e-ISSN 2320 –7876 www.ijfans.org
Vol.11, Iss.9, Dec 2022

Research Paper

APPLICATIONS IN SUPRAMOLECULAR CHEMISTRY AND SOLID-STATE REACTIVITY

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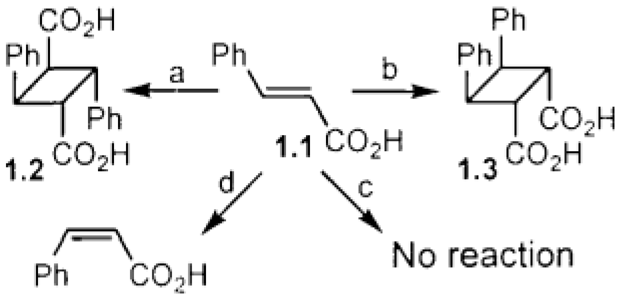
INTRODUCTION

A literature review of organic solid-state reactions and acyl transfer in molecular crystals of cyclitol derivatives. From its beginnings in the early 19th century, knowledge in the area of organic chemistry has mostly been accumulated through the study of reactions in solution. The earliest chemists were probably prejudiced by the Greek philosopher Aristotle's reflection 'No coopora nisi fluida' or 'No reaction occurs in the absence of solvent', in the times when philosophy and religion had a major influence on science. However, today there are many examples of reactions known to proceed in the absence of solvent or in the crystalline state, with many reviews and a few books" dealing with the subject. Solid-state reactions can be developed as green reactions on account of their solvent-free nature and simplicity in workup and purification. While spectroscopic methods have been used for understanding solution-state phenomena, techniques developed to study solid-state reactions include single crystal and powder X-ray diffraction, differential scanning calorimetry, electron microscopy, infrared and solid-state nuclear magnetic resonance spectroscopy. Because of the topochemical control imposed by the crystal lattice, reactions in crystals often occur with ease and great selectivity. Reactivity in the crystalline form is mainly determined by weak contacts and the closeness of reactive groups, while reactivity in solution is determined by the electrical characteristics of molecules. In contrast to the gaseous and solution states, where molecules are free to constantly reorient with respect to each other, the crystal lattice in the solid state serves to predispose the reactants in a favourable orientation for the reaction and thwart changes in their relative orientation with respect to the neighbouring molecules. The crystal lattice's pre-organization of the reactive groups is a factor that contributes to the increased rate and/or stereochemistry of the product produced in crystallisation processes. Crystal packing pressures may reduce the entropy of a reaction's activation by either limiting the molecule conformation, resulting in an intramolecular reaction, or by fixing the relative orientation of the sites in the crystal lattice, allowing for intermolecular processes. However, a variety of additional interactions in the crystal lattice (such as hydrogen bonding, halogen bonding, electrophile-nucleophile interactions, and so on) may prevent potentially reactive groups from forming reactive organisations. As a result, unlike solution state reactions, crystallised reactions often show extreme behaviour, i.e., they may be extremely simple and selective (stereo-, regio-, etc.) or they may not proceed at all in comparison to their solution state counterparts. Solution state reactions, on the other hand, may not be very selective, but they often produce necessary products in isolable amounts. Since relative orientation of the neighbouring molecules is a major factor deciding the facility of the reactions in crystals, unlike in solution state reactions, electronic factors may not contribute much to the facility of the reactions. Amongst the earliest known and well-studied solid-state reactions are addition to C=C bonds. Photodimerization of cinnamic acid (Scheme 1.1) was studied by Schmidt and Cohen.'' which led to the reiteration of Kohlschutter's postulate that reaction in the solid state occurs with a minimum amount of atomic or molecular movement'.

