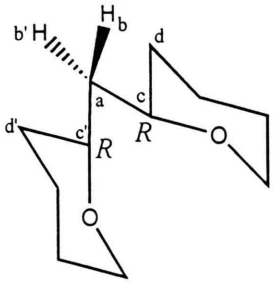
correlation energy calculated with the MP2 method [10] in single point calculations. Beside the semiempirical CNDO/2S method [11] we also applied the nonempirical CIS procedure (*CI-Singles*)[12] to predict the sign of the longest wavelength Cotton effect.

2. Computational Methods

To obtain initial coordinates for geometry optimizations we started from a molecular model defined by means of standard structural parameters assuming the chair conformation for the six-membered rings and equatorial[a] C_a-C_c and C_a-$C_{c'}$ bonds (Scheme 1).



666[b] conformers of (*R,R*)-bis(tetrahydropyran-2-yl)-methane were then generated by variation of the dihedral angles ϑ_1(b-a-c-d) and ϑ_2(b'-a-c'-d') defined in Scheme 1 (stepwidth: 10°). At fixed dihedral angles ϑ_1 and ϑ_2, the remaining structural parameters were energetically optimized employing the semiempirical AM1 method and the MM3 force field. Both hypersurfaces reveal seven minima, three with $\vartheta_1 = \vartheta_2$ and four with $\vartheta_1 \neq \vartheta_2$. Since those with $\vartheta_1 \neq \vartheta_2$ are pairwise equivalent we end up with five energetically different local minima. Starting from the corresponding molecular coordinates we performed further geometry optimizations without constraints.

Additional unconstrained geometry optimizations with the 6-31G* [13 - 16] basis set were carried out at the *ab initio* one-determinant level (Hartree Fock, HF) starting from the MM3-optimized structural parameters. The normal frequencies were calculated to characterize the resulting stationary points and all five optimized geometries turned out to be local minima (**1a** - **1e**, Figure 1).

[a] For the equatorial preference of the alkyl substituent in 2-methyltetrahydropyran see [24].

[b] The total number of points on the hypersuface is 1296. However, due to symmetry only half of the conformers with $\vartheta_1 \neq \vartheta_2$ (i. e. 630) plus those with $\vartheta_1 = \vartheta_2$ (36) have to be considered.

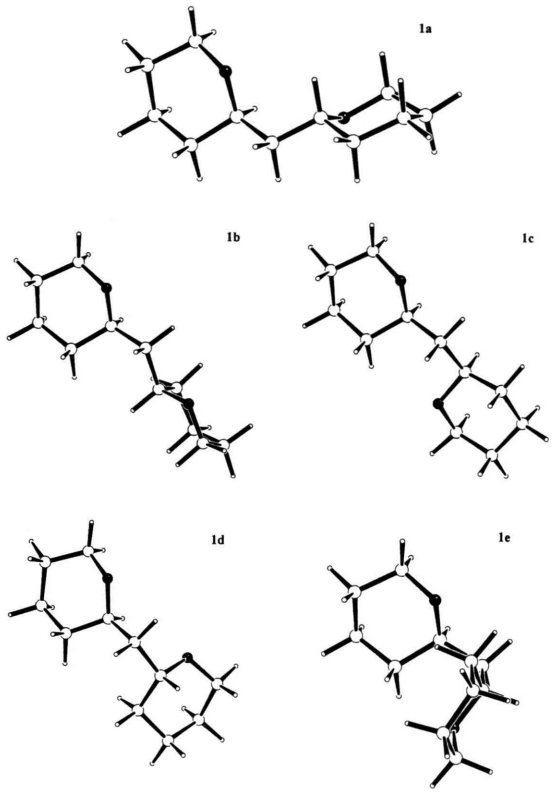


Fig. 1. Conformers of (*R,R*)-bis(tetrahydropyran-2-yl)methane (**1a** - **1e**) optimized at the HF/6-31G* level.

Correlation energy was included by means of single point calculations with the MP2 method employing the 6-31G*, 6-31G** [16], and 6-31+G* [17 - 18] basis sets. To obtain the final relative energies (Table 5) the unscaled zero point vibrational energies calculated at the HF/6-31G* level were added to the MP2/basis set//HF/6-31G* energies.

