Determination of the Absolute Configuration of 1,5-Diaza-*cis*-decalin by Comparison of Measured and Calculated CD-Spectra

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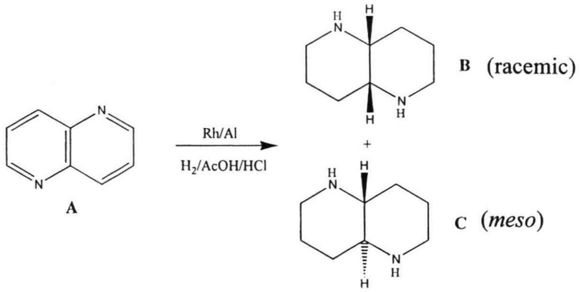
The absolute configurations of both 1,5-diaza-*cis*-decalin enantiomers were determined by comparison of measured and calculated CD spectra.

CD spectra for both enantiomers were recorded. Theoretical CD spectra for one of the isomers were calculated by means of the semiempirical CNDO/2S method. Eight 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 one-determinant *ab initio* calculations using the split valence 6-31G* basis set. Boltzmann factors were then obtained using relative energies calculated with three different basis sets and including correlation(MP2)- and zero point vibrational energy.

Comparing the sign of the observed and calculated longest wavelength Cotton effect, we assign an absolute configuration to the compound. This assignment was verified by means of X-ray structure determination of one of the enantiomers' α-methoxy-α-trifluoromethylphenyl aceticacid (MTPA, Mosher's reagent) derivative.

1. Introduction

Synthesis of 1,5-diaza decalin by catalytic hydrogenation of naphtyridine (**A**) results in an 85:15 mixture of *cis* (racemic, **B**) and *trans* (*meso*, **C**) isomers [1] (cf. Scheme 1).



Scheme 1.

The enantiomers of the racemic mixture of the 1,5-diaza-*cis*-decalines (**B1**, **B2**) could be separated by reaction with 10-camphorsulfonic acid. An NMR study [1] revealed that at room temperature the equilibrium mixture contains only those isomers where the nitrogen atoms are in an axial position relative to the neighbouring ring (cf. Scheme 2)[a]).


nitrogen atoms axial≡*proximal*

nitrogen atoms equatorial≡*distal*

Scheme 2.

It was not possible to obtain single crystals of sufficient quality of one of the pure enantiomers or of the camphorsulfonic acid derivatives. Therefore, this problem could not be solved directly by means of X-ray structure determination (however, see Part 3). The absolute configuration can also be elucidated by comparison of experimentally determined and calculated CD spectra [2 - 7]. We therefore calculated the

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[a)] Only *R,R* enantiomers are shown.

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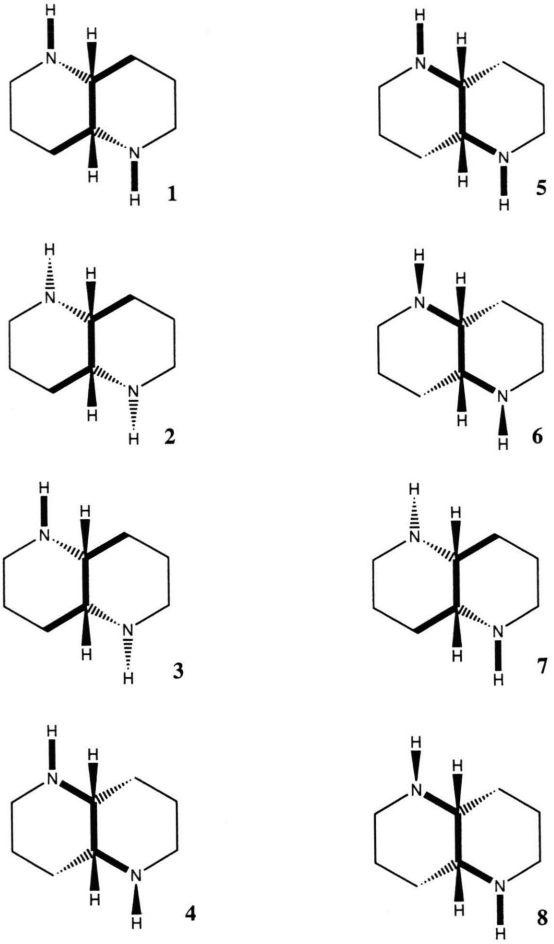

Scheme 3.

