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Determination of the absolute configuration of 1,3,5-triphenyl-4,5-dihydropyrazole enantiomers by a combination of VCD, ECD measurements, and theoretical calculations

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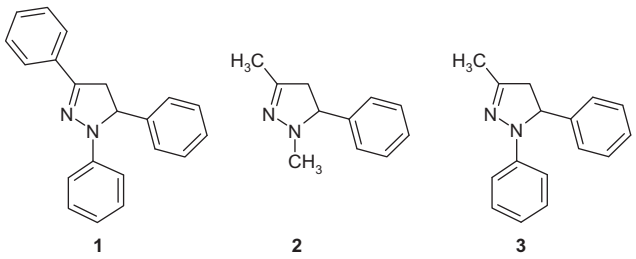
ABSTRACT

The enantiomers of 1,3,5-triphenyl-4,5-dihydropyrazole (an intense blue fluorescent compound) have been separated for the first time and their absolute configuration was established by a combination of VCD and ECD measurements and theoretical calculations. The enantiomers of 1,3,5-triphenyl-4,5-dihydropyrazole which are highly fluorescent both in solution (CH_2Cl_2) and in the solid state may find application in the very active field of enantioselective fluorosensors.

1. Introduction

In 2001, some of us reported that 1,3,5-triphenyl-2-pyrazoline (or 4,5-dihydropyrazole) **1** (Scheme 1) shows spontaneous resolution when crystallizing, being a conglomerate.[1] To date, this remains the only reported example of a conglomerate in 2-pyrazolines. 1,3-Dimethyl-5-phenyl-2-pyrazoline **2** crystallizes enantiomerically pure when included in chiral Toda's host.[2] We have also resolved both enantiomers of 1,5-diphenyl-3-methyl-2-pyrazoline **3** using chiral HPLC.[3] Other authors have resolved other 2-pyrazolines via crystallization with a chiral auxiliary or by chiral HPLC.[4]



Scheme 1. Chiral 2-pyrazolines.

1,3,5-Triaryl-2-pyrazolines have important applications as drugs[5] and as optical devices,[6] particularly those described by Prasanna de Silva.[7] In recent years, the enantioselective synthesis of 2-pyrazolines has received much attention,[8] due to the fact that some pharmaceutical compounds are chiral pyrazolines.[9]

We decided to use compound **1** (QUMZUT,[10] Fig. 1) to test the possibilities offered by VCD and ECD plus theoretical calculations to assign the absolute configuration of the enantiomers of this compound. We have successfully used this combination in previous work.[11,12] In the case of **1** the lack of heavy atoms prevents the use of Bijvoet's anomalous dispersion method.[13]

2. Results and discussion

In the first step, HPLC screening of different chiral columns (see Section 4) showed that Chiralcel OD-3 and Chiralpak AD-H

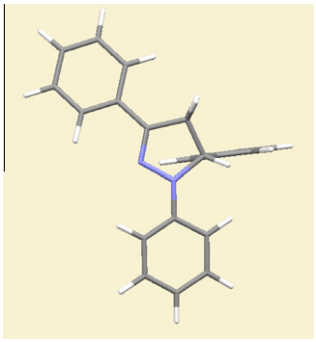


Figure 1. The X-ray molecular structure of 1,3,5-triphenyl-2-pyrazoline **1**.

