Crystal polymorphism of methyl 2,3,4-tri-*O*-acetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucopyranouronate

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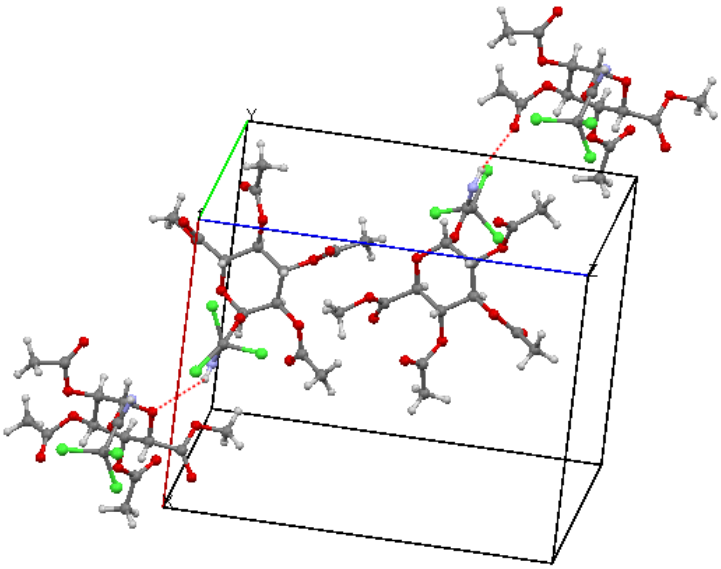
Structures of two polymorphs of methyl 2,3,4-tri-*O*-acetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucopyranouronate were determined.



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Abstract

The polymorphism of the glycoside donor methyl 2,3,4-tri-*O*-acetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucopyranouronate (**1**) has been investigated. Two polymorphic forms (labelled Forms **I** and **II**) have been elucidated and fully characterised by DSC, PXRD and single crystal analysis, both crystallizing in the space group $P2_1$. Form **I** was obtained by crystallization from a wide range of solvents, while Form **II** was obtained only from ethyl acetate or isopropanol on certain occasions. Unit cell dimensions for Form **I** are *a* 14.0292(12), *b* 8.9641(8), *c* 16.8580(14) Å, *β* 94.285(2)°, and for Form **II** *a* 11.266(3), *b* 6.8889(17), *c* 13.921(4) Å, *β* 101.161(6)°. Z' is 2 for Form **I** and 1 for Form **II**. Form **I** displays two moderate intermolecular hydrogen bonds in the unit cell whereas Form **II** shows

no moderate hydrogen-bonding motifs. All three molecules in the two polymorphs differ significantly in their conformations, especially with respect to the methyl carboxylate and trichloroacetimidoyl groups.

Keywords: Methyl 2,3,4-tri-*O*-acetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucopyranouronate, Polymorphism, Imine hydrogen bonding.

Introduction

Crystal polymorphism can be defined as differing crystal structures formed from the same molecular components. Instances of crystal polymorphism are relatively common in fields in which preparation and characterisation of crystalline solids are core activities [1] while over 16000 entries in the CSD are tagged as polymorphs [2]. In a significant number of cases, polymorphism in molecular crystals in associated with differences in molecular conformations [3]. Crystal polymorphs of the same compound can display differences in key physical properties such as stability, melting point and dissolution rate. Many instances are observed where conditions such as process impurities may induce the nucleation of less stable phases of a system and subsequently metastable polymorphs are observed [4]. For reactive synthetic intermediates such as methyl 2,3,4-tri-*O*-acetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucopyranouronate **1**, (Fig. 1), the crystal forms and polymorphs, if observed, are significant in determining the stability of the compounds as materials.

The synthetic utility of trichloroacetimidates [5] as glycoside donors has long been realized and has resulted in increased application in both glycoside formation [5] and glucuronidation [6-8]. The mild conditions required and the high selectivity for β-glycoside formation make trichloroacetimidates highly attractive choices as the main intermediates for many syntheses.

