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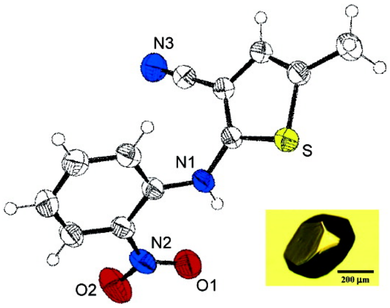

YT04

- The ninth polymorph of ROY
- The seventh crystal structure solved (new CSD record)
- The densest at 25°C
- The second most stable at 0K

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New Polymorphs of ROY and New Record for Coexisting Polymorphs of Solved Structures

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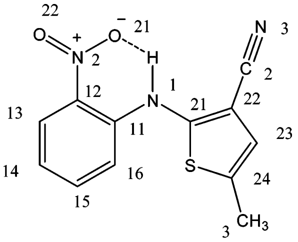
Abstract: With six polymorphs coexisting at room temperature, 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY) is the top system in the current Cambridge Structural Database (Feb. 2005) for the number of polymorphs of solved crystal structures. Here we report two new ROY polymorphs, Y04 and YT04, and the crystal structure of YT04. Y04 is a metastable polymorph that tends to crystallize first from a melt at room temperature, and YT04 is a product of solid-state transformation of Y04. Despite its late discovery, YT04 is the densest among the polymorphs at 25 °C and likely the second most stable at 0 K. The conformation of ROY in YT04 is similar to those in the other two yellow polymorphs (Y and YN) but significantly different from those in the orange and red colored polymorphs (ON, OP, ORP, and R). Having escaped years of solution crystallization in several laboratories, Y04 and YT04 exemplify polymorphs that are likely missed by solvent-based screening and discovered through alternative routes.

Introduction

5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile has been crystallized in seven polymorphs: yellow prisms (Y), red prisms (R), orange needles (ON), orange plates (OP), yellow needles (YN), orange-red plates (ORP), and red plates (RPL).[1,2] The system has been named ROY for its red, orange, and yellow crystal colors. The structures of the first six polymorphs, all crystallized from solution, have been solved,[1] which makes ROY the "most polymorphic" organic compound in the current Cambridge Structural Database (CSD).[3,4] The seventh polymorph (RPL) crystallized from vapor on succinic acid (010).[2]



ROY

A remarkable property of ROY is that many polymorphs are stable at room temperature to allow detailed studies at leisure. The red, orange, and yellow crystal colors of ROY arise from different molecular conformations in different polymorphs.[5]

Herein we report two new polymorphs of ROY, Y04 and YT04, and the crystal structure of YT04. We observed Y04 and YT04 during our studies of cross-polymorph nucleation[6] using ROY as a model system. Y04 was obtained from melt crystallization, and YT04, as a product of solid-state transformation from Y04. Despite this late discovery, YT04 is remarkably stable: it is the densest polymorph at room temperature and likely the second most stable at 0 K.

Polymorph screening is now recognized as an important step in the development of drugs and other specialty chemicals.[7,8] Solution crystallization is the method of choice today for polymorph screening. YT04, however, had escaped years of solution crystallization in several laboratories and was discovered through melt crystallization and solid-state conversion. In fact, none of the last three polymorphs of ROY were found through solution crystallization. This experience underscores the importance of alternative approaches to polymorph screening. With many polymorphs of known structures, systems such as ROY provide special opportunities to study the origin of polymorphism, structure−property relations, and the control of crystallization in polymorphic systems.

Experimental Section

ROY (as polymorphs Y and R) was a gift from Eli Lilly and Company. Raman microscopy was performed with a Renishaw System

