Crystal polymorphs and transformations of 2-iodo-4-nitroaniline

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ABSTRACT Full crystal structural characterization of three crystal polymorphs of 2-iodo-4-nitroaniline was carried out: the triclinic, orthorhombic and a new monoclinic form. PXRD, DSC and IR data on the three of these are reported. Solvent-mediated transformations were observed on the basis of changes in crystal morphology and data from an *in situ* laser probe. Transformation to the monoclinic form was observed in all cases.

KEYWORDS Crystal polymorphism, solution-mediated transformations, 2-iodo-4-nitroaniline.

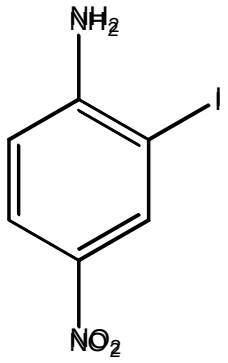
Introduction

Polymorphism is the ability of a molecule to adopt more than one crystal structure. When more than one polymorphic form is simultaneously obtained from the same growth solution, these are referred to as concomitant polymorphs.[1] Crystalline polymorphs have the same chemical composition but different internal crystal structures and this can give rise to different physicochemical properties including variations in melting points, solubility, bioavailability, colour and density to name a few.[2, 3] Previous

studies on the title compound, 2-iodo-4-nitroaniline (**1**), have reported the existence of two polymorphic forms based on single-crystal structure analysis. These forms are the triclinic ($P\bar{1}$) and the orthorhombic (*Pbca*) phases, grown concomitantly from saturated room temperature ethanolic solutions.[4, 5] We have been unable to find any literature on the crystal forms of compound (**1**) which precede these single-crystal studies.

Appearance of polymorphs often adds to the operating complexity of manufacturing scale crystallizations. Metastable polymorphs may initially appear which transform during the crystallization process to more stable polymorphs[6]. Such processes may often, but not always, follow Ostwald's rule of stages, i.e. with the most accessible highest energy form first appearing, followed by the next highest and so on[7]. Polymorphic transformations are challenging for industrial crystallizations, in which consistent product quality is required. In some cases process analytical technologies such as the use of *in situ* laser probes and microscopy techniques can allow these transformations to be observed and controlled[8].

2-Iodo-4-nitroaniline is a polymorphic compound which can be prepared from 4-nitroaniline by iodination. As it forms concomitant polymorphs, reliable preparation of polymorphically pure material on a larger scale is challenging, and would be a suitable test case for the application of process analytical technology. In this study, we have reexamined the crystal polymorphism of 2-iodo-4-nitroaniline, and have examined the transformation of polymorphs in scales of up to 500 mL of solvent.



(**1**)

Experimental Procedures

Materials and Physical Measurements. All chemicals purchased were of reagent grade and were used without further purification. Materials used were purchased from Sigma-Aldrich. Water used in the reactions was distilled water. Infra-red spectra were recorded on a Perkin-Elmer 1000 spectrometer in the range of 4000 to 500 cm^{-1}. All melting points were recorded on a Vickers Microscope model M14/2 and are uncorrected. ^1H NMR spectra were recorded on a Bruker Avance 300 spectrometer at 300MHz. Thermal analysis was recorded on a DSC Q1000 instrument. Crystal habits were observed using a Nikon ECLIPSE 50i POL Polarizing Microscope. Crystal pictures were obtained using a Nikon COOLPIX 8400 digital camera with 8.0 effective megapixels. Powder X-ray diffraction (PXRD) was performed at ambient temperature using a Stoe Stadi MP PXRD operating in reflectance mode with a linear PSD detector with an anode current of 40 mA, an accelerating voltage of 40 kV and Cu $K\alpha_1$ X-radiation (λ = 1.5406 Å) over a scan range of 3.5° to 60° 2θ, scanning in steps of 2° for 90 s per step. Samples were placed on a flat holder and were ground. Calculated patterns were generated from crystallographic information files downloaded from the Cambridge Structural Database, using the THEO function on the Stoe $WinX^{POW}$ software with a pseudo-Voigt profile-shape function and a Gauss component of 0.8 (and from single crystal analysis using our own machine to solve the crystal structure).

Preparation of 2-Iodo-4-nitroaniline (1)[9]. A solution of 4-nitroaniline (1.28g, 9.26mmol), potassium iodide (1.03g, 6.22mmol) and potassium iodate (0.66g, 3.08mmol) was prepared in methanol (5ml) and water (30ml). The mixture was treated at room temperature with conc. hydrochloric acid (3ml) over 40-45 mins and stirred for an additional 2-3 hrs. It was then diluted with water (50ml) which caused the product to precipitate out of solution as a yellow solid. This was collected by suction filtration and dried to afford a yellow solid: 1.94g (88% yield); mp 116-118°C; ν_{max}(KBr/cm^{-1}) 3480, 3452, 3378, 3346, 1612, 1580, 1475, 1300, 1263, 1156, 1114, 1018. ^1H NMR ($CDCl_3$): δ 8.57 (d J = 2.5Hz, 1H, Ar-H), 8.06 (dd J = 2.5Hz, J = 9Hz, 1H, Ar-H), 6.70 (d J = 9Hz, 1H, Ar-H), 4.84 (br s, 2H, $-NH_2$). Use of ethanol (30ml) as the solvent in place of the water:methanol mixture prevented the product from precipitating out of solution following addition of the 50 ml deionised water. On completion of the reaction and addition of 50 ml of deionised water the reaction mixture was washed with dichloromethane (1 x 50ml). The aqueous ethanolic layer was separated and allowed to sit at 10°C overnight. The resulting crystalline material was collected by filtration and dried under vacuum. For large scale crystallisations from solution, a 1L HEL AutoLab jacketed crystalliser was used. The system was equipped with a HEL $LaserTRACK^{TM}$ probe and a temperature sensor inside the vessel. The glass vessel had a jacketed wall attached to a Huber Unistat 851 unit capable of controlling the temperature of the circulator oil allowing for efficient control of heating and cooling.

Preparation of the triclinic form (1a) Crystals of the triclinic polymorph were prepared by completely melting about 5 mg of 2-iodo-4-nitroaniline powder (which may be either commercial material or recrystallized by one of the procedures described below) on a microscopic slide, at 150°C, using a temperature controlled hot-stage microscope (Vickers Microscope model M14/2). The slide was then rapidly cooled by placing it on a cold aluminium surface and covered with a petri dish to avoid contamination. The sample was allowed to sit for 30 mins to allow for complete crystallisation and following this DSC analysis was performed on a small portion of the crystallised melt (3mg) to ensure the existence of the pure triclinic form. The remaining crystalline material on the slide was kept in a desiccator over phosphorous pentoxide until required for PXRD analysis and further reaction. This procedure was repeated several times in order to collect a sufficiently large enough sample for PXRD analysis. A comparison of the theoretical and experimental PXRD patterns showed the crystalline material obtained from the melt to be the triclinic polymorph. Larger quantities (ca. 500 mg) of the

triclinic form could be obtained by recrystallization from ethanol using triclinic seeds. Polymorphic purity was again confirmed by PXRD.