CD spectrum of one of the isomers (*R,R*). Because the CD spectrum of a flexible molecule depends on the molecular conformation, prediction of its absolute configuration requires knowledge of the conformational equilibrium. In the case of 1,5-diaza-*cis*-decalin we considered eight different isomers (cf. Scheme 3, **1** - **8** and Fig. 1)[a)], which might be devided into two classes.

In the molecules assigned to the first group, which we call *proximal* isomers (**1**, **2**, **3**, **7**), both nitrogen atoms occupy axial positions. In these isomers both N-H bonds can either be in an equatorial (**1**) or axial position (**2**). Moreover, one N-H bond might be axial while the other occupies an equatorial position (**3**). In this case we have to consider a second isomer, **7**, which is related to **3** by rotation about a twofold axis passing through the middle of the C-C bond connecting the two chiral carbon atoms. In the second group, the so-called *distal* isomers (**4**, **5**, **6**, **8**), the nitrogen atoms are in equatorial positions. Again, the N-H bonds might occupy equatorial (**5**), axial (**6**), or one axial and one equatorial position (**4**, **8**). As in the case of **3** and **7**, **4** and **8** are related to each other by a twofold rotation.

While **2** and **5** or **1** and **6** might be interconverted by a simultaneous inversion of both six-membered rings, generation of e. g. **3** from **1** or **2** requires inversion at one of the nitrogen atoms.

In order to obtain relative energies of the different isomers we applied not only the MM3 forcefield [8 - 10] but also performed *ab initio* calculations to locate stationary points on the hypersurface. In these calculations the geometries were optimized at the Hartree-Fock (HF) level. To obtain more reliable final relative energies, we included correlation energy calculated by means of Møller-Plesset perturbation theory [11] to the second order (MP2) and zero point vibrational energy in single point calculations. We then used the semiempirical CNDO/2S method [12] to calculate the transition energies and the transition moments. Further details of these calculations are described below.

2. Computational Methods

To obtain initial coordinates for geometry optimizations we started from molecular models defined by means of standard structural parameters and assuming the chair conformation for the fused piperidine rings. All structural parameters were energetically optimized employing the MM3 force field. Starting from the resulting molecular coordinates, we performed further unconstrained geometry optimizations at the *ab initio* one determinant level (Hartree Fock, HF) with the 6-31G* [13 - 16] basis set. The normal frequencies were then calculated to characterize the resulting stationary points and to obtain zero point vibrational energies. All six optimized geometries turned out to be local minima (**1** - **6**; Figure 1).

In order to include correlation energy we performed single point calculations at the HF/6-31G*-optimized structures with the MP2 method, employing not only the 6-31G* contraction of Gaussians but also the 6-31+G* [17, 18], and the 6-31++G** [17, 18] basis sets. Unscaled zero point vibrational energies calculated at the HF/6-31G* level were then added to the

