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Investigation of a Privileged Polymorphic Motif: a Dimeric ROY Derivative

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Abstract

Bis(5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrilyl)acetylene, a derivative of the highly polymorphic compound 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY) that possesses two chromophores electronically coupled through a triple bond, was found to be trimorphic. Structural data for two of these forms indicates that symmetry is maintained in one structure and broken in the other leading to spontaneous differentiation of the methyl-thiophenecarbonitrile units. This study contributes to the mounting evidence that ROY and its derivatives are particularly prone to polymorphism.

1. Introduction

The notion that some structure types are privileged has gained widespread acceptance in the pharmaceutical field^{1,2}. The recognition that these scaffolds are likely to yield bioactive compounds aids discovery efforts greatly. Similarly in the area of asymmetric catalysis, a handful of ligand types have been identified that, under a variety of conditions and with an array of metals, lead to catalysts with good levels of stereocontrol.³ These examples serve to illustrate the principle that we had in mind when asking if there are privileged structures in the area of crystal polymorphism; in analogy to pharmacophores these could be termed polymorphophores.⁴ It certainly appears that pharmaceuticals containing sulfonamide functionality are prone to polymorphism^{5,6}, but exceptions exist^{6–8} and often many other functional groups are present in these molecules. Factors that may favor polymorphism in structure types have been much discussed and include conformational flexibility and hydrogen bonding.⁹ Clearly these are not necessary factors for polymorphism, because some highly polymorphic systems such as carbamazepine have conserved strong hydrogen bonding networks and conformations across all four polymorphs.¹⁰ Furthermore there are examples of highly polymorphic compounds that possess no classical hydrogen bonding or rotatable bonds and yet display many forms as found in pentacene (4 forms)¹¹ and copper phthalocyanine (5 forms established, 4 more claimed)¹² (Figure 1).

When trying to understand if there are privileged structure types in crystal polymorphism, it is natural to begin inquiry with 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY) (Figure 2). This compound currently holds the record for the highest number of crystallographically characterized polymorphs with 7^{13,14} in addition to 3 forms without crystal structures for a total of 10 polymorphs.¹⁵ Furthermore, the related compounds 5-methyl-2-[(4-methyl-2-nitrophenyl)amino]-3-thiophenecarbonitrile and 2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile display 4 (3 crystallographically characterized)^{16–18} and 3 (2 crystallographically characterized)¹⁹ forms respectively (Figure 2). A common theme arising

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in ROY and its derivatives is the presence of molecules with different conformations leading to a modulation of the conjugation between the nitrophenyl and thiophenecarbonitrile groups and a corresponding change in the color of the crystals.²⁰ To add an additional layer of complexity in studying the ROY polymorphophore, a molecule containing two chromophores that are in electronic communication was synthesized (Scheme 1). This raises the possibility of symmetry breaking in the solid state leading to two different conformations of the chromophore within the same molecule.

2. Experimental

Synthesis of 2-(4-bromo-2-nitrophenylamino)-5-methylthiophene-3-carbonitrile (Br-ROY)

In a two-neck flask, dry THF (10 mL) was added to NaH (60% dispersion in mineral oil, 1.22 g, 0.0305 mol) under a N₂ atmosphere. In a different flask, 2-amino-5-methyl-3-thiophenecarbonitrile (1.40 g, 0.0101 mol) and 4-bromo-1-fluoro-2-nitrobenzene (2.23 g, 1.25 ml, 0.0101 mol) were dissolved in dry THF (10 mL). This mixture was transferred by cannula dropwise into the NaH/THF mixture at 0 °C; the solution turned dark purple and was allowed to stir overnight. The reaction mixture was poured over ice water and it immediately turned red. Extraction with CH₂Cl₂ (3 × 100 mL) was followed by combining the organic layers, and washing with 1 M HCl and brine. The organic layer was dried over anhydrous Na₂SO₄ and the solvent removed by rotary evaporation. The orange solid obtained was recrystallized from absolute ethanol. Yield: 2.057 g (60%). mp 160 °C. ¹H NMR (400 MHz, CDCl₃, δ): 2.484 (s, 3H), 6.800 (s, 1H), 7.052 (d, J = 9.0 Hz, 1H), 7.580 (dd, J = 9.2, 2.4 Hz, 1H), 8.391 (d, J = 2.4 Hz, 1H), 9.495 (s, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 15.63, 105.57, 111.25, 113.38, 117.68, 124.14, 128.86, 134.27, 137.08, 138.94, 140.47, 147.8. Anal. Calcd for C₁₂H₈N₃O₂SBr: C, 42.62; H, 2.38; N, 12.43. Found: C, 42.64; H, 2.17; N, 12.46. The crystal structure is monoclinic in C2/c with *a*=34.013(3), *b*=4.4489(4), *c*=22.1431(18), and β=130.5450(10). See Supporting Information.