Preparation of the orthorhombic form (1b) One batch of predominantly orthorhombic crystals was obtained by the preparation of 2-iodo-4-nitroaniline described above using ethanol as reaction solvent. Other batches obtained by this method gave either mixtures of either two or all three forms.

Preparation of the monoclinic form (1c) In our experience, the monoclinic form is that obtained by recrystallization of pure 2-iodo-4-nitroaniline from solvents, for example from ethanol. 2-Iodo-4-nitroaniline was obtained commercially (Sigma-Aldrich) and was found to be of the monoclinic form.

Crystallisations from solution were carried out on a small scale using 50 ml conical flasks and a temperature controlled heater. Varying concentrations of 30-100 g/L of commercial 2-iodo-4-nitroaniline in organic solvents (abs. ethanol, toluene, water:methanol 1:1, methanol, THF and ethyl acetate) were heated to refluxing temperature and allowed to cool slowly to room temperature. The crystallised material was collected by filtration and dried under vacuum. Hot filtration was carried out before cooling in instances where any undissolved material remained in the refluxing solutions.

Crystal structure determination X-ray diffraction measurements were made on a Bruker APEX II DUO diffractometer using graphite monochromatised MoKα radiation (λ = 0.71073 Å) and cooled with an Oxford Cryosystems COBRA fitted with a N_2 generator. All calculations were made using the APEX2 software[10, 11] and the diagrams prepared using Mercury.[12] CCDC numbers are 763634 – 763636 for the triclinic, monoclinic and orthorhombic forms respectively. Suitable crystals of each of the three forms were selected from batches for the three forms.

Solvent mediated transformations A 0.5g amount of the triclinic polymorph was stirred in 5ml of hexane at 25°C in a 10ml round bottom flask for 24h. A 5g amount of orthorhombic 2-iodo-4-nitroaniline was stirred in 500ml of hexane at 25°C for 24h using the HEL AutoLab 1litre crystalliser and HEL LaserTRACK^{TM} probe to monitor any changes in crystal size distribution as a possible indication of a solvent mediated transformation. Following this a similar process was carried out using a 10g amount of a mixture of all three polymorphic forms, monoclinic, triclinic and orthorhombic, using identical conditions but using toluene as the solvent.

Results and Discussion

2-Iodo-4-nitroaniline (**1**) was obtained commercially and was also prepared by iodination of 4-nitroaniline[9] using potassium iodide / potassium iodate / hydrochloride acid mixtures. Compound **1** was obtained by watering out when aqueous methanol was used as the solvent system. However, when ethanol was used as solvent, addition of further water did not result in precipitation. Following a dichloromethane wash, the product crystallized upon cooling to 10 ºC and several hours standing. When aqueous methanol was used as the solvent system only the monoclinic polymorph was produced. When ethanol was used as the solvent system this resulted in the production of mixtures of polymorphs in

combinations of either two or three different forms of those reported in this paper and in one instance it resulted in a batch of exclusively orthorhombic crystals.

To clarify the crystal polymorphism of 2-iodo-4-nitroaniline, we recrystallized samples from the following solvents: absolute ethanol, toluene, water / methanol (1:1), methanol, THF and ethyl acetate; and analyzed the resulting materials by IR, DSC and PXRD. In addition, we carried out full structure analysis on all crystal polymorphs obtained. The crystallographic data obtained is summarized in Table 1, which shows that in addition to the known triclinic [CSD reference code YEJLII01][4] and orthorhombic [CSD reference code YEJLII][4] forms, we also observed a separate monoclinic polymorph. The Niggli values for the three forms are (i) 50.42, 62.67, 64.39, 23.48, 2.89, 22.75 (ii) 56.87, 167.98, 242.68, 0.00, -8.95, 0.00 and (iii) 55.40, 160.07, 273.71, 0.00, 0.0, 0.00 for the triclinic, monoclinic and orthorhombic forms respectively, making it unlikely that the monoclinic structure is a twin or an incorrectly solved version of the orthorhombic form rather than a true polymorph. Experimental PXRD patterns of the three forms and comparison with theoretical patterns generated from the crystal structures are given in the ESI. The data for the triclinic and orthorhombic forms indicate our results are a better model of the electron density in the unit-cell, on the basis of R-factors, unassigned electron density etc.

<Table 1 about here>

In the triclinic polymorph of 2-iodo-4-nitroaniline, the molecules are linked by two crystallographically unique N-H···O hydrogen bonds into C(8) chains, the combination of which give rise to $[R_2^2(6)]$ rings, leading to one-dimensional chains along the $[01\bar{1}]$ direction, (Figure 1).[4] These chains are linked into sheets by nitro···I interactions, and the sheets are pairwise linked by aromatic π-π stacking interactions.

<Figure 1 about here>

In the orthorhombic polymorph,[4] the molecules are linked by single N-H···O hydrogen bonds into 2_1 generated spiral C(8) chains. Combination of these with nitro….I interactions form a sheet of $R_4^2(12)$ and $R_4^4(28)$ rings (Figure 2), each of which is linked to its two immediate neighbors by aromatic π-π stacking interactions, so producing a continuous three-dimensional structure.

<Figure 2 about here>

In the monoclinic polymorph, space group $P2_1/c$, the molecules are linked by single N-H···O hydrogen bonds into spiral C(8) chains, the chains are linked into sheets by aryl hydrogen…nitro interactions, resulting in sheets of $R_2^1(4)$, $R_1^2(6)$, $R_2^2(7)$, $R_5^5(27)$ and $R_6^6(36)$ rings (Figure 3a). In addition, the C(8) spiral chains are linked into sheets via paired molecules using nitro···I and C-H···I interactions into sheets of $R_4^4(20)$ and $R_8^8(48)$ rings (Figure 3b). Figures 4, 5 and 6 show the thermal ellipsoids for the three forms.

<Figure 3 about here>

<Figures 4, 5 and 6 about here>

In the DSC measurement for the three polymorphs (Figure 7) it was found that the monoclinic polymorph had the highest melting temperature at 118.1°C, the orthorhombic polymorph melted at 116.4°C and the triclinic measured at 105.0°C.