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(1) Yu, L.; Stephenson, G. A.; Mitchell, C. A.; Bunnell, C. A.; Snorek, S. V.; Bowyer, J.; Borchardt, T. B.; Stowell, J. G.; Byrn, S. R. *J. Am. Chem. Soc.* **2000**, *122*, 585−591.
(2) Mitchell, C. A.; Yu, L.; Ward, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 10830−10839.
(3) Allen, F. H. *Acta Crystallogr.* **2002**, *B58*, 380−388. The Nov. 2004 Full Release (CSD V5.26) has 325 709 entries. The Feb. 2005 Intermediate Release has 12 736 entries. The total number of entries is now 338 445.
(4) In the current CSD, ROY (hexamorphic) is followed by one pentamorphic (sulphathiazole), 14 tetramorphic, and 102 trimorphic compounds. To obtain these statistics, we retrieved all entries containing the qualifier "polymorph", "form", "phase", or "modification", allowing for structures of one or more components determined at room or other temperatures, but excluding organometallic compounds and entries for which atomic coordinates are unavailable. The resulting 4717 hits were sorted by hand to yield all compounds with three or more polymorphs (see Supporting Information).
(5) Yu, L. *J. Phys. Chem. A* **2002**, *106*, 544−550.
(6) Yu, L. *J. Am. Chem. Soc.* **2003**, *125*, 6380−6381.
(7) Byrn, S. R.; Pfeiffer, R. R.; Stowell, J. G. *Solid State Chemistry of Drugs*, 2nd ed.; SSCI Inc.: West Lafayette, IN, 1999.
(8) Bernstein, J. *Polymorphism in Molecular Crystals;* Oxford University Press: New York, 2002.

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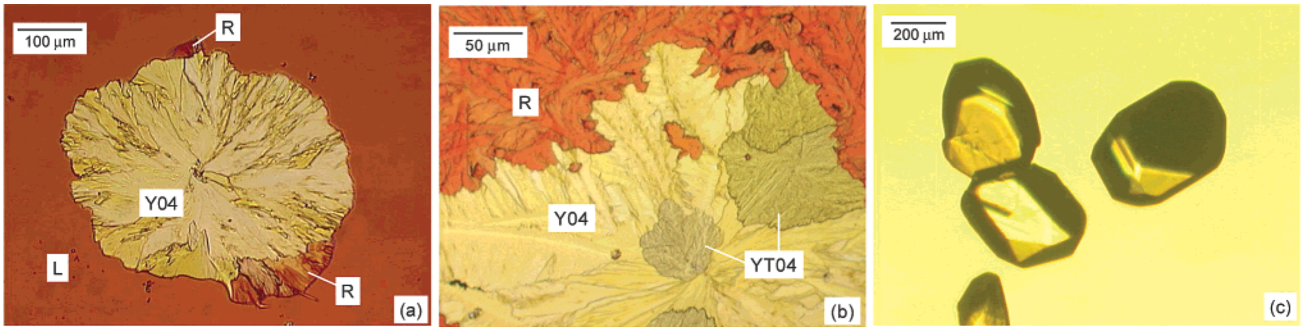

Figure 1. (a) ROY liquid crystallized first as Y04 and then as R, with R nucleating on Y04. (b) Y04 is metastable and converted to YT04. (c) Single crystals of YT04 obtained by seeding a supersaturated solution.

1000 Micro-Raman spectrometer equipped with a HeNe laser and peltier-cooled CCD detector. With a 50× objective, it offered a spatial resolution of 0.5 μm. Hot-stage microscopy was performed with a Linkam THMS 600 hot-stage and a Nikon Optiphot2-Pol light microscope. Powder X-ray diffraction was performed with a Bruker D8 Advance diffractometer (Cu Kα radiation, voltage 40 kV, and current 40 mA). Approximately 5 mg of ground powders was sprinkled on the surface of a zero-background silicon (510) sample holder and scanned from 2° to 50° 2θ at a speed of 1.2° 2θ/min and a step size of 0.02° 2θ.

Differential scanning calorimetry (DSC) was conducted in crimped aluminum pans using a TA Instruments Q1000 unit under 50 mL/min N_2 purge. From the melting data of two polymorphs, i and j, the free energy and entropy differences were calculated by[9]

$$(G_j - G_i)_{T_{mi}} = \Delta H_{mj}(T_{mi} - T_{mj})/T_{mj} + \Delta C_{pmj}[T_{mj} - T_{mi} - T_{mi}\ln(T_{mj}/T_{mi})] \quad (1)$$

$$(S_j - S_i)_{T_{mi}} = \Delta H_{mi}/T_{mi} - \Delta H_{mj}/T_{mj} + \Delta C_{pmj}\ln(T_{mj}/T_{mi}) \quad (2)$$