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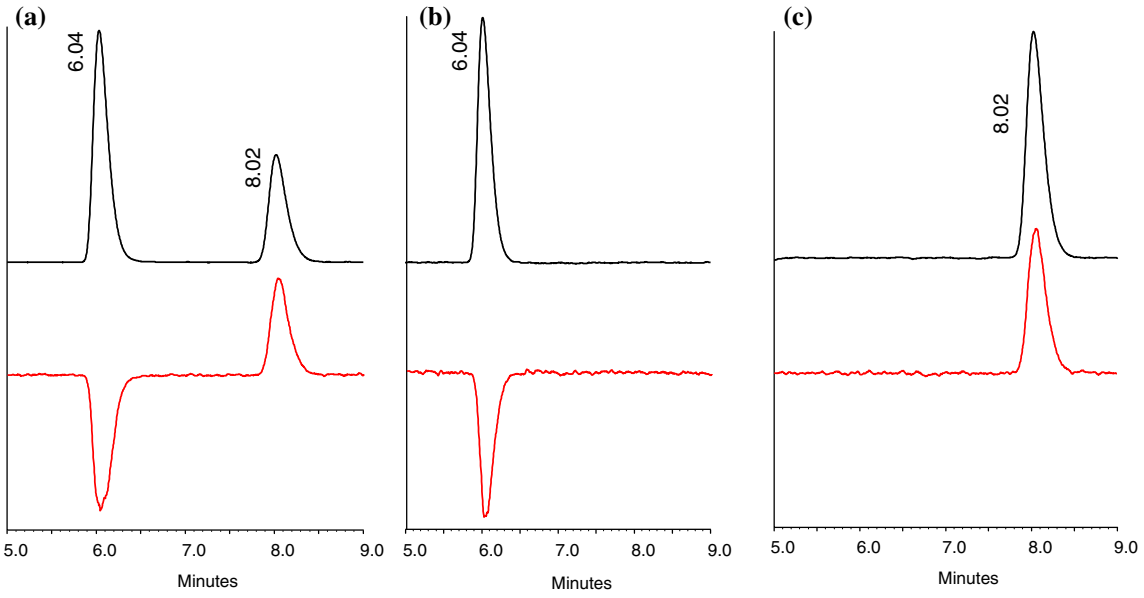

Figure 2. Separation of the enantiomers of **1** on Chiralpak AD-H. (eluent 90:10 Hexane/2-PrOH, Flow rate 1 mL/min, 25 °C, UV 254 nm (black trace) and CD 220 nm (red trace). (a) a reassembled mixture of enantiomers; (b) example of an enantiomerically pure crystal composed of the first eluted enantiomer; and (c) example of an enantiomerically pure crystal composed of the second eluted enantiomer.

columns were suitable for separation of the enantiomers of **1** in a 90:10 Hexane/2-PrOH mixture of solvents (Fig. 2a). Chiralcel OD-3 and Chiralpak AD-H columns were composed of cellulose and amylose tris(3,5-dimethylphenyl)carbamate coated on silica, respectively.

In the second step, the individual crystals of **1** grown in different solvents were submitted to liquid chromatography on Chiralpak AD-H. The objective was to verify if conglomerates were obtained under different crystallization conditions. This method has been already used to detect the formation of conglomerates of pyrimidin-2(1*H*)-(thi)ones by Sakamoto et al.[14] Some of us further improved the method by using on line chiroptical detection which allows a safer assignment in case of a possible drift of the retention time or poor separation.[15,16] Chromatography on chiral support with chiroptical detection (Pol or ECD) is particularly efficient in detecting the occurrence of a conglomerate when the crystals are quite small; the only requirement is to obtain peaks with an opposite sign and different retention depending on the crystal picked. In the case of large crystals a small piece of the picked crystal is submitted to chromatography and crystals of high enantiomeric purity with the same retention and sign can be gathered in the same flask. It is worth noting that chiral chromatography immediately gives information on the enantiomeric purity of the crystals while this type of information is not attainable without considerable effort and time consumption by other classical methods such as polarimetry.

The crystals of **1** could be obtained via recrystallization in various solvents. Six crystals were selected from a recrystallization in 2-PrOH/CH_2Cl_2 (1:1) and four crystals were selected from recrystallization in EtOH/CH_2Cl_2 (1:1) or 2-PrOH, respectively. Each selected crystals was solubilized in ethanol and analyzed on a Chiralpak AD-H column with CD detection at 220 nm. Amongst the 14 crystals which were analyzed, 5 were enantiomerically pure: 3 corresponded to the first eluted enantiomer (R_t = 6.01–6.11 min) (Fig. 2b) and 2 to the second eluted (R_t = 7.90–8.09 min) (Fig. 2c). These results are in accordance with X-ray data which gave a $P2_1$ space group for **1**.

