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Cocrystallization out of the blue: DL-mandelic acid/ethyl-DL-mandelate cocrystal

Natalia Tumanova [a], Ricky Payen [a], Géraldine Springuel [a], Bernadette Norberg [b], Koen Robeyns [a], Cécile Le Duff [a], Johan Wouters [b], Tom Leyssens [a, *]

[a] Institute of Condensed Matter and Nanosciences, Université catholique de Louvain, Louvain-la-Neuve, Belgium
[b] Unité de Chimie Physique, Théorique et Structurale, University of Namur, Namur, Belgium

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ABSTRACT

This work focuses on a peculiar behavior of racemic mandelic acid in ethanol solution. Dissolution of racemic mandelic acid in ethanol followed by evaporation to dryness results in a DL-mandelic acid/ethyl-DL-mandelate cocrystal. This behavior indicates that racemic mandelic acid tends not only to transform into an ester in ethanol, but also to cocrystallize with untransformed acid molecules. Cocrystal formation for mandelic acid in ethanol was found to be reproducible under various conditions. DL-tropic acid and DL-phenyllactic acid that contain similar functional groups and that were tested as well, on the other hand, showed no cocrystal formation: DL-phenyllactic acid partly converted into an ester, whereas DL-tropic acid mostly recrystallized.

1. Introduction

Cocrystallization has been studied extensively during recent years from both the fundamental and application points of view. Fundamental aspects of cocrystallization mostly deal with structural peculiarities that predispose compounds to cocrystal formation, involving analysis of functional groups and their ability to form hydrogen bonds, with packing being also one of the factors responsible for polymorphism in cocrystals; identifying stable synthons (*e.g.*, between an amide and carboxyl groups) serve as guidelines in designing cocrystals [1–7]. In the context of applications, cocrystals are considered good alternatives to existing pharmaceutical formulations, as they may help to improve pharmacological properties of drugs, *e.g.*, bioavailability, dissolution rate, hygroscopicity [8–10]. Recent works also show that cocrystals can be applied for separation, purification, or chiral resolution [11–16]. Although cocrystal studies have already uncovered some of the thermodynamic and kinetic factors driving cocrystal formation [17–21], cocrystallization still remains poorly predictable; polymorphism issues may also be underestimated, as recent works report that cocrystal systems may be extremely complex [22,23].

In this contribution, we discuss the formation and structure of the DL-mandelic acid/ethyl-DL-mandelate cocrystal. Crystallization and various properties of mandelic acid have been studied extensively in various solvents [24–27]. Mandelic acid is a useful precursor to various drugs, for example homatropine and cyclandelate, which are esters of mandelic acid, and it is also known to have antibacterial properties [28]. The compound is furthermore used as a cocrystallization co-former [11,29]. In this paper, we report an unusual behavior of racemic mandelic acid. When recrystallized from ethanol solution, it partially transforms into an ester which cocrystallizes with the remaining acid molecules, forming a DL-mandelic acid/ethyl-DL-mandelate cocrystal. This system presents a cocrystal involving an ester, which is quite rare, and is also an example of a cocrystal with four chiral centers. This system also raises awareness to unexpected cocrystallization phenomenon, which is especially important when selecting an appropriate solvent for recrystallization or even when performing synthesis.

2. Experimental

DL-mandelic acid (99+%), L-mandelic acid (99%), D-mandelic acid (99%), DL-tropic acid (97%), DL-3-phenyllactic acid (97%) were purchased from Acros Organics and used as received without further

* Corresponding author. Institute of Condensed Matter and Nanosciences Molecules, Solids and Reactivity, Université Catholique de Louvain, Place Louis Pasteur 1, bte L4.01.03, B-1348, Louvain-La-Neuve, Belgium.
E-mail addresses: natalia.tumanova@uclouvain.be (N. Tumanova), johan.wouters@unamur.be (J. Wouters), tom.leyssens@uclouvain.be (T. Leyssens).
URL: http://www.uclouvain.be/leyssens-group

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purification. Ethanol (absolute), methanol and isopropanol (HPLC grade) were purchased from VWR International.

2.1. Crystallization from solution

100 mg of a selected compound (DL-mandelic acid, D-mandelic acid, L-mandelic acid, DL-tropic acid or DL-3-phenyllactic acid) were dissolved in 1 mL of a corresponding solvent (methanol, ethanol or isopropanol) upon stirring at room temperature or 75 °C for a varied period of time; after that, solutions were cooled to room temperature and left to evaporate to dryness. The resultant phases were analyzed with powder X-ray diffraction (PXRD) if solid or by ^{1}H NMR if oily. Table 1 summarizes selected experimental conditions and outcomes for DL-mandelic acid dissolved in ethanol (Table 1S in ESI lists all the experiments performed).

2.2. X-ray powder diffraction

X-ray powder diffraction patterns (CuKα radiation, λ = 1.5418 Å) were measured using a Siemens D5000 diffractometer; 2θ was scanned from 2 to 50° with a step of 0.02° and exposure time of 2 s per step.