where T_{mi} and T_{mj} are the melting points of i and j, ΔH_{mi} and ΔH_{mj} are their enthalpies of melting, and ΔC_{pmj} is the heat capacity change upon melting j (estimated from the baseline shift across melting endotherms). The subscript $_{T_{mi}}$ signifies that $(G_j - G_i)$ and $(S_j - S_i)$ are evaluated at T_{mi}. Equations 1 and 2 thus provide the segment of the $(G_j - G_i)$ vs T curve at T_{mi}: eq 1 the value and eq 2 the temperature slope $[d(G_j - G_i)/dT = -(S_j - S_i)]$. Eutectic melting with common additives (acetanilide, benzil, azobenzene, and thymol)[10] were used to calculate $(G_j - G_i)$ at lower, eutectic melting temperatures:[1]

$$x_{ej}(G_j - G_i)_{T_{ei}} = \Delta H_{mej}(T_{ei} - T_{ej})/T_{ej} - \Delta C_{pej}[T_{ei} - T_{ej} - T_{ei}\ln(T_{ei}/T_{ej})] + RT_{ei}\{x_{ej}\ln(x_{ej}/x_{ei}) + (1 - x_{ej})\ln[(1 - x_{ej})/(1 - x_{ei})]\} \quad (3)$$

where T_{ei} and T_{ej} are the eutectic melting points of i and j with a common additive, x_{ei} and x_{ej} are the eutectic compositions, ΔH_{mei} and ΔH_{mej} are enthalpies of eutectic melting, ΔC_{pej} is the heat capacity change upon melting the eutectic of j and the additive, and R is the ideal gas constant. The subscript $_{T_{ei}}$ signifies that $(G_j - G_i)$ is evaluated at T_{ei}. By symmetry, $(G_j - G_i)$ at T_{ej} is given by eq 3 upon exchanging i and j. The additives were obtained from Aldrich and used as received.

Single-crystal diffraction was performed with a Bruker CCD-1000 diffractometer with Mo Kα radiation (λ = 0.710 73 Å) and the diffractometer to a crystal distance of 4.9 cm. The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 20 frames collected at intervals of 0.3° in a 6° range about ω with the exposure time of 10 s per frame. A total of 51 reflections was obtained. The reflections were successfully indexed by an automated indexing routine built in the SMART program. The final cell constants were calculated from a set of 3287 strong reflections from the actual data collection. The data were collected by using the hemisphere data collection routine. The reciprocal space was surveyed to the extent of a full sphere to a resolution of 0.80 Å. A total of 5068 data were harvested by collecting three sets of frames with 0.25° scans in ω with an exposure time 30 s per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements.[11] The systematic absences in the diffraction data were uniquely consistent for the space group $P2_1/n$ that yielded chemically reasonable and computationally stable results of refinement.[11] A successful solution by the direct methods provided most non-hydrogen atoms from the E-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. The final least-squares refinement of 164 parameters was performed with 2312 reflections. The final difference Fourier map was featureless.

Results and Discussion

Discovery of Y04 and YT04. We observed Y04 and YT04 unexpectedly during our studies of cross-polymorph nucleation[6] using ROY as a model system. We melted ROY between two cover glasses at 130 °C and cooled the sample to 22 °C. The liquid began crystallizing after ca. 30 min, and the first phase to appear tended to be yellow crystals (Figure 1a). The yellow crystals showed a distinct Raman spectrum and a morphology different from those of YN and Y, two known yellow-colored polymorphs (at 22 °C YN is fine-grained spherulite and Y is opaque clusters of small crystals). On heating, the yellow crystals in Figure 1a often converted to polymorph R (confirmed by Raman microscopy and melting point). This ruled out the yellow crystals being polymorph Y, which melts at 109.8 °C without solid−solid transformation. Together, the evidence indicates that the yellow crystals that crystallized first from a 22 °C melt were a new polymorph of ROY. We named this polymorph Y04 (yellow, discovered in 2004).

Y04 never grew to consume the entire liquid. Instead, red crystals of polymorph R nucleated on Y04 (Figure 1a) and grew faster to encircle Y04. Y04, meanwhile, was observed to transform to another yellow crystal, of duller color (Figure 1b). The new yellow crystal had a distinct Raman spectrum and melting point (106.9 °C). We concluded that the transformed

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[9] Yu, L. *J. Pharm. Sci.* **1995**, *84*, 966−974.

