

A Facile Method to Determine the Absolute Structure of Achiral Molecules: Supramolecular-Tilt Structures

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Dedicated to Dr. Patrick Batail on the occasion of his 65th birthday

Abstract: Achiral compounds 4-methoxy-4-(*p*-methoxyphenyl)cyclohexanoneethylene ketal (**2**), 4-hydroxy-4-(*p*-methoxy phenyl)cyclohexanoneethylene ketal (**3**), and 3,5-dimethyl-4-nitropyrzole (**4**) crystallized in chiral structures and the samples showed an enantiomeric excess. We have determined the absolute structures of these compounds by using X-ray diffraction with

copper radiation at low temperatures. Moreover, we have also established the prevalent absolute structures in these samples, by comparing their calculated

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and solid-state vibrational circular dichroism (VCD) spectra. The consistency of this method was confirmed by using (*R,R*)-2,8-diiodo-4,10-dimethyl-6*H*,12*H*-5,11-methano-dibenzo[b,f]-[1,5]diazocine, Tröger's base, (*R,R*)-**1**, as a chiral compound of known absolute configuration.

Introduction

The topic of absolute configuration (AC, that is, the spatial arrangement of the atoms of a chiral molecule) and/or absolute structure (AS, that is, the spatial arrangement of the atoms of a noncentrosymmetric crystal) is of great importance in the science and technology of chiral systems in general and in the investigation of reaction mechanisms, in particular spontaneous resolution and molecular recognition in fields such as material sciences, nonlinear optics, or pharmacology.^[1] In this context, spontaneous resolution continues

to be an intriguing issue, the explanation of which is often elusive.^[2] Pidcock evaluated that about 11% of achiral organic compounds in the Cambridge structural database give rise to chiral crystal structures, mainly in *P*₂,*2*₁ or *P*₂₁ space groups.^[3] Furthermore, recently, Dryzun and Avnir showed that the proportion of non-biological chiral crystals was as high as 23%.^[4] The knowledge of the absolute configurations of solid materials is necessary to understand this phenomenon, as well as the origin of enantiomeric excess in the crystal (or solid-state *ee*).^[5] In addition, chiral solids from achiral compounds have been used to perform "absolute asymmetric synthesis"^[6] and as the source of asymmetry in autocatalytic reactions.^[7]

The most commonly used techniques to establish the absolute configuration are X-ray diffraction of single crystals and VCD in solution.^[8] To accurately determine AC or AS by X-ray diffraction, it is necessary to take into account the X-ray anomalous dispersion effect beyond Friedel's law. This difference in intensity (the "Bijvoet difference") depends on both the type of atoms present in the molecule and on the wavelength of the radiation used.^[9] In general, the anomalous differences increase as a function of the atomic number and the wavelength of the X-rays. For light-atom structures (that is, those that only contain C, H, N, or O atoms), the anomalous scattering with molybdenum radiation is very small and, therefore, a copper X-ray source is preferable.^[10] Given high-quality samples and appropriate hardware and software, X-ray crystal-structure determination offers the possibility of an *ab initio* determination of the absolute structure and, hence, the absolute configuration of chiral organic materials.^[11]

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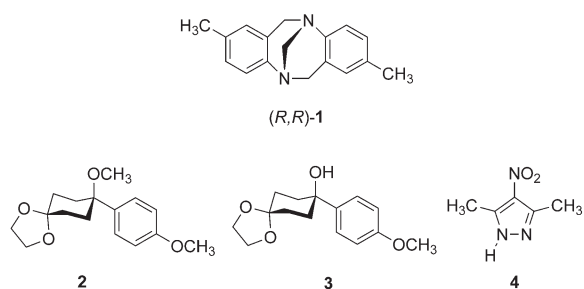
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For enantiopure bulk samples, it can be assumed that the structure as revealed by X-ray analysis of a single crystal is the same as that of the rest of the sample and, thus, the analysis simply has to distinguish between one hand and its opposite. However, if it cannot be guaranteed that the bulk sample is enantiopure, the interpretation of the crystallographic results becomes much more complicated. Thus, one needs, especially for the determination of AC, a rapid and simple method for establishing that the one single crystal that is used for the X-ray diffraction measurements is characteristic of the bulk compound.^[12]

A comparison of the calculated and experimental VCD spectra in solution is widely used to establish the absolute configuration when no single crystals can be obtained. However, this technique has some limitations because it can only be applied to chiral compounds and it requires complex calculations, because it is necessary to evaluate the contribution of different conformers that are present in solution.