Hence, specific trichloroacetimidates, such as 2,3,4,6-tetra-*O*-benzyl-1-*O*-trichloroacetimidoyl-α-D-glucopyranose [10] and methyl 2,3,4-tri-*O*-acetyl-1-*O* (trichloroacetimidoyl)-α-D-glucopyranouronate **1** [6], are stable but reactive compounds. The physical form of such compounds is significant in conferring stability on samples of the pure material and affects practical issues such as isolation and storage. In commercial scale syntheses, the physical properties and stability of intermediate products, including reactive compounds such as glycosylating agents, are important considerations. When such compounds are crystalline solids, issues such as crystal structure and particle morphology are particularly important. These issues are even more challenging for compounds of the complexity and reactivity of trichloroacetimidate **1**. We have investigated the crystal forms of compound **1** and herein report two novel polymorphic forms, denoted Forms **I** and **II**.

<Fig 1 about here>

Experimental

Synthesis

All commercial reagents were purchased from Sigma-Aldrich and were used without further purification. All solvents were either of HPLC grade or distilled prior to use. Synthesis of the target glycoside donor was as follows [6, 9]:

Methyl 2,3,4-tri-*O*-acetyl-α,β-glucopyranuronate (12.0 g, 36 mmol) and trichloroacetonitrile (18 mL, 180 mmol) were stirred in dry CH_2Cl_2 at 0 °C for 30 min. DBU (1.5 mL, 10 mmol) was added dropwise and the solution was allowed to warm to room temperature and stirred overnight. The solvent was removed *in vacuo* and the residue was subjected to flash chromatography (40:59:1 EtOAc: hexane: Et_3N). Appropriate fractions were pooled and the

solvent removed under reduced pressure to yield a syrup which was triturated with diethyl ether. Recrystallisation with EtOAc:hexane (50:50) yielded 8.5g (65%) of compound **1** as a white solid. mp 108-109 °C, lit. [10] 109-110 °C; IR (KBr) ν 3320 (N-H), 2958 (C-H), 1755 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H, N**H),** 6.64 (d, 1H, *J* 3.6 Hz, H-1), 5.63 (t, 1H, *J* 10 Hz, H-3), 5.27 (t, 1H, *J* 10 Hz, H-4), 5.16 (dd, 1H, *J* 3.6 Hz, 10 Hz, H-2), 4.49 (d, 1H, *J* 10 Hz, H-5), 3.75 (s, 3H, CO_2**Me**), 2.05 (s, 3H, O**Ac**), 2.04 (s, 3H, O**Ac**), 2.02 (s, 3H, O**Ac**). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.78 (**C**=O), 169.72 (**C**=O), 169.47 (**C**=O), 167.14 (**C**=O), 160.58 (**C**=N), 92.64 (**C**-H), 70.49 (**C**-H), 69.47 (**C**-H), 69.10 (**C**-H), 68.96 (**C**-H), 53.04 (CO_2**Me**), 21.04, 20.66, 20.48, 20.39 (3 x O**Ac** and 1 x **C**Cl_3).

Thermal analysis

DSC was performed using a TA Q1000 DSC with RSC 40 cooling system. The sample cell was heated under a nitrogen purge at a rate of 5 °C min^{-1}, from 25 °C up to a final temperature of 160 °C.

Crystallography

Single-crystal X-ray diffraction measurements were made on a Bruker APEX II DUO diffractometer using graphite monochromatized Cu Kα (1.54178 Å) X-radiation and an Oxford Cryosystems COBRA fitted with an N_2 generator. All calculations involving data collection, structure solution and refinement were made using the APEX2 v2009.3-0 software [11] containing the SHELX suite of programs [12]. Diagrams were prepared using Mercury [13] and PLATON [14] was used for the Cremer-Pople analysis [15]. The absolute configuration was determined from the diffraction data using the Flack parameter [16] within SHELXL-97 [12]. Hydrogen atoms associated with the N atom were located from a difference map and the position and isotropic displacement parameters were refined freely.

All other hydrogen atoms were placed in calculated positions and treated as riding atoms.

