CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	Crystal polymorphism of methyl 2,3,4-tri-O-acetyl-1-O-(trichloroacetimidoyl)-α-d-glucopyranouronate
Authors	Hayes, John A.;Eccles, Kevin S.;Elcoate, Curtis J.;Daly, Carla A.;Lawrence, Simon E.;Moynihan, Humphrey A.
Publication date	2013-03
Original Citation	HAYES, J. A., ECCLES, K. S., ELCOATE, C. J., DALY, C. A., LAWRENCE, S. E. & MOYNIHAN, H. A. 2013. Crystal Polymorphism of Methyl 2,3,4-tri-O-acetyl-1-O-(trichloroacetimidoyl)-α-d-glucopyranouronate. Journal of Chemical Crystallography, 43, 138-143. DOI: http://dx.doi.org/10.1007/s10870-013-0397-y
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1007/s10870-013-0397-y
Rights	© Springer Science+Business Media New York 2013. The final publication is available at Springer via http://dx.doi.org/10.1007/s10870-013-0397-y
Download date	2026-09-08 03:48:58
Item downloaded from	https://hdl.handle.net/10468/1589

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

The final publication is available at Springer via http://dx.doi.org/10.1007/s10870-013-0397-y

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

John A. Hayes, Kevin S. Eccles, Curtis J. Elcoate, Carla A. Daly, Simon E. Lawrence and Humphrey A. Moynihan*

Analytical and Biological Chemistry Research Facility / Department of Chemistry, University College Cork, College Road, Cork, Ireland

* Corresponding author: Tel. +353 21 4902488; Fax. +353 21 4274097.

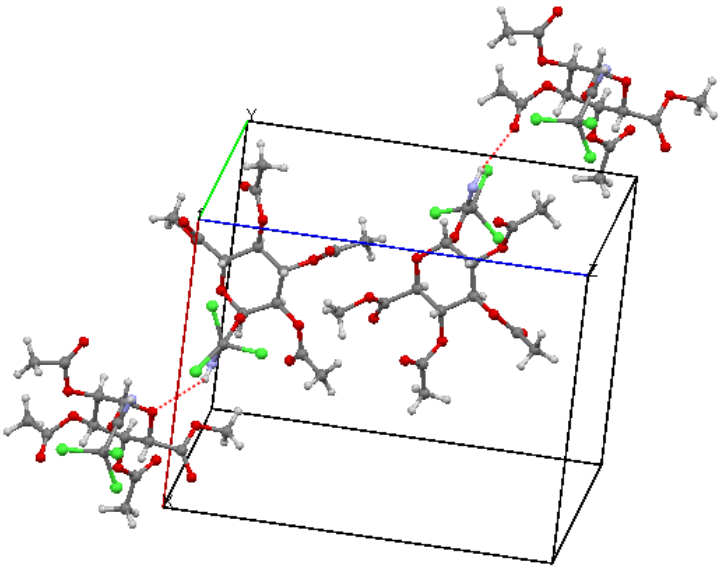
E-mail address: h.moynihan@ucc.ie

Polymorphism of a trichloroacetimidate

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

John A. Hayes, Kevin S. Eccles, Curtis, J. Elcoate, Carla A. Daly, Simon E. Lawrence and Humphrey A. Moynihan*

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



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

John A. Hayes, Kevin S. Eccles, Curtis J. Elcoate, Carla A. Daly, Simon E. Lawrence and Humphrey A. Moynihan*

Analytical and Biological Chemistry Research Facility / Department of Chemistry, University College Cork, College Road, Cork, Ireland

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

This publication has emanated from research conducted with the financial support of Science Foundation Ireland under Grant Numbers 07/SRC/B1158, 08/RFP/MTR1664 and 05/PICA/B802/EC07.

References

1. Bernstein J (2002) Polymorphism in Molecular Crystals. Oxford Science Publications, Oxford.

2. Braga D, Grepioni F, Maini L. (2010) Chem Commun 46: 6232

3. Bernstein J, Hagler A.T. (1978) J Am Chem Soc 100: 673

4. Mukuta T, Lee AY, Kawakami T, Myerson A.S. (2005) Cryst Growth Des 5:1429

5. Schmidt R.R. (1986) Angew Chem Int Ed Engl 25:212

6. Fischer B, Nudelman A, Ruse M, Herzig J, Gottlieb H.E. (1984) J Org Chem 49: 4988

7. Stachulski AV, Jenkins G. (1998) Nat Prod Rep 15**:**173

8. Brown RT, Carter NE, Mayalarp SP, Scheinmann F. (2000) Tetrahedron 56:7591

9. Hayes JA, Eccles KS, Lawrence SE, Moynihan H.A. (2012) Carbohydr Res 349:108

10. Kuszmann J, Medgyes G, Boros S. (2004) Carbohydr Res 339: 1569

11. Bruker AXS (2009) APEX2 v2009.3-0; Madison, WI

12. Sheldrick GM (2008) Acta Crystallogr A 64: 112

13. Macrae CF, Bruno IJ, Chrisholm JA, Edgington PR, McCabe P, Pidcock E, Rodriguez-Monge L, Taylor R, van de Streek J, Wood P.A. (2008) J Appl Crystallogr 41: 466