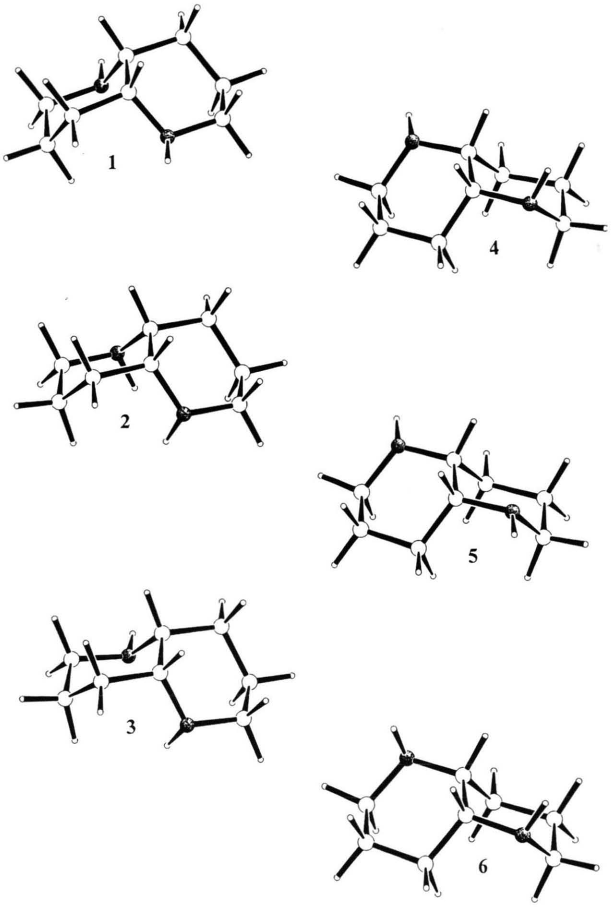

Fig. 1. Isomers of (*R*,*R*)-1,5-diaza-*cis*-decalin. **1 - 3** are the so-called *proximal* and **4 - 6** the *distal* isomers.

MP2/basis set//HF/6-31G* energies to obtain the final relative 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. 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][b]. The total CD spectrum was obtained as a Boltzmann-weighted superposition of the $\Delta\varepsilon$ curves of the conformers[c].

Table 1. Total energies of **1 - 6** calculated at the Hartree Fock level employing 6-31G*-optimized geometries (HF/basis set//HF/6-31G*). ε is the zero point vibrational energy, calculated at the HF/6-31G*//HF/6-31G* level. All energies are in Hartrees. The numbers of basis functions in the different basis sets are: 6-31G*: 182; 6-31+G*: 222; 6-31++G**: 286.

	6-31G*	6-31+G*	6-31++G**	ε
1	–421.150661	–421.157876	–421.185880	0.260111
2	–421.148190	–421.156191	–421.184183	0.260115
3	–421.152780	–421.160132	–421.188006	0.260434
4	–421.146976	–421.155046	–421.183022	0.260347
5	–421.147429	–421.155441	–421.183407	0.260349
6	–421.146067	–421.154240	–421.182243	0.260335

Table 2. Total energies (in Hartrees) of **1 - 6** calculated at the MP2 level employing 6-31G*-optimized geometries (MP2/basis set//HF/6-31G*).

	6-31G*	6-31+G*	6-31++G**
1	–422.565206	–422.590920	–422.727803
2	–422.563615	–422.589873	–422.726439
3	–422.568298	–422.593942	–422.730495
4	–422.561208	–422.587856	–422.724669
5	–422.561390	–422.588134	–422.724979
6	–422.560673	–422.587292	–422.724105

All *ab initio* calculations were carried out employing the GAUSSIAN94 set of quantum chemical routines [21] running on an SNI-s600/20 computer of the Rechenzentrum der RWTH-Aachen. MM3 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].

3. Results and Discussion

Total energies obtained with *ab initio* methods are listed in Tables 1 and 2. Relative energies (ΔE_{rel}) and the corresponding Boltzmann factors at room temperature (w_i) of the six local minima are listed in Tables 3 - 5, while wavelengths (λ) and rotational strenghts (R in Debye-Bohr magneton (DBM)) of the four energetically lowest transitions are compiled in Table 6.

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

[c] $\Delta\varepsilon = \Sigma_{i=1}^{N} w_i \Delta\varepsilon_i$, $w_i = (\exp(-E_i/RT))/[\Sigma_j \exp(-E_j/RT)]$. 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 3. Relative energies (ΔE_{rel} in kcal/mol) and Boltzmann factors (w_i, in % at 298 K) of **1 - 6**, calculated with different basis sets (6-31G*, 6-31+G*, 6-31++G**) at the HF level using 6-31G*-optimized geometries (HF/basis set//HF/6-31G*).