We recently published a method that allowed us to establish the absolute structure of a solid sample of an achiral molecule that only contained light atoms.^[13] This method is based on a comparison between quantum-mechanical calculations (DFT methods) and experimental solid-state VCD spectra. This method was developed for achiral 4-methoxy-4-(*p*-methoxyphenyl)cyclohexaneethylene ketal (**2**), which showed spontaneous resolution. Compound **2** has a calculated racemization barrier between its enantiomeric conformations of 23 kJ mol⁻¹ and contains no functional groups, which can give rise to strong noncovalent interactions in the solid state.^[13]

Herein, we first compare various conditions for determining the absolute structure of chiral and achiral compounds that are comprised of light atoms (Scheme 1) by using X-ray diffraction. Furthermore, we used Tröger's base, enantiomer (*R,R*)-**1**, to establish the consistency between the results that



Scheme 1. Chiral (**1**) and achiral compounds (**2-4**) whose absolute structure have been determined.

were obtained by X-ray diffraction and those that were obtained by comparing the calculated and solid state experimental VCD spectra. Finally, we present the application of our method to determine the predominant absolute structure in a sample and these results are compared with those obtained by X-ray diffraction.

Results and Discussion

Compounds **2**, **3**, and **4** are achiral, they are only comprised of light atoms, and they crystallize in chiral conglomerates. Tröger's base (**1**) is a chiral compound that we used as a standard and its enantiomers were resolved by the selective crystallization of its diastereoisomeric salts and the subsequent recovery of its enantiomers.^[14]

Although the structures of compounds (*R,R*)-**1**, **2**, and **4** have been described previously, we re-determined them at different X-ray wavelengths and temperatures (Table 1) to verify that it was possible to determine the absolute structure of crystals that were formed from achiral molecules that were composed of light atoms. Suitable crystals for structure determination of all of these compounds were obtained by their slow evaporation from solutions in appropriate solvents.

As shown in Table 2, the parameters and uncertainties as defined by Flack and Hooft have values that allow us to establish, with a high degree of confidence, the absolute structure of a compound when the data collection is performed with copper radiation at low temperatures.^[10a,12] Moreover, by using the method described by Hooft and because the calculations involve distributions, there is the possibility of directly estimating the probability, $P(2)$, that the assigned hand of an enantiopure material is correct. For a material of unknown enantiopurity, the probabilities of three outcomes, $P(3)$ (correct assignment, 50:50 twin, and incorrect assignment), can be computed. The $P(2)$ probability is decisive for assigning the absolute structure of Tröger's base, whilst the values of the $P(3)$ probabilities of structures **2-4** are indicative that the allocation of absolute structure is correct. Some differences may be attributed to not only the data-collection conditions but also to the quality of the crystals that are used because we used different crystals for each data collection.

Compounds **1** and **2** have different degrees of conformational flexibility: Compound **1** is rigid, whilst compound **2** is flexible. Neither of these compounds contains groups that can form strong noncovalent interactions. Their crystal packing is characterized by the presence of only weak interactions. Thus, we can assume that these molecules are isolated in the solid state. Contrary to Tröger's base (**1**), in which the chirality is intrinsic, the chirality in compound **2** results from the adoption of a chiral conformation. The conformer of compound **2** in the crystal structure presents an angle (θ) between the planes that are defined by the aryl group and by carbon atoms C(1) and C(4) on the cyclohexane ring and the oxygen atom on the methoxy group that is attached to carbon, $\theta = -14.4^\circ$, as well as the conformation of the ethylene ketal ring. By using the θ angle, as defined previously, and by viewing the molecule from the ketal side, the structure in Figure 1, right, has an *R* configuration ($\theta > 0$) and the structure in Figure 1, left, has an *S* configuration ($\theta < 0$). The crystal structure of compound **2** at 100 K with copper radiation has an *S* configuration.

Table 1. Crystallographic data for compounds **1** to **4** under different conditions.