The nine remaining crystals were contaminated by the other enantiomer (up to 20%). From that screening on a limited set of crystals, we suggest that isopropanol alone or in mixture with CH_2Cl_2 gave a cleaner spontaneous resolution than ethanol.

In all the cases, the enantiopure crystals of **1** were too small to attempt a preparative separation in an efficient way as we did for the hydrobenzoine case which gave enantiopure crystals weighing ca 14 mg each.[15]

The chromatographic screening experiments yielded a lot of information: the separation of the enantiomers on Chiralpak AD-H is amenable to a semi-preparative scale. The first eluted enantiomer gave a (−) CD sign at 220 nm and a (+) CD sign at 254 nm in a 90:10 Hexane/2-PrOH mixture of solvent. Furthermore, detection using a JASCO polarimeter on-line shows that the first eluted enantiomer is the dextrogyre one (data not reported).

It is worth noting that Chiralcel OD-3 also provided very nice separation of the enantiomers of **1**. Since the same mobile phase was used for Chiralpak AD-H and Chiralcel OD-3,[17] CD detection at 220 nm revealed that the two chiral stationary phases produced the opposite order of elution (see Section 4.2).

The semi-preparative resolution of *rac*-**1** was performed with the same eluent as for analytical analysis on a (250 × 10 mm) Chiralpak AD-H column. Strictly speaking, we did not obtain *rac*-**1** but a reassembled mixture obtained by grinding a large crop of more or less enantiomerically pure crystals of each configuration.

The semi-preparative separation afforded ca. 20 mg of each enantiomer within 6 h. The first eluted enantiomer corresponded to the (−)ECD_{220nm} form according to CD detection in the mobile phase. The specific rotation of the first and second eluted enantiomers was determined in CH_2Cl_2 at different wavelengths (Table 3, Section 4), the first eluted enantiomer is dextrogyre, while the second is levogyre. It is worth noting that the determination of the specific rotation at 365 nm was not possible due to the intense absorption about that wavelength which is associated with an intense blue fluorescence[18] (see Graphical abstract).

The experimental IR spectra of the enantiomers (red line in Fig. 3a) and VCD spectra for the first eluted (red line in Fig. 3b) and second eluted enantiomer (green line in Fig. 3b) were recorded in CD_2Cl_2 and compared to the spectra calculated for (*R*)-**1** (blue line in Figs. 3a and 3b). As expected, the IR absorptions are identical and VCD spectra are mirror images. Conformational studies