	6-31G*		6-31+G*		6-31++G**	
	ΔE_{rel}	w_i	ΔE_{rel}	w_i	ΔE_{rel}	w_i
1	1.33	4.99	1.42	4.28	1.33	4.94
2	2.88	0.36	2.47	0.73	2.40	0.81
3	0.00	94.25	0.00	94.14	0.00	93.32
4	3.64	0.25	3.19	0.44	3.13	0.44
5	3.36	0.15	2.94	0.33	2.89	0.35
6	4.21	0.00	3.70	0.08	3.62	0.14

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

	6-31G*		6-31+G*		6-31++G**	
	ΔE_{rel}	w_i	ΔE_{rel}	w_i	ΔE_{rel}	w_i
1	1.94	1.85	1.90	1.96	1.69	2.77
2	2.94	0.35	2.55	0.65	2.54	0.66
3	0.00	97.71	0.00	97.08	0.00	96.18
4	4.45	0.00	3.82	0.15	3.66	0.19
5	4.33	0.00	2.64	0.10	3.46	0.14
6	4.78	0.00	4.17	0.06	4.01	0.06

Table 5. Relative energies (ΔE_{rel} in kcal/mol) and Boltzmann factors (w_i, in % at 298 K) of **1 - 6**, calculated with different basis sets (6-31G*, 6-31+G*, 6-31++G**) 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*		6-31++G**	
	ΔE_{rel}	w_i	ΔE_{rel}	w_i	ΔE_{rel}	w_i
1	1.74	2.56	1.69	2.77	1.49	3.83
2	2.74	0.47	2.35	0.91	2.34	0.91
3	0.00	96.85	0.00	96.00	0.00	94.83
4	4.39	0.06	3.76	0.17	3.60	0.22
5	4.28	0.04	3.59	0.10	3.41	0.15
6	4.72	0.02	4.11	0.05	3.95	0.06

Table 6. Wavelengths λ (nm) and rotational strengths R (DBM) of the four energetically lowest transitions (Trans. 1 - 4) of **1 - 6** 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	λ	R
1	123.2	–0.41	122.9	1.25	120.5	0.38	120.4	–1.24
2	130.3	0.29	123.8	–1.74	123.1	1.11	121.4	0.75
3	126.4	0.42	122.0	–2.64	121.2	1.18	120.0	1.43
4	127.3	–1.54	124.6	5.18	122.9	–3.87	122.5	–0.49
5	125.9	–5.35	125.1	6.24	122.8	–2.52	122.6	1.65
6	130.6	–0.52	123.8	1.55	123.1	–0.03	121.6	–1.52

The structures of the six local minima (**1 - 6**) obtained at the HF/6-31G* level are shown in Figure 1. At all levels of theory employed in this study the *proximal* isomers are more stable than the *distal* structures. Among the members of the first group **3** has the lowest total energy and this might be due to an energetically favourable interaction between the hydrogen atom of the axial N-H bond with the other nitrogen atom (r_{N-H}: 1.00 Å, r_{NN}: 3.00 Å, $r_{N \cdots H}$: 2.67 Å, $\angle_{N-H \cdots N} = 97.3°$). Semiempirically calculated CD spectra of the six local minima are diplayed in Figure 2. The total Boltzmann-weighted CD spectrum, calculated using our best relative energies from Table 5 (ZPE+MP2/6-31++G**//HF/6-31++G**) is given in Figure 3. Finally, the experimentally determined CD spectra of both enantiomers (**B1**, **B2**) are plotted in Figure 4.

Compared with the experimental transition wavelength in Fig. 4 (193 nm), the calculated values are strongly blue-shifted. However, we believe that in spite of this obvious shortcoming, the method predicts the sign of the first Cotton effect correctly, as has been shown in previous investigations [2 - 7].