Photochemical reactivity in crystals of Frans-cinnamic acid

Photochemical reactivity in crystals of *trans*-cinnamic acid[6]



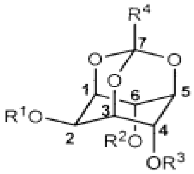
Scheme 1.1 (a) hν , α form (b) hν, β form (c) hν, γ form (d) hν, solution

However, this postulate could not be applied to gas-solid and solid-solid reactions wherein the crystal structures of the reactant and product vary greatly." " Kaupp and co-workers used atomic force microscopy to study the crystal surfaces in such reaction processes and demonstrated that molecules could migrate to great distance within the crystals. often resulting in destruction of the reactant crystal. They concluded that in a solid-state reaction, three processes must occur: namely molecules must be able to migrate within the crystal, the product phase must form at a reasonable rate and the crystal must disintegrate for the generation of a new surface. Additionally, a mechanochemical inter-solid reaction may involve phenomena such as local melting and formation of intermediate eutectic phases resulting in formation of the product in a liquid phase followed by solidification with recrystallization yielding the product crystal lattice.

THE MOLECULAR DESIGN, SYNTHESIS AND CHARACTERIZATION OF MYO-INOSITOL DERIVATIVES

INTRODUCTION

The facility of reactions in solution may be manipulated by the use of suitably modified substrates, reagents and solvents based on their electronic and steric properties. Facile intermolecular reactions in crystals often depend on the molecular pre-organization and the interactions of the reactive groups. Hence, the key to performing solid-state intermolecular reactions is to design molecules and grow crystals in which the reactive groups are prearranged with the required geometry to facilitate the interaction between the reactant molecules without significantly disturbing the crystal lattice during new bond formation. In the preceding chapter, the solid-state reactivities of some di-O-benzoylated myoinositol 1.3.5-orthoesters and the associated acyl transfer mechanism was discussed based on the crystal structures of the reactants. In order to study the scope of this reaction, explore its possible synthetic utility, and examine the impact of small perturbations in chemical structure on the crystal structure and reactivity in the solid state, a series of compounds was prepared by modification of ester groups at various positions. The hydroxyl group at the C4 position was replaced by methyl and allyl groups retaining the benzoates at C2 and C6. The benzoyl group at the C6 position was replaced by acrylate. crotonate and furoate esters, to determine the effect of replacing the benzoate group (which engages in C-H…π interactions. Chapter 1. pg. 31. Fig. lb) with olefinic esters and other aromatic esters, on the molecular structure of the reactive dibenzoate. Secondly, the benzoates at C2 and C6 were replaced by ρ-halobenzoyl (halo = fluoro. chloro, bromo, iodo) and ρ-toluoyl groups to study the effect of substitution on the aromatic ring on molecular pre-organization and electronic effects in solid-state transesterification reactions (Scheme 2.1). Finally, based on the reactivity displayed by the 2-0-benzoyl myo-inositol 1.3.5-orthoesters, some mono-acylated myo-inositol 1,3,5-orthoformate derivatives were also prepared and studied. The synthesis and characterization of these derivatives is described in this chapter. Crystal structures, thermal studies and reactivities of these compounds are discussed in the following chapters.



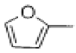
$R^4 = H$

	R^1	R^2	R^3
2.1	H	H	H
2.2	PhCO	PhCO	CH_3
2.3	PhCO	PhCO	$CH_2\text{-}CH{=}CH_2$
2.5	*p*-Br-C_6H_4CO	*p*-Br-C_6H_4CO	H
2.6	*p*-Br-C_6H_4CO	*p*-Br-C_6H_4CO	*p*-Br-C_6H_4CO
2.7	*p*-Cl-C_6H_4CO	*p*-Cl-C_6H_4CO	H
2.8	*p*-Cl-C_6H_4CO	*p*-Cl-C_6H_4CO	*p*-Cl-C_6H_4CO
2.9	CH_3CO	H	H
2.10	PhCO	$CH_2{=}CHCO$	H
2.11	PhCO	 CO	H
2.12	PhCO	$CH_3CH{=}CHCO$	H

