High-Pressure Nucleation of Low-Density Polymorphs

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Submitted date: 29/10/2020 • Posted date: 02/11/2020
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Citation information: Sobczak, Szymon; Ratajczyk, Paulina; Katrusiak, Andrzej (2020): High-Pressure Nucleation of Low-Density Polymorphs. ChemRxiv. Preprint. https://doi.org/10.26434/chemrxiv.13161956.v1

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File list (1)

OrgMANu.pdf (841.10 KiB)
High-pressure nucleation of low-density polymorphs

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Supporting Information Placeholder

ABSTRACT: The crystallized above 0.3 GPa polymorphs β and γ of bis-3-nitrophenyl disulphide, are less dense than the ambient-pressure polymorph α. This counterinitiative density relation results from the kinetic high-entropy nucleation, the work performed by pressure compensates the product of increased entropy and temperature. This high-entropy nucleation illustrates the molecular-scale mechanism of empirical Ostwald’s rule of stages. This method, in contrast to mechanochemical techniques, is ideally suited the kinetic nucleation of new low-density conformational polymorphs.

The rational control over polymorphic forms of organic compounds is one of the greatest challenges of materials sciences, modern chemistry, and related industries.\textsuperscript{1-3} Apart from the environment (solvent, pressure, temperature, composition, evaporation rate, etc.) also the intrinsic features (intra- and intermolecular interactions of conformers, tautomerism, different solvates forms, etc.) need to be taken into account for designing the robust process aimed at the desired polymorphic form.\textsuperscript{4-5} Precisely defined technological procedures are applied for obtaining required forms of pharmaceuticals, pesticides, food, plastics, dyes and various other products. Despite a considerable progress in the crystal-structure prediction,\textsuperscript{6-9} in most cases, the experimental screening of polymorphs provides the most reliable information about crystal forms of compounds.

Generally, the crystal form results from the initial aggregation of molecules, either primary or secondary nucleation, and from the time-dependent crystal growth, either dynamic or kinetic.\textsuperscript{1,2,5,9} The dynamic crystallizations proceed slowly, in the nearly equilibrated systems, whereas the kinetic crystallizations take place off the thermodynamic equilibrium, for example in quickly cooled molten or dissolved compounds. The dynamic and kinetic crystallizations often lead to different polymorphs. Some compounds, irrespective of thermodynamic conditions of their nucleation, have been obtained in only one crystalline form, for example naphthalene and CS\textsubscript{2}.\textsuperscript{10,12} The thermodynamic conditions of nucleation can be extended by subjecting the sample to the high-pressure, which increases the range of accessible temperature, high excited states, rota-vibrations, conformations or disorder.

Presently we report a simple method of high-pressure nucleation, capable of generating new polymorphs, in this case study on bis-3-nitrophenyl disulphide (3-NO\textsubscript{2}-PhS)\textsubscript{2}. The family of biphenyl disulphides is important due to their applications as drugs,\textsuperscript{13} sensors,\textsuperscript{14} lubricants,\textsuperscript{15} polymers;\textsuperscript{16-19} in organic reactions bisfenyldisulphides are substrates as a source of PhS substituents;\textsuperscript{20,21} and precursors leading to supramolecular systems.\textsuperscript{22-25} Recently we showed di-p-tolyl disulphide (4-CH\textsubscript{3}-PhS\textsubscript{2}) is capable compensating the stress and absorbing the energy of compression, which explain at the molecular level the lubricating performance of this class of compounds.\textsuperscript{24} We also observed that exchange reaction between bis(4-chlorophenyl)disulphide (4-Cl-PhS)\textsubscript{2} with bis(2-nitrophenyl)disulphide (2-NO\textsubscript{2}-PhS)\textsubscript{2}, yields a low-density polymorph A 4-Cl-PhSSPh-2-NO\textsubscript{2} at high-pressure conditions, and also at catalyst-promoted reactions at normal conditions.\textsuperscript{25-27} The 3-NO\textsubscript{2} analogue, of those disulphides is known, and commercially available in the centrosymmetric form of monoclinic space group C2/c, with molecules located on the 2-fold axes (hereafter referred as polymorph α).\textsuperscript{28} Our systematic study on (3-NO\textsubscript{2}-PhS)\textsubscript{2} combines the effects of primary nucleation with dynamic and kinetic crystallization, viewed from the perspective of high-pressure conditions. We observed that the high-pressure nucleation yields two new polymorphs, labelled β and γ, both with density lower compared to that of polymorph α obtained at the ambient conditions, sheds new light on empirical Ostwald’s rule of stages and Wallach’s rule relating the densities of enantiomers and racemates.