[10] McCrone, W. C. *Fusion Methods in Chemical Microscopy*; Interscience Publishers: New York, 1957.

[11] Bruker-AXS. SADABS V.2.05, SAINT V.6.22, SHELXTL V.6.10 & SMART 5.622 Software Reference Manuals. Bruker-AXS: Madison, Wisconsin, USA, 2000−2003.

Table 1. Crystal Structure of YT04 (Other Polymorphs Included for Comparison)[a]

form	YT04[b]	Y	ON	OP	R	YN	ORP
crystal system	monoclinic	monoclinic	monoclinic	monoclinic	triclinic	triclinic	orthorhombic
space group [no.]	$P2_1/n$ [14]	$P2_1/n$ [14]	$P2_1/c$ [14]	$P2_1/n$ [14]	$P\bar{1}$ [2]	$P\bar{1}$ [2]	*Pbca* [61]
description	yellow prism	yellow prism	orange needle	orange plate	red prism	yellow needle	orange-red plate
crystal size	0.45 × 0.31 × 0.26	0.49 × 0.47 × 0.25	0.30 × 0.15 × 0.08	0.27 × 0.22 × 0.13	0.25 × 0.13 × 0.10	0.04 × 0.075 × 0.5	0.1 × 0.2 × 0.3
a, Å	8.2324(4)	8.5001	3.9453	7.9760	7.4918	4.5918	13.177
b, Å	11.8173(5)	16.413	18.685	13.319	7.7902	11.249	8.0209
c, Å	12.3121(6)	8.5371	16.3948	11.676	11.9110	12.315	22.801
α, deg	90	90	90	90	75.494	71.194	90
β, deg	102.505(1)	91.767	93.830	104.683	77.806	89.852	90
γ, deg	90	90	90	90	63.617	88.174	90
volume, Å^3	1169.36(9)	1190.5	1205.9	1199.9	598.88	601.85	2409.8
Z	4	4	4	4	2	2	8
D_{calcd}, g cm^{-3}	1.473	1.447	1.428	1.435	1.438	1.431	1.429
T, K	296	293	293	295	293	296	296

[a] Empirical formula: $C_{12}H_9N_3O_2S$. MW: 259.29. Error in the last digit is given in parentheses. [b] $R = 0.0387$, $wR = 0.1086$, GOF = 1.069.

Y04 is a new, thermally stable polymorph of ROY and named it YT04 (Y04 transformed).

We next attempted to grow single crystals of YT04 by seeding a saturated solution. To prepare seeds of YT04, we redid the melt crystallization at 4 °C, which gave YT04 at a higher yield. We isolated YT04 seeds under a microscope with a tungsten needle. We used the following procedure to prepare a saturated solution devoid of crystal nuclei: dissolve 68 mg of ROY in 5 mL of hot EtOH, filter the solution through a pipet filter, reheat the solution with a heat gun, add 1 mL of EtOH to rinse down and redissolve crystals that might have formed during heating, and cool the solution to room temperature. The solution was seeded, covered with an aluminum foil with ventilation holes, and stored undisturbed. After ca. 19 h, yellow, prismlike single crystals appeared (Figure 1c). They were confirmed to be YT04 by Raman spectroscopy and melting point.

Crystal Structure of YT04. We solved the crystal structure of YT04 and give its crystallographic parameters in Table 1, along with those of other ROY polymorphs. An interesting property of YT04 is its higher density than the previous six polymorphs. This is unexpected in view of its late discovery and even suggests, according to the Density Rule,[12] that YT04 is the most thermodynamically stable polymorph at 0 K (see later). The molecule in YT04 adopts a conformation similar to those in Y and YN but significantly different from those in the other polymorphs. The torsion angle of C11−N1−C21−S (θ_{thio}) of YT04 (112.8°) is similar to those of Y (104.7°) and YN (104.1°) but significantly larger than those of the other polymorphs (ON, 52.6°; OP, 46.1°; ORP, 39.4°; R, 21.7°).[1] This is consistent with the yellow color of YT04, YN, and Y and the red or orange colors of the other polymorphs.[5]