Semiempirical CD spectra were calculated using the CNDO/2S method as implemented in the DZDO/MCD3SP program package [19]. Configuration interaction (CI) included 196 singly excited configurations formed from the 14 highest filled orbitals and 14 lowest empty orbitals. Non-empirical CD spectra were calculated employing the CIS method and the 6-31G* basis set. The calculated $\Delta\varepsilon$ curves for the conformers were represented as sums of Gaussians centered at the wavelengths of the corresponding transitions and multiplied with the rotational strength [20][c]. The total CD spectrum was

[c] The Gaussians were generated using an empirical half bandwith of 7 nm at e^{-1} of the maximum.

Table 1. Selected structural parameters of **1a** - **1e** from MM3, AM1, and HF/6-31G* geometry optimizations. $r_{O\cdots O}$ is the oxygen-oxygen distance (in Å), and ϑ_1 and ϑ_2 are the dihedral angles defined in Scheme 1 (in degrees).

	MM3			AM1			HF/6-31G*		
	$r_{O\cdots O}$	ϑ_1	ϑ_2	$r_{O\cdots O}$	ϑ_1	ϑ_2	$r_{O\cdots O}$	ϑ_1	ϑ_2
1a	3.58	60	60	3.80	73	73	3.60	65	65
1b	4.74	175	175	4.71	155	155	4.66	176	176
1c	4.36	67	170	4.36	70	149	4.35	63	159
1d	3.95	–65	144	3.71	–59	137	3.88	–63	146
1e	3.88	–71	–71	3.92	–71	–71	3.90	–67	–67

Table 2. Results of MM3- and AM1 calculations. ΔE_{rel} and $\Delta H_{f,rel}$ are the energy and the heat of formation relative to the most stable isomer (in kcal/mol). w_i is the Boltzmann factor at 298 K.

	MM3		AM1	
	ΔE_{rel}	w_i [%]	$\Delta H_{f,rel}$	w_i [%]
1a	0.00	84.7	0.00	54.0
1b	1.77	4.2	0.94	11.0
1c	1.63	10.8	0.71	32.5
1d	4.14	0.2	2.27	2.3
1e	3.91	0.1	3.46	0.2

Table 3. Relative energies (ΔE_{rel} in kcal/mol) and Boltzmann factors (w_i, at 298 K) of **1a** - **1e** calculated with different basis sets (6-31G*, 6-31+G*, 6-31G**) at 6-31G* – optimized geometries (HF/basis set//HF/6-31G*).

	6-31G*		6-31+G*		6-31G**	
	ΔE_{rel}	w_i [%]	ΔE_{rel}	w_i [%]	ΔE_{rel}	w_i [%]
1a	0.00	94.8	0.00	96.0	0.00	94.6
1b	3.14	0.5	3.08	0.5	3.17	0.5
1c	2.19	4.7	2.38	3.5	2.16	4.9
1d	13.32	0.0	13.29	0.0	12.97	0.0
1e	12.93	0.0	13.62	0.0	12.51	0.0

obtained as a Boltzmann-weighted superposition of the $\Delta\varepsilon$ curves of the conformers[d].

All *ab initio* calculations were carried out employing the GAUSSIAN94 set of quantum chemical routines [21] running on a SNI-s600/20 computer of the Rechenzentrum der RWTH-Aachen. MM3 and AM1 calculations were performed using the IBM RS6000 (OS: AIX 3.2.5) cluster of the Rechenzentrum and on a local SUN SPARCstation, respectively (OS: Solaris 2.5.1). The DZDO/MCD3SP program was running on a local SUN SPARCstation. Drawings of the molecular structures were generated using the program SCHAKAL [22].

[d] $\Delta\varepsilon = \Sigma_{i=1}^{N} w_i \cdot \Delta\varepsilon_i$, $w_i = \exp(-E_i/R \cdot T)/[\Sigma_j \exp(-E_j/R \cdot T)]$. N is the number of located stationary points, $\Delta\varepsilon_i$ the superposition of Gaussians. w_i and E_i are the Boltzmann factor and the energy of the ith local minimum, respectively.

Table 4. Relative energies (ΔE_{rel} in kcal/mol) and Boltzmann factors (w_i, at 298 K) of **1a** - **1e** calculated with different basis sets (6-31G*, 6-31+G*, 6-31G**) and including correlation energy at 6-31G* - optimized geometries (MP2/basis set//HF/6-31G*).

