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The Use of Co-crystals for the Determination of Absolute Stereochemistry: An Alternative to Salt Formation

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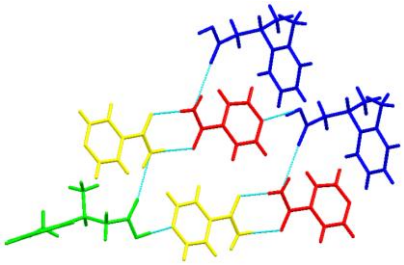

Absolute stereochemistry of oils and viscous liquids can be difficult to determine. Co-crystallization involves generating a crystalline material consisting of more than one neutral compound. The combination of co-crystallization with both X-ray diffraction and chiral HPLC was particularly powerful in overcoming these difficulties for a series of chiral 3-arylbutanoic acids. Co-crystallization offers advantages over salt formation because co-crystals dissociate in solution, meaning identical HPLC conditions can be used for both the materials of interest and their co-crystals.

Despite major advances in asymmetric synthesis over the past thirty years,[1] one of the major challenges which remains is definitively assigning absolute stereochemistry,[2] especially with materials which are not readily crystalline. This is increasingly important as new synthetic products are often difficult to crystallise,[3] and many can only be isolated as viscous oils.

The two main synthetic strategies which have been employed to circumvent these problems involve modification of the material, via either additional chemical transformations or salt formation.[4] Both of these strategies, however, have limitations. The use of chemical transformations can be limited by the availability of only small quantities of enantiopure material, and furthermore, additional reaction steps may affect the stereochemical integrity of the required compound. For salt formation, in addition to the limitations mentioned above, the compound also requires ionizable sites. For both strategies, chiral HPLC analysis has to be developed not only for the pure material but also for the derivatives, since in many cases the conditions are non-transferrable.[4]

As part of an on-going program of research into enantioselective biotransformations, we have been interested in determining the absolute stereochemistry of a series of substituted 3-arylbutanoic acids **1a**–**1d**, obtained via enzymatic hydrolysis of the corresponding ethyl ester **(**Figure 1).[5] The enantiopure products were isolated as liquids at room temperature. The enantioselectivity of the enzyme catalyzed reactions was investigated by chiral HPLC analysis,[5] and appropriate conditions to separate and quantify the enantiomers of **1a**–**1d** were identified. However, knowledge of absolute stereochemistry was necessary to determine the sense of enantioselection with each of the biocatalysts employed. Chemical transformations were not attempted, as the enantiopure samples were available in limited quantities.

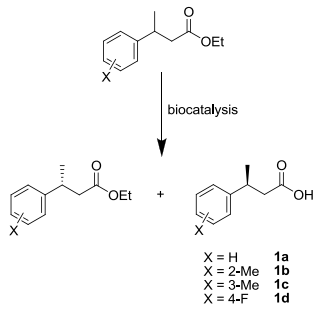

Figure 1. The enzymatic biotransformation employed in this work.[5]

Co-crystallization, involving crystallizing two (or more) neutral molecules together in one crystalline material, has recently garnered great interest as an alternative to salt formation for improving the physical properties of active pharmaceutical ingredients, without detrimental effects on the chemical properties.[6] Therefore, we decided to investigate if co-crystals involving the carboxylic acids **1a**–**1d** would be suitable materials for determining their absolute stereochemistry.

A search of the Cambridge Structural Database[7] revealed that monocarboxylic acids often co-crystallize with nicotinamide and isonicotinamide.[8-10] Initial co-crystal screening was performed by neat grinding with the racemic acid, and isonicotinamide was identified by powder X-ray diffraction (see Supporting Information) as a suitable co-crystal former for each of the acids (Figure 2).

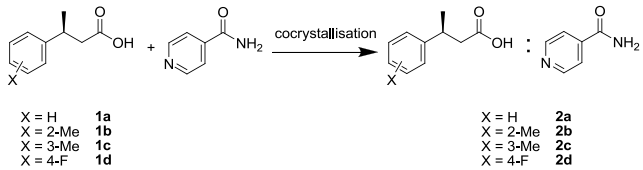

Figure 2. Co-crystallization of the 3-arylbutanoic acids with isonicotinamide.

Suitable conditions for growing single crystals from solution were identified using the racemic acids and similar conditions were applied to the enantiopure analogs. The advantage of this approach was that once the conditions were developed, a small sample of the enantiopure material (< 8 mg) was sufficient. All co-crystals, both enantiopure and racemic, were grown by slow evaporation of acetonitrile : acetone (70 : 30) solutions.

Single crystal diffraction data, in combination with the chromatographic experiments, allowed the unambiguous assignment of absolute configuration.[11] Each enantiopure co-crystal was formed with the (*S*)-enantiomer of the acid. Each of the co-crystals display a common set of intermolecular interactions (Figures 3 and 4) with amide-amide [N-H...O=C] and acid-pyridine [COOH...N] hydrogen bonds linking the co-crystal components.