Compound	(<i>R,R</i>)- 1 ^[c]	2 ^[a]	2 ^[c]	3 ^[a]	3 ^[c]	4 ^[a]	4 ^[b]	4 ^[c]
empirical formula	C ₁₇ H ₁₈ N ₂	C ₁₆ H ₂₂ O ₄	C ₁₆ H ₂₂ O ₄	C ₁₅ H ₂₀ O ₄	C ₁₅ H ₂₀ O ₄	C ₅ H ₇ N ₃ O ₂	C ₅ H ₇ N ₃ O ₂	C ₅ H ₇ N ₃ O ₂
formula weight	250.33	278.34	278.34	264.31	264.31	141.14	141.14	141.14
wavelength [Å]	1.5418	0.71073	1.5418	0.71073	1.5418	0.71073	1.5418	1.5418
crystal system	orthorhombic	monoclinic	monoclinic	orthorhombic	orthorhombic	hexagonal	hexagonal	hexagonal
<i>a</i> [Å]	6.04092(12)	6.4942(2)	6.4800(13)	9.5376(2)	9.5300(19)	12.2170(5)	12.2400(17)	12.3100(17)
<i>b</i> [Å]	7.95113(18)	7.3340(2)	7.2000(14)	10.3334(2)	10.330(2)	12.2170(5)	12.2400(17)	12.3100(17)
<i>c</i> [Å]	27.2870(6)	15.1138(4)	14.980(3)	13.6591(2)	13.660(3)	4.0924(4)	4.0900(8)	3.8900(8)
α [°]								
β [°]		94.397(3)	94.81(3)					
γ [°]								
<i>V</i> [Å ³]	1310.65(5)	717.73(4)	696.4(2)	1346.18(4)	1344.8(5)	528.98(6)	530.66(15)	510.50(14)
<i>T</i> [K]	100.01(10)	293(2)	100.00(10)	293(2)	100.1(2)	293(2)	297(1)	99.99(10)
space group	<i>P</i> 2 ₁ 2 ₁	<i>P</i> 2 ₁	<i>P</i> 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 3 ₁ 21	<i>P</i> 3 ₁ 21	<i>P</i> 3 ₁ 21
	4	2	2	4	4	3	3	3
absorption coefficient [mm ⁻¹]	0.576	0.091	0.766	0.094	0.767	0.127	0.894	0.929
θ range [°]	3.24 to 74.17	2.70 to 26.37	2.96 to 73.58	2.91 to 33.32	5.37 to 73.57	3.34 to 28.80	4.17 to 74.17	4.15 to 74.77
total reflns	24685	13974	13719	23837	25498	9664	4448	18626
unique reflns/ <i>R</i> _{int}	2629/0.0434	2875/0.0528	2738/0.0269	4672/0.0388	2634/0.0250	862/0.0409	716/0.0334	702/0.0502
<i>R</i> ₁ / <i>wR</i> ₂ (<i>I</i> > 2 σ)	0.0367/0.0949	0.0359/0.0631	0.0252/0.0643	0.0468/0.0895	0.0233/0.0582	0.0469/0.1075	0.0385/0.0983	0.0312/0.0750
<i>R</i> ₁ / <i>wR</i> ₂	0.0373/0.0953	0.0650/0.0683	0.0258/0.0649	0.0991/0.0987	0.0239/0.0586	0.0630/0.1141	0.0426/0.1061	0.0317/0.0758
max shift	0.002	0.002	0.003	0.002	0.004	0.002	0.002	0.002
residual ρ [e Å ⁻³]	0.179 and -0.242	0.148 and -0.124	0.193 and -0.184	0.269 and -0.259	0.182 and -0.153	0.151 and -0.108	0.129 and -0.107	0.130 and -0.177

[a] molybdenum radiation, ambient temperature (293 K); [b] copper radiation, ambient temperature (293 K); [c] copper radiation, low temperature (100 K).

Table 2. The absolute structures of all of the samples were determined by using four different techniques: The Flack *x* parameter, the Hooft *y* parameter, and the two- and three-hypotheses models.^[a]

Compound	Flack <i>x</i> (u)	Hooft <i>y</i> (u)	<i>p</i> 2(correct)	<i>p</i> 3(correct)	<i>p</i> 3(twin)	<i>p</i> 3(incorrect)
1 ^[d]	0.3(6)	-0.03(15)	1.000	0.999	0.001	0.2 × 10 ⁻¹⁰
2 ^[b]	-1.6(9)	0.0(9)	0.635	0.410	0.354	0.236
2 ^[d]	0.06(12)	0.00(5)	1.000	1.000	0.1 × 10 ⁻¹⁷	0.5 × 10 ⁻⁷²
3 ^[b]	-0.4(9)	-0.4(3)	1.000	0.955	0.045	0.2 × 10 ⁻⁰³
3 ^[d]	-0.07(11)	-0.02(4)	1.000	1.000	0.2 × 10 ⁻³⁹	0.3 × 10 ⁻¹⁵²
4 ^[b]	2(3)					
4 ^[c]	-0.1(6)	-0.25(18)	1.000	1.000	0.5 × 10 ⁻⁰³	0.1 × 10 ⁻⁰⁹
4 ^[d]	0.0(4)	0.02(9)	1.000	1.000	0.3 × 10 ⁻⁰⁶	0.6 × 10 ⁻²⁷

[a] The Flack *x* parameter was refined, together with all other structural parameters. For the two-hypotheses model (i.e., the structure is either correct or incorrect), the probability *p*2(correct) that the absolute structure assignment was right is given. For the three-hypotheses model (the structure is either correct, incorrect, or a 50% inversion twin), the probabilities *p*3(correct), *p*3(twin), and *p*3(incorrect) that each of the hypotheses was right are given. [b] Molybdenum radiation, ambient temperature (293 K). [c] Copper radiation, ambient temperature (293 K). [d] Copper radiation, low temperature (100 K).