$R^4 = Ph$

	R^1	R^2	R^3
2.4	H	H	H

$R^4 = H$

	R^1	R^2	R^3
2.13	 CO	 CO	H
2.14	 CO	H	H
2.15	*p*-CH_3-C_6H_4CO	*p*-CH_3-C_6H_4CO	H
2.16	*p*-CH_3-C_6H_4CO	H	H
2.17	*p*-CH_3-C_6H_4CO	*p*-CH_3-C_6H_4CO	*p*-CH_3-C_6H_4CO
2.18	*p*-I-C_6H_4CO	*p*-I-C_6H_4CO	H
2.19	*p*-I-C_6H_4CO	H	H
2.20	*p*-Br-C_6H_4CO	H	H
2.21	*p*-Cl-C_6H_4CO	H	H
2.22	*p*-F-C_6H_4CO	*p*-F-C_6H_4CO	H
2.23	*p*-F-C_6H_4CO	H	H
2.24	*p*-F-C_6H_4CO	*p*-F-C_6H_4CO	*p*-F-C_6H_4CO

Scheme 2.1 myo-Inositol orthoester derivatives: perturbation of functional groups at C2. C4 and C6. Cl.

Experimental

Benzoyl chloride, thionyl chloride, p-toluene sulfonic acid and all the solvents were purified according to the literature procedures before use. Acryloyl chloride was prepared by heating acrylic acid with benzoyl chloride in the presence of hydroquinone and distillation under vacuum. p-Toluoyl chloride and ρ-halobenzoyl chlorides were prepared by refluxing the respective acids with freshly distilled thionyl chloride for 2-3 h. followed by distillation and drying under vacuum. All air or moisture sensitive reactions were conducted under argon or nitrogen atmosphere. 'Usual work up' of the residue / reaction mixture involved washing of organic layer successively with water, 2% dil. HCl solution (when acid sensitive groups were not present), water, saturated sodium bicarbonate solution and water followed by brine. drying over anhydrous sodium sulfate and evaporation of the solvent under reduced pressure. Light petroleum refers to the 60-80° C boiing fraction of petroleum ether. Thin layer chromatography was performed on E. Merck precoated 60 F254 plates and the spots were rendered visible either by shining UV light or by charring the plates with concentrated

H_2SO_4. Flash column chromatographic separations were carried out on silica gel 230-400 mesh with light petroleum-ethyl acetate mixtures, unless otherwise mentioned. Preparative TLC was carried out on Merck pre-coated 60 F254 glass plates and the spots were rendered to visible by shining UV light. The fractions were isolated by extraction of the appropriate region of the TLC plate with suitable solvents. Compounds previously reported in the literature were characterized by comparison of their melting points and / or ’H N M R spectra with reported data. IR spectra were recorded either as Nujol mull or as thin film (neat) on a Shimadzu F FIR8400 spectrophotometer. NM R spectra were recorded in deuterated solvents on Bruker AV200 (or DRX 500MHz for 'H) spectrometer. Chemical shifts (8) reported are referred to internal tetramethyl silane. F N M R spectra were recorded on Bruker 400MFIz spectrometer with C_6F_6 (hexafluoro benzene) as internal standard. Microanalytical data were obtained using a Carlo-Erba CHNS-0 EA 1108 elemental analyzer. All the melting points were recorded on a Buchi B-540 electro-thermal melting point apparatus. All the asymmetrically substituted myo-inositol derivatives reported are racemic; however, only one of the enantiomers is shown in all the schemes.

The following compounds were prepared as reported in the literature:

myo-inositol 1.3.5-orthoformate (2.1), racemic 2,6-di-0-benzoyl-4-0-methyl myo-inositol 1.3.5- orthoformate (2.2). racemic 2,6-di-O-benzoyl-4-0-allyl myo-inositol 1,3,.5-orthoformate (2.3), 2-0-benzoyl myo-inositol 1,3,5-orthoformate. myoinositol 1,3,5-orthobenzoate (2.4), racemic 2,6-di-O-benzoyl myo-inositol 1,3,5- orthobenzoate (1.179), racemic 2,6-di-(9-(4-bromobenzoyl) inositol 1,3,5- orthoformate (2.5), 2,4,6-tri-0-(4-bromobenzoyl) myo-inositol 1,3,5 orthoformate''' (2.6), racemic 2,6-di-0-(4-chlorobenzoyl) myo-inositol l,3,5-orthoforrnate (2.7). 2.4.6-tri-O-(4-chlorobenzoyl) myo-inositol 1,3,5-orthoformate (2.8) and 2 O-acetyl myo-inositol 1,3,5-orthoformate (2.9).

