



The crystal packing of a strongly dipolar piperazinedione[†]

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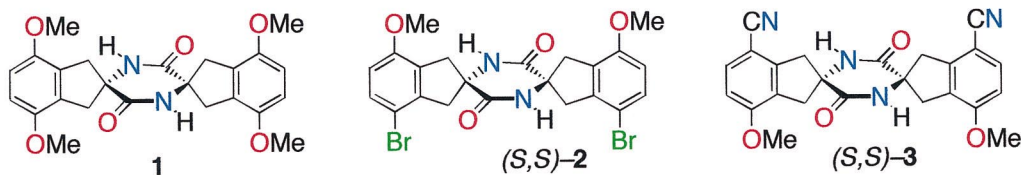
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Abstract

A strongly dipolar piperazine-2,5-dione was synthesized in enantiomerically pure form, crystallized from DMSO, and the supramolecular organization of the crystals determined by X-ray crystallography. In contrast with non-polar or weakly polar piperazinediones of similar molecular topography, which form tapes by reciprocal intermolecular amide-to-amide hydrogen bonding, the strongly dipolar piperazinedione participated in hydrogen bonding with occluded DMSO. The dipoles of the piperazinedione molecules were aligned and were opposed by the dipoles of the DMSO molecules. The cocrystals exhibited second harmonic generation when subjected to pulsed irradiation. © 2000 Elsevier Science Ltd. All rights reserved.

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A number of studies have provided insight into the relationship between molecular structure and crystal packing of organic molecules.¹ For instance, certain molecules have been shown to adopt identifiable packing motifs if they contain complementary atoms or functional groups. We postulated that order in three dimensions might be predictable for molecules that simultaneously participate in three independent packing interactions. In order to test this postulate we designed a class of molecules that could support three geometrically and chemically independent molecular recognition elements.² The core of our molecular scaffold is a piperazine-2,5-dione ring, a moiety known to favor formation of supramolecular tapes through reciprocal amide-to-amide hydrogen bonding.³ A number of non-polar and weakly polar molecules, including **1** and (*S,S*)-**2**, were synthesized and their crystal packing determined by X-ray crystallography.^{4,5}



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[†] Dedicated to Harry and Elga Wasserman on the occasion of Harry's 80th birthday.

The crystal packing of **1** and (*S,S*)-**2** were very similar and appeared insensitive to molecular dipoles.^{4b} In each case the expected one-dimensional tapes were established through reciprocal amide-to-amide hydrogen bonding (Fig. 1). Tape topography permitted edge-to-face arene interactions between molecules of neighboring tapes and resulted in two-dimensional grooved sheets. Tongue-in-groove stacking of the sheets produced three-dimensional solids. These results suggested that all piperazinediones topographically related to **1** and (*S,S*)-**2** might pack similarly and afforded a unique opportunity to study the effect of molecular dipoles on crystal packing. Herein we report the synthesis and characterization of piperazinedione (*S,S*)-**3**, which contains the *p*-methoxybenzotrile chromophore.⁶