Compounds **3** and **4** also differ in their conformational flexibility, but both compounds contain groups that can establish strong noncovalent interactions. The crystal packing in both cases is characterized by the formation of hydrogen-bonding interactions. The crystal structure of compound **3** has a chiral conformation; if we apply the same criterion as for compound **2**, it has an angle of $\theta = -44.4^\circ$, which indicates a solid-state *S* configuration. The crystal packing provides hydrogen-bonding organization around a 2₁ screw axis. The crystal structure of compound **4** is composed of propellers around a 3₂ screw axis, with individual molecules that

interact through hydrogen bonds (N–H...N 2.879 Å, $\theta = 169.66^\circ$; as measured with Cu radiation at ambient temperatures). As proposed in the original article, it is possible that the small rotation of the nitro group with respect to the pyrazole ring ($\theta = 1.7^\circ$) is sufficient to determine the chirality of the structure.^[15] The two enantiomers differ in the tilt of the molecule with respect to the helical axis. By viewing the molecule with the nitro group oriented away from the eye and following the rule that requires a counter-clockwise turn to match the molecule with the screw axis, we assigned this structure as the *S* configuration and, reciprocally, the structure that requires a clockwise turn corresponded to the *R* configuration (Figure 2).

The crystal structures of compounds **3** and **4** can be considered as 1D because the hydrogen bonds help to form the propellers, whilst only weak non-covalent interactions are established between neighboring helices.

X-ray crystallography is a successful technique for a single crystal, which weighs perhaps no more than 1 µg, that is selected from a batch of crystals; however, this crystal may not be typical of the whole batch. To verify (after the X-ray data have been measured) that the chosen single crystal has the same characteristics as the bulk sample, various techniques, such as circular dichroism (CD) in solution or enantioselective chromatography, can be employed on the whole sample, although these techniques are only applicable to intrinsically chiral compounds. Moreover, solid-state techniques, such as Kurtz–Perry, second harmonic generation

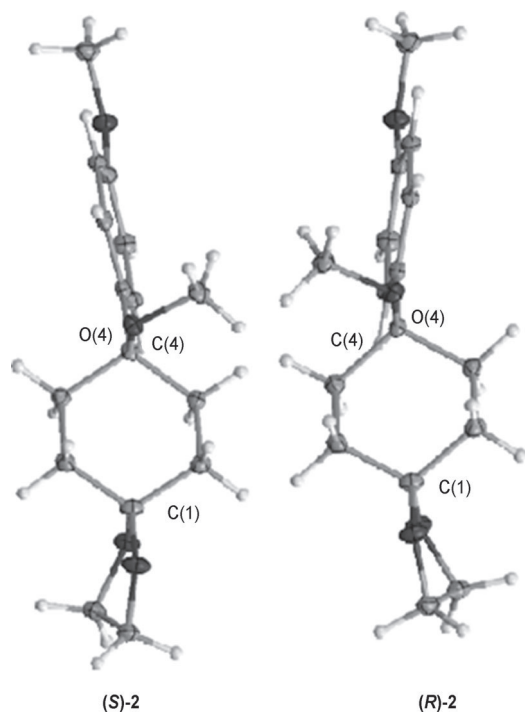


Figure 1. ORTEP of the *S* and *R* configurations in the crystal structure of compound **2**.

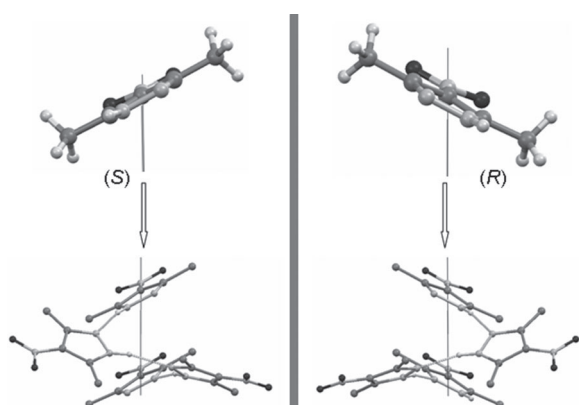


Figure 2. Definition of handedness in the crystal structure of compound **4**, with respect to the helical axis.

measurements (NLO),^[16] CD spectroscopy,^[17] and optical microscopy,^[18] are useful to assess the presence of enantiomeric excess of both chiral and achiral compounds.