2.3. Single crystal X-ray diffraction analysis

Single crystal X-ray diffraction analysis for DL-mandelic acid/ethyl-DL-mandelate was performed on a Gemini Ultra R system (4-circle kappa goniometer, Ruby CCD detector) using MoKα radiation. A data set was collected at 150(2) K; the exposure time was chosen so that average I/σ is more than 15. The data were integrated using the CrysAlisPro software [30].

The structure of the $P2_1/c$ polymorph of DL-phenyllactic acid was solved from single-crystal X-ray diffraction data, collected using a MAR345 image plate detector at MoKα radiation (Rigaku UltraX 18 rotation anode, Xenocs Fox3D focusing multilayer mirror) at 150(1) K; the exposure time was chosen so that average I/σ is more than 15. The data were integrated using the CrysAlisPro software.

Both structure were solved by direct methods with the SHELXS-97 program and refined on $|F|^2$ using SHELXL-2014 software [31]. Non-hydrogen atoms were refined anisotropically. All hydrogen atoms were localized from the Fourier difference map; hydrogen atoms not involved in H-bonds were refined in the riding mode with isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms (1.5 times for methyl groups); and hydrogen atoms involved in H-bonds were refined independently.

The figures were generated using Mercury [32]; and the *cif* were finalized using the Encifer [33] program. Table 2 summarizes the experimental details on crystal data, data collection, and refinement for the DL-mandelic acid/ethyl-DL-mandelate cocrystal, see Table 2S, supplementary info for crystallographic data on the DL-phenyllactic acid polymorph.

Table 1
Selected experiments performed for DL-mandelic acid in ethanol solution ("cocrystal" stands for DL-mandelic acid/ethyl-DL-mandelate cocrystal; "acid" stands for DL-mandelic acid).

Sample	Treatment	Outcome
1	from solution, 3 days, 75 °C	Cocrystal
2	from solution, 3 days, RT	acid ($P2_1/c$) + cocrystal
3	from solution, 25h, 75 °C	acid ($P2_1/c$) + cocrystal
4	from solution, 6h, 75 °C	acid ($P2_1/c$) + cocrystal
5	from solution, 2h, 75 °C	acid ($P2_1/c$) + cocrystal

2.4. Computational details

Molecular geometries were optimized without constraints via DFT calculations using the B3LYP functional. Frequency calculations at the same level of theory have also been performed to identify all the stationary points as minima (zero imaginary frequencies) and to provide free energies at 298.15 K in order to calculate equilibrium constants. These calculations include entropic contributions by taking into account the vibrational, rotational, and translational motions of the species. The 6-31G(d,p) basis set was used for all atoms (C, H, N and O). All the DFT calculations were performed with the Gaussian 09 package and the molecular structures built in GaussView [34].

3. Results and discussion

We will start by discussing the conditions that predispose transformation of racemic mandelic acid into racemic ethyl mandelate followed by cocrystallization of both constituents. Secondly, we will dwell on structural peculiarities of this cocrystal that can help understand why this cocrystal is stable. Finally, we will move on to the question whether or not a similar situation holds for other compounds and will discuss results using theoretical calculations for acid/ester equilibrium.

3.1. Crystallization from solution

As mentioned above, the mandelic acid/mandelate cocrystal was obtained from a mandelic acid/ethanol solution that was left to evaporate. As the formation of this cocrystal may depend on the acid/ester equilibrium, multiple factors, such as percentage of water in the solvent, temperature, reaction and evaporation rates, likely impact cocrystal formation and yield. In this context, we studied some of these factors. Although we cannot be sure that the equilibrium has been reached under conditions used, we assumed that system was close to equilibrium before being evaporated to simplify further calculations of equilibrium constants.

In a first set of experiments, we studied the temperature effect, dissolving DL-mandelic acid in a closed vial with ethanol, after which a 3 day isothermal hold was applied (either 75 °C or room temperature). After this period, the solution was left to evaporate at room temperature and the solid residual was analyzed with PXRD; the diffraction patterns are shown in Fig. 1, the inset to Fig. 1 shows low-angle peaks, intensities of which allow qualitative estimation for the amount of the acid and the cocrystal (the peak at 6° corresponds to mandelic acid and the peak at 7.4° to the cocrystal; a higher relative intensity corresponds to a larger amount of the phase). The cocrystal phase emerged in both experiments, but for the vial that was left to stir at room temperature, we obtained a mixture of DL-mandelic acid (metastable polymorph with $P2_1/c$ space group) and the DL-mandelic acid/ethyl-DL-mandelate cocrystal; whereas at 75 °C, we obtained almost pure cocrystal. A mild grinding of sample ***2*** (see Table 1) provokes a polymorphic transition of mandelic acid, resulting in the more stable *Pbca* polymorph, leaving the DL-mandelic acid/ethyl-DL-mandelate cocrystal intact. Isothermal hold at higher temperatures (75 °C compared with room temperature) seems to displace the acid/ester equilibrium, leading to an increased amount of cocrystal being formed. At the same time, ^{1}H NMR shows an excess of ester in sample ***2*** (see Table 5), which cannot be detected by PXRD. This is an indication that the esterification reaction in the case of mandelic acid cannot be controlled by crystallization as it would have stopped after reaching 1: 1 stoichiometry, which is not the case.

In a second set of experiments, we varied the isothermal holding period (upon stirring); and the solid residual was analyzed by