<Figure 7 about here>

On inspection of the IR spectra of the three polymorphs of 2-iodo-4-nitroaniline it was noticed that there are three regions where the peaks differ. The first area of difference lies in the region for NH_2 stretching peaks (3500 to 3340 cm^{-1}). In the triclinic polymorph there are two single peaks of about equal intensity which correlates well with the orthorhombic polymorph which also has two single NH_2 stretching peaks. This differs when looking at the monoclinic polymorph for the same region where there is a splitting of both peaks. This splitting may be associated with the fact that there are two independent molecules in the unit cell of the monoclinic form, whereas there is only one independent molecule in the unit cells of the triclinic and orthorhombic forms. The second region of significance is 1000 to 450 cm^{-1}, contains more subtle differences in the peaks. Figure 8 highlights these regions for all three polymorphs to give a visual of these subtle differences while Figure 9 summarizes the difference in the region 1000 to 800 cm^{-1}.

<Figure 8 about here>

<Figure 9 about here>

The monoclinic form generally provides the most prismatic morphology, with the orthorhombic form tending to produce needles and the triclinic form plates (Figure 10).

<Figure 10 about here>

All solvent mediated transformations carried out resulted in the formation of the monoclinic polymorph. PXRD and DSC analysis along with photographs of the crystalline material before and after

transformation (Figure 11) correlates well with this finding.

<Figure 11 about here>

The case of the orthorhombic transformation was looked at more closely using an *in situ* laser probe, the HEL LaserTRACK^{TM}, to ascertain if the solvent-mediated transformation could be detected with this device. Previous research[8,13] has suggested evidence for the possibility of following a solution mediated transforation of one polymorph to another using *in situ* laser probes. Sampling took place during the stirred slurrying of a largely orthohombic batch of 2-iodo-4-nitroaniline crystals in hexane. PXRD analysis of material before and after the slurrying shows that transformation from the orthorhombic to the monoclinic form has taken place, therefore it is sensible to examine the *in situ* laser probe to ascertain how well this transformation is detected. Very high counts, both total counts and of each fraction but in particular the fines (0-80 μm) fraction, are observed over the first two hours of slurry (Figure 12) attributable to the presence of a mixture of morphologies in the crystalliser. Over the next few hours the data shows a considerable levelling out and this can be attributed to at least two phenomena: one, the growth of crystals, and two, a transformation from a population dominated by needle-like crystals (orthorhombic form) to one having the characteristics of prismatic crystals (monoclinic form). Similar behaviour was observed by Barthe *et al* in the polymorphic system paracetamol[13]. In that case, early spiking in laser probe counts was attributed to the existence of multiple morphologies associated with different polymorphs in the system. As transformation to the most stable form, and one dominant morphology, completed, laser probe counts leveled off to steady values. It is questionable, however, whether the polymorphic transformation would be detected without the benefit of before and after PXRD data. Chord length (dimensions of particles as measured by reflection of the laser beam) distribution histograms taken at various times during the slurrying experiments (Figure 13) also indictate formation of a greater proportion of larger crystals.

<Figure 12 about here>

<Figure 13 about here

Conclusions

Reexamination of the crystal polymorphism of 2-iodo-4-nitroaniline identified three polymorphs: a triclinic, an orthorhomic and a monoclinic form. These could be differentiated by XRD, DSC and IR studies. In our studies, solvent-mediated transformations of the orthorhombic form and of mixtures of forms tended to result in formation of the monoclinic form.

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Table of Contents Graphic

Crystallizations of batches of synthetic and commercial 2-iodo-4-nitroaniline has resulted in the observation of a new monoclinic crystal polymorph in addition to the known triclinic and orthorhombic polymorphs. Samples of the triclinic and orthorhombic polymorphs transform to the monoclinic polymorph under the conditions studied.

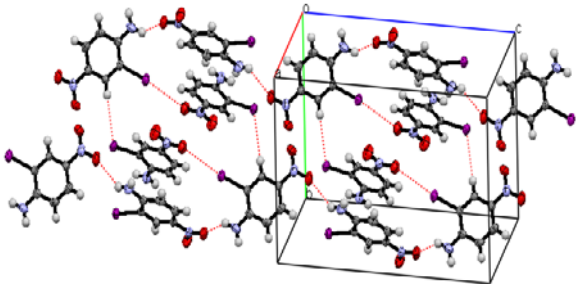


Table 1. Crystallographic Data and Structure Refinement Details for 1a-c

	1a	***1b***	***1c***
formula	$C_6H_5IN_2O_2$	$C_6H_5IN_2O_2$	$C_6H_5IN_2O_2$
Mr	*264.02*	*264.02*	*264.02*
crystal system	*Triclinic*	*Orthorhombic*	*Monoclinic*
space group	*P-1*	*Pbca*	$P2_1/c$
a(Å)	*7.1095(4)*	*7.4433(5)*	*7.7617(15)*
b(Å)	*7.9514(5)*	*12.6520(11)*	*12.912(3)*
c(Å)	*8.0469(6)*	*16.5442(13)*	*15.663(3)*
α(°)	*68.1020(10)*	*90*	*90.00*
β(°)	*87.0300(10)*	*90*	*95.141(6)*
γ(°)	*66.089(2)*	*90*	*90.00*
V(Å^3)	*383.194*	*1558.01*	*1563.42*
Z, ρ_{calc} (Mg/m^3)	*8, 2.251*	*2, 2.288*	*8, 2.243*
μ (mm^{-1})	*4.060*	*4.127*	*4.046*
F(000)	*992*	*248*	*992*
θ range (°)	*3.2203-23.6526*	*2.75-26.48*	*3.05-25.18*
limiting indices	$-7 \le h \le 9$	$-8 \le h \le 5$	$-9 \le h \le 8$
	$-16 \le k \le 16$	$-9 \le k \le 7$	$-15 \le k \le 14$
	$-22 \le l \le 16$	$-10 \le l \le 10$	$-18 \le l \le 17$
reflns collected	*1944*	*2088*	*2797*
GOF on F^2	*0.931*	*1.046*	*1.028*
R_1/wR_2 [$I > 2\sigma(I)$]	*R_1 = 0.0321*	*0.0174*	*0.0257*
	wR_2 = 0.0684	*0.0438*	*0.0534*
R_1/wR_2 (all data)	*R_1 = 0.0672*	*0.0184*	*0.0382*
	wR_2 = 0.0819	*0.0442*	*0.0572*

Temp	*100 K*	*292 K*	*100K*
# independent reflections (I>2σ(I))]	*1893*	*1994*	*3368*
# parameters	*108*	*108*	*215*

Figure 1. The two unique C(8) hydrogen-bonded chains and resulting [$R_2^2(6)$] chains of rings linked by nitro···I interactions into a sheet for the triclinic form.

Figure 2. The C(8) spiral N-H…O chains in the orthorhombic form, which form a sheet of $R_4^2(12)$ and $R_4^4(28)$ rings involving this hydrogen bond and the nitro….I interactions.