As in the previous six polymorphs, an intramolecular hydrogen bond exists between the amino and nitro groups in each molecule in YT04. Similar to Y, but unlike other polymorphs, YT04 crystals contain weak intermolecular hydrogen bonds between the cyano group of one molecule and the amino group of another [$d(\mathrm{CN\cdots H}) = 2.52$ Å, $d(\mathrm{N\cdots N}) = 3.24$ Å, and $\angle(\mathrm{N-H\cdots N}) = 141°$]. The corresponding parameters for Y are $d(\mathrm{CN\cdots H}) = 2.42$ Å, $d(\mathrm{N\cdots N}) = 3.13$ Å, and $\angle(\mathrm{N-H\cdots N}) = 140°$.[1] The intermolecular hydrogen bonds in YT04 are thus deemed slightly weaker than those in Y.

Relative Stability of Polymorphs. The highest density of YT04 raises the question of whether the new polymorph is in fact the most stable at 0 K. To answer this question, we relied on melting[9] and eutectic melting[1] data and solvent-mediated polymorphic conversion. We compared the thermodynamic stability of YT04 to Y, which is the most stable polymorph at low temperature among the previous polymorphs. Figure 2a and Table 2 show the melting and eutectic melting data of YT04 referenced to those of Y. The resulting free energy−temperature diagram is shown in Figure 2b, along with results of other polymorphs.[1] As described in ref 1, the line for YN was constructed from two data points obtained from eutectic melting with thymol and the slope of the line obtained from the enthalpy of transformation from YN to Y. The YN line cuts the liquid line at 99 °C, which corresponds to YN's melting point. We could not confirm YN's melting point in the work reported in ref 1 because of rapid transformation of YN to R, but we subsequently confirmed it with (presumably more perfect) crystals of YN grown on pimelic acid (101).[2] We have added the melting point of YN in Figure 2b.

Figure 2b shows that within the temperature range of measurement, YT04 is less stable (higher G) than Y, ON, and OP but more stable (lower G) than R and YN. The free-energy difference between YT04 and Y is approximately constant and increases slowly with decreasing temperature. Thus, it seems unlikely that their free-energy curves cross with decreasing temperature such that YT04 becomes more stable than Y at 0 K. But the YT04 curve should cross the ON and OP curves at lower temperatures (24 °C and 9 °C, respectively). This suggests that the relations between YT04 and ON and between YT04 and OP are enantiotropic; that is, YT04 is less stable than ON and OP at high temperature but more stable than ON and OP at low temperature. The relations between YT04 and R and between YT04 and YN are monotropic, with YT04 being more stable than R and YN at any temperature. The free energy curves of ORP, RPL, and Y04 have not been measured because the polymorph is unstable to heating (Y04) or because insufficient material is available for analysis (ORP and RPL). Observations of polymorphic conversions suggest Y04, ORP, and RPL are significantly less stable than YT04. Thus, YT04 is likely the second-most stable polymorph at 0 K (only to Y).

To gain more confidence in the monotropic relation between YT04 and Y suggested by Figure 2b, we performed direct

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(12) Burger, A.; Ramberger, R. *Mikrochimica Acta [Wien]* **1979 II**, 259−271 and 273−316.

