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COMMUNICATIONS

Crystallization of an Achiral Cyclohexanone Ethylene Ketal in Enantiomorphs and Determination of the Absolute Structure

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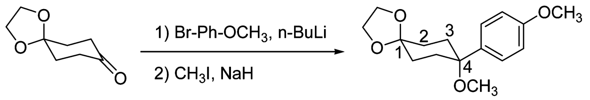
Since the days of Louis Pasteur, chirality has become a fundamental topic of research with influence in every aspect of science.[1] Not only covalently bonded molecules with defined configuration and conformation but also noncovalently interacting supramolecular assemblies with conformational flexibilites can form chiral structures.[2] Therefore, two main classes of spontaneous resolution have to be distinguished according to the racemization barrier that separates the conformational enantiomers. If the barrier is high enough, the enantiomers exist indefinitely or for a long time in solution; consequently many techniques are available to determine their absolute configurations. However, if the enantiomers are only stable in the solid state, the usual method is crystallography based on anomalous scattering,[3] but with a few exceptions,[4] the presence of a heavy atom is required.[5]

In this communication, we describe an example of spontaneous resolution of an achiral compound together with absolute structure determination in the absence of heavy atoms. It concerns acetal **1** (Scheme 1) and is based on the use of solid state VCD together with calculated VCD.

Scheme 1. Formation of 4,4-Disubstituted Cyclohexanone Ethylene Ketal (**1**) from Cyclohexandione Monoethylene Ketal



1 (55%)

Vibrational circular dichroism (VCD) spectroscopy is a powerful tool in the study of chiral systems, which has helped to reach a deeper understanding of conformations of chiral molecules in different solvents or supramolecular aggregates present in solution.[6] The combination of the VCD spectra in solution and theoretical calculation has been used for the determination of the absolute configuration of chiral compounds.[7] These facts prompted us to use VCD spectroscopy associated with computation of chiroptical signatures to assign the absolute structure by way of the study of solid-state conformations.

4-Methoxy-4-(*p*-methoxyphenyl)-cyclohexanone ethylene ketal (**1**) was obtained by treatment of 4-hydroxy-4-(*p*-methoxyphenyl)-cyclohexanone ethylene ketal with methyl iodide and NaH. This last compound was, in turn, prepared as briefly described by Chu et al.[8] Slow evaporation of dichloromethane solutions of compound **1** gave rise to good quality crystals. The crystal structure of **1** is chiral, in space group $P2_1$ with one molecule in the asymmetric unit. The cyclohexane rings in the crystal structures of **1** adopt a chair conformation, with the methoxy at the 4-position, occupying an axial position. The chirality in ketal **1** is due to the angle ($\theta = 15.8°$) between the aryl group and the plane defined by carbon atoms C1 and C4 of the cyclohexane ring and the oxygen of the methoxy group attached to carbon C4 as well as the conformation of the ethylene ketal ring. The racemization barrier was calculated to be 23 kJ mol^{-1} that situates this compound in the fourth group of Pidcock's classification of molecules with no chiral center that crystallize in a Sohncke space group: "the molecule is conformationally flexible and there are low steric energy barriers to interconversion between the molecule and its mirror image. Thus a chiral crystal structure results from a molecule which displays no chirality".[9]

The crystal packing in the structure of compound **1** is characterized by the presence of a 2_1 axis. Throughout it, weak interactions between the oxygen of the methoxy group attached to carbon C4 and one hydrogen of the ketal moiety ($CH_3O\cdots H{-}C_{ketal}$ 2.544 Å, 155.44°) are established (Figure 1). The Flack parameter value [−1.6(9)] makes it impossible to determine the absolute structure. Using the θ angle as defined previously (between C1−C4−O8 and C10−C12−C13−C14−C15−C16 planes) and viewing the molecule from the ketal side, we then determined the left side structure is R ($\theta > 0$) and the right side is S ($\theta < 0$).

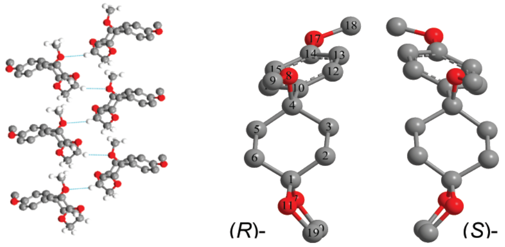


Figure 1. Left: packing view of 4-methoxy-4-(*p*-methoxyphenyl)-cyclohexanone ethylene ketal (**1**) along axis *b*. Right: minimized structures of two enantiomers of ketal **1**.