	6-31G*		6-31+G*		6-31G**	
	ΔE_{rel}	w_i [%]	ΔE_{rel}	w_i [%]	ΔE_{rel}	w_i [%]
1a	0.00	92.8	0.00	94.4	0.00	91.5
1b	3.23	0.5	3.07	0.5	3.06	0.5
1c	1.97	6.7	2.16	4.9	1.86	7.9
1d	5.72	0.0	5.23	0.0	7.27	0.0
1e	3.93	0.1	4.24	0.1	5.43	0.0

Table 5. Relative energies (ΔE_{rel} in kcal/mol) and Boltzmann factors (w_i, at 298 K) of **1a** - **1e** calculated with different basis sets (6-31G*, 6-31+G*, 6-31G**) and including correlation as well as zero point energy at 6-31G* – optimized geometries (ZPE+MP2/basis set//HF/6-31G*).

	6-31G*		6-31+G*		6-31G**	
	ΔE_{rel}	w_i [%]	ΔE_{rel}	w_i [%]	ΔE_{rel}	w_i [%]
1a	0.00	67.4	0.00	73.3	0.00	87.8
1b	3.24	0.3	3.09	0.4	3.07	0.5
1c	1.87	5.7	2.06	4.5	1.76	9.0
1d	2.36	2.5	1.87	6.2	3.91	0.2
1e	0.61	24.1	0.92	15.5	2.12	2.5

Table 6. Wavelengths λ (nm) and rotational strengths R (DBM) of the four energetically lowest transitions (Trans. 1 - 4) of **1a** - **1e** calculated using the HF/6-31G* geometries and the CNDO/2S method.

	Trans. 1		Trans. 2		Trans. 3		Trans. 4	
Conf.	λ	R	λ	R	λ	R		
1a	120.3	1.0	120.2	–2.2	118.5	0.7	118.5	0.4
1b	121.0	–2.5	120.9	2.3	118.6	2.1	118.6	–1.6
1c	121.0	–5.6	120.2	6.4	118.6	–1.7	118.5	1.1
1d	120.8	5.5	120.8	–5.0	118.5	–2.6	118.5	2.0
1e	121.0	6.5	120.8	–6.8	118.7	1.9	118.6	–1.8

Table 7. Wavelengths λ (nm) and rotational strengths R (DBM) of the four energetically lowest transitions (Trans. 1 - 4) of **1a** - **1e** calculated using the HF/6-31G* geometries and the *ab initio* CIS method.

	Trans. 1		Trans. 2		Trans. 3		Trans. 4	
Conf.	λ	R	λ	R	λ	R		
1a	113.8	–0.10	113.5	–0.14	106.0	–0.16	105.8	0.11
1b	113.6	0.01	113.6	–0.19	107.1	–0.23	106.6	0.12
1c	114.3	–0.14	113.6	–0.14	106.5	0.41	105.5	0.10
1d	114.7	0.09	114.2	–0.20	106.6	–0.07	106.3	–0.82
1e	113.9	–0.11	113.8	–0.05	106.5	–0.10	106.1	0.21