General procedure for crystallization:

All crystallization experiments were performed under comparable conditions A clear solution of the compound (typically 3-10 mg) in a solvent (1-2 depending on solubility), obtained by vigorous shaking / gentle warming was allowed to stand for 1 to 6 days at ambient temperature. In some experiments (particularly those involving volatile solvents) light petroleum vapour (bp 40-60 ◦ C) was diffused into the solution.

Racemic 2-0-benzoyl-6-0-acryoyl myo-inositol 1,3,5-orthoformate (2.10): Freshly prepared acryloyl chloride (0.182 g, 2 mmol) was added to a cooled solution of the benzoate 1.183 (0.588 g, 2 mmol) and dry triethylamine (0.405 g, 6 mmol) in dry dimethylformamide (DMF, 12 mL) and the reaction mixture was stirred at room temperature for 12 h. The DM F was evaporated under reduced pressure, and the residue was diluted with dichloromethane and washed with water, dilute HCl, saturated sodium bicarbonate solution and brine. The organic layer was dried with anhydrous sodium sulfate and concentrated, and the product purified by column chromatography to obtain racemic 2.10. (0.25 g, 36%).

Mp: 148-150 °C; IR(Nujol,cm^{-1})v:3451,1728,1701;
'H NMR (200 MHz, $CDCl_3$): δ 2.58 (IH, dJ = 6.1 Hz), 4 .4 3 -4 9 (IH, m), 4.50-4.58 (2H, m), 4 63-4,74 (IH. m). 5.53 (IH, q. 1.6 Hz), 5.62 (IH, d, J = 1,3 Hz), 5.68 (IH. td, - 3.9 and 1,6 Hz), 5.91-6.02 (IH, m), 6.07-6.24 (IH, m), 6.45-6.58(IH,m),7.42-7.66(3H.m).8,10-8.22(2H,m)ppm; **CNMR** (125 MHz, CDCI3): 5 63.4, 67.2, 68.1, 68.2, 69.2, 71.5. 102.6, 126.9, 128.2, 129.2, 129.7, 132.7, 133.3, 164.2, 165.9 ppm; **Elemental analysis**: Calcd. for $C_{17}H_{16}O_8$: C, 58.62; H, 4.63. Found: C, 58.86; H, 4.92 %.

Crystallization: Rac-2.10, upon crystallization from ethyl acetate (containing a trace of light petroleum), toluene, methanol, tetrahydrofuran, chloroform and benzene yielded exclusively plate-like crystals (form I). Crystallization from an ethyl acetate light petroleum mixture (1:1 v/v, by vapour diffusion) produced needle-shaped crystals (form II), whereas crystallization from dichloromethane yielded both forms concomitantly, with the relative yield of the form I crystals consistently greater than that of form II crystals. Co-crystallization of rac-2.10 with 2,6-di 0-benzoyl myoinositol 1,3,5-orthoformate (rac-1.177) in ethyl acetate and chloroform with diffusion of light petroleum did not yield crystals.

Racemic 2-0-benzoyl-6-0-(2-furoyl) myo-inositol 1,3,5-orthoformate (2.11): 2-Furoylchloride (0.11 mL, 1.1 mmol) was added to a cooled solution of 1.183, (0.294 g, 1 mmol) in dry pyridine (3 mL) and the reaction mixture stirred at room temperature for 12 h. Pyridine was removed by co-evaporation with toluene and the residue was dissolved in methanol and allowed to stand. Crystals of the benzoate 1.183 appeared over a period of two days and they were filtered out, I he mother liquor when allowed to stand for a further 24 h yielded crude racemic 2.11 (0.1 g. 26%) as a solid, which was extracted with dichloromethane. The residue (0.05 g) obtained from dichloromethane was purified by preparative TLC to obtain 2.11 (0,01 8 g).