Table 1
Frequencies and descriptions of the bands selected in Figs. 3a and 3b

Bands	$\bar{\nu}_{calc}$ (cm^{-1})	$\bar{\nu}_{exp.}$ (cm^{-1})	Description
1	1593	1598	Stretching C=$C_{arom.}$
2	1583	–	Stretching C=$C_{arom.}$ and C=N
3	1577	1577	Stretching C=$C_{arom.}$ with bending $C_{arom.}$–C_{sp3}*–H
4	1567	1562	Stretching C=$C_{arom.}$
5	1557	–	Stretching C=$C_{arom.}$ and C=N
6	1492	1502	Stretching $C_{arom.}$–N and $C_{arom.}$–C_{sp2} with bending C–$H_{arom.}$
7	1485	1495	Stretching $C_{arom.}$–N and $C_{arom.}$–C_{sp2} with bending C–$H_{arom.}$
8	1448	1455	Bending H–C_{sp3}–H, $C_{arom.}$–C_{sp3}*–H and C–$H_{arom.}$
9	1442	1448	Bending H–C_{sp3}–H, $C_{arom.}$–C_{sp3}*–H and C–$H_{arom.}$
10	1374	1392	Breathing of the five-membered heterocycle and bending C–$H_{arom.}$
11	1346	1350	Bending $C_{arom.}$–C_{sp3}*–H and C–$H_{arom.}$
12	1322	1334	Rocking C–$H_{arom.}$, H–C_{sp3}–H and $C_{arom.}$–C_{sp3}*–H
13	1306	1324	Rocking C–$H_{arom.}$, H–C_{sp3}–H and $C_{arom.}$–C_{sp3}*–H
14	1291	1302	Deformations of the five-membered heterocycle and of two phenyl groups
15	1282	–	Deformations of the five-membered heterocycle and of two phenyl groups
16	1271	1283	Deformations of the five-membered heterocycle and of one phenyl group
17	1260	1268	Deformations of the five-membered heterocycle and of two phenyl groups
18	1233	1240	Deformations of the five-membered heterocycle and of two phenyl groups
19	1116	1125	Stretching N–N with twist of H–C_{sp3}–H, $C_{arom.}$–C_{sp3}*–H and bending C–$H_{arom.}$
20	1066	1069	Stretching N–N with bending C–$H_{arom.}$

showed that there was one conformation for (*R*)-**1** which has a geometry close to the one determined by X-ray diffraction analysis. The geometry optimizations, vibrational frequencies, IR absorption and VCD intensities were calculated with Density Functional Theory (DFT) using B3LYP combined with TZVP basis set. A very good agreement was observed between the experimental and calculated spectra (Figs. 3a and 3b). The VCD spectrum of the first eluted enantiomer (red line in Fig. 3b) matches the calculated one for (*R*)-**1** (blue line in Fig. 3b). Among all the bands attributed on the spectra, bands 1, 2, 6, 7, 8, 10, 11, 12, 13, 14, 15, 18, and 20 must be highlighted due to their particularly good correspondence. The normal modes corresponding to those bands are described in Table 1.

Following Polavarapu's recommendation that more than one chiroptical spectroscopic method should be applied for the absolute configuration determination, the ECD spectra of the enantiomers were recorded in *n*-hexane.[19]

The bands at 220 and 254 nm (Fig. 4) were in perfect agreement with the observed signals during chiral HPLC CD detection. The first eluted enantiomer (red line in Fig. 4b) presents a negative signal at 220 nm and a positive one at 254 nm. The ECD and UV spectra were calculated using time dependent density functional theory (TDDFT) with CAM-B3LYP functional and 6-31++G(d,p) basis set (Figs. 4a and 4b). Considering that the calculations were carried out in the gas phase and that the calculated results have not been shifted, the agreement between calculated and experimental spectra is satisfactory. Particularly, the large band above 300 nm confirms the assignment of the (*R*)-configuration to the first eluted enantiomer.

3. Conclusion

Chromatography on chiral support associated with chiroptical detection confirmed the X-ray observation that compound **1** affords a conglomerate when crystallized in different solvents. The absolute configuration of the enantiomers of 1,3,5-triphenyl-2-pyrazoline **1** which were readily obtained by chromatography on Chiralpak AD-H was established using vibrational and electronic

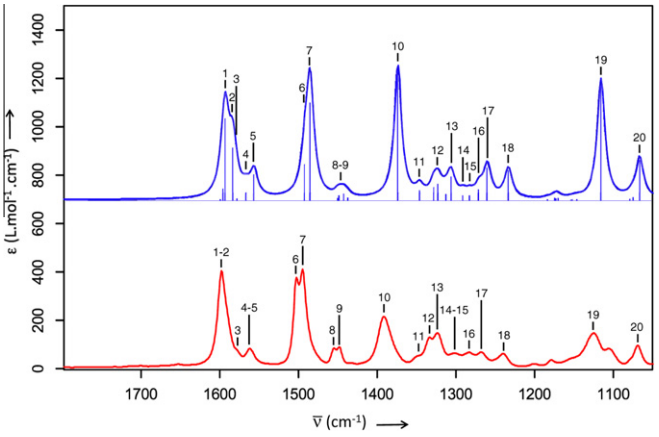

Figure 3a. IR absorption spectra of **1** calculated for the (*R*)-enantiomer (in blue) and measured in CD_2Cl_2 (in red). A scaling factor of 0.97 has been applied on the frequencies of the calculated spectrum. The blue bars correspond to the calculated dipole strengths.