Results and discussion

Samples of compound **1** were recrystallized from the following solvents: methanol, ethanol, isopropanol, acetonitrile, diethyl ether, THF, ethyl acetate and ethyl acetate-hexane mixtures. In each case, solutions were allowed to evaporate at ambient temperature to provide crystals. These recrystallizations generally yielded crystals of the polymorph designated Form **I**. A second polymorph, designated Form **II**, was obtained on some occasions by recrystallization from ethyl acetate by evaporation, or by rapid cooling of isopropanol solutions. However, it should be noted that these methods also more often provided crystals of Form **I**. Crystals of Form **I** were generally of prismatic habit, while those of Form **II** were needle-like (Fig. 2). Crystal structure analysis showed that both forms crystallise in the monoclinic crystal system with space group $P2_1$. Crystallographic information for both forms is summarised in Table 1. Form **I** contains two molecules of compound **1** in the asymmetric unit, while Form **II** contains one. Atomic numbering for all molecules of compound **1** is shown in Fig 3 and Fig 4. Views of the unit cells for both structures are shown in Fig. 5.

<Fig 2 about here>

<Table 1 about here>

<Fig 3 about here>

<Fig 4 about here>

<Fig 5 about here>

For both molecules of the asymmetric unit of Form **I**, two discrete imine NH···O hydrogen bonds are present (Fig 5a), involving both a carbonyl O-atom acceptor of the acetate ester at C3 of an adjacent molecule (N1-H···O16) and a heterocyclic O-atom acceptor (N2-H···O11) (Table 2). This latter motif is similar to that reported in the crystal structure of methyl 2,3-di-*O*-acetyl-4-*O*-levulinoyl-1-*O*-(2,2,2-trichloro-2-iminoethyl-L-idopyranosiduronate [17]. By contrast, Form **II** is characterised by the absence of hydrogen bonds when forming the crystal lattice. The pyranose rings in both forms are in the $^4C_1$ conformation. Cremer-Pople [15] total puckering amplitudes (Q), distortions (θ), phase angles (φ) and puckering amplitudes q_2 and q_3 for the two pyranose chairs in Form **I** and that in Form **II** are given in Table 3. The values are close to the corresponding values for an ideal cyclohexane chair (Q = 0.63 Å, θ = 5.0°). They are also similar to values reported for 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronic acid monohydrate and 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose [18].

In both forms, the trichloroacetimidate group is in the α anomeric position with the trichloromethyl group in an *anti*-periplanar conformation with respect to the pyranose ring (C-O-C-CCl_3 torsion angles of −179.2(2)° and −177.25(19)° in Form **I**, and −179.6(2)° in Form **II**). The imidate NH group is *syn*-periplanar to the anomeric carbon in both forms (C-O-C-NH torsion angles of 1.5(4)° and 3.3(4)° in Form **I**, and 3.1(4)° in Form **II**). There is significant variation in the orientation of the imidate group relative to the pyranose ring, with the torsion angle formed by the bond sequence O(pyranose)-C-O-C(imidate) having values of

101.5(2)° and 137.6(2)° in Form **I**, and 69.2(3)° in Form **II**. Conformational differences are also observed in the orientations of the carboxymethyl groups in the two forms. In both molecules of Form **I**, the carboxymethyl carbonyl group oxygen is oriented away from the pyranose ring (O(pyranose)-C-C=O angles of 143.4(2)° and 135.9(3)°), whereas in Form **II**, the carboxymethyl carbonyl group oxygen is oriented towards the pyranose ring (O(pyranose)-C-C=O angle of −80.7(4)°). The acetoxy groups have essentially the same conformations in all three molecules. By virtue of the observed variation in the conformations of the imidate and carboxymethyl groups, the two forms of compound **1** are an example of conformation polymorphism [3]. In all three conformations, an intramolecular interaction between the imidate N-H group and one of the Cl atoms appears to be present. The bond distances and angles for these are given in Table 4.

<Table 2 about here>

<Table 3 about here>

<Table 4 about here>

DSC scans for samples of both forms are shown in Fig 6. Form **I** showed a melting endotherm at 111.4 °C and no other thermal events. The thermal behaviour of samples of Form **II** is more complex, showing a broad melting endotherm with a maximum at 114.8 °C, with a subsequent small endothermic event at 119.6 °C. It is possible that this is due to the presence or formation of small quantities of a further form.