14. Spek A.L. (2009) Acta Cryst D65: 148

15. Cremer D, Pople J.A. (1975) J Am Chem Soc 97:1354

16. Flack H.D. (1983) Acta Crystallogr A39: 876

17. Cai C, Wei G, Du Y. (2010) Acta Cryst E66: o949

18. Baddeley TC, Howie RA, Skakle JMS, Wardell, J.L. (2005) Acta Cryst C61: o711

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 (°)
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

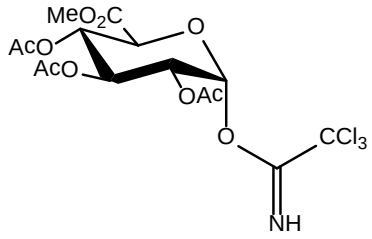


Fig 2

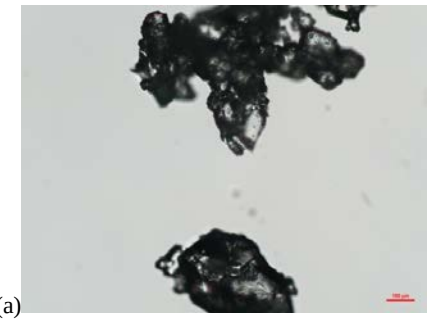
(a)  (b)

Fig 3

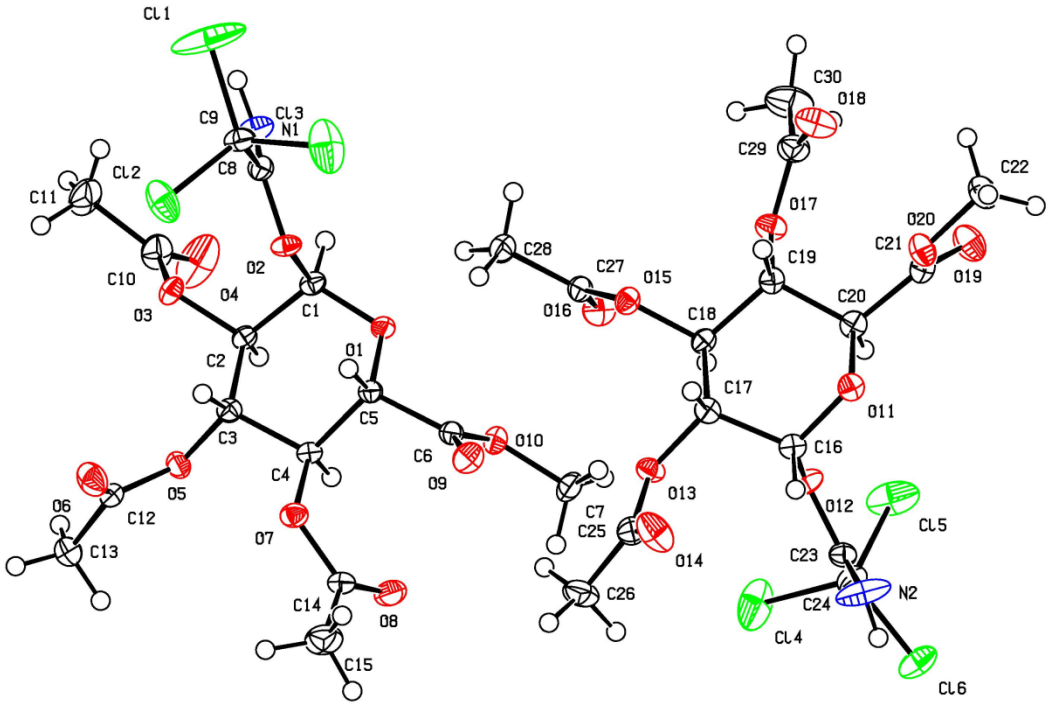

CL1
C9
CL3
N1
C8
CL2
C11
C10
O3
O4
O2
C1
C2
O1
C5
C3
C4
O5
C12
O6
C13
O7
C14
O8
C15
C6
O9
O10
C7
C25
O13
O14
C26
C28
C27
O15
O16
C18
C17
C19
O17
C29
C30
O18
C20
O11
C16
O12
C23
CL5
C24
N2
CL4
CL6
C21
O20
O19
C22