The minimum energy conformation of enantiomer (*R*)-**1** calculated at the B3LYP/6-31G(d) level (Figure 1) is very similar to the experimental geometry, although the θ angle is larger (38.4°), which is not unusual when comparing gas phase calculations to crystal structures.[10]

To evaluate the agreement between the calculated and experimental IR spectrum of compound **1**, IR spectra were registered in

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dichloromethane and deuterochlorophorm solutions, as well as in solid state; in particular, a Nujol mull was prepared with a monocrystal of compound **1**. No noticeable difference in its main features were detected upon viewing the IR (Figure 2 left), except for the splitting of the 1252 cm^{-1} band observed in the solid state IR (1255 and 1245 cm^{-1}). The few differences that are present are due to the fact that only weak interactions occur in the supramolecular arrangement in the solid state. Also, there is good agreement between solution and solid state experimental and gas phase calculated spectra, as shown in Figure 2 left. The two highest frequencies in the experimental and calculated IR spectrum of **1**, assigned to the stretching of the ketal group (1097 cm^{-1}) and to asymmetric stretching of the aromatic ether group (1252 cm^{-1}), show a good fit. In the less intense bands slight displacements are observed.

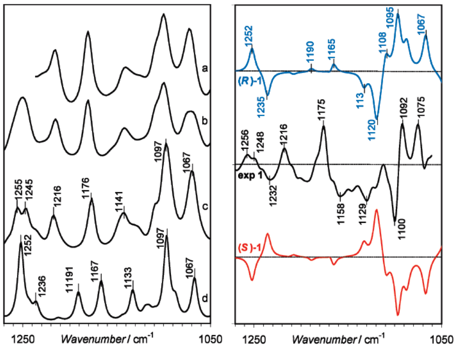

Figure 2. Left: IR spectra of **1** in CH_2Cl_2 solution (a), $CDCl_3$ solution (b), Nujol mull (c), and calculated IR spectrum of **1**. Right: ((*R*)-**1**) calculated VCD for (*R*)-**1**, (exp 1) experimental VCD absorption spectra of **1** in Nujol mull, and ((*S*)-**1** calculated VCD for (*S*)-**1**).

The good agreement observed between the experimental and calculated conformation as well as between the solid-sate experimental and gas-phase calculated IR spectra allows us to have confidence in the computational level employed to calculate VCD spectrum. Thus, the experimental VCD spectrum of the a monocrystal (Figure 2 right, middle) was compared with theoretical DFT-calculated results for the optimized conformation of enantiomers *R* and *S* (top and bottom). The overall profile of the experimental VCD spectrum nicely coincides with that of the enantiomer (*R*)-**1** calculated VCD, although the calculated VCD does not simulate accurately the intensity of some peaks in the experimental spectrum due to the interactions that are established in the solid. Actually, apart from the overall coincidence of the spectrum, the most important data for the assignment of the *R* or *S* absolute crystal configuration is the sign of the bands at 1250 (split) and 1232 cm^{-1}. Moreover, the IR band at 1097 cm^{-1} appears in the experimental VCD as a positive couplet at 1100 and 1092 cm^{-1}. The positive sign of the 1092 cm^{-1} peak in the experimental VCD corresponds to the *R* conformation as shown by the calculated VCD of enantiomer (*R*)-**1**. All these facts are enough to decide without doubt that the experimental VCD corresponds to the (*R*)-**1**.

To check the repeatability of experimental results, we carried out two random crystallizations and from each batch, five crystals were selected. By recording their X-ray data we assured that all of them were monocrystals (same unit cell). We determined their VCD spectra in Nujol mulls (Figure 3) and obtained 9 crystals with *R* configuration and the 10th with an inverse VCD. We have also carried out five random crystallizations of *ca.* 5 mg of **1** in CH_2Cl_2 and have used the whole sample (all the crystals, no remaining solvent) to record their VCD spectra in a Nujol mull. In all cases, we obtain VCD signals, meaning that there is an enantiomeric excess in all the samples, but the preferred enantiomer seems random (we obtained a 3:2 ratio of the *R* and *S* configuration).

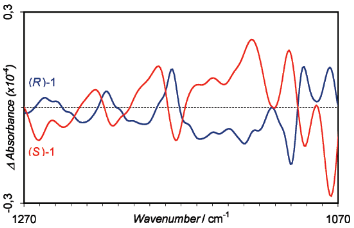

Figure 3. Experimental VCD absorption spectra of (*R*)-**1** (blue) and (*S*)-**1** (red) in Nujol mull.

In conclusion, we describe a method for determining the absolute structure of flexible molecules composed of light atoms, based on the combination of single crystal X-ray diffraction, solid state VCD, and DFT calculations. This method has been applied to nonchiral 4-methoxy-4-(*p*-methoxyphenyl)-cyclohexanone ethylene ketal (**1**) which describes the synthesis, crystal structure, and spontaneous resolution. The procedure is simple and does not require a lengthy calculation time, due to no conformational distribution analysis being required before VCD calculation. Subsequently, we are currently working on the implementation of this method to other chiral materials.

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Supporting Information Available: Experimental details for synthesis, characterization and X-ray structure determination (in CIF format) for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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