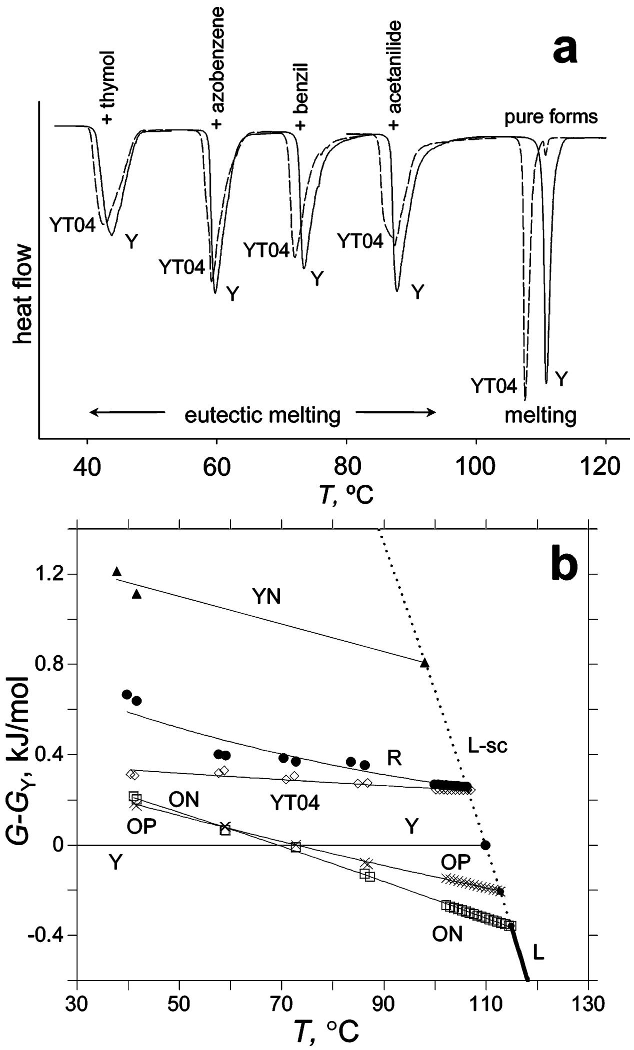

Figure 2. (a) Melting and eutectic melting data of YT04 and Y. (b) Free-energy difference between ROY polymorphs. Each line represents the free energy of a polymorph relative to Y (i.e., $G - G_Y$).

experiments of solvent-mediated conversion. Slurries of YT04 and Y (1:1) in EtOAc or EtOAc/hexanes (1:3) were stirred and analyzed after time intervals for polymorphic changes by Raman microscopy or powder X-ray diffraction. We found that, at 4 °C and −78 °C, YT04 converted to Y (see Figure 3 for −78 °C results). These results are consistent with Figure 2b. It is likely that YT04 and Y are related monotropically, with Y being more stable at any temperature.

The temperature slope of $G_{YT04} - G_Y$ yields the entropy difference $S_{YT04} - S_Y = 2.0$ J/K/mol. This is to be compared with the $S - S_Y$ value for other polymorphs (in J/K/mol): 7.7 (ON), 5.3 (OP), and 3.0 (R).[1] The slope of the $(G_{YT04} - G_Y)/T$ vs $1/T$ plot yields the enthalpy difference $H_{YT04} - H_Y = 0.9$ kJ/mol. This is to be compared with the $H - H_Y$ value for other polymorphs (in kJ/mol): 2.6 (ON), 1.9 (OP), 1.4 (R), and 3.0 (YN).[1] The enthalpy of YT04 is thus the second lowest (only to Y). This suggests that YT04 is the second most stable at 0 K.

Table 2. Melting and Eutectic Melting Data[a]

form	YT04	Y
	Melting	
T_m, °C	106.9	109.8
ΔH_m, kJ/mol	26.6	27.2
	Eutectic Melting	
	with acetanilide	
x_e	0.48	0.47
T_e, °C	84.42	86.28
ΔH_{me}, kJ/mol	23.3	23.2
	with benzil	
x_e	0.38	0.38
T_e, °C	71.11	72.72
ΔH_{me}, kJ/mol	23.9	22.7
	with azobenzene	
x_e	0.22	0.22
T_e, °C	58.07	59.09
ΔH_{me}, kJ/mol	22.6	21.8
	with thymol	
x_e	0.15	0.15
T_e, °C	40.83	41.64
ΔH_{me}, kJ/mol	17.4	17.6

[a] The second decimal place of T_e has been included to preserve the precision of the *differences* between eutectic temperatures, which was approximately ±0.03 °C, even though the *accuracy* of these temperatures, limited by indium calibration, was ±0.1 °C.