To overcome these difficulties, solid-state techniques, such as solid-state VCD, are highly suitable because they combine the features of IR spectroscopy, which are dependent on the characteristics of the molecule and its solid-state supramolecular organization, with circular dichroism, which show different absorptions of right- and left-circularly polarized light and, thus, these techniques are sensitive to the handedness of the sample. Solid-state VCD has been used to determine the absolute structure of compounds that are only chiral in the solid state. This method requires the com-

parison of experimental and calculated VCD spectra for each enantiomer.^[13,19]

First, we compared the calculated and experimental VCD spectra of (*R,R*)-**1** in the solid state, as an enantiopure sample of known absolute configuration. This comparison allowed us to establish the consistency between the VCD method and the configuration that was obtained by X-ray diffraction. To compare the solid-state and calculated VCD spectra, it was necessary to determine the level of the calculations, as well as the number of molecules (catemers) to be used. To achieve these objectives, we compared the calculated and experimental solid-state IR spectra. In this way, the theoretical level could be determined, because the comparison between experimental and calculated spectra was easier by IR spectroscopy than by VCD spectroscopy. To determine the number of molecules that are necessary for the calculations, it is necessary to compare the solution- and solid-state IR spectra.

Considering the solid-state and calculated IR spectra for one molecule of (*R,R*)-**1** (Figure 3, left), no notable differences in its main features were observed. This result was due to the fact that these molecules were isolated in the solid

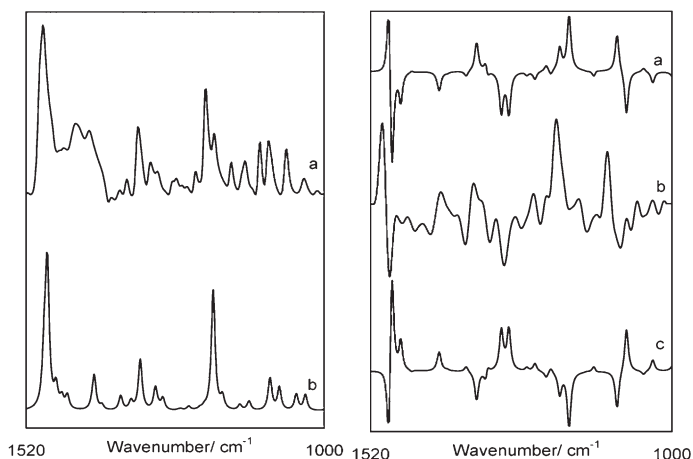


Figure 3. Left: IR spectra of (*R,R*)-**1**: a) As a Nujol mull and (b) calculated for an isolated molecule. Right: VCD spectra: a) Calculated spectrum of (*R,R*)-**1**, b) as a Nujol mull of (*R,R*)-**1**, and c) calculated for (*S,S*)-**1**.

state, as shown in the crystal structure, because Tröger's base (**1**) contained no groups that could lead to strong non-covalent interactions. Consequently, it was sufficient to only use one molecule for calculating the IR and VCD spectra, which were calculated from the optimized conformation as obtained from the X-ray data by using the B3LYP/6-31G(d) approach. Good agreement was observed between the solid-state experimental and gas-phase-calculated VCD and IR spectra (Figure 3). This result allows us to have confidence in the computational level that was employed to calculate the VCD spectrum.

The solid-state VCD spectrum of enantiomer (*R,R*)-**1** (Figure 3b, right) is well-predicted by its calculated VCD spectrum (Figure 3a, right). The fair agreement between the

sign of the experimental bands at 1491, 1207, 1111, and 1095 cm^{-1} and the calculated bands permits us to assign the absolute configuration of the bulk sample of Tröger's base (**1**). Moreover, this result is consistent with that obtained by X-ray diffraction and that previously described to resolve the enantiomers of Tröger's base. Therefore, we have demonstrated that it is possible to establish the absolute configuration of the prevalent structure in a solid sample, regardless of the chiral or achiral nature of the compound that formed, it by using solid-state VCD and DFT methods.

Acetals **2** and **3** have conformational flexibility; however, compound **2** does not contain groups that can form strong noncovalent interactions, whilst compound **3** contains a hydroxy group that can form hydrogen bonds. However, within the wavenumber range 1000–1300 cm^{-1} , the IR spectra of both compounds, both in solution and in the solid state, are similar (Figure 4, left and Figure 5, left). These results support the conclusion that only one isolated molecule is required to calculate the IR and VCD spectra of these compounds.

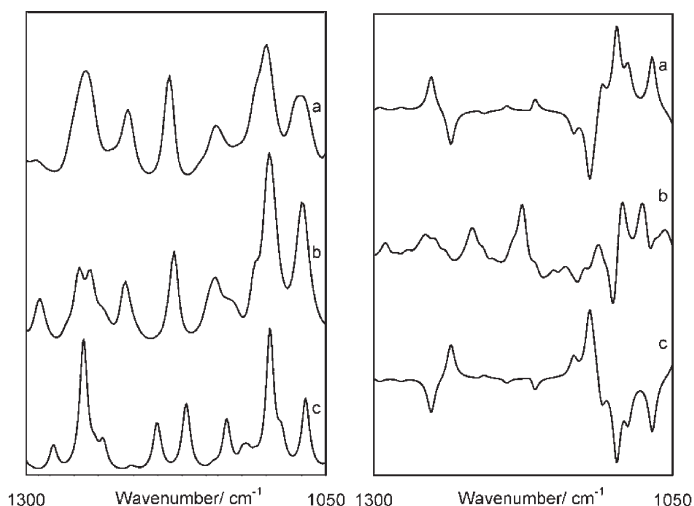


Figure 4. Left: IR spectra of compound **2**: a) As a solution in CDCl_3 , b) as a Nujol mull, and c) calculated spectrum of an isolated molecule. Right: VCD spectra of compound **2**: a) calculated for (*R*)-**2**, b) as a Nujol mull, and c) calculated for (*S*)-**2**.