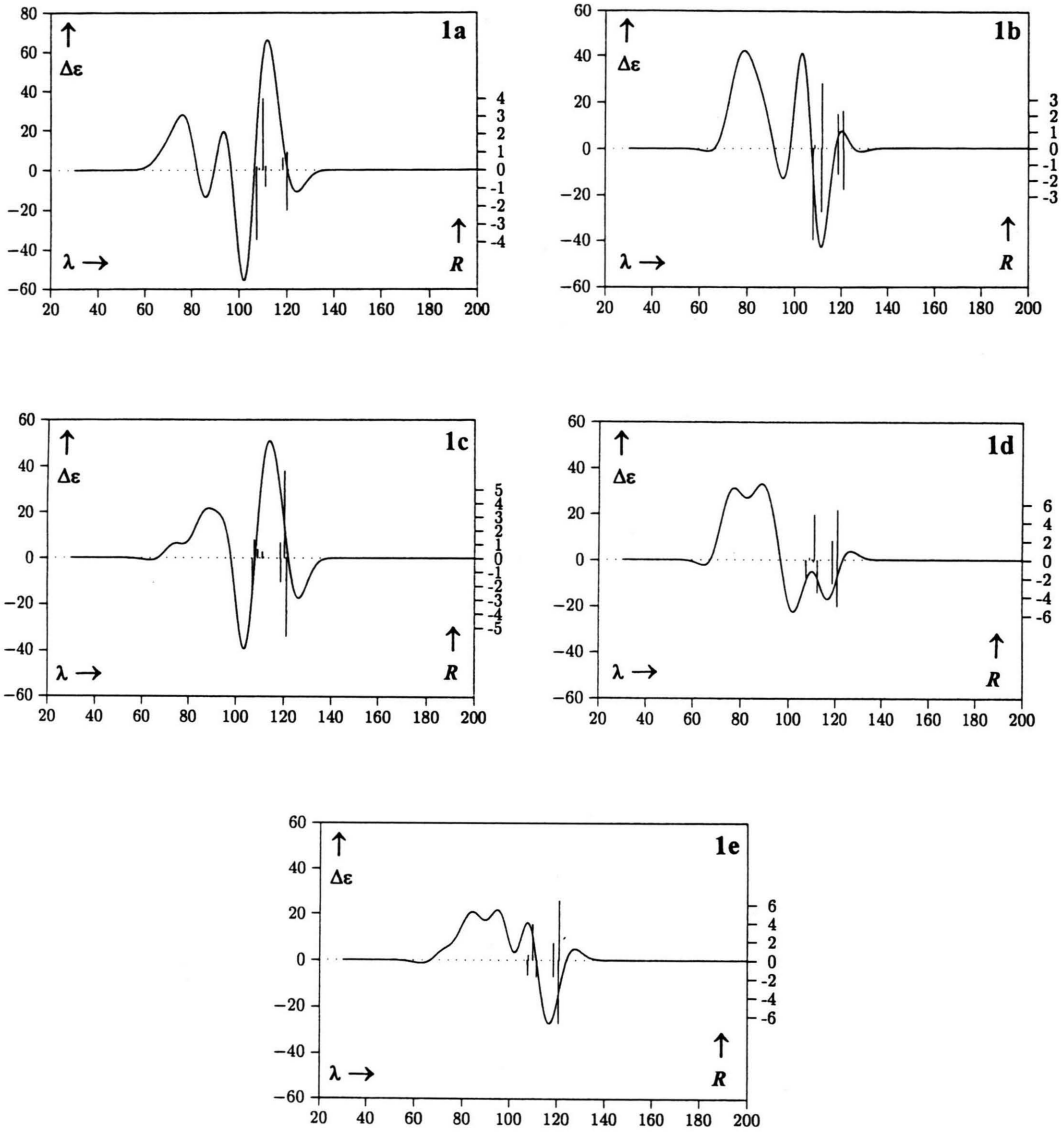


Fig. 2. CD spectra of conformers **1a** - **1e** calculated by means of the CNDO/2S method using HF/6-31G*-optimized geometries. $\Delta\varepsilon$ in $l \cdot mol^{-1} \cdot cm^{-1}$, rotational strenght ($R$) in DBM, and λ in nm.

Results and Discussion

Selected structural parameters of **1a** - **1e** obtained with different methods are given in Table 1. Relative energies (ΔE_{rel}), enthalpies ($\Delta H_{f,rel}$), and the corresponding Boltzmann factors at room temperature (w_i) of the five local minima are listed in Tables 2 - 5. Wavelengths (λ) and rotational strenghts (R in Debye·Bohr magneton (DBM)) of the four energetically lowest transitions are compiled in Tables 6 and 7. Total energies obtained with *ab initio* methods are listed in Tables 8 and 9.