Mp: 185.5-187.5 °C; **IR** (Nujol. cm ") v: 3563, 1719. 1701; 'H NMR (200 MHz.$CDCl_3$): 5 2.92 (IH, br s) 4.49-4.53 (IH. m), 4.56-4.62 (2H, m). 4,66-4.76 (IH. m). 5.58-5.60 (IH, q, J - 1.6 Hz), 5.64-5.65 (IH, d, 1.3 Hz), 5.81-5 86 (IH, td, J = 4 and 1.7 Hz), 6.54-6.57 (IH, m), 7.30-7.32 (IH, d, J = 3 Hz). 7.45 7,51 (2H, m). 7.57-7.65 (2H, m). 8.13-8.19 (2H, m) ppm; **CNMR (**125 MHz,($CDCl_3$,): 6 63.4. 67.7, 68.3, 68.4, 69.3, 71.9, 102.3, 112.4, 120.1, 128.5, 129.4, 1 M), 133,6, 143.1. 147.4, 156.3, 166.1 ppm; **Elemental analysis**: Calcd. For $C_{19}H_{16}O_9$: C. 58.77; H. 4.15. Found: C, 59.22; H, 4.39 %.

Crystallization: Rac-2.11, upon crystallization (by slow evaporation) from acetone, ethyl acetate, dichloromethane and chloroform yielded plate-like crystals.

CRYSTALLIZATION AND REACTIVITY OF DI-O-ACYLATED MYO INOSITOL DERIVATIVES

In the introductory chapter of this thesis, the importance of helical hydrogen bonded molecular assemblies in crystals of benzoylated myo-inositol 1,3,5-orthoester derivatives in the context of benzoyl group transfer that occurs along adjacent molecules in these helices was described. The scope of this acyl transfer reaction was briefly examined by synthesising molecules containing esters other than benzoate groups at the equatorial and axial positions. It was consistently observed that the reactive crystals displayed (a) good electrophile - nucleophile geometry, (b) weak interactions which held the migrating group in the p roper orientation for the reaction and (c) discretely packed helices which acted as reaction tunnels for the acyl transfer resulting in high rate of conversion to products. In order to examine the effect of other functional groups at different positions in the myo-inositol {orthoformate framework on the molecular pre-organization and crystalline-state reactivity, the crystal structures of some trisubstituted myo-inositol orthoformates and di acylated myo-inositol orthoformates were studied (Scheme 3.1).

Experimental Details

X-ray crystallography: Intensity data was collected for all crystals on a Bruker SMART APEX CCD diffractometer with graphite-monochromatized (Mo K_α = 0.71073Å) radiation. Diffraction data were collected with a (o scan width of 0.3° at different settings of cp (0, 90, 180 and 270°) keeping the sample-to detector distance fixed at 6,145 cm and the detector position (20) fixed at -28°. The Xray intensities at low temperatures (in some experiments) were measured using an OXFORD LN2 cryosystem. The X-ray data acquisition was monitored by SMART program (Bruker.2003).All the data were corrected for Lorentz-polarization effects using SAINT programs (Bruker, 2003).A semi-empirical absorption correction (multi- scan) based on symmetry equivalent reflections was applied using the SADABS program (Bruker. 2003). Lattice parameters were determined from least-squares analysis of all reflections. The structures were solved by direct methods and refined by full matrix least squares, based on using SHELX-97 software package. Thermal ellipsoid plots were generated using ORTEP-32, packing diagrams were prepared using Mercury-2,3" and geometrical calculations were performed using PLATION.

Differential Scanning Calorimetry (DSC):

The thermal behaviour of crystals was investigated by measuring enthalpy change on a Mettler Differential Scanning Calorimeter. Crystals (2 - 4 mg) placed in a sealed aluminium pan (40 μL) were analyzed from ambient temperature to ~ 35 °C above the melting point of the compound using an empty pan as the reference. The heating rate was 5◦C min (or 10 °C min * in some experiments) and nitrogen gas was used for purging.