The minimum energy conformations of enantiomers (*R*)-**2** and (*R*)-**3**, calculated from X-ray data at the B3LYP/6-31G(d) level, are very similar to the experimental geometries, although the angle in compound **2** is larger ($\theta = 38.4^\circ$), which is not unusual when comparing gas-phase calculations to crystal data.^[20]

The more-intense bands in the experimental and calculated IR spectra of compound **2**, which are assigned to stretching of the ketal group (calculated band at 1097 cm^{-1}) and to asymmetric stretching of the aromatic ether group (calculated band at 1252 cm^{-1}), show a good fit. A slight displacement is detected for the less-intense bands, despite the fact that the correlation between the calculated and experimen-

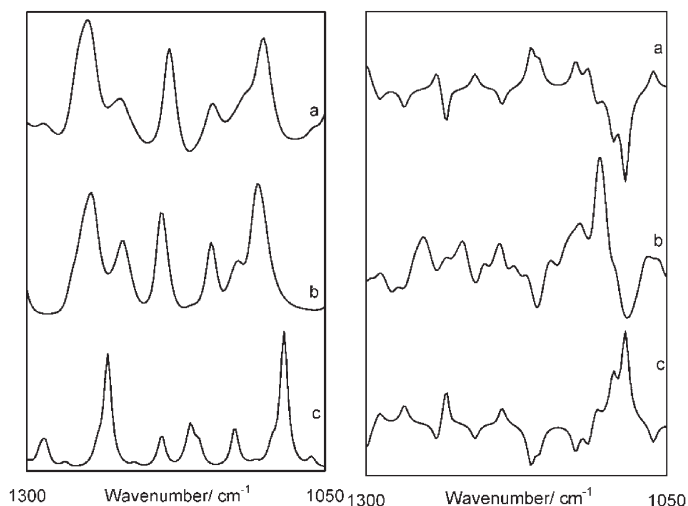


Figure 5. Left: IR spectra of compound **3**: a) As a solution in CDCl_3 , b) as a Nujol mull, and c) calculated spectrum of an isolated molecule. Right: VCD spectra of compound **3**: a) Calculated for (*R*)-**3**, b) as a Nujol mull, and c) calculated for (*S*)-**3**.

tal (Nujol mull and solution in CDCl_3) IR spectra is very good.

The experimental VCD spectrum of a polycrystalline sample of compound **2** (Figure 4b, right) was compared with calculated spectra for the optimized conformation of enantiomers *R* and *S* (Figure 4a,c, right). The most important data for the assignment of the *R* or *S* absolute configuration of the crystal are the signs of the couplets at about 1250 and 1097 cm^{-1} . The positive sign of the couplet at about 1097 cm^{-1} in the experimental VCD spectrum corresponds to the *R* configuration, as shown by the calculated VCD spectrum of enantiomer (*R*)-**2**.

Proceeding in a similar manner, a good fit between the signs of the experimental bands at 1250, 1218, 1187, 1121, and 1105 cm^{-1} (Nujol mull) and the corresponding bands in the calculated VCD spectrum for (*R*)-**3** is shown in Figure 5, right (a). This result allows us to establish the chirality of the majority of the polycrystalline sample.

However, the IR spectra of compound **4** in CDCl_3 and as a Nujol mull in the range 1200–1000 cm^{-1} show one main band at 1173 and 1175 cm^{-1} , respectively, which is assigned to a combination of vibrations that involve the pyrazole ring (breathing mode). Moreover, the IR spectrum in Nujol mull exhibits five supplementary bands at 975, 1010, 1035, 1070, and 1128 cm^{-1} , as shown in Figure 6, left. The presence of these five bands should be due to the formation of hydrogen bonds, as shown by X-ray diffraction, because IR and VCD spectroscopy are very sensitive to hydrogen bonds that maintain the supramolecular chiral structure. As mentioned above, the crystal structure of compound **4** can be considered to be 1D; thus, we had to determine the number of molecules of compound **4** that are necessary for the calculations to obtain a good description of the experimental IR spectrum. Calculations of the different catemers (up to six) were performed by using the optimized geometry of the