Figure 3. Part of the crystal structure of the monoclinic polymorph, (**1c**), (a) showing the linking of C(8) spiral chains by single molecules each of which is linked to its two nearest neighbours via another single molecule resulting in sheets of $R_2^1(4)$, $R_1^2(6)$, $R_2^2(7)$, $R_5^5(27)$ and $R_6^6(36)$ rings and (b) showing the linking of C(8) spiral chains by pairs of molecules into sheets of $R_4^4(20)$ and $R_8^8(48)$ rings. For clarity, H atoms bonded to C atoms have been omitted.

Figure 4 A view of the triclinic form of 2-iodo-4-nitroaniline showing the atomic labelling. Thermal ellipsoids are shown at the 50% probability level.

Figure 5 A view of the orthorhombic form of 2-iodo-4-nitroaniline showing the atomic labelling. Thermal ellipsoids are shown at the 30% probability level.

Figure 6 A view of the monoclinic form of 2-iodo-4-nitroaniline showing the atomic labelling. Thermal ellipsoids are shown at the 50% probability level.

Figure 7. DSC thermodiagrams of triclinic, orthorhombic and monoclinic polymorphs of 2-iodo-4-nitroaniline.

Figure 8. IR spectra of the three polymorphic forms of 2-iodo-4-nitroaniline triclinic (top), orthorhombic (middle) and monoclinic (bottom).

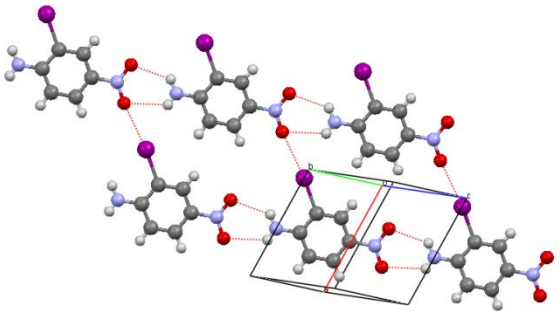
Figure 9. IR spectra of triclinic, orthorhombic and monoclinic polymorphs of 2-iodo-4-nitroaniline highlighting the differences in the region 700-1000cm^{-1}

Figure 10. Optical micrographs of 2-iodo-4-nitroaniline (a) monoclinic crystal, (b) triclinic plates and (c) orthorhombic needles.

Figure 11. shows photographic evidence of the solvent mediated transformation of (a) triclinic to monoclinic, (b) orthorhombic to monoclinic and (c) a mixture of all three polymorphic forms to monoclinic.

Figure 12. Orthorhombic crystals stirred in hexane leading to a solution mediated transformation to the monoclinic form. The black line shows the turbidity counts (no. of particles observed per second); the red line shows the vessel temperature (° C); the dark blue line shows the number of particles in the size range 0 to 80 μm; the pink line 80 to 150 μm; and the light blue line 150 to 1000 μm.

Figure 13. Particle size distributions taken at three time intervals during the slurry experiment.



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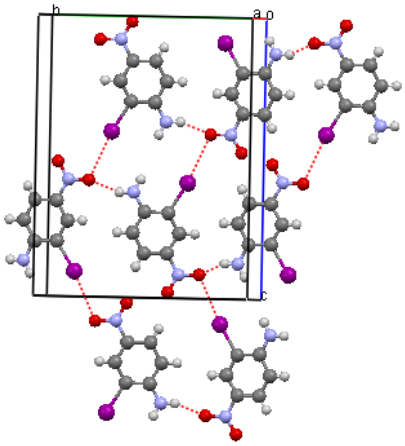

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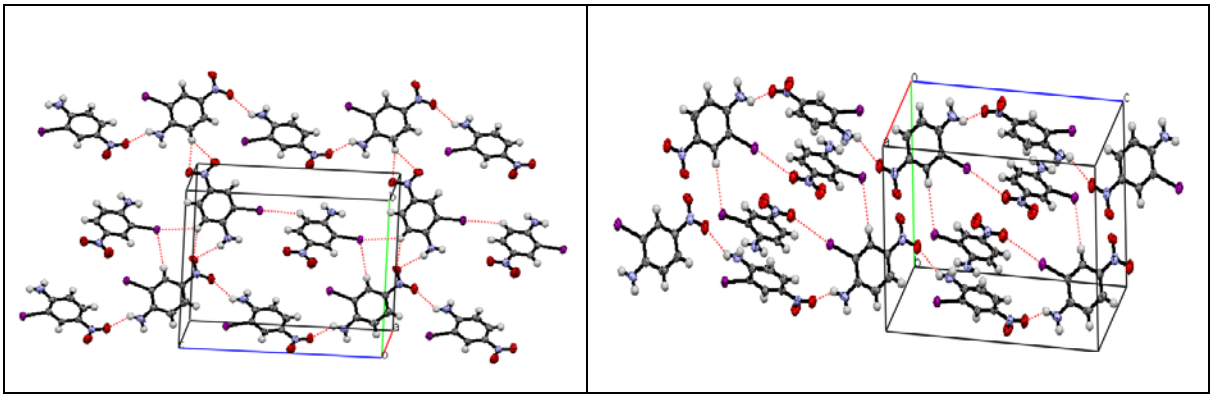
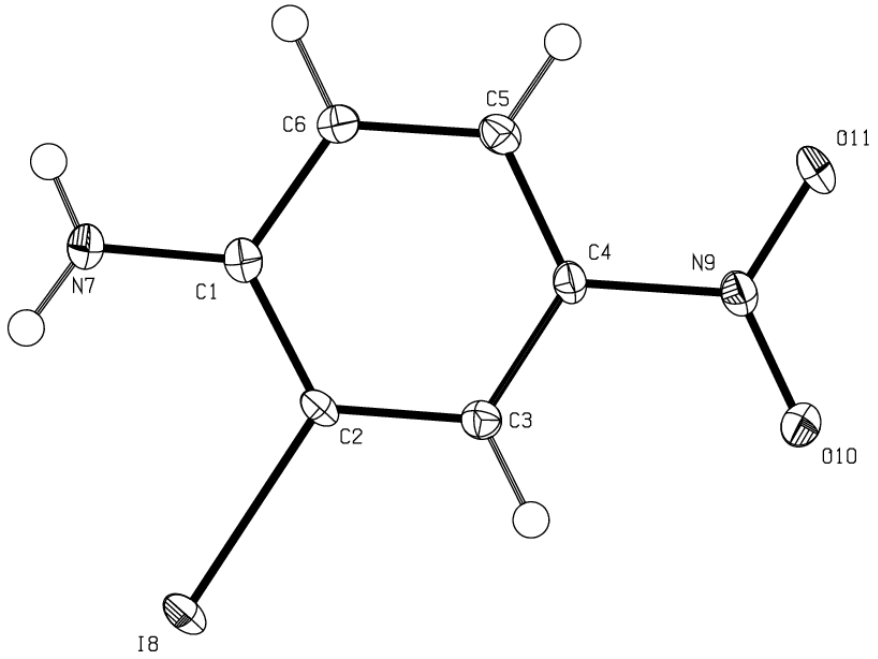


Figure 3.