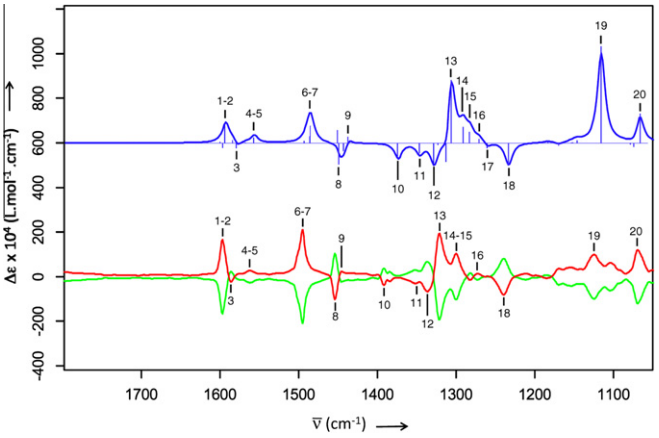

Figure 3b. VCD spectra of **1** calculated for the (*R*)-enantiomer (in blue) and measured in CD_2Cl_2 for the first eluted (in red) and the second eluted (in green) enantiomers. A scaling factor of 0.97 has been applied on the frequencies of the calculated spectrum. The blue bars correspond to the calculated VCD rotary strengths.

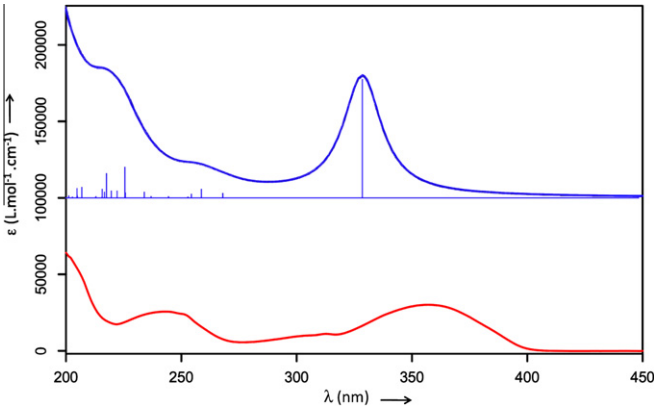

Figure 4a. UV spectra of **1** calculated for the (*R*)-enantiomer (in blue) and measured in hexane for the first and second eluted enantiomers (in red). The blue bars correspond to the calculated oscillator strengths.

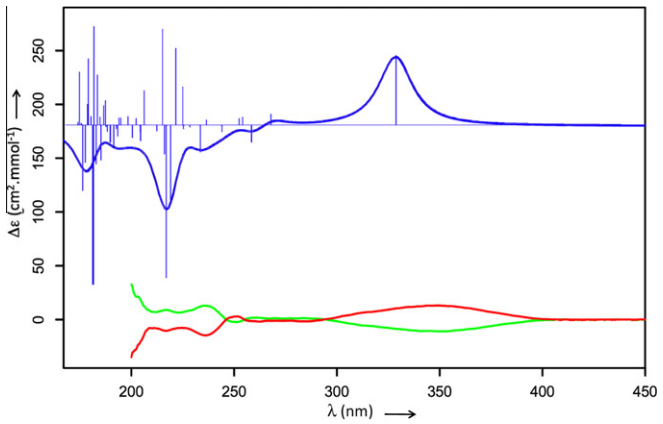

Figure 4b. ECD spectra of **1** calculated for the (*R*)-enantiomer (in blue) and measured in hexane for the first eluted (in red) and the second eluted (in green) enantiomers. The blue bars correspond to the calculated ECD rotary strengths.