The structures of the five local minima (**1a** - **1e**) obtained at the HF/6-31G* level are shown in Figure 1. Figure 2 displays the semiempirically calculated CD spectra of the five local minima, while Fig. 3 shows the corresponding CD spectra calculated with the nonempirical CIS method. The total Boltzmann-weighted CD spectra obtained with these methods are shown in Figs. 4 (CNDO/2S) and 5 (CIS), respectively. Finally,

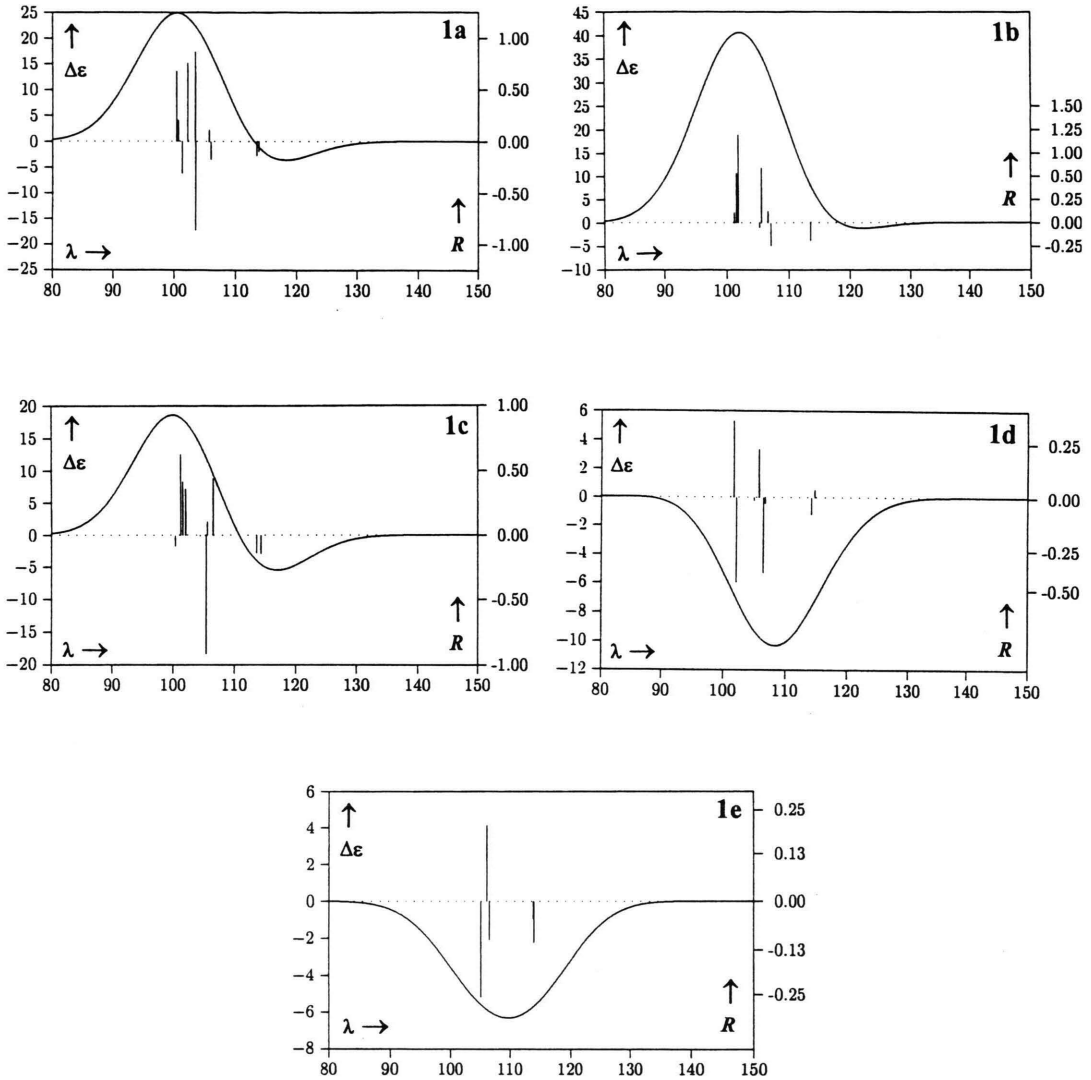


Fig. 3. CD spectra of conformers **1a** - **1e** calculated by means of the non-empirical CIS method using HF/6-31G*-optimized geometries. $\Delta\varepsilon$ in $l \cdot mol^{-1} \cdot cm^{-1}$, rotational strenght ($R$) in DBM, and λ in nm.

the experimentally determined CD spectrum of **1** is plotted in Figure 6.