Figure 4



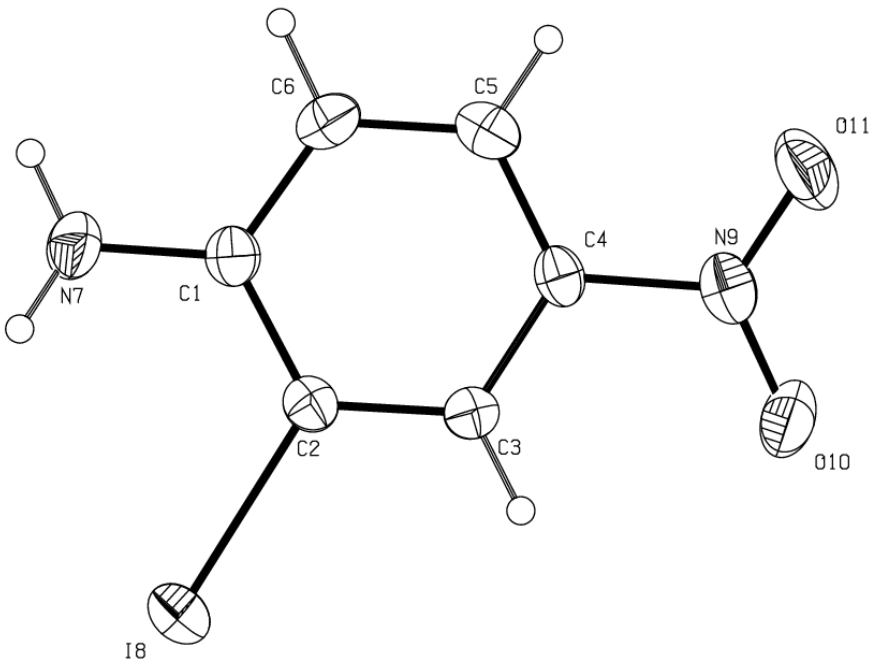


Figure 5

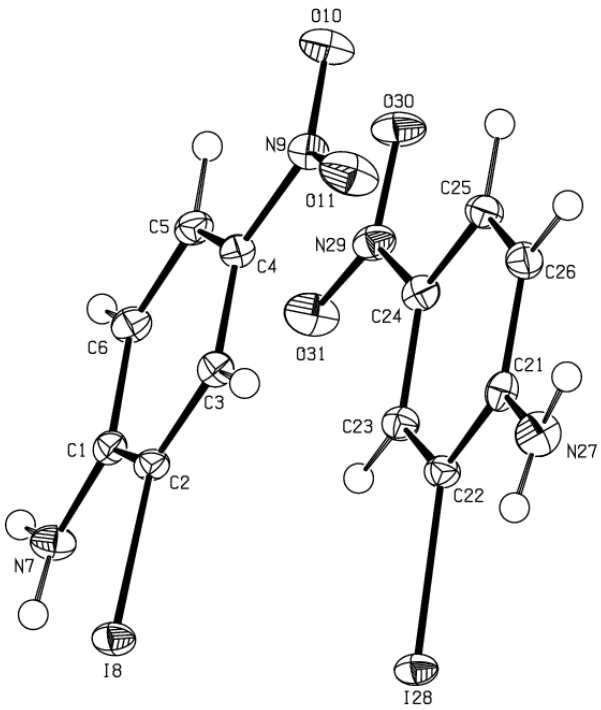

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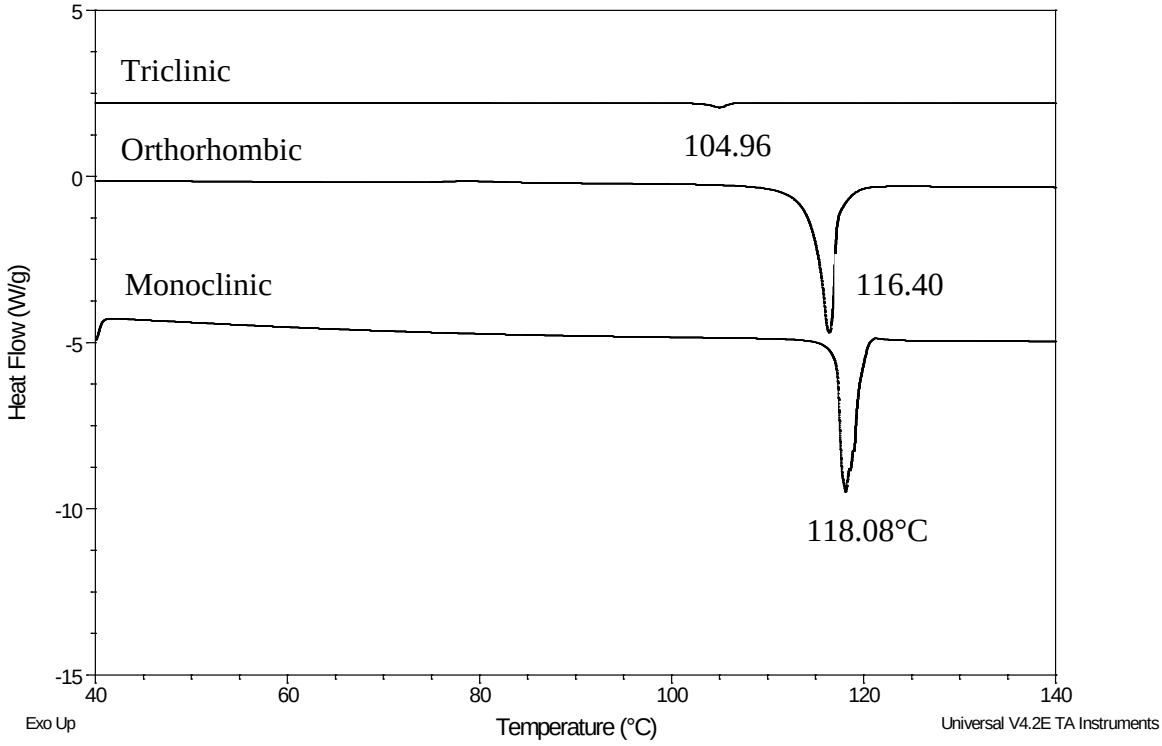
Figure 6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Exo Up
Temperature (°C)
Universal V4.2E TA Instruments

Figure 7.