CD spectroscopy experiments in comparison with the calculated spectra for the (*R*)-form. The first eluted enantiomer on a Chiralpak AD-H column, which gives a (−) CD sign at 220 nm and a (+) specific rotation in CH_2Cl_2 presents the (*R*)-absolute configuration. The first separation of the enantiomers of **1** and their intense blue fluorescence, which was observed both in the solution and in the solid state, paves the way for further studies in the field of enantioselective fluorescent sensors.[7e,20]

4. Experimental

4.1. Preparation of 1,3,5-triphenyl-2-pyrazoline 1

This compound was prepared in a crystalline form as previously described.[1] The samples were not stable on standing in $CHCl_3$ and they are highly fluorescent under UV lamp.

4.2. Enantioseparation

The analytical chiral HPLC experiments were performed on a unit composed of a Merck D-7000 system manager, Merck-Lachrom L-7100 pump, Merck-Lachrom L-7360 oven, Merck-Lachrom L-7400 UV-detector, and on-line Jasco OR-1590 polarimeter. Hexane and isopropanol, HPLC grade, were degassed and filtered on a 0.45 μm membrane before use. Semi-preparative separations were performed on a Knauer unit with pump, UV detector and a software to collect the different fractions.

The columns (250 × 4.6 mm) used for the analytical separation of **1** were: Chiralpak AD-H, Chiralcel OD-3, Chiralpak AS-3 and Chiralpak AZ-H from Chiral Technologies Europe (Illkirch, France), Lux-Amylose-2, Lux-Cellulose-2 and Lux-Cellulose-4 from Phenomenex, Le Pecq (France), Whelk-O1 (*S*,*S*) and Ulmo (*S*,*S*) are from Regis Technologies, Morton Grove (USA).

A Chiralpak AD-H column (250 × 10 mm) from Chiral Technologies Europe (Illkirch, France) was used for semi-preparative separation (flow-rate = 5 mL min^{-1}, UV detection at 254 nm, eluent: Hexane/2-PrOH (90:10)).

Retention times Rt in minutes, retention factors $k_i = (Rt_i - Rt_0)/Rt_0$ are given. Rt_0 was determined by injection of tri-*t*-butylbenzene. The CD detector was set at 220 or 254 nm. The analyses were performed at 25 °C, with 1 mL min^{-1} as flow-rate, detections by UV at 254 nm and CD. The sign given by the on-line JASCO CD-1595 detector is the CD sign of the product in the solvent used for the chromatographic separation at the selected wavelength. The screening of the chiral columns is reported in Table 2.

Table 2
Screening of chiral columns for the separation of **1** (flow-rate = 1 mL min^{-1}, UV detection at 254 nm, eluent: Hexane/2-PrOH (90:10))

Column	t_{R1}	k_1	t_{R2}	k_2	α	Rs
Chiralpak AS-3	5.55	0.81			1	0
Lux-amylose-2	5.17	0.69			1	0
Whelk-O1 (*S*,*S*)	4.02	0.31			1	0
Ulmo (*S*,*S*)	4.21	0.38			1	0
Lux-cellulose-2	4.42 (+)	0.44	4.65 (−)	0.51	1.13	<0.5
Lux-cellulose-4	4.44	0.45			1	0
Chiralpak AZ-H	5.42 (−)	0.81	5.93 (+)	0.98	1.21	1.76
Chiralcel OD-3	6.26 (+)	1.09	9.45 (−)	2.15	1.97	8.43
Chiralpak AD-H	6.04 (−)	1.01	8.02 (+)	1.67	1.65	5.66

The associated sign corresponds to the sign of the CD trace at 220 nm.