Synthesis of bis(5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrilyl)acetylene (el-ROY)

In a microwave reaction vessel, Br-ROY (186 mg, 0.554 mmol), copper (II) chloride (24.7 mg, 0.186 mmol), and bis(tributylstannyl) acetylene (0.13 mL, 0.254 mmol) were stirred in dry toluene (3.5 mL) while sparging with nitrogen. After 10 minutes, Pd(PPh₃)₄ (57.8 mg, 5 mol % based on halide) was added to the reaction mixture. The vessel was capped and placed in a microwave reactor. The reaction was conducted for 60 minutes at a temperature of 130 °C with a maximum power of 255 W and a maximum pressure of 300 psi. The reaction mixture was diluted with CH₂Cl₂ and the combined organic layers were washed with 1 M HCl (3 × 100 mL). The solvent was removed under reduced pressure and the resulting solid was purified by column chromatography on silica gel eluting with 3:1 CHCl₃:CH₂Cl₂. Yield 60.9 mg (45%, form I). mp 286.7 °C. ¹H NMR (400 MHz, CDCl₃, δ): 2.498 (s, 6H), 6.816 (s, 2H), 7.155 (d, J = 8.8 Hz, 2H), 7.611 (dd, J = 8.6, 1.8 Hz, 2H), 8.423 (d, J = 1.8 Hz, 2H), 9.688 (s, 2H). ¹³C NMR (100 MHz, CDCl₃, δ): 15.16, 87.37, 105.01, 112.76, 113.88, 117.49, 124.22, 128.98, 134.02, 137.36, 138.14, 149.49.

Single Crystal X-Ray Diffraction

Crystal structures were obtained on a Bruker SMART CCD-based X-ray diffractometer equipped with a LT-2 low temperature device and normal focus Mo-target X-ray tube (λ=0.71073) operated at 2000 W power (50 kV, 40 mA). The X-ray intensities were measured at 123(2) K; the detector was placed at a distance 4.980 cm from the crystal. Analysis of the data showed negligible decay during the data collection; the data were processed with SADABS and corrected for absorption. Structures were solved and refined with the Bruker SHELXTL (version 6.12) software package. All non-hydrogen atoms were refined

anisotropically with the hydrogen atoms placed in idealized positions. Form I was obtained from evaporation of toluene while heating. Form II was obtained from evaporation of CH_2Cl_2 at room temperature.

Vibrational Spectroscopy

Raman spectra were recorded on a Renishaw inVia Raman Microscope equipped with a 20 $\times$ objective utilizing a 785 nm laser. The scan range was 3200-100 cm^{-1} . A silicon standard was used to calibrate the instrument.

IR spectra were obtained with a Perkin Elmer AutoIMAGE FTIR microscopy system in transmission mode.

3. Results and Discussion

Investigation of the crystallization of ethynyl linked ROY (el-ROY) revealed three forms. Form I was obtained as red needles by evaporation of a toluene solution (Figure 3). Form II, which crystallizes as red-orange plates, was obtained by the evaporation of a CH_2Cl_2 solution. Form III, was only obtained through polymer-induced heteronucleation^{21–23} in a combinatorial screen. It is conveniently prepared by evaporation of a CH_2Cl_2 solution in the presence of a polymer derived from 21.5 μL of hydroxyethyl methacrylate, 26.5 μL of methacrylic acid and 25.0 μL of divinyl benzene. It crystallizes as small and thin red-orange ellipsoidal plates. The onset of melting in forms I, II, and III occurs at 286.7, 279.4, and 282.9 $^{\circ}\text{C}$ respectively and is accompanied by decomposition of the resulting red liquid.

The Raman spectra of el-ROY show a distinctive difference in the nitrile/alkyne region (Figure 4). Form I exhibits 1 peak at 2225 cm^{-1} , whereas the spectrum for form II possesses 2 distinct peaks at 2226 and 2214 cm^{-1} . Form III show a peak at 2224 cm^{-1} with a slight shoulder. This difference may be attributed to the asymmetry of the el-ROY molecules in forms II and III, but based on infrared data more likely results from a shifting of the alkyne stretch to lower energy (vide infra). There is a characteristic peak observed at 1618 cm^{-1} in form I, 1622 cm^{-1} in form II and 1616 cm^{-1} in form III, which also enables the polymorphs to be distinguished from one another.

The IR absorption spectra show several diagnostic regions (Figure 5). In form I there are a peaks at 1622 cm^{-1} and 1238 cm^{-1} , while the same peaks in forms I and II are observed at 1626 cm^{-1} and 1239 cm^{-1} and 1622 cm^{-1} and 1235 cm^{-1} respectively. Another diagnostic peak is around 820 cm^{-1} observed at 829 cm^{-1} in form I, 827 cm^{-1} in form II, and at 825 cm^{-1} in form III.