<Fig 6 about here>

In conclusion, full crystal structural analyses have been performed on two polymorphs of the important glucuronidating agent methyl 2,3,4-tri-*O*-acetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucopyranouronate **1**. The physical properties and forms of important synthetic intermediate compounds can affect stability and use. In the case of compound **1**, one polymorph, Form **I**, is readily obtainable. Another polymorph, Form **II**, has also been observed and the existence of other forms cannot be ruled out. Actual samples of compound **1** have the potential to exist in one or more of these forms, potentially impacting physical stability over time, the ability to purify, filter and dry batches, and process issues such as dissolution in solvents.

Supplementary data

The crystallographic data Forms **I** and **II** have been deposited with the Cambridge Crystallographic Data Centre, CCDC numbers 869321 and 869322. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgements

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Table 1 Crystallographic information for the polymorphic forms of compound **1**.

Compound reference	**1** Form **I**	**1** Form **II**
Chemical formula	$C_{15}H_{18}Cl_3NO_{10}$	$C_{15}H_{18}Cl_3NO_{10}$
Formula Mass	478.65	478.65
Crystal System	Monoclinic	Monoclinic
a/Å	14.0292(12)	11.266(3)
b/Å	8.9641(8)	6.8889(17)
c/Å	16.8580(14)	13.921(4)
β/°	94.285(2)	101.161(6)
Unit cell volume/Å^3	2114.1(3)	1060.0(5)
Temperature/K	100(2)	100(2)
Space group	$P2_1$	$P2_1$
No. of formula units per unit cell, *Z*	4	2
Absorption coefficient, μ/mm^{-1}	0.485	0.483
No. of reflections measured	24125	12970
No. of independent reflections	9277	4182
R_{int}	0.0281	0.0513
Final R_1 values ($I > 2\sigma(I)$)	0.0402	0.0406
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.0875	0.0903
Final R_1 values (all data)	0.0434	0.0544
Final $wR(F^2)$ values (all data)	0.0893	0.0977
Goodness of fit on F^2	1.025	1.057
Flack parameter	0.01(4)	-0.13(6)

Table 2 Hydrogen bonds in Form **I**

Type	D-H···A	D-H (Å)	D-H···A(Å)	D···A(Å)	Angle D-H···A (^{o})
Moderate	N1-H1A···O16	0.84	2.29	3.13	160.5
Moderate	N2-H2A···O11	0.60	2.63	3.23	132.5

Table 3 Cremer-Pople ring puckering coordinates [15] calculated using PLATON [14]

Coordinate	Form **I** Molecule 1	Form **I** Molecule 2	Form **II**
Q / Å	0.560(18)	0.555(3)	0.597(3)
θ / °	6.30(3)	3.40(4)	6.00(3)
φ / °	280.0(2)	331.0(4)	254.0(3)
q_2 / Å	0.062	0.033	0.062
q_3 / Å	0.557	0.554	0.594

Table 4 Bonds distances and angles for the intramolecular N-H---Cl interactions

N-H···Cl	N-H (Å)	N-H···Cl(Å)	N···Cl(Å)	Angle N-H···Cl (^{o})
Form **I** Molecule 1	0.81(4)	2.561(4)	3.014(3)	116.70(4)
Form **I** Molecule 2	0.87(5)	2.570(4)	3.003(3)	111.73(3)
Form **II**	0.86(4)	2.460(4)	3.030(3)	123.96(3)

List of Figure Legends

Fig. 1. Methyl 2,3,4-tri-*O*-acetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucopyranouronate (**1**)

Fig. 2. Crystal habit for (a) polymorphic Form **I** and (b) Form **II**

Fig 3. Atomic numbering scheme for the two molecules in the asymmetric unit of Form **I**. Displacement parameters are drawn at the 30% probability level.

Fig. 4. Atomic numbering scheme for the asymmetric unit of Form **II**. Displacement parameters are drawn at the 30% probability level.