Well known are the structural features usually valid for the polymorphs obtained under kinetic regime: (i) their symmetry is lower; (ii) their Z' number is higher; and (iii) they are less dense, when compared to the dynamic-regime polymorphs. It is also characteristic of conformational polymorphs that (iv) the kinetic polymorphs are built of conformers of higher potential energy (E\textsubscript{p}) than those of the dynamic polymorphs.

Both polymorphs β and γ of (3-NO\textsubscript{2}-PhS)\textsubscript{2} are text-book examples of kinetic polymorphs, with all their characteristic features (i-iv). Both forms crystallize in the chiral space group P2\textsubscript{1}, which is a subgroup of space group C2/c and their density is significantly lower than that of
polymorph α (Figure 2, Table 1). The disulphide molecules are conformationally flexible and their ‘soft’ torsion angles about bonds C-S and S-S can be modified by momentary environment changes in the liquid and by crystal field in the solid state. The Z’ number is 0.5 in dynamic polymorph α, while in kinetic polymorphs β and γ the Z’ number is 4. In polymorph β four independent conformers (A, B, C and D) are located at general positions, in pseudo-centrosymmetric relations between conformers A to C, and B to D. This relation is most prominently visible for torsion angles τ, τ D and τ E (Table 2). Similar pseudo-symmetry relations are also apparent in the structure of polymorph γ.

The (3-NO2-PhS)2 molecule has two favoured conformations; in the lower-Ep (LE) conformer angels τ, τ B and τ E are close to 90°, 0° and 0°, whereas in the somewhat higher Ep (HE) conformer these angles are close to 90°, 0° and 165°, respectively. Figure 1 and Table 2 show that polymorph α is built LE conformers, in polymorph β half of conformers is of LE and half of HE, and in polymorphs γ only HE conformers are present. The average conformational energies of polymorph α, β, and γ are 1.18, 1.57 and 3.42 kJ mol⁻¹, as shown in the inset in Figure 1c. In all polymorphs there are equal numbers of rotational enantiomers (Table 2) and in this respect they are true kryptoracemates.²⁹

Table 1. Selected crystal data of (3-NO2-PhS) polymorphs α, β and γ.

| Polymorph  | α  | β   | γ       |
|-----------|----|-----|---------|
| Space group | C2/c | P2₁ | P2₁ |
| a (Å)    | 13.673(9) | 8.1298(16) | 8.1069(10) |
| b (Å)    | 8.9078(6) | 26.951(4) | 22.406(3) |
| c (Å)    | 12.4539(8) | 12.6250(18) | 14.7478(16) |
| β (°)    | 120.070(1) | 105.220(1) | 94.087(12) |
| V (Å³)   | 1372.704 | 2669.10 | 2672.1(6) |
| Z /Z'    | 4/0.5 | 8/4 | 8/4 |
| D s (g/cm³) | 1.573 | 1.534 | 1.533 |

Apart from the molecular conformation the crystal structure and packing motifs in polymorph α of (3-NO2-PhS)2 strongly differ from those observed in isomers (2-NO2-PhS)2 and (4-NO2-PhS)2. In their crystals, molecules are linked into chains by C-H–O hydrogen bond, absent α-(3-NO2-PhS)2, where sheets are formed through π-π stacking of aromatic rings.²⁸,³⁰ On the other hand, in (3-NO2-PhS)2 polymorphs β and γ, the shortest intermolecular distances (Figure S2) mark a combination of various cohesions forces, involving hydrogen bonds C-H–O, π-π stacking and S–S contacts.