To elucidate the structural differences among el-ROY polymorphs, single crystal X-ray diffraction was performed on forms I and II (Table 1). In both cases the molecules possess intramolecular hydrogen bonds between the NH and NO_2 groups and molecules are in the anti-conformation; in form I this conformation is rigidly enforced by the presence of an inversion center (Figure 6). The torsion angle describing the twisting of the orientation of the amine relative to the thiophene ring in form I is 0.1 $^{\circ}$ and the angle between the planes defined by the thiophene and phenyl rings in form I is 3.3 $^{\circ}$. This indicates that this is the most planar conformation among the polymorphs of ROY and ROY derivatives. Previously the smallest torsion angle observed was that of the red form of 2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile at 4.0 $^{\circ}$. These angles in el-ROY are relatively small, leading to a molecule that is almost planar and possesses a high degree of conjugation consistent with the deep red color (Figure 3). The angle between the benzene rings connected by the triple bond is 1.0 $^{\circ}$ signaling the potential for extended delocalization. Stacks of molecules extend along the *b*-axis with molecules tilted at an angle of 56 $^{\circ}$ from normal. This slipped π -stacked

arrangement places thiophene rings over benzene rings and there are extensive close contacts. The distance between planes of adjacent molecules is approximately 3.3 Å. Adjacent columns are connected into sheets through nearly coplanar molecules by close CN $\cdots$ S interactions at 3.20 Å and CH $\cdots$ O $_2$ N contacts. Finally, sheets with two different molecular orientations come together in a herringbone fashion with edge-to-face contacts between thiophene rings.

In contrast to form I, form II does not have an inversion center present within the molecule. This gives rise to two different torsion angles for S-C-N-C of 9.1° and 4.1°. The angles between the planes defined by the thiophene and phenyl rings are 17.4° and 6.6° (Figure 7). The combination of these angles leads to a molecule that is significantly less planar than form I and this conformation impacts conjugation somewhat as evidenced by the orange color of the crystals (Figure 3). The angle between the benzene rings connected by the triple bond is 7.6°. In form II, the slipping of the infinite π -stacks takes place along both the short and long axes of the molecule and this diagonal displacement results in close contacts between chemically equivalent rings at approximately 3.3 Å. Columns are connected, in an analogous manner to form I, through close CN $\cdots$ S interactions at 3.22 Å and 3.27 Å and CH $\cdots$ O $_2$ N contacts. The methyl groups on the thiophene rings at the edges of these sheets are interdigitated with neighboring sheets resulting in the observed three-dimensional structure.

4. Conclusion

If, as these studies and previous studies on ROY derivatives suggest, privileged structures exist in the area of crystal polymorphism it must also be recognized that even compounds demonstrated to be highly polymorphic do not necessarily have polymorphic analogs. As an example from the present study, Br-ROY gave rise to only a single form despite screening hundreds of crystallization conditions. Expanded study is certainly desirable on analogs of highly polymorphic compounds to validate the concept of a polymorphophore and to illuminate which structural traits can be used to predict the crystallization behavior of new molecules, a key issue in drug development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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pentacene

copper phthalocyanine

Figure 1.
Examples of rigid molecules that exhibit abundant polymorphism.

Figure 2.
ROY and ROY derivatives. 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY, left), 5-methyl-2-[(4-methyl-2-nitrophenyl)amino]-3-thiophenecarbonitrile (center), and left 2-[(2-nitrophenyl)-amino]-3-thiophenecarbonitrile (right).

Figure 3.
Photomicrographs of form I (upper left), form II (upper right), and form III (bottom) of el-ROY.

Figure 4.
Raman spectra of el-ROY forms I, II, and III.

Figure 5.
IR spectra of el-ROY forms I, II, and III recorded in transmission mode.

Figure 6.

a) Top and side views of form I revealing an anti-configuration and a planar conformation b) view down the *a*-axis c) view down the *b*-axis

Figure 7.

a) Top and side views of form II showing the anticonfiguration and the non-planarity of the conformation b) view down the *a*-axis c) view showing the packing of the columns into sheets.

Scheme 1.

Synthetic scheme for el-ROY through the intermediate Br-ROY.

Table 1
X-Ray Crystallographic Data for Two el-ROY Polymorphs (C₂₆H₁₆N₆O₄S₂)

	form I	form II
Crystal System	monoclinic	triclinic
Space Group	C2/c	<i>P1</i>
Temperature (K)	123(2)	123(2)
a(Å)	15.327(2)	7.7327(12)
b(Å)	5.8949(9)	8.1178(13)
c(Å)	26.692(4)	21.309(3)
α(°)	90	95.762(4)
β(°)	92.763(4)	91.092(4)
γ(°)	90	117.525(4)
Cell Volume (Å³)	2408.8(6)	1177.0(3)
Calculated Density (g/cm³)	1.491	1.525
Z	4	2
Unique reflections	2722	3124
R (I>2σ(I))	0.0407	0.0650
R_w (I>2σ(I))	0.0870	0.1674