At an average difference of about 1° the values of the optimized dihedral angles ϑ_1 and ϑ_2 calculated with the MM3 forcefield and those obtained at the HF/6-31 G* level agree quite well (cf. Table 1). The results of the AM1 method differ somewhat more strongly from the *ab initio* values (average difference: 4.2°). Moreover, as far as the energetic order of the conformers is concerned, AM1 predicts the energy of **1d** to be lower than that of **1e** (cf. Table 2). This result is at odds with both our MM3 and best *ab initio* data (Table 5), which predict that **1d** is higher in energy than **1e**. In addition, according to the AM1 results the conformational equilibrium should be dominated by two isomers occurring at relative abundancies of 54% (**1a**) and 33% (**1c**), respectively. Such a composition of the equilibrium mixture, however, contradicts the experimental findings [5]. In the present paper we therefore only report CD spectra calculated using the *ab initio* geometries (cf. Figures 2-5). In order to study the basis set dependence and the influence of correlation corrections we used the relative energies obtained with different basis sets at the HF- and the

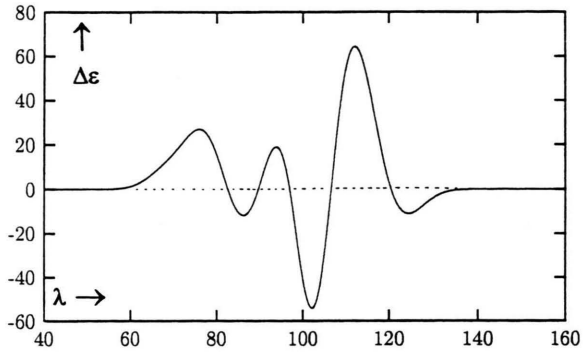


Fig. 4. Total CD spectrum of (*R,R*)-bis(tetrahydropyran-2-yl)methane calculated by means of the CNDO/2S method using HF/6-31G*-optimized geometries ($\Delta\varepsilon$ in $l \cdot mol^{-1} \cdot cm^{-1}$, λ in nm).

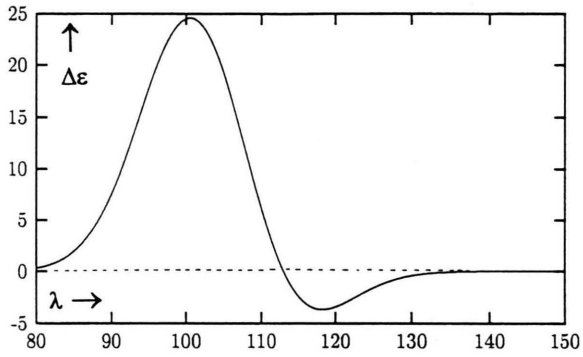


Fig. 5. Total CD spectrum of (*R,R*)-bis(tetrahydropyran-2-yl)methane calculated by means of the non-empirical CIS method using HF/6-31G*-optimized geometries ($\Delta\varepsilon$ in $l \cdot mol^{-1} \cdot cm^{-1}$, λ in nm).

MP2 level to calculate Boltzmann factors. The results mainly differ as far as the relative abundance of **1e** is concerned (cf. Tables 2 - 5). Although the contribution of this conformer is negligible with both the HF- and and MP2 method, it amounts to 24.1% at the ZPE+MP2/6-31G*//HF/6-31G* level. However, at the highest level of theory employed in this paper (ZPE+MP2/6-31G**//HF/6-31G*) the contribution of **1e** is reduced to 2.5% and the conformer equilibrium is dominated by isomer **1a** (87.8%) followed by **1c** (9.0%). This result is supported by the data obtained in NMR experiments [5].

The four energetically lowest transitions and rotational strengths of each conformer calculated by the CNDO/2S method are compiled in Table 6. Compared with the experimental data, the calculated transition energies are strongly blue-shifted. However, several

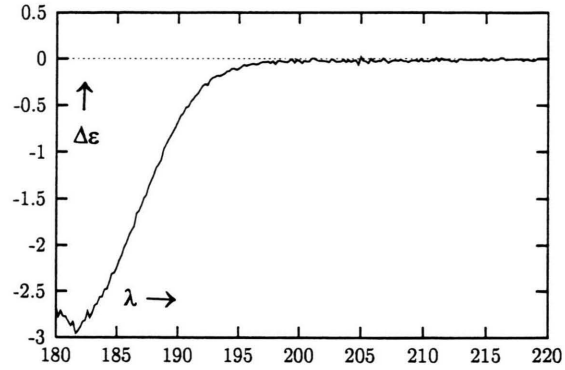


Fig. 6. Experimental CD spectrum ($\Delta\varepsilon$ in $l \cdot mol^{-1} \cdot cm^{-1}$, λ in nm) of (*R,R*)-bis(tetrahydropyran-2-yl)methane.

examples showed that the obvious shortcomings in the prediction of the transition energies do not impair the ability of the method to predict the sign of the first Cotton effect [1 - 4].