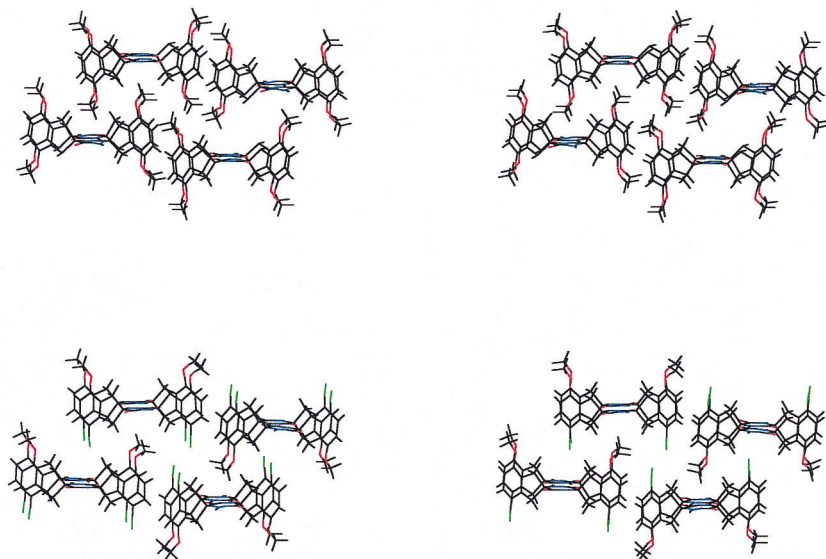
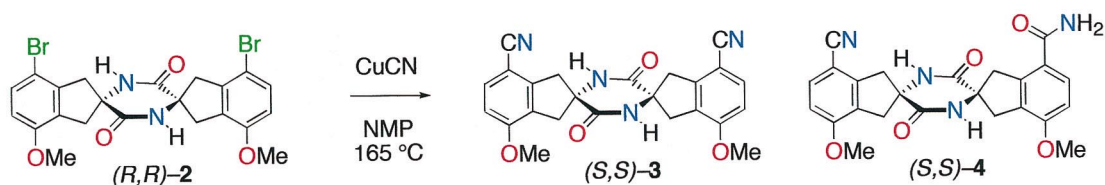


Figure 1. Stereoviews of 2×2×2 arrays from the crystal structures of **1** (top) and (*S,S*)-**2** (bottom)

Treatment of (*R,R*)-**2**⁷ with cuprous cyanide in 1-methyl-2-pyrrolidinone at 165°C for 10.5 hours gave (*S,S*)-**3** and (*S,S*)-**4** in 53 and 28% yields, respectively, after purification by column chromatography (Scheme 1).⁸ Crystallization of (*S,S*)-**3** from dimethylsulfoxide (DMSO) gave colorless irregular blocks suitable for X-ray diffraction analysis.⁹ The crystals so obtained were of the monoclinic space group *C*2. The asymmetric unit contained one molecule of (*S,S*)-**3** and three molecules of DMSO, one of which was disordered (Fig. 2).



Scheme 1. Synthesis of (*S,S*)-**3**

In the cocrystal, the piperazinedione ring of (*S,S*)-**3** adopts a shallow twist-boat conformation and the cyclopentene rings of the indane moiety are in an envelope conformation folded toward



Figure 2. Stereoview of the asymmetric unit from the crystal structure of (*S,S*)-3

the proximal nitrogen atom. The methoxy groups of (*S,S*)-3 are symmetrically rotated with respect to the plane of the arene ring to which they are attached. The ordered DMSO molecules hydrogen bond with the amide N–H groups and sit on the nitrile side of the piperazine-dione ring. The disordered DMSO molecule sits on the same side in a pocket above the piperazine-dione ring. Thus, a twofold rotational symmetry element exists in the crystal which is coincident with the two fold rotational symmetry axis of the molecule of (*S,S*)-3. Opposition of the dipoles due to the two *p*-methoxybenzotrile moieties and the three DMSO molecules is noteworthy.⁶

It can be seen in expanded stereoviews from the crystal structure that all dipoles due to (*S,S*)-3 are similarly oriented, all dipoles due to DMSO are similarly oriented, and these two groups of dipoles are opposed (Fig. 3, unit cells are outlined). These acentric cocrystals should possess second order non-linear optical properties. Both a microcrystalline powder sample of (*S,S*)-3 obtained by column chromatography and the cocrystals of (*S,S*)-3 with DMSO were subjected to the Kurtz and Perry powder test.¹⁰ Whereas the powder sample of (*S,S*)-3 gave no signal, the crystals containing DMSO exhibited a signal comparable to that of urea.