Fig.5. Unit cell for (a) polymorphic Form **I** and (b) Form **II**

Fig. 6. DSC scans for samples of Form **I** (red) and Form **II** (black)

Fig 1

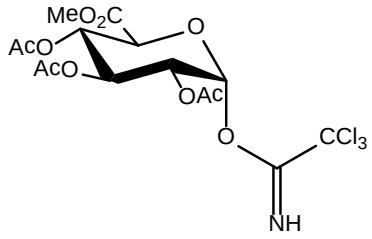


Fig 2

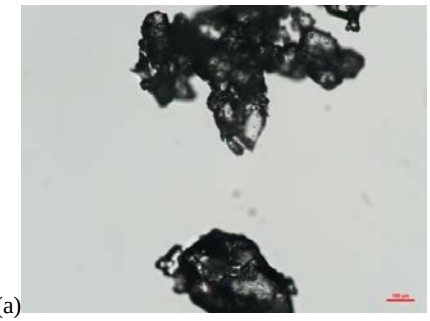
(a)  (b) 

Fig 3

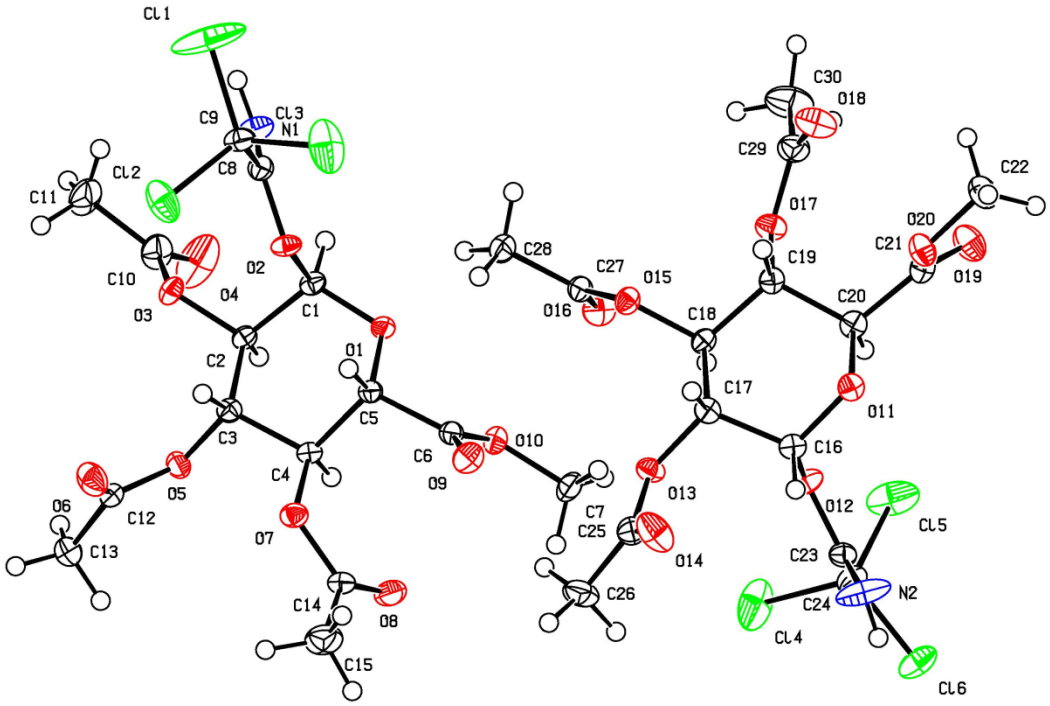

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Fig 4