4.3. Specific rotation of the enantiomers of 1

The specific rotations were determined on a Perkin-Elmer MC-241 in CH_2Cl_2 at 25 °C. They are reported in Table 3. It was not possible to determine the specific rotation at 365 nm, as the transmitted energy was too low.

Table 3
Specific rotation in CH_2Cl_2

λ (nm)	$[\alpha]_D^{25}$ (*c* 0.5, CH_2Cl_2) for the first eluted enantiomer on Chiralpak AD-H (*R*)-form	$[\alpha]_D^{25}$ (*c* 0.3, CH_2Cl_2) for the second eluted enantiomer on Chiralpak AD-H (*S*)-form
589	+425	−424
578	+452	−451
546	+569	−567
436	+1929	−1927

4.4. IR, VCD and UV, ECD measurements

Infrared (IR) and vibrational circular dichroism (VCD) spectra were recorded on a Bruker PMA 50 accessory coupled to a Vertex 70 Fourier transform infrared spectrometer. A photoelastic modulator (Hinds PEM 90) set at 1/4 wave retardation was used to modulate at 50 kHz the handedness of the circular polarized light. Demodulation was performed by a lock-in amplifier (SR830 DSP). An optical low-pass filter (<1800 cm^{-1}) before the photoelastic modulator was used to enhance the signal/noise ratio. A transmission cell equipped with sealed CaF_2 windows of 200 μm of optical pathlength was used. Solutions with a concentration of 0.18 mol L^{-1} were prepared by dilution of solid samples in CD_2Cl_2. The VCD spectra of each pure enantiomer were measured and the baseline of the spectra was corrected by taking the half difference of the spectra of the two enantiomers. For the individual spectra of the enantiomers, approximately 12,000 scans were averaged at 4 cm^{-1} resolution (corresponding to 3 h measurement time). For IR absorption spectra, the cell filled with CD_2Cl_2 served as a reference.

UV and ECD spectra were measured on a JASCO J-815 spectrometer equipped with a JASCO Peltier cell holder PTC-423 to maintain the temperature at 20.0 ± 0.2 °C. A cell of 1 mm of optical pathlength was used. Solutions with a concentration of 7.5 mg/100 mL were prepared by dilution of solid samples in *n*-hexane (HPLC grade). The CD spectrometer was purged with nitrogen before recording each spectrum, which was baseline subtracted. The baseline was always measured for the same solvent and in the same cell as the samples.

The spectra are presented without smoothing and further data processing.

4.5. DFT calculations

Calculations were performed on the (*R*)-enantiomer of **1** starting from the X-ray structure available in the CSD database (QUMZUT).[10] The geometry optimizations, vibrational frequencies, IR absorption and VCD intensities were calculated with Density Functional Theory (DFT) using B3LYP functionals combined with TZVP basis set.[21,22] Frequencies were scaled by a factor of 0.97. IR absorption and VCD spectra were constructed from calculated dipole and rotational strengths assuming lorentzian band shape with a half-width at half maximum of 6 cm^{-1}. Based on the B3LYP/TZVP optimized geometry (Fig. 5), the ECD and UV spectra were calculated using time dependent density functional theory (TDDFT)[23] with CAM-B3LYP functional and 6-31++G(d,p) basis set.[24] Calculations were performed for vertical 1A singlet excitation using 50 states. For a comparison between the theoretical results and the experimental values, the calculated UV and ECD spectra have been modeled with lorentzian functions, using a half-width of 0.21 eV. All calculations were performed using Gaussian09 Revision A02.[25]

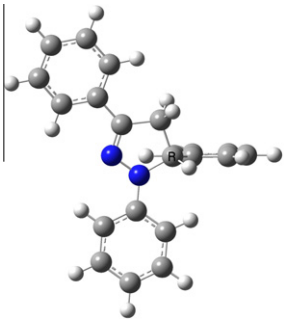

Figure 5. B3LYP/TZVP optimized structure of **1**.

Acknowledgments

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