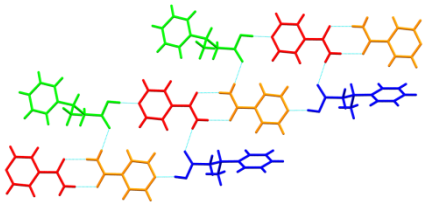

Figure 3. Hydrogen bonding interactions in **(*S*)-2a**. The different colors indicate unique, symmetry-independent **(*S*)-2a** (green and blue) and isonicotinamide (red and orange) molecules. The same motif is formed in **(*S*)-2c**, **(*S*)-2d**, **(±)-2b** and **(±)-2c**, see Supporting Information.

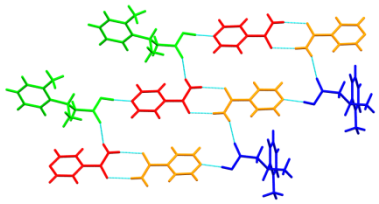

Figure 4. Hydrogen bond motif in **(*S*)-2b**. The same color scheme is applied as for Figure 1.

Interestingly, irrespective of the chiral or enantiopure nature of the acid molecules, similar infinite one-dimensional hydrogen-bonded ribbons are formed in all the co-crystals except **(±)-2d**, which exhibits two-dimensional puckered sheets (see Supporting Information). Thus, the overall core hydrogen-bonded motif is retained across the structures, with the conformation of the acids varying. Presumably, this conformational variation is necessary to maintain both a close-packed arrangement of molecules with asymmetric shapes and a (topologically) symmetrical hydrogen bond network. Further details of the structural features present in these co-crystals are in the Supporting Information.

An important consideration was whether the diffraction experiment was a true representation of the bulk sample. To ensure this was the case, powder X-ray diffraction, PXRD, was performed on each of the ground materials **2a**–**2d** and compared to the theoretical PXRD patterns calculated from the single crystal data.

We anticipated that acid molecules, once dissolved, would have the same properties irrespective of whether they are obtained by dissolving the pure acid or the co-crystal, as co-crystallization only affects the properties of the solid phase. Thus, co-crystallization has the clear advantage that the conditions developed to separate the enantiomers of the pure compound by chiral HPLC can be applied directly for analysis of the co-crystal employed for X-ray crystallography, enabling direct correlation with the chiral HPLC peak for the enantiomer. The only potential concern is the impact of the co-crystal former. To check for possible interference, chiral HPLC of the racemic acids, in the presence of isonicotinamide, was recorded, clearly showing that chromatographic behavior of **1a**–**1d** was unaffected, confirming the validity of the methodology employed. Thus, chiral HPLC were recorded on the individual crystals used for the X-ray diffraction experiments. This enabled the use of chiral HPLC to directly monitor the direction of enantioselection in the enzyme mediated resolutions, Figure 5.[5] Thus, while **(*S*)-1a** has been previously described in the literature,[12] this is the first time the absolute stereochemistry of this compound has been definitively determined by X-ray diffraction. This procedure was successfully employed to determine the absolute stereochemistry of the novel enantiopure acids **(*S*)-1b**–**1d**.

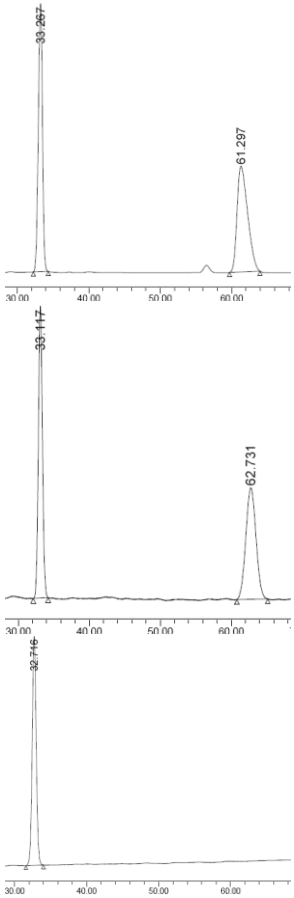

Figure 5. Chiral HPLC trace for **(±)-1b**, top; **(±)-2b**, middle; and **(*S*)-2b**, bottom. For **(±)-2b** and **(*S*)-2b**, the data is obtained using the individual crystal from the single crystal analysis.

Co-crystallization involving achiral compounds with enantiopure and racemic partners is known; in particular interest has centred on the different physical properties that are obtained for the racemic and enantiopure co-crystals, such as density and stability.[8,13] It has been used to introduce heavy atoms into a chiral structure, enabling absolute stereochemistry determination of known materials using Mo-Kα radiation.[14] To date the stereochemistry of the starting material has always been known.

Our results demonstrate for the first time that the application of co-crystallization methodology can be utilized successfully for determination of the absolute stereochemistry of compounds that are oils or viscous liquids at ambient conditions. The advantage of co-crystals over salt formation is that the chromatographic conditions developed to separate the enantiomers do not change on co-crystallization, unless the co-crystal former interferes with the separation of the enantiomers. Furthermore, co-crystals do not require ionizable sites, which in principle means that co-crystallization should be more universally applicable than salt formation. In conclusion, co-crystallization and X-ray diffraction, in combination with chiral HPLC, provides an effective method in synthetic research to identify absolute stereochemistry in novel compounds.