Correlation between Crystal and Conformational Energies. The different conformations of ROY in different polymorphs provide an opportunity to probe how crystal environment affects molecular conformation and how the choice of different conformers as building units affects crystal stability. The analysis has been performed for five polymorphs (Y, R, ON, OP, and YN),[1] and Figure 4 updates this analysis for YT04. The lower part of Figure 4a shows how the conformational energies of ROY differ among polymorphs in reference to the gas-phase potential energy curve along θ_{thio}. As in ref 1, we obtained the conformational energy of ROY in YT04 at the RHF/6-31G* level[13] by geometry optimization with θ_{thio}, θ_{phen}, and θ_{nitro} (and thus the conformation of ROY) fixed at the crystal values.[14] The YT04 point (No. 7) is near the Y and YN points

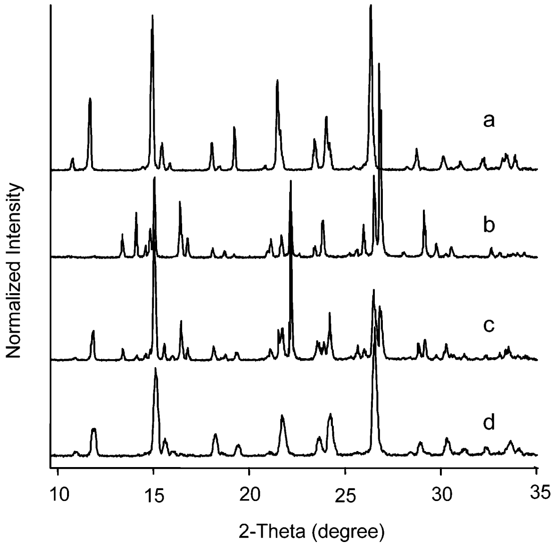

Figure 3. Slurry experiment to determine the relative stability of YT04 and Y at −78 °C. Shown are X-ray powder diffraction patterns of Y (a), YT04 (b), and Y−YT04 mixture (1:1 w/w) before (c) and after (d) solvent-mediated conversion. Solvent was ethyl acetate. Conversion time was 14 h.

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(13) Spartan 02 (Wavefunction, Inc., 18401 Van Karman Ave., #370, Irvine, CA 92612, USA).

(14) As explained in ref 1, the residual errors in crystallographic determination of atomic coordinates can cause anomalously high single-point energies. It is reasonable to relax not only hydrogen positions but also heavy atom positions while fixing the conformation of the molecule.

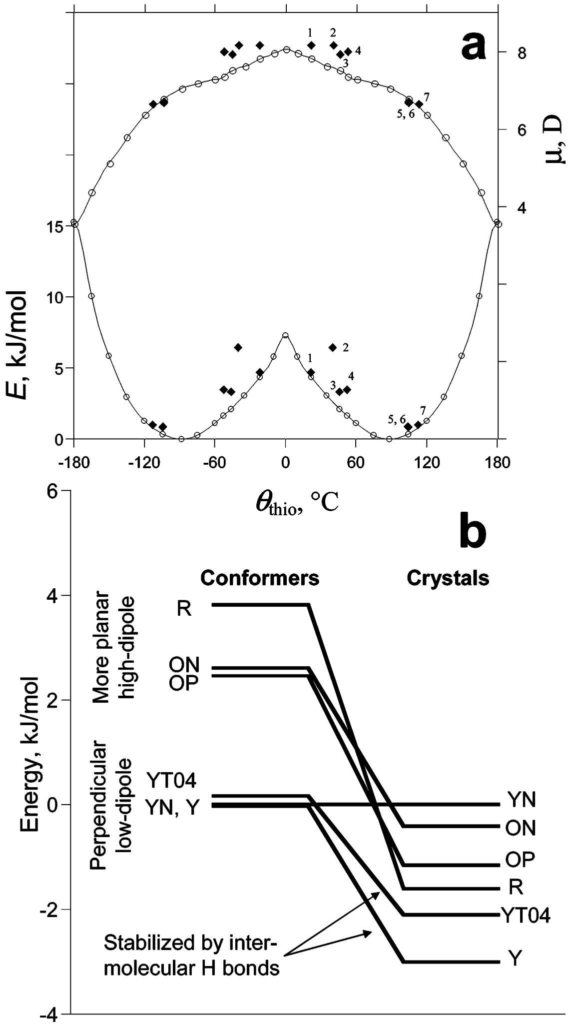

Figure 4. (a) Conformational energies E and dipole moments μ of crystal conformers. 1-R, 2-ORP, 3-OP, 4-ON, 5-Y, 6-YN, 7-YT04. (b) Correlation between conformational and crystal energies.