Fig 4

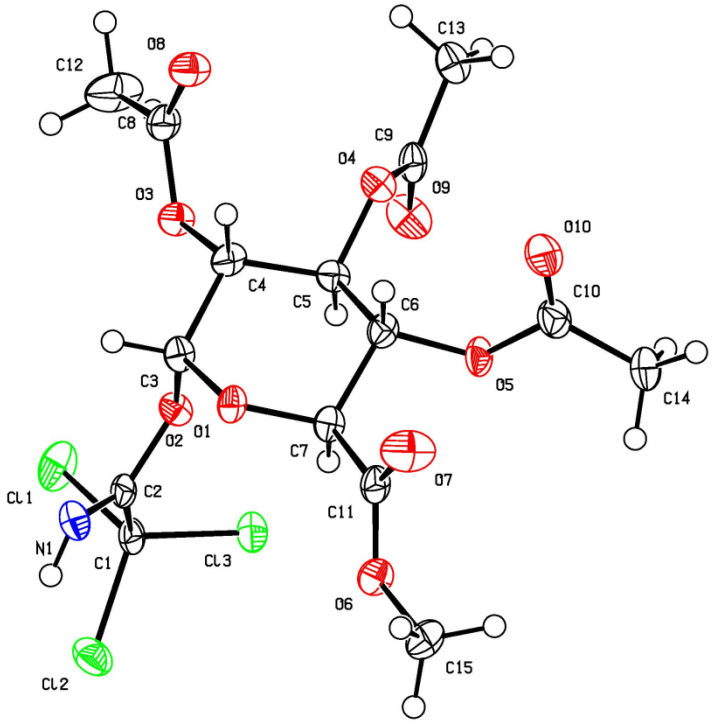
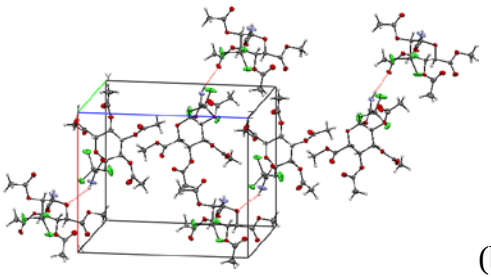

C13
O8
C12
C8
C9
O4
O3
O9
O10
C4
C5
C6
C10
C3
O5
C14
O2
O1
C7
O7
CL1
C2
C11
N1
C1
CL3
O6
C15
CL2

Fig 5

(a)



(b)

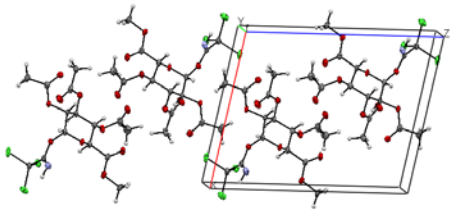
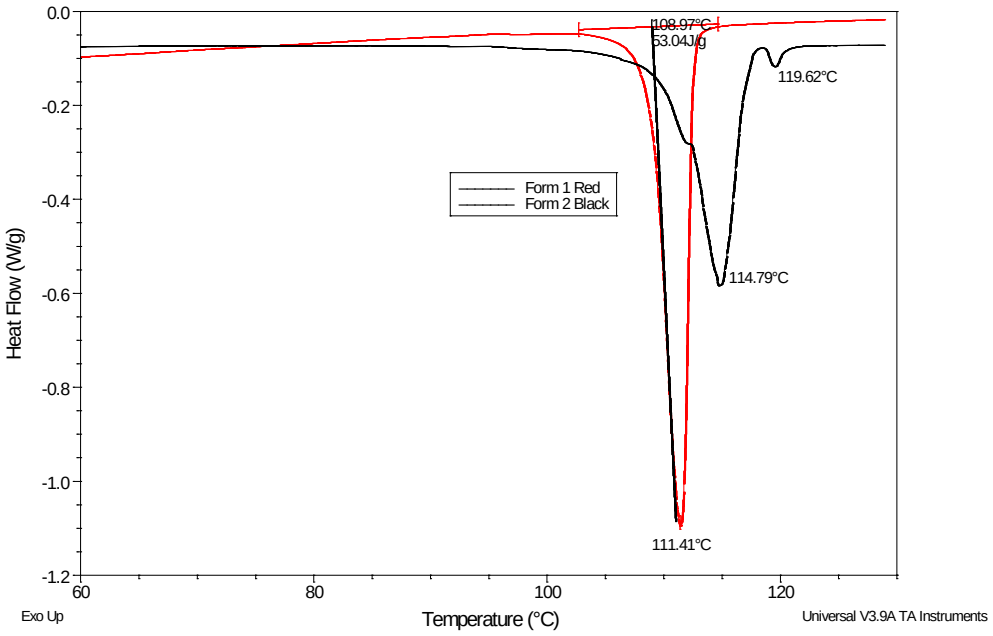


Fig 6


0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
Heat Flow (W/g)
60
80
100
120
Temperature (°C)
Exo Up
Universal V3.9A TA Instruments
Form 1 Red
Form 2 Black
108.97°C
53.04J/g
119.62°C
114.79°C
111.41°C