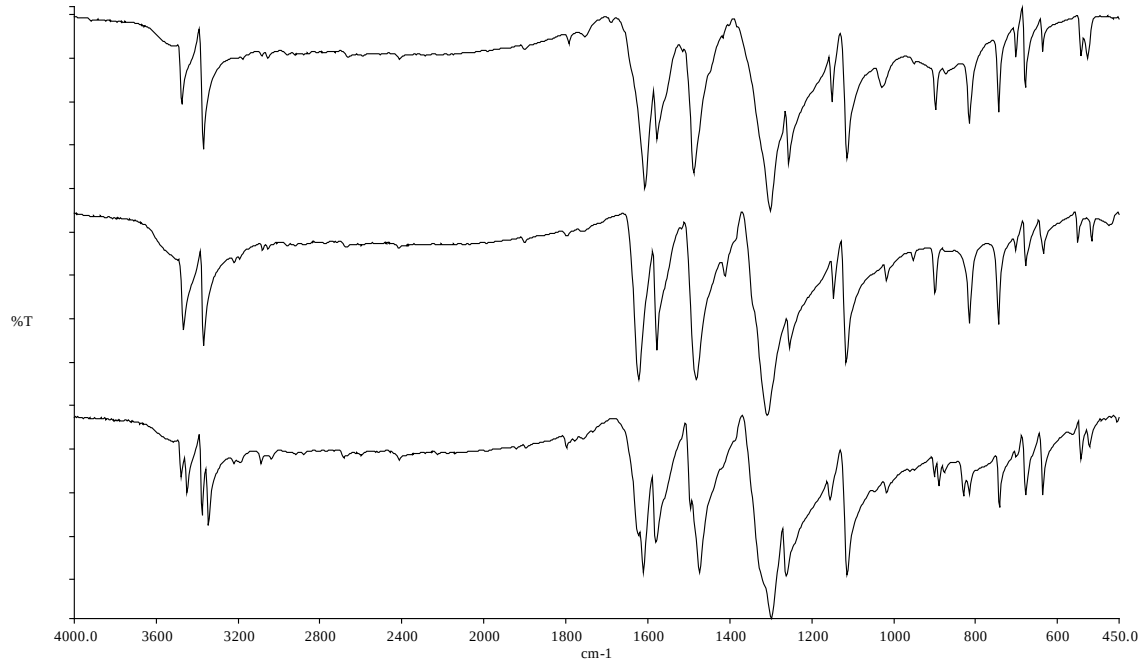


Figure 8.

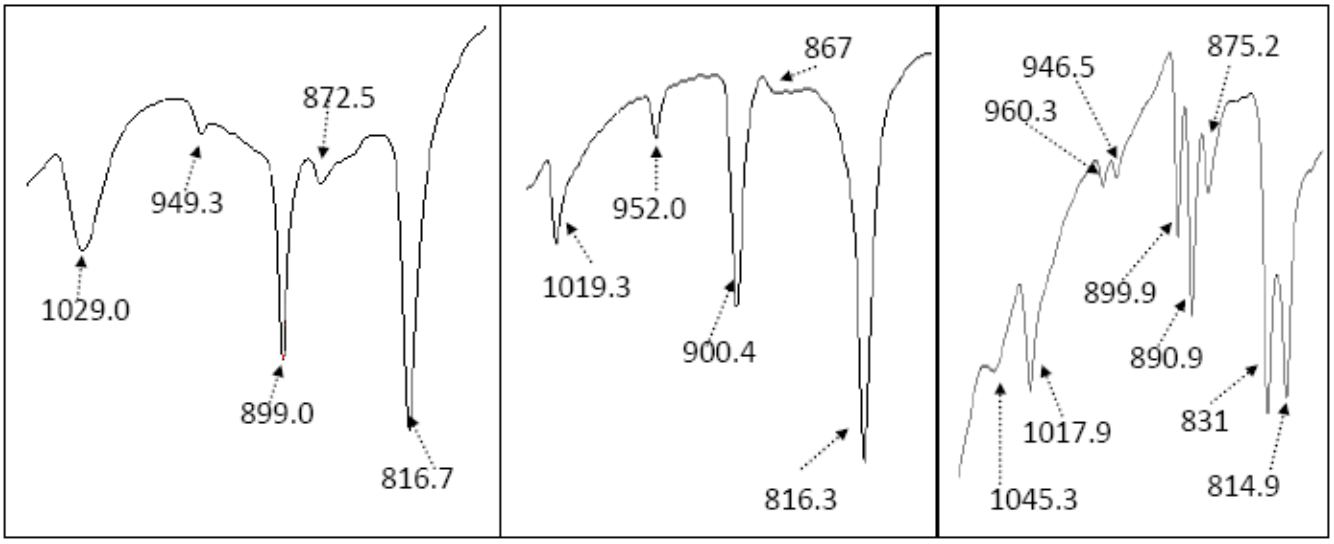
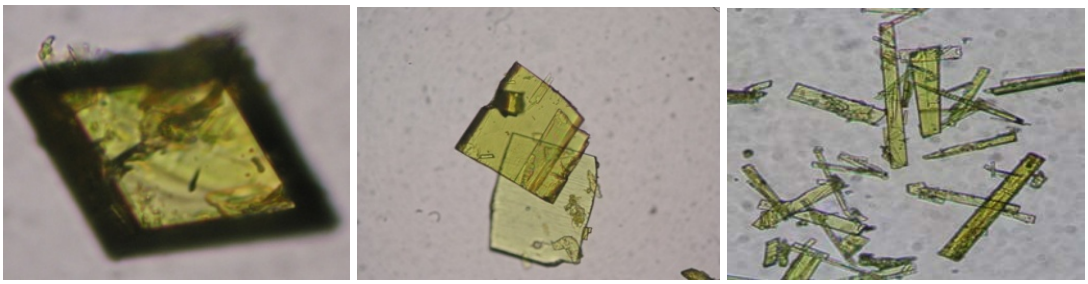
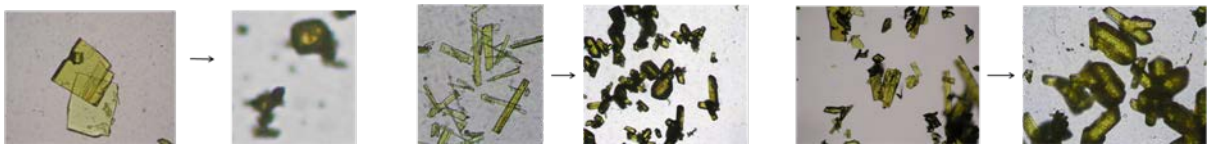


Figure 9 .....



(a) (b) (c)

Figure 10.



(a) (b) (c)

Figure 11.