(No. 5 and 6) and the potential energy minima. The upper part of Figure 4a shows how the molecular dipole moments differ among polymorphs in reference to the molecular dipole moment in the gas phase as a function of θ_{thio}. Again, the YT04 point (No. 7) is near the Y and YN points (No. 5 and 6). The molecules in these polymorphs have lower conformational energies and lower dipoles than the molecules in the other polymorphs.

Figure 4b shows how the conformational energy of ROY correlates with its crystal energy. Here the crystal energies are taken to be their enthalpies referenced to the enthalpy of YN[15] and the conformational energies are taken to be those from ab initio calculations (Figure 4a). The correlation between crystal and molecular energies shows that lower-energy crystals can be built from higher-energy, higher-dipole conformers (see the lines connecting ON, OP, and R). This effect may arise from favorable packing geometry of more planar conformers and greater electrostatic interactions between larger dipoles. In ref 1, we identified Y as an outlier from this trend and attributed it to the intermolecular hydrogen bonds present in Y, but not in other polymorphs. Our new data show that polymorph YT04 also deviates from the trend. This deviation may also result from intermolecular hydrogen bonds, which exist in YT04 but seem weaker than those in Y according to the hydrogen bond distances given above.

Concluding Remarks

We have discovered two new polymorphs of ROY (Y04 and YT04) through careful observation of melt crystallization and solid-state transformation. Single crystals of YT04 were obtained by seeding a supersaturated solution with seeds harvested from solidified melt. Despite its late discovery, YT04 has the highest density at 25 °C among all known polymorphs and is likely the second-most stable at 0 K. The discovery of YT04 sets a new record (seven) for the number of coexisting polymorphs for which crystal structures have been solved and affords new opportunities for studying structure−property relations and crystallization in polymorphic systems.

It is questionable that we have found all the polymorphs of ROY. Laboratory experiments such as ours identify polymorphs stable enough to be isolated and characterized. Less stable forms, of which there could be many, may escape our experiments and are obtained only under special conditions or with special care. It is even doubtful that we have found all *stable* polymorphs of ROY (say, within 1 kcal/mol of free energy). That the ninth polymorph of ROY (YT04) is probably the second-most stable at 0 K is a reminder that even well studied systems may have low-energy polymorphs yet to be discovered.

The two new polymorphs of ROY had escaped years of solution crystallization and were observed through melt crystallization and solid-state transformation. This way of discovering polymorphs was mastered by chemical microscopists[10,16] and today can be augmented by Raman microscopy. This approach complements solution crystallization, the method of choice today for polymorph screening, as do other approaches involving solvent-free synthesis,[17] drying of solvated crystals,[18] and nucleation templates.[2,19]

Acknowledgment. We thank University of Wisconsin - Madison for supporting this work.

Supporting Information Available: Crystallographic data, results of Cambridge Structural Database search on crystal polymorphs, and results of ab initio calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) At 1 atm, the difference between ΔH and ΔE, the enthalpy and energy differences between polymorphs, is negligible for ROY polymorphs. This is seen from $\Delta H = \Delta E + P\Delta V$, where $P = 1\text{atm}$ and ΔV is the difference in molar volumes between two polymorphs. At room temperature, the $P\Delta V$ term for the polymorphic pair of YT04 (most dense) and ON (least dense) is $(1\ \text{atm})(1/d_{\text{ON}} - 1/d_{\text{YT04}})$ (259.29 g/mol) = 0.56 J/mol, which is much smaller than the ΔH values (at least several hundred J per mol).

(16) Kuhnert-Brandstätter, M. *Thermomicroscopy in the Analysis of Pharmaceuticals;* Pergamon: New York, 1971.

(17) Cheung, E. Y.; Kitchin, S. J.; Harris, K. D. M.; Imai, Y.; Tajima, N.; Kuroda, R. *J. Am. Chem. Soc.* **2003**, *125*, 14658−14659.

(18) Burger, A.; Griesser, U. J. *Eur. J. Pharm. Biopharm.* **1991**, *37*, 118−124.

(19) Lang, M.; Grzesiak, A. L.; Matzger, A. J. *J. Am. Chem. Soc.* **2002**, *124*, 14834−14835.