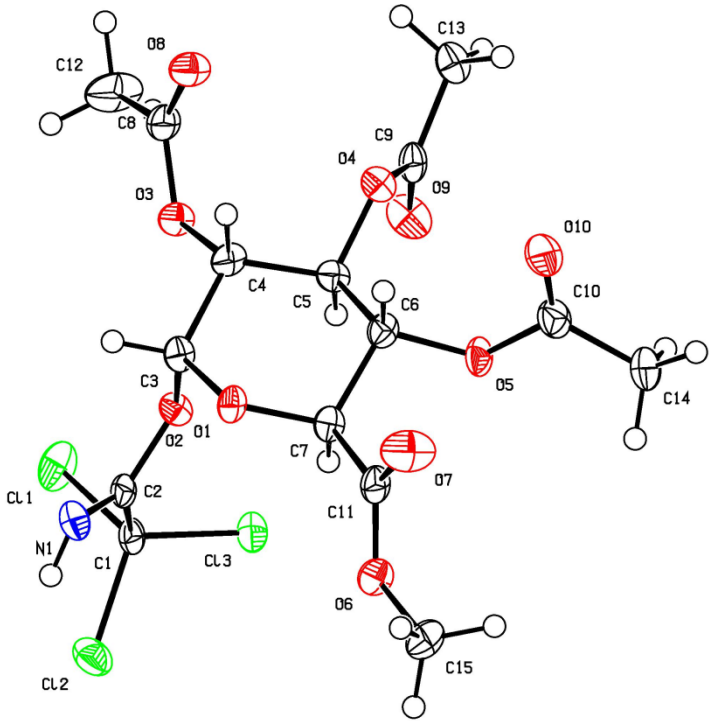
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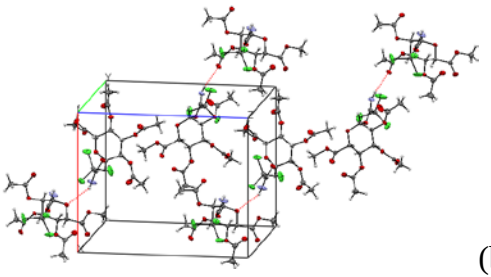
Fig 5

(a)



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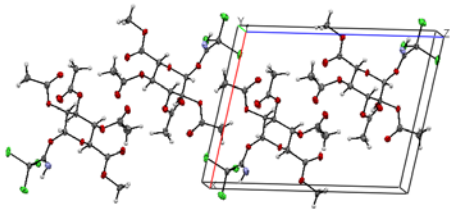
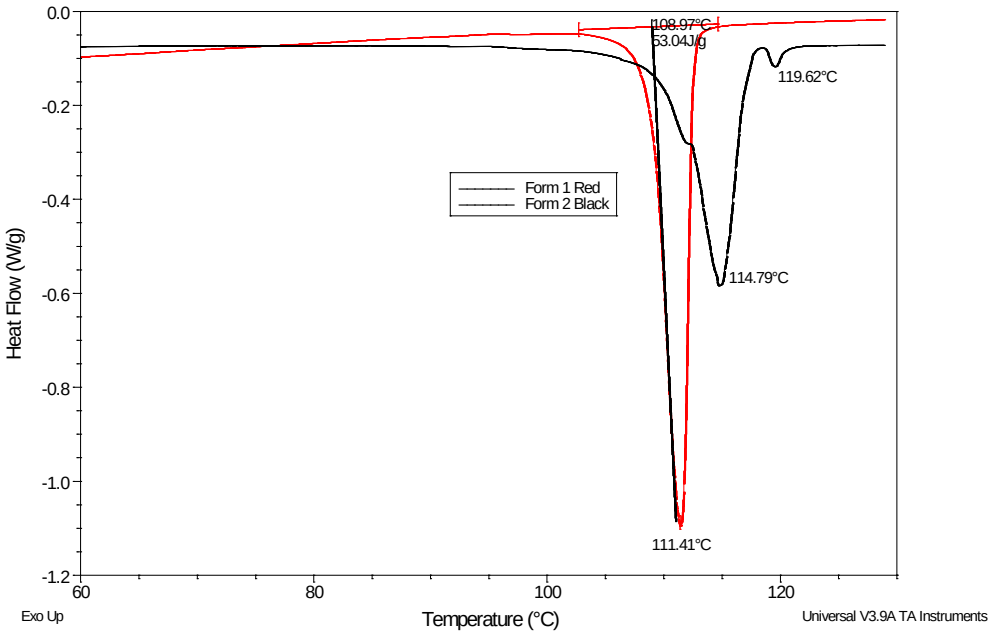


Fig 6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