It is apparent that the conditions of nucleation affect the hierarchy of interactions in the crystal structure. It was demonstrated that the intermolecular hydrogen bonds are strongly modified under pressure,³⁹⁻⁴¹ when they have to compromise with the increased role of close packing. Most importantly, ambient pressure molecular crystals easily sublime, melt and evaporate, but under high-pressure the temperature of the system can be increased to higher values, which increases the kinetic energy of molecular motion. According to Boltzmann’s statistics for ideal gas molecules, their average kinetic energy increases linearly with temperature and is equal to kₜ/2 (where kₜ is Boltzmann constant) per each degree of freedom. This kinetic energy at normal conditions is of the order of the Ep energy of cohesion forces in (3-NO2-PhS)2, and high temperature can easily destabilize these interactions (mainly C-H–O, cf. Figure S2) and promote a variation of conformers in polymorphs β and γ. It is characteristic that the Ep values of these polymorphs nucleated at high temperature are higher, compared to the potential energy of the conformer present in polymorph α (Table 2).

Indeed, our high-pressure high-temperature crystallizations yielded new polymeric forms. The crystals obtained by the high-pressure kinetic crystallizations have all features of kinetic polymorphs listed above. Most surprisingly, these features of new high-pressure polymorphs also include that their density is lower compared to the density of the dynamic polymorph α obtained at ambient pressure (Table 1). This counterinitiative result at first glance seems to contradict numerous high-pressure crystallizations and syntheses that led to high-density polymorphs. In fact, high-pressure techniques are generally aimed at obtaining harder, high-density forms of crystals.³⁴ However, such crystallizations are performed slowly under the dynamic regime, allowing the system to equilibrate. Listed above all characteristic features (i-iv) of kinetic polymorphs can be rationalized in

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Figure 1. Conformers present in (3-NO2-PhS)2 crystals: (a) polymorph α with torsion angles τ, τ B and τ E indicated; (b) all molecules of polymorphs α, β, and γ superimposed on the C1-S1-S1’ fragment; (c) all molecules in three polymorphs superimposed after the rotational enantiomers have been changed to those with torsion angle τ positive (in order to visualise the presence of low- and high-Ep conformers).
the thermodynamic conditions of the crystallization process: (i) the low symmetry is a consequence of the conformational and orientational variety consistent with the high entropy of the system at high-temperature, which is also connected with (ii) the high \( Z^\prime \) number; the high \( T \) also explains the high \( E_p \) states of excited molecules (compared to lower \( E_p \) conformer in the dynamic polymorph \( \alpha \)). The quick crystallization leaves no sufficient time for the molecules to reorient or change the positions of substituents. Finally, the low density (iii) despite the high-pressure conditions, can result of several reasons: (a) the low-density polymorph is more compressible than the high-density one, hence their density difference diminishes with pressure; (b) the nucleation takes place at high temperature and high entropy strongly favouring the low-density form, because strong rota-vibrations require an additional space; and (c) the nucleation directs the crystallization leaving no space for other polymorphs, particularly that the crystallization is the fastest close to the melting curve.