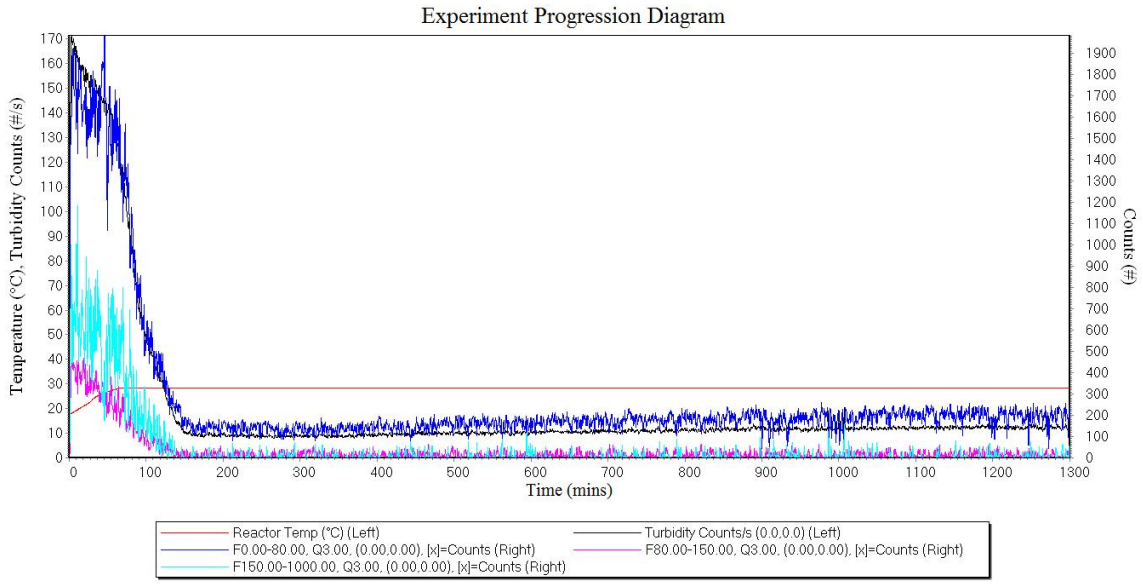


Figure 12.

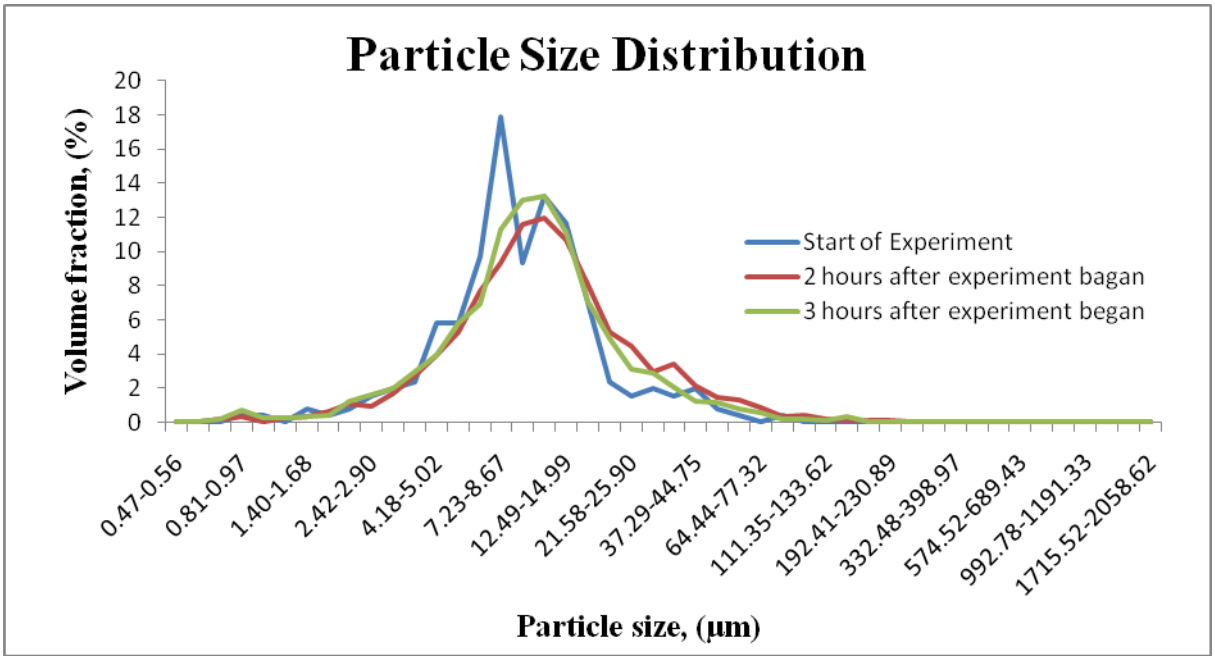


Figure 13.

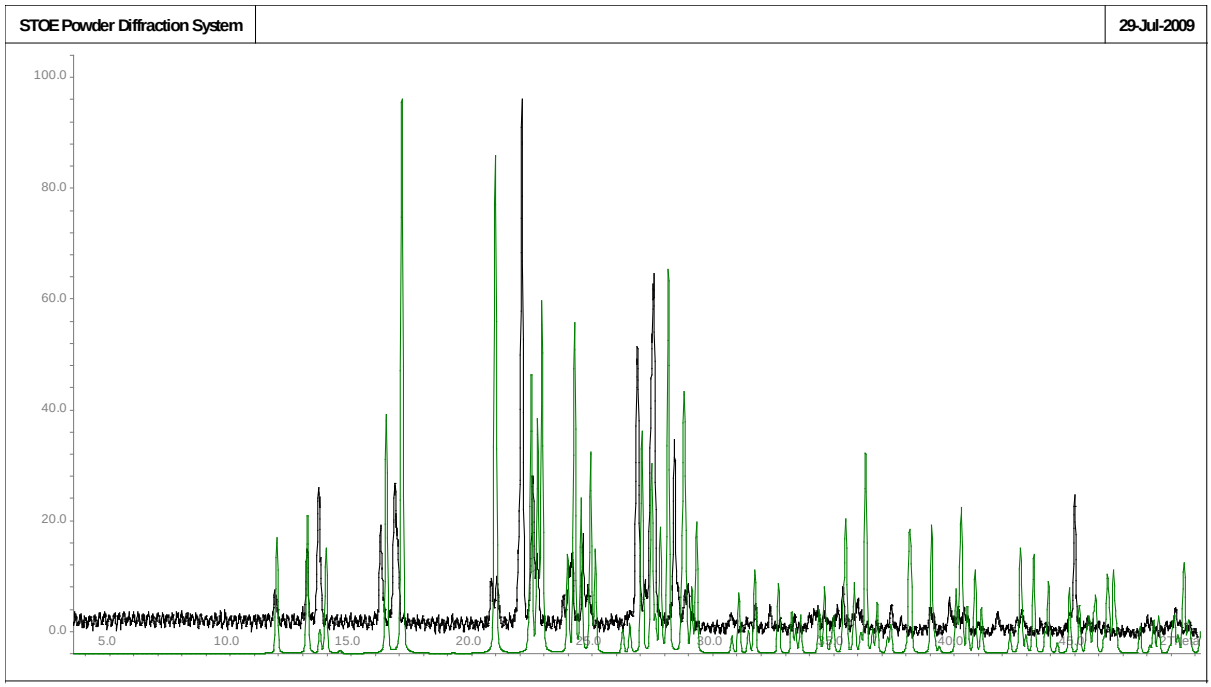
Crystal polymorphs and transformations of 2-iodo-4-nitroaniline

