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Determination of absolute configuration using heavy atom based co-crystallization method: Halogen atom effects

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ABSTRACT

Heavy atom (chloride, bromide, and iodide) based co-crystals for determination of absolute configuration (AC) for chiral molecules were synthesized and evaluated. Co-crystals of cholestanol and L-ascorbic acid were analysed and the effects and potential benefits of varying the heavy atom are discussed. Changing the halogen atoms (chloride, bromide, or iodide) affects the co–crystal formation, X-ray absorption, and anomalous dispersion, and hence the ability to determine AC.

1. Introduction

The absolute configuration (AC) is one of the most important and challenging features of chiral compounds that need to be revealed during structure elucidation process. The available methods to determine AC of chiral molecules, including single crystal X-ray diffraction (SCXRD), chemical synthesis, NMR spectroscopy/chiral derivatization, and chiroptical approaches [1–4]. Among these, SCXRD provides direct structural information at the atomic level and is recognized as the most powerful and effective structure determination method [5]. This cornerstone methodology was pioneered by Bijvoet in the early twentieth century [6]. The useful indicator to determine the likelihood of a reliable determination of AC using the effects of anomalous dispersion is the Friedel pairs (the couple of reflections *h*, *k*, *l* and -*h*, -*k*, -*l*) [6,7]. The Flack and Hooft parameters calculated from Friedel pairs, can be used to differentiate between enantiomers to a high degree of precision and accuracy [8]. In particular, the recent technology has made AC assignment possible without introduction of a heavy atom in the molecule [9–11]. However, compounds composed only of light atoms, i.e., those having low Friedel pairs give rise to standard uncertainties on the Flack and Hooft parameters even with a longer wavelength Cu Kα radiation, which are too large for determination of AC.

The Friedel pairs and hence the ability to determine AC, depends upon several factors, including the X-ray wavelength, the atomic numbers of the atoms composing the crystal, and the quality of the X-ray diffraction data. With compounds containing only light atoms a significant difference of anomalous dispersion is not guaranteed. Friedel pairs increase with increasing atomic number, and hence it is an advantage to have a heavy atom in the crystal to maximize these differences. Just as with heavy atom introduction into the compound prior to the X-ray analysis, there are four methods: namely, salts formation, chemical transformation, crystal sponge [12] and co-crystallization with the target molecule by hydrogen bonds or other relatively weak intermolecular interactions [13–15] (Fig. 1). Salt formation is of course reliant on some acidic or basic functionality in the target molecule that can be manipulated by pH. For chemical transformation, one must be mindful that the introduction of a heavy atom does not affect the AC of the stereo centers. In the case of crystal sponge, there are also some critical limitations to the current ZnMOF crystal sponge system that most compounds

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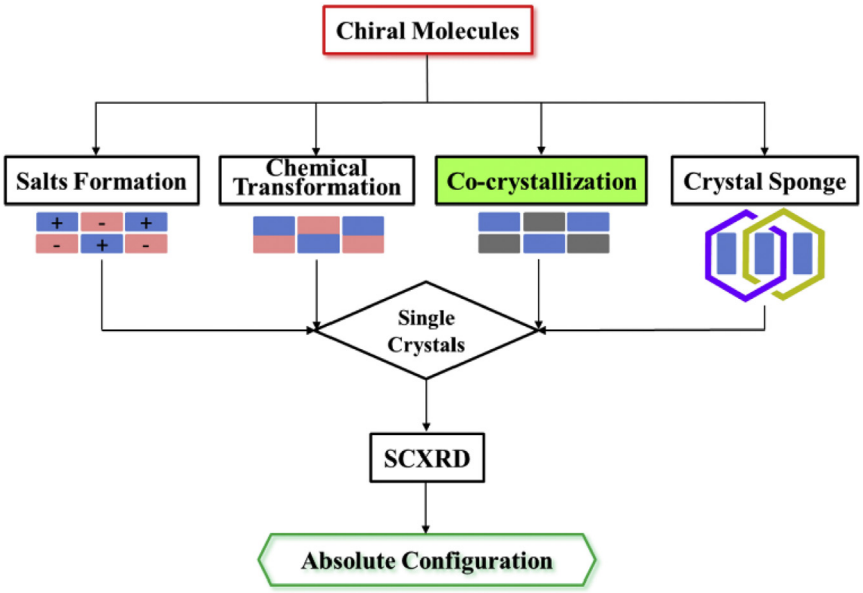