The calculated CD spectra of the two most abundant conformers (**1a**, **1c**) show a negative first and a positive second Cotton effect (Figure 2) This is also true for **1b**, however the areas under the curves are much smaller in this case. On the contrary, the first and second CD bands of **1d** and **1e** are positive and negative, respectively. However, due to their small Boltzmann factors the contributions of **1d** and **1e** to the total spectrum (Fig. 4) are negligible. As a result, the CD spectrum of (*R,R*)-bis(tetrahydropyran-2-yl)-methane calculated with the CNDO/2S method shows a negative first and a positive second band and we assign the first one calculated at 124 nm (cf. Fig. 4) to the negative CD band observed at about 182 nm in the experimentally determined CD spectrum (cf. Figure 6).

To further confirm our semiempirical results, we also calculated the rotational strengths of the ten lowest transitions of each conformer by means of the non-empirical CIS (*CI-Singles*) method using the 6-31G* basis set. The calculated wavelengths and the rotational strengths for the four energetically lowest transition of each conformer calculated with the *ab initio* method are listed in Table 7. As in the case of the CNDO/2S results, the transitions are strongly shifted to the blue. This might in part be due to the neglect of solvent effects. The signs of the first two Cotton effects of conformers **1a - 1c** obtained with the CIS method (Figure 3) agree with those calculated by means of the CNDO/2S procedure (Figure 2). Thus, both the non-empirical CIS method (Figure 5) and the

Table 8. Total energies of **1a** -**1e** calculated at the Hartree Fock level employing 6-31G*-optimized geometries (HF/basis set//HF/6-31G*). Zero point vibrational energies calculated at the HF/6-31G*//HF/6-31G* level are given in parentheses. All energies are in Hartrees. The numbers of basis functions in the different basis sets are: 6-31G*: 235; 6-31G**: 295; 6-31+G*: 287.

Basis set	1a	1b	1c	1e	1d
6-31G*	-577.922354	-577.917353	-577.918865	-577.901750	-577.901133
6-31+G*	-577.932122	-577.927212	-577.928334	-577.910420	-577.910943
6-31G**	-577.952794	-577.947746	-577.949351	-577.932852	-577.932123
	(0.324806)	(0.324834)	(0.324647)	(0.319519)	(0.319449)

Table 9. Total energies (in Hartrees) of **1a** - **1e** calculated at the MP2 level employing 6-31G*-optimized geometries (MP2/basis set//HF/6-31G*).

Basis set	1a	1b	1c	1e	1d
6-31G*	-579.705385	-579.700242	-579.702245	-579.699128	-579.696274
6-31+G*	-579.737065	-579.732175	-579.733620	-579.730307	-579.728730
6-31G**	-579.867748	-579.862876	-579.864784	-579.859087	-579.856155

CNDO/2S method predict the same signs for the first two bands of the total CD-spectrum of **1**.

Since the calculated and observed signs of the first Cotton effect agree, we conclude that the absolute configuration of the measured compound is also *R,R*. This result is in perfect agreement with the reaction mechanism assumed for synthesis of **1** [5].

4. Experimental

The circular dichroism in terms of the ellipticity Θ (in deg) was measured on an AVIV 62 DS spectrometer (Lakewood, NJ, USA). Θ and $\Delta\varepsilon$, are interrelated by the equation $\Delta\varepsilon = 0.0303 \cdot \Theta/(c \cdot d)$. Dimensions: Numerical coefficient 0.0303 (in deg^{-1}); concentration c (in $mol \cdot l^{-1}$); pathlength d (in cm). The instrument was calibrated according to Chen and Yang [23]. The spectral bandwidth was 1.5 nm, the time constant 2 s and the temperature 27 °C. It is not possible to measure the CD spectrum at wave numbers higher than 55555 cm^{-1} (180 nm) with the spectrometer used.

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