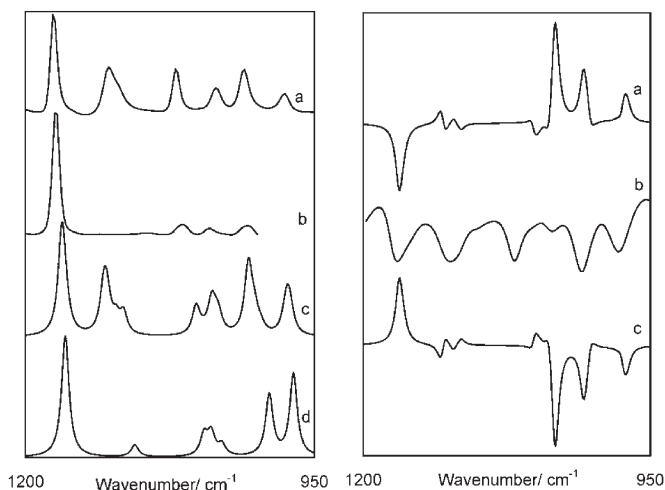


Figure 6. Left: IR spectra of compound **4**: a) As a Nujol mull, b) as a solution in CDCl_3 , c) calculated for a hexamer M helix, and d) calculated for an isolated molecule. Right: VCD spectra of compound **4**: a) Calculated for a hexamer M helix, b) as a Nujol mull, and c) calculated for a hexamer P helix.

monomer and the crystal arrangement. As shown in Figure 6, the calculations with six molecules (hexamer) of compound **4** showed six main bands, as in the experimental spectrum, with good agreement (experimental/calculated): 975/973, 1010/1007, 1035/1039, 1128/1132 and 1175/1168 cm^{-1} . The band at 1070 cm^{-1} could correspond to the band at 1053 cm^{-1} in the experimental spectrum.

Thus, the peak at 1175 cm^{-1} in the experimental IR spectrum appears in the VCD spectrum as a couplet centered at 1178 cm^{-1} , whilst a single band is observed in the calculated spectrum. Therefore, this band cannot be used to assign the handedness of the helical structure. It is possible that the disparity in the shape of the signal is due, as mentioned above, to the combination of vibrations that involve the pyrazole ring. However, this difference does not prevent the assignment of absolute structure, because this peak appears in both IR spectra, that is, in solution and in the solid state, thus indicating that it is mainly related to the compound and not to its supramolecular organization. The most important data for the assignment of the *R* or *S* absolute structure is the sign of the three most intense bands at 973, 1008, and 1033 cm^{-1} in the calculated VCD spectrum. The negative sign of these three peaks in the experimental VCD spectrum (975, 1009, and 1033 cm^{-1}) corresponds to the P helix, as shown in the calculated VCD spectrum (Figure 6, right).

To test the robustness of our method and the potential prevalence of a given configuration, we carried out five random crystallizations of about 5 mg of compounds **2**, **3**, and **4** in CH_2Cl_2 and we determined the predominant chiral structure in each batch. To record their VCD spectra in Nujol mull, we used the whole sample (all of the crystals, no remaining solvent). All of the samples of compound **2** showed VCD signals in a 3:2 ratio (*R* and *S* configuration). Figure 7 shows the opposite VCD spectra of compound **2**. The four samples of compound **3** exhibited a VCD response

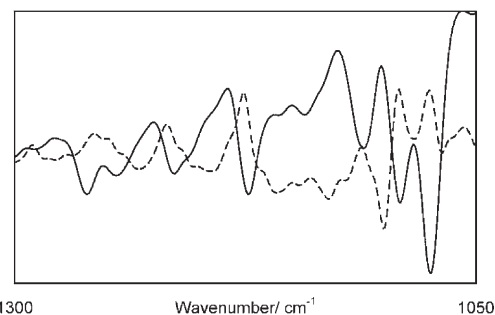


Figure 7. Experimental VCD absorption spectra of (*R*)-**2** (---) and (*S*)-**2** (—) in Nujol mull.

with a 4:1 enantiomeric ratio. Figure 8 shows the opposite VCD spectra of compound **3**, which were obtained after random crystallizations. Only four of the five randomly crystallized samples of compound **4** showed evidence of chiral

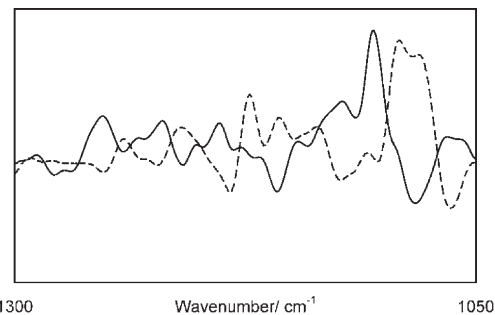


Figure 8. Experimental VCD absorption spectra of (*R*)-**3** (---) and (*S*)-**3** (—) in Nujol mull.

response. The ratio of the helix “handedness” was 3:1 (*R/S*). Figure 9 shows the opposite VCD spectra of randomly crystallized compound **4**. In most cases, the samples were formed by a non-equal mixture of crystals with opposite handedness (crystal enantiomeric excess) without the presence of a chiral source. In samples in which there was an enantiomeric excess, it was possible to establish the predominant enantiomer by comparing the spectra in the solid state with the calculated VCD spectra, as we have shown herein.