The calculated CD spectra of the three energetically lowest conformers (**1 - 3**) show a positive first Cotton effect (Figure 2). On the contrary, the first CD bands of **4 - 6** are negative. However, due to the small Boltzmann factors of these isomers, their contributions to the total spectrum (Fig. 3) are negligible. As a result, the CD spectrum of (*R*,*R*)-1,5-diaza-*cis*-decalin, calculated with the CNDO/2S method shows a positive first band. Since the first measured Cotton effect of **B2** is also positive (cf. Fig. 4), we conclude that this compound is the (*R*,*R*) isomer. Consequently, **B1** is (*S*,*S*)-1,5-diaza-*cis*-decalin.

The latter assignment could be verified experimentally since it was possible to crystallize the *R*-(+)-MPTA derivative (**D**) of enantiomer **B1**. The structure of the molecule in the solid state [24] is shown in Figure 5. The absolute configuration of both bridging carbon atoms (C4 and C5) is *S*. While 1,5-diaza-*cis*-decalin occurs almost exclusively as a *proximal* isomer in solution, the MPTA derivative crystallizes as a *distal* isomer (cf. Fig. 6) corresponding to **5** in Scheme 3. This might be explained by the bulkiness of the substituents and by the fact that in **D** no stabilization due to formation of an internal hydrogen bridge is possible.