Table 2. Torsion angles \( \tau \), \( \tau_2 \) and \( \tau_3 \) (cf. Figure 1) in the conformers present in polymorphs \( \alpha \) (half molecule independent), \( \beta \) and \( \gamma \) (both with 4 independent molecules labelled A, B, C and D), as well as their potential energy \( \Delta E_p \) related to the fully optimized isolated conformer. LE - indicates low \( E_p \) and HE denotes high \( E_p \) conformer.

| Torsion angle [°] | \( \tau \) | \( \tau_2 \) | \( \tau_3 \) | \( \Delta E_p \) [kJmol\(^{-1}\)] |
|-------------------|-----------|-----------|-----------|----------------|
| Optimized mol.    |           |           |           |                |
| \( \phi \)        | 84.78     | 4.13      | 4.13      | 0              | LE          |
| Phase \( \alpha \) |           |           |           |                |
| A                 | -88.07    | -22.32    | 12.06     | 0.67           | LE          |
| B                 | 87.08     | -1.24     | 171.13    | 2.28           | HE          |
| C                 | 91.21     | -14.30    | 21.27     | 0.97           | LE          |
| D                 | -87.01    | 1.46      | -169.62   | 2.35           | HE          |
| Phase \( \beta \) |           |           |           |                |
| A                 | -84.77    | -5.30     | -162.45   | 2.98           | HE          |
| B                 | 91.05     | 8.26      | 163.13    | 2.95           | HE          |
| C                 | 89.39     | 16.49     | 165.05    | 3.29           | HE          |
| Phase \( \gamma \) |           |           |           |                |
| A                 | -91.05    | -22.65    | -165.42   | 4.06           | HE          |

Interestingly, all our attempts to obtain the kinetic polymorphs \( \beta \) and \( \gamma \) by mechanochemical methods, liquid-assisted grinding (LAG) with acetonitrile and isopropanol, dry ball milling, failed. This contrasts with the successful production of heterodimeric low-density polymorph A of 4-Cl-PhSSPh-2-NO\(_2\),\(^{36,37}\) but it also shows the importance of the high-entropy nucleation in the process of obtaining low-density polymorphs \( \beta \) and \( \gamma \) of (3-NO\(_2\)-PhS).\(^{36,37}\)

To conclude, the high-pressure crystallization of low-density polymorphs \( \beta \) and \( \gamma \) of (3-NO\(_2\)-PhS), provides new information about this counterinitiative phenomenon, previously considered as a sporadic event in the case of heterodimeric 4-Cl-PhSSPh-2-NO\(_2\), obtained as a product of high-pressure disulphide exchange reaction.\(^{37}\) The high-pressure coordinates added in the thermodynamic space to those of usually applied, temperature and concentration extend the space for the interpretation of mechanism leading to the formation of different polymorphs. The Ostwald’s rule of stages appears as a natural consequence of the kinetic effect ‘enhanced’ under pressure. It can be noted that (3-NO\(_2\)-PhS), low-density polymorphs \( \beta \) and \( \gamma \) are noncentrosymmetric, unlike polymorph \( \alpha \), which is consistent with Wallach’s rule, stating that the density of racemates in higher than those of enantiomers. Numerous exemptions from Wallach’s rule\(^{38}\) can be regarded as a premonition that more experimental results and studies are needed for the rigorous description of the crystallization process, which still today is often considered to be more ‘art’ than ‘science’.\(^{1}\)

ASSOCIATED CONTENT

Supporting Information

Detailed experimental data including protocol for obtaining high-pressure nucleated polymorphs, single-crystals of polymorphs \( \beta \) and \( \gamma \), the shortest intermolecular contacts plotted for all polymorphic forms, A, B, C and D conformers present in form \( \beta \) and \( \gamma \), as well as the results of ball-mill experiments can be
find in Supporting Information. The CIF files have been deposited in Cambridge Structural Database (CCDC, www.ccdc.cam.ac.uk) as supplementary publications with reference numbers 2040892 and 2040891 for phase β and γ, respectively. The Supporting Information is available free of charge on the ACS Publications website. CSD

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank the Polish National Science Centre (grant PRELUDIUM 2017/27/N/ST5/00693) for financial support. This research was supported in part by PLGrid Infrastructure.

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