Fig. 1. Strategies in introducing heavy atom into the chiral molecules for AC determination.

may not enter the pores due to their size or their inability to form favorable interactions with the host framework [16–18]. The heavy atom based co-crystallization method escape from these potentially intractable issues. Moreover, co-crystallization is carried out through a retrosynthetic analysis with supramolecular synthons [19] and may be made to dissociate easily to their original components by dissolution, sublimation or a similar method [20,21]. The prior report, using this methodology, Desiraju and co-workers determined the absolute configurations of pregnenolone, cholesterol, and zidovudine without chemical modification [13]. We were interested in knowing whether changing the halogen atoms (chloride, bromide, or iodide) would affect the co–crystal formation, X-ray absorption, and anomalous dispersion. Herein we communicate the synthesis, effects, and potential benefits of varying the halogen atom.

2. Experimental

2.1. Preparation of co-crystals *1*–*4*

Co-crystals **1**–**4** were synthesised using the reaction crystallization method. The co-former was added to 5 mL of ethyl acetate (methanol or tetrahydrofuran) solvent in a 10 mL glass vial to give a saturated solution and the excess solid was removed by filtration. Then, an excess amount of cholestanol or L-ascorbic acid (0.1 mmol) was added to the saturated solution. The resulting suspension was allowed to react overnight at room temperature and was subjected to centrifugation to separate out the solid phase. The co–crystal solid was harvested at the bottom of the centrifuge tubes and vacuum dried at 50 °C for 24 h to give the corresponding co-crystals as a fine crystalline powder. Single crystals of co–crystals **1**–**4** that were suitable for X-ray diffraction were successfully obtained by slowly evaporating the final filtrate. The compositions of **1**–**4** were determined by single-crystal X-ray diffraction.

2.2. Single crystal X-ray diffraction

Single crystal X-ray diffraction of co-crystals **1** (0.15 × 0.12 × 0.10 mm^3), **2** (0.15 × 0.12 × 0.10 mm^3), **3** (0.12 × 0.08 × 0.08 mm^3), and **4** (0.12 × 0.10 × 0.10 mm^3) was performed on a Bruker Apex II CCD diffractometer using Mo Kα radiation (λ = 0.71073 Å) at 100(2) K. The collected data integration and reduction were processed with SAINT software [22], and multi-scan absorption corrections were performed using the SADABS program [23]. The structures were solved by direct methods using SHELXTL [24] and were refined on F^2 by the full-matrix least-squares technique using the SHELXL-97 and SHELXL-2014 program package [25]. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms of O–H and N–H were found from a Fourier difference map, and refined with a fixed distance of 0.86 (0.01) Å and isotropic displacement parameters of 1.50 times U_{eq} of the parent atoms. The remaining hydrogen atoms were placed in calculated positions and refined with a riding model with distance of 0.95 Å (sp^2) and 0.98 Å (sp^3) with isotropic displacement parameters set to 1.20 (sp^2) and 1.50 (sp^3) times U_{eq} of the parent atom.

3. Results and discussion

Cholestanol is a typical steroid which contains only C, H, and O atoms (Scheme 1). There are three crystal data reported in Cambridge Structural Database (CSD) with only unit cell and space group information (refcode: ZZZDGS, ZZZDHA, and ZZZDKI). Our recent work revealed the relative configuration of cholestanol through co-crystallization with vitamin D_3 [26]. But the direct determination of AC is still not conducted. We herein report the direct determination of AC of this important steroid using heavy atom (chloride, bromide, and iodide) based co-crystallization method.

Single crystals of pure cholestanol were repeatedly measured at a longer wavelength Cu Kα radiation under low temperature (100 K). The best one showed that low Friedel pairs give rise to high uncertainties on the Flack parameter −0.5(6) and high *R* value. Cholestanol crystallized as ethanol solvate in *P*1 space group with $Z' = 4$. This symmetry is shown not to arise from twinning or other artefacts. Small but significant deviations are observed particularly in the flexible side chains. The structure of native cholestanol comprises a lipid bilayer-like structure, while the steroid backbones form the much wider lipophilic portion as shown in Fig. 2. The origins of the $Z' > 1$ in cholestanol are likely to be linked to the