EXPERIMENTAL SECTION

General Experimental. Compounds **(±)-1a**, **(±)-1b**, **(±)-1c**, **(±)-1d**, **(*S*)-1a**, **(*S*)-1b**, **(*S*)-1c**, **(*S*)-1d** were prepared according to the literature methods.[5] Grinding was undertaken using a mixer mill equipped with stainless steel 5 mL grinding jars and one 2.5 mm stainless steel grinding ball per jar. Powder diffraction experiments were performed using graphite monochromatized Cu-Kα radiation at room temperature. Single crystal diffraction experiments were performed using either graphite monochromatized Mo-Kα or doubly curved silicon crystal monochromatized Cu-Kα radiation at 100 K. Analysis was undertaken using the SHELX suite of programs[15] and diagrams prepared with Mercury 2.3.[16] Differential Scanning Calorimetry was undertaken over the temperature range 40 – 140 °C and the sample was heated at a rate of 4 °C min^{-1}. Chiral HPLC analysis was undertaken using a chiral column (Chiralcel OJ-H for **2a**, **2b**, and **2c**, Chiralcel AS-H for **2d**) at 0 °C.

General Procedure for Preparation of the Racemic Acid : Isonicotinamide Co-crystals. The corresponding racemic acid (1 equiv) and isonicotinamide (1 equiv) were placed in the grinding jars, and the mill was operated at 30 Hz for 30 min. The material obtained was analyzed by PXRD. It was then dissolved in a minimum amount of acetonitrile and acetone added until the solvent ratio was 70 : 30 respectively. The solution was allowed to stand at ambient conditions and crystals suitable for single crystal diffraction were obtained by slow evaporation over 3-4 d. After single crystal analysis, chiral HPLC analysis was performed on the actual crystal used in the diffraction experiment.

Synthesis of (±)-3-*o*-tolylbutanoic acid : isonicotinamide co-crystal, (±)-2b. Isonicotinamide (27 mg, 0.22 mmol) and **(±)-1b** (40 mg, 0.22 mmol) were used; mp 84 – 86 °C. Crystal data: $C_{17}H_{20}N_2O_3$, M = 300.35, triclinic, a = 9.6495(16) Å, b = 12.915(2) Å, c = 13.390(2) Å, α = 102.007(3)°, β = 103.616(4)°, γ = 92.047(4)°, V = 1580.0(4) $Å^3$, T = 100.(2) K, space group $P\bar{1}$, Z = 4, 43120 reflections measured, 7818 unique (R_{int} = 0.0647). The final R_1 values were 0.0402 ($I > 2\sigma(I)$) and 0.0570 (all data). The final $wR(F^2)$ values were 0.1009 ($I > 2\sigma(I)$) and 0.1070 (all data). HPLC data: Chiralcel OH-J, eluent hexane : *i*-PrOH (3% trifluoroacetic acid), 94 : 6, flow rate 0.25 $mLmin^{-1}$, λ = 209.8 nm, RT (min): S = 33.1 and R = 62.7.

General Procedure for Preparation of the Enantiopure Acid : Isonicotinamide Co-crystals. The corresponding enantiopure acid (1 equiv) and isonicotinamide (1 equiv) were treated in an identical fashion to the racemic compounds, except the initial grinding and subsequent PXRD analysis steps were omitted.

Synthesis of (*S*)-3-*o*-tolylbutanoic acid : isonicotinamide co-crystal, (*S*)-2b. Isonicotinamide (5 mg, 0.06 mmol) and **(*S*)-1b** (7 mg, 0.05 mmol) were used; mp 89 – 91 °C. Crystal data: $C_{17}H_{20}N_2O_3$, M = 300.35, triclinic, a = 7.1279(4) Å, b = 8.8202(5) Å, c = 13.1405(8) Å, α = 102.542(3)°, β = 92.659(3)°, γ = 95.430(3)°, V = 800.90(8) $Å^3$, T = 100.(2) K, space group $P1$, Z = 2, 18797 reflections measured, 5028 unique (R_{int} = 0.0238). The final R_1 values were 0.0278 ($I > 2\sigma(I)$) and 0.0285 (all data). The final $wR(F^2)$ values were 0.0773 ($I > 2\sigma(I)$) and 0.0781 (all data). Flack parameter = -0.10(9), Hooft y parameter = 0.05(6). HPLC data: Chiralcel OH-J, eluent hexane : *i*-PrOH (3% trifluoroacetic acid), 94 : 6, flow rate 0.25 $mLmin^{-1}$, λ = 209.8 nm, RT (min): S = 32.7.

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Supporting Information Available: Additional figures, HPLC traces, DSC data, PXRD data and the cif files for **(±)-2a–d** and **(*S*)-2a–d**. The crystallographic data for **(±)-2b–d** and **(*S*)-2a–d** have been deposited with the Cambridge Crystallographic Data Centre, CCDC numbers 790893 to 790899. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. This material is available free of charge via the Internet at http://pubs.acs.org.

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