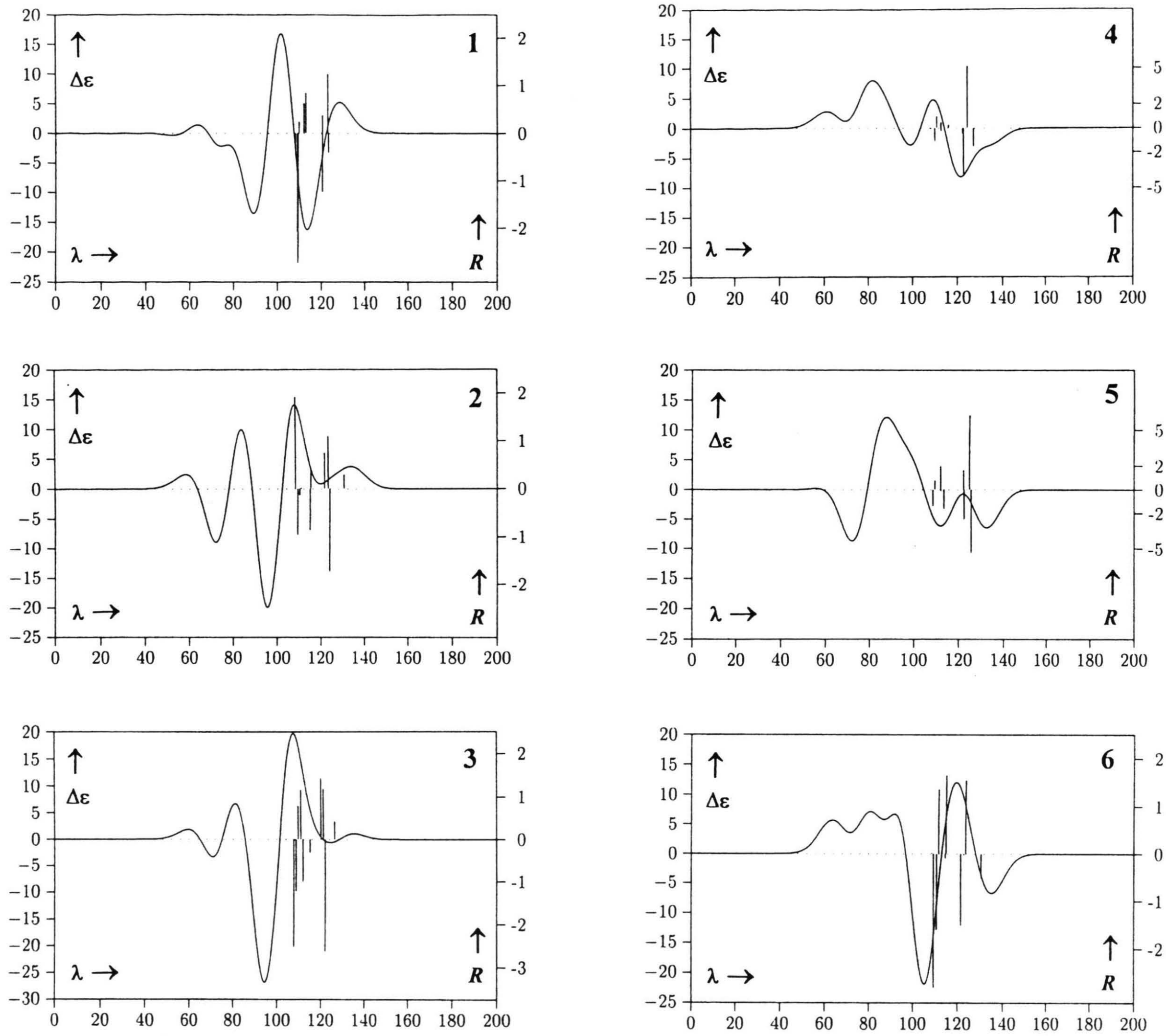

Fig. 2. CD spectra of conformers **1** - **6**, calculated by means of the CNDO/2S method using HF/6-31G*-optimized geometries. $\Delta\varepsilon$ in l·mol^{-1}·cm^{-1}, rotational strength (R) of the ten lowest transitions in DBM, and λ in nm.

4. Experimental

CD spectra of compounds **B1** *and* **B2**

The circular dichroism in terms of the ellipticity Θ (in deg) was measured on an AVIV 62 DS spectrometer (Lakewood, NJ, USA). The molar ellipticity $[\Theta]$ and the molar extinction coefficient $\Delta\varepsilon$ are interrelated by the equation $\Delta\varepsilon = 0.0303 \cdot \Theta/(c \cdot d)$. Dimensions: Numerical coefficient 0.0303 (in deg^{-1}); concentration c (mol·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.

X-ray structure determination of **D**

Colourless crystals of sufficient quality were obtained from a chloroform/hexane mixture. 6726 reflections (Friedel pairs) were collected at 200K on an ENRAF-NONIUS CAD4 diffractometer equiped with a copper anode and a graphite monochromator (CuKα, λ = 1.54179 Å). Averaging resulted in 2744 observed reflections ($I > 2\,\sigma(I)$, $R_{\text{int}} = 0.05$). The com-

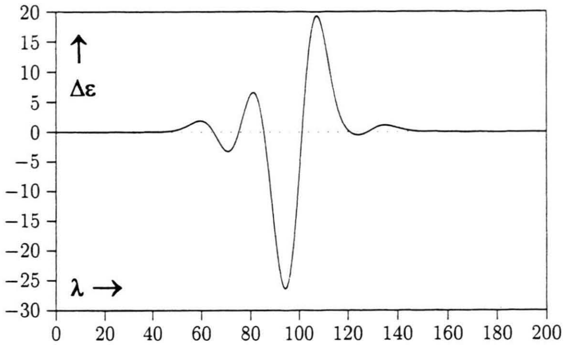

Fig. 3. Total CD spectrum of (*R*,*R*)-1,5-diaza-*cis*-decalin calculated by means of the CNDO/2S method using HF/6-31G*-optimized geometries and the relative energies (ZPE+MP2/6-31++G**//HF/6-31++G**) from Table 5. $\Delta\varepsilon$ in $l \cdot mol^{-1} \cdot cm^{-1}$, λ in nm.