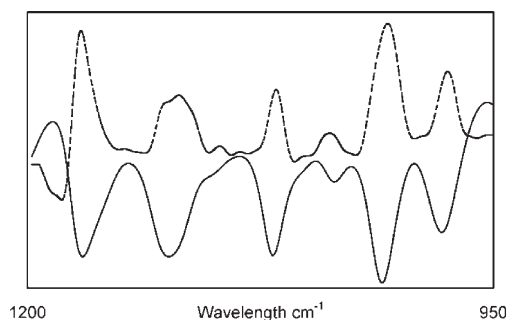


Figure 9. Experimental VCD absorption spectra of 4 M helix (····) and P helix (—) in Nujol mull.

Conclusion

X-ray diffraction on single crystals, by using copper radiation at low temperatures, is a suitable method to determine the absolute structure of achiral compounds that only contain light atoms. Hooft's parameter and the P(3) probabilities are crucial for establishing absolute structure.

The combination of solid-state VCD and quantum-mechanical calculations allowed us to establish the absolute configuration of the major enantiomer in a sample with an enantiomeric excess. The B3LYP/6-31G(d) computational level was suitable for geometry optimization from the data that were obtained by X-ray diffraction and for the calculation of the theoretical IR and VCD spectra. If the experimental IR spectra in solution and in the solid state are similar, it is enough to use a single molecule for calculating the VCD spectra. Otherwise, it is necessary to determine the number of molecules to be used in the theoretical calculations, thereby increasing that number to obtain a good fit between the experimental and calculated spectra.

Experimental Section

Crystal-structure determination: Single crystals suitable for X-ray diffraction were obtained by the slow evaporation of solutions of (*R,R*)-**1** in MeOH, compounds **2** and **3** in CH₂Cl₂, and compound **4** in water. The crystals were air stable and one of them was mounted onto the tip of a glass fiber with the use of epoxy cement. X-ray diffraction experiments were performed on Oxford-Diffraction Xcalibur S (MoK α) X-ray source and Xcalibur, Onyx, Nova (CuK α) X-ray diffractometers. The CrysAlis software package was used to process the data.^[21]

Final cell parameters were obtained by the global refinement of reflections that were obtained from an integration of the data from all of the frames. The structures were solved by using direct methods and refined by using the full-matrix method based on F2 by using the SHELXTL program.^[22] The non-hydrogen atoms of structures (*R,R*)-**1**, **2**, **3**, and **4** were refined anisotropically; the hydrogen atoms were observed in difference electron density maps and were refined isotropically. The crystal parameters and basic information relating to the data collection and structure refinement are summarized in Table 1.

IR and VCD spectroscopy and instrumentation: IR spectra were recorded on a Bruker Vertex 70 FTIR spectrometer and VCD spectra were recorded on a Bruker PMA 50 optical bench coupled with the Vertex 70 spectrometer.

Solution-state IR absorptions were recorded in CDCl₃ at a resolution of 4 cm⁻¹ from 16 scans. The sample concentrations were 0.05 M and the solutions were held in a cell (path length: 100 μ m) with BaF₂ windows. VCD spectra of these solutions were recorded by the accumulation of spectra over 1 h. Baseline correction of the IR and VCD spectra was performed by subtracting the raw VCD spectra of the solvent. In a typical experiment to obtain the solid-state IR and VCD spectra, a complete batch of random crystallization (5 mg) was employed. All samples were crushed into powders and mixed with two drops of Nujol to form a mull. This mull was placed in a cell (path length: 25 μ m) with BaF₂ windows. The IR spectra were recorded at a resolution of 4 cm⁻¹ as the sum of 16 scans. VCD spectra of these samples were recorded by the accumulation of spectra over 6 h. Baseline correction of the IR and VCD spectra was performed by subtracting the raw VCD spectrum of the Nujol.

Quantum-mechanical calculations: The geometries of the systems were optimized at the B3LYP/6-31G(d) level of theory^[23] with the Gaussian 03 package^[24] by using the geometries that were obtained from X-ray diffraction as the starting geometries for the non-hydrogen atoms. Frequent

cy calculations were performed at the same computational level to confirm that the structure corresponded to an energetic minimum or a true transition state. The IR spectra were scaled by a factor of 0.9613, as proposed by Moran, Radom, and co-workers.^[25] The calculation of the theoretical VCD spectra of different catemers was performed at the previously indicated computational level.

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