*Dawn M. Kelly, Kevin Eccles, Curtis Elcoate, Simon E. Lawrence and Humphrey A. Moynihan**

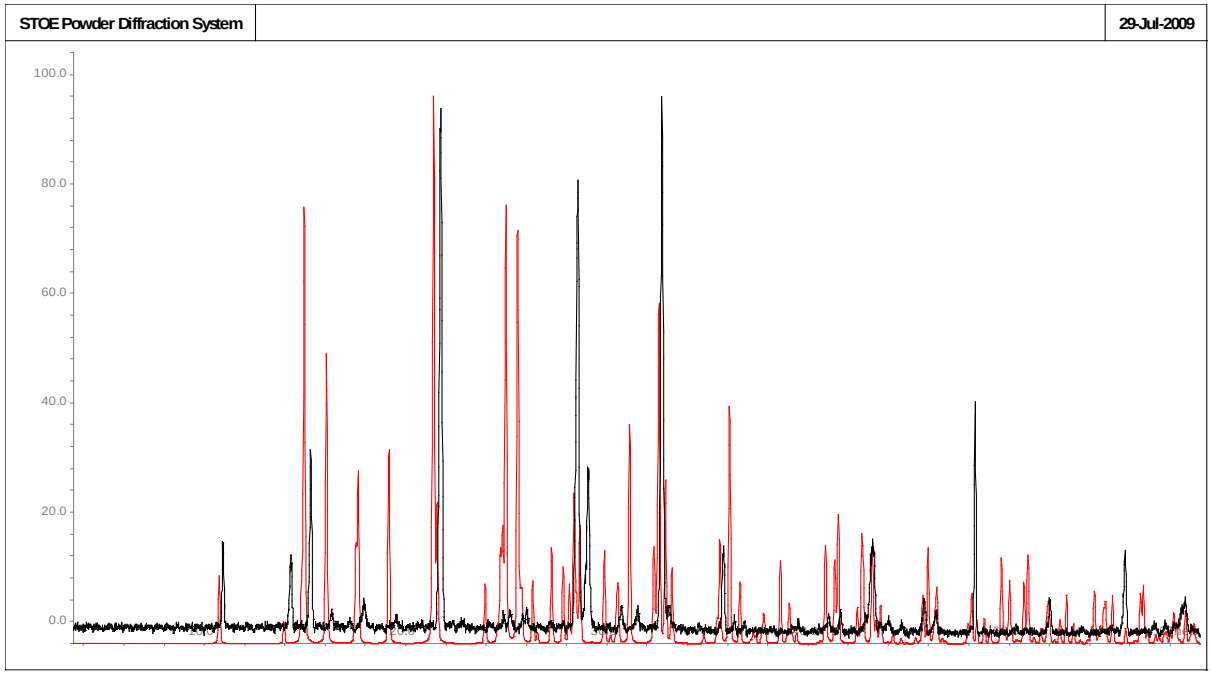
Supplementary Information

Experimental and theoretical PXRD of the three observed polymorphs of 2-iodo-4-nitroaniline

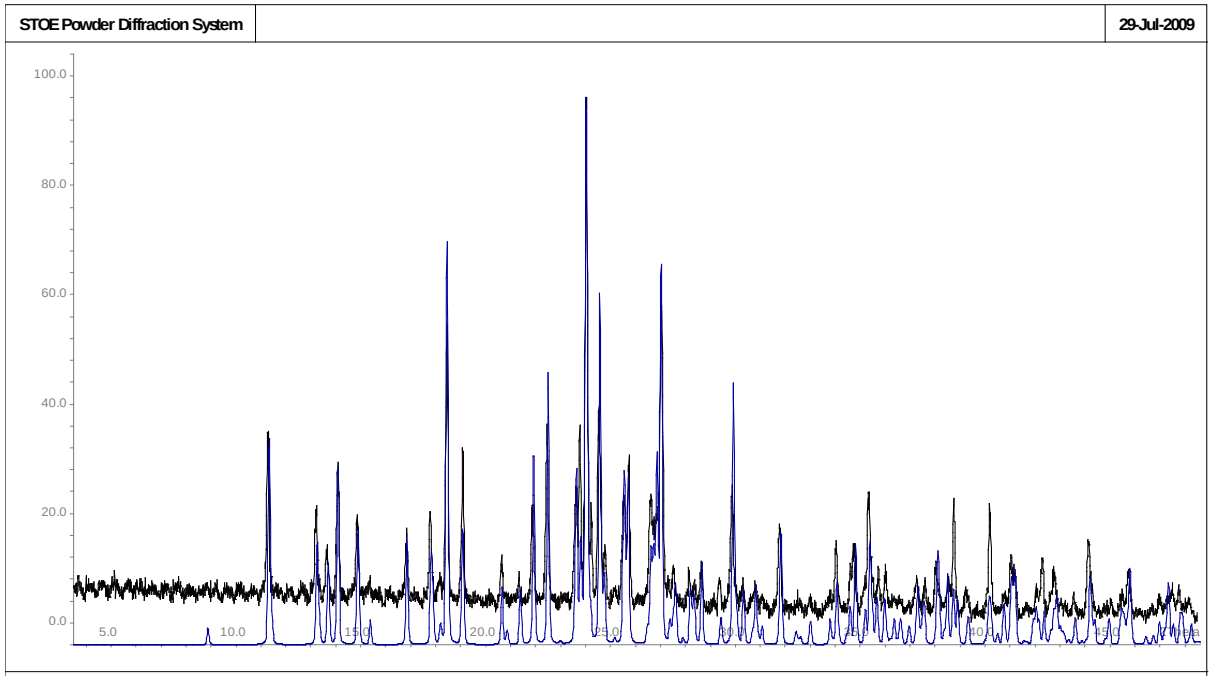
Experimental PXRD recorded at 293 K. Theoretical patterns generated from data obtained at 100 K.



Triclinic polymorph (theoretical in green with experimental pattern overlaid in black)



Orthorhombic polymorph (theoretical in red with experimental overlaid in black)



Monoclinic polymorph (theoretical in blue with experimental overlaid in black)