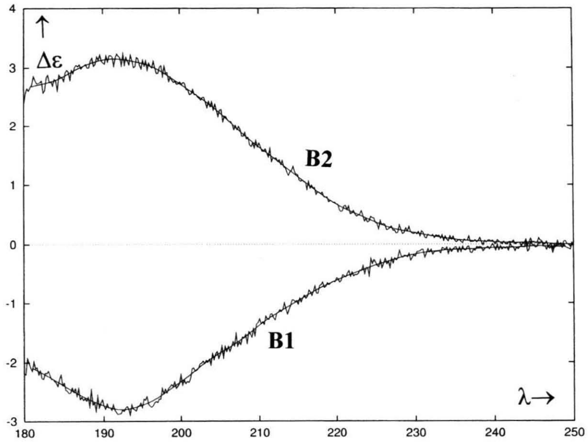

Fig. 4. Experimental CD spectra ($\Delta\varepsilon$ in $l \cdot mol^{-1} \cdot cm^{-1}$, λ in nm) of compound **B1** ((*S*,*S*)-1,5-diaza-*cis*-decalin) and compound **B2** ((*R*,*R*)-1,5-diaza-*cis*-decalin).

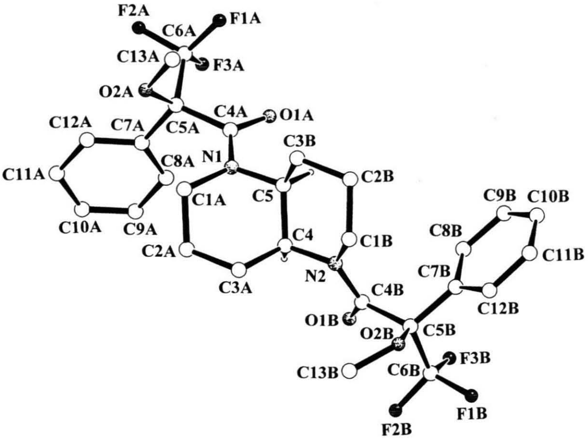

Fig. 5. Structure of the *R*-(+)-MPTA derivative **D** in the solid state [24].

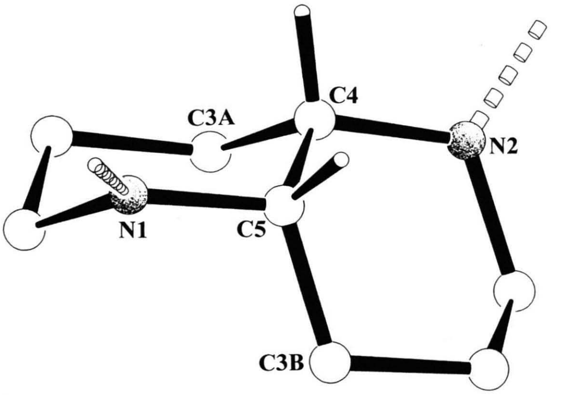

Fig. 6. Part of the solid state structure of **D** in Fig. 5 showing the *distal* arrangement of the nitrogen atom N1 and N2.

pound crystallizes in the orthorhombic space group $P2_12_12_1$ (No. 19), a = 11.9028(4), b = 13.194(2), and c = 17.789(1) Å. Z = 4, V = 2793.7 Å^3, and M_r = 572.5 resulting in a calculated density of D_{cal} = 1.361 g·cm^{-3}. μ = 9.88 cm^{-1}, no absorption correction. The structure was solved using direct methods as implemented in the XTAL3.2 package of crystallographic routines [25], employing GENSIN [26] to generate structure invariant relationships and GENTAN [27] for the general tangent phasing procedure. Final least-squares full-matrix refinement of 361 parameters terminated at $R = 0.078$ ($R_w = 0.057$, $w = \sigma^{-2}$), a final shift/error $< 10^{-3}$, a residual electron density of –0.7/+0.6 e·Å^{-3}, and a goodness of fit of 1.828. Hydrogen positions were calculated and not refined. Their U_{eq} were fixed at $1.5 \cdot U_{eq}$ of the relevant heavy atom prior to final refinement. The absolute structure of the molecule as shown in Fig. 5 was determined by calculation of Flack's absolute structure parameter [28] in a separate refinement.

Acknowledgement

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