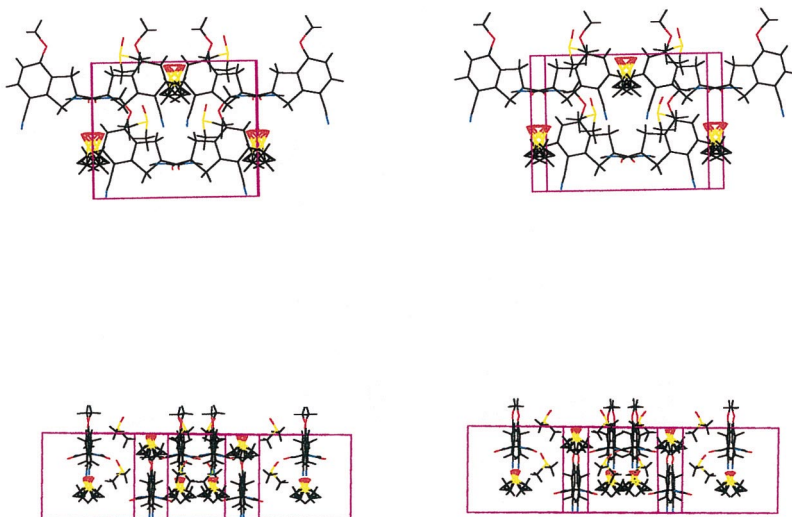


Figure 3. Stereoviews from the crystal structure of (*S,S*)-3

The molecular topography of (*S,S*)-3 should not preclude crystal packing similar to that observed for (*S,S*)-2. Such packing would result in opposition of the *p*-methoxybenzotrile dipoles on adjacent tapes engaged in edge-to-face arene interactions. However, crystals of (*S,S*)-3 free of DMSO suitable for single crystal diffractometry have not yet been obtained. It

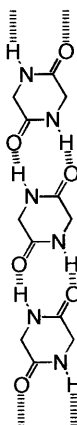
is possible that the need for compensation of the stronger dipole of the *p*-methoxybenzotrile moiety leads to kinetically controlled inclusion of DMSO.¹¹ Crystal growth under different conditions and additional work with piperazinediones bearing stronger dipoles is underway.

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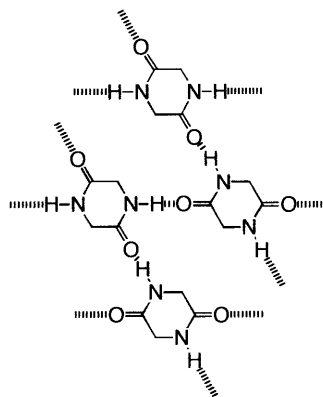
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- Many examples of 'ladder-like' tapes (*i*) have been reported. Less commonly observed are two-dimensional hydrogen bonded networks (*ii*). Tape structures involving piperazinedione side chains and occluded small molecules are also known. See: MacDonald, J. C.; Whitesides, G. M. *Chem. Rev.* **1994**, *94*, 2383–2420.



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- The molecular dipoles for (*S,S*)-**2** and (*S,S*)-**3**, calculated at the semi-empirical AM1 level using MacSpartan v1.1, were 3.25 and 8.77 D, respectively. The dipole calculated for DMSO was 3.90 D. The experimental value for DMSO is 3.96 D; see: Gordon, A. J.; Ford, R. A. *The Chemist's Companion: A Handbook of Practical Data, Techniques, and References*; John Wiley & Sons: New York, 1972; p. 7.
 - (*R,R*)-**2** was prepared as described for the synthesis of (*S,S*)-**2** in Ref. 4b.
 - All new compounds exhibited satisfactory spectroscopic and HRMS data.
 - Crystal data for the cocrystal of DMSO with (*S,S*)-**3**: C₃₀H₃₈N₄O₇S₃; *M*=662.82 g mol⁻¹, monoclinic *C*2, colorless irregular block measuring 0.05×0.15×0.22 mm, *T*=170(2) K, *a*=16.4321(11), *b*=10.3701(7), *c*=12.2684(8) Å, β=130.2420(10)°, *V*=1595.78(18) Å³, *Z*=2, *D*_c=1.379 Mg m⁻³, μ=0.285 mm⁻¹; *T*_{max}=1.000, *T*_{min}=0.936; GOF on *F*²=0.965; *R*₁=0.0406, *wR*₂=0.0836 for all 3692 independent observed reflections.
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