Hot stage microscopy (HSM): Crystals heated on the stage (equipped with a temperature probe) were viewed through the eyepiece of a Leica polarizing microscope. Their images were captured using an on-board Leica camera.

General experimental procedure for solid-state reactions: Freshly grown crystals of the compound (1 equiv.) were ground together with activated solid Na_2C0_3 (8 equiv.) into a fine powder using a mortar and pestle. This powder was transferred to a hard glass test-tube and heated in an oil bath (in an inert atmosphere) maintained at a temperature below the melting point of the compound.

The acrylate rac-2.10: A mixture of form I crystals of rac-2.10 (0.052 g, 0.15 mmol) and activated Na_2C0_3 (0.127 g, 1.2 mmol) ground together into a powder, was heated at 100 °C for 40 h. TLC analysis showed the presence of several products and absence of rac-2.10. The mixture was dissolved in dry pyridine and acetylated with excess acetic anhydride. Pyridine was evaporated under reduced pressure and the reaction mixture was diluted with ethyl acetate and washed with water, dilute HCl, $NaHC0_3$ solution, brine. The organic layer was dried with Na_2S0_4 and concentrated to obtain a gum. Analysis by proton NMR spectroscopy revealed the presence of di-acetylated 1.183, i.e., 2-O-benzoyl 4,6-di-O-acetyl myo-inositol 1,3,5-orthoformate amongst other unidentified products.

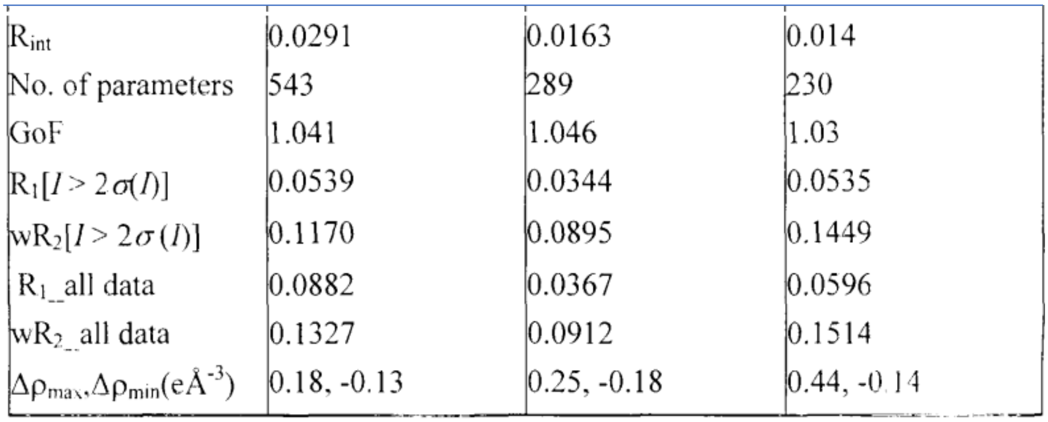
The di-ρ-toluate rac-2.15: A mixture of crystals of rac-2.15 (0.149g,0.35mmol) and activated Na_2C0_3(0.297 g, 2.8 mmol) ground together into a powder, was initially heated at 110 °C for 17 h. TLC indicated the presence of only rac-2.15. The temperature was increased up to 130 °C and heating was continued for 47 h, at the end of which rac-2.15 was recovered quantitatively.

The di-ρ-iodobenzoate rac-2.18: A mixture of crystals of rac-2.15 (0.0195 g, 0.03 mmol) and activated Na_2C0_3(0.0254 g, 0.24 mmol) ground together into a powder, was heated at 130 °C for 72 h. TLC analysis indicated a mixture of products, including rac-2.18 and the diol rac-2.19, which were not separated. The solid-state reactivities of rac-2.10 - form II, rac-2.11 and rac-2.13 could not be studied due to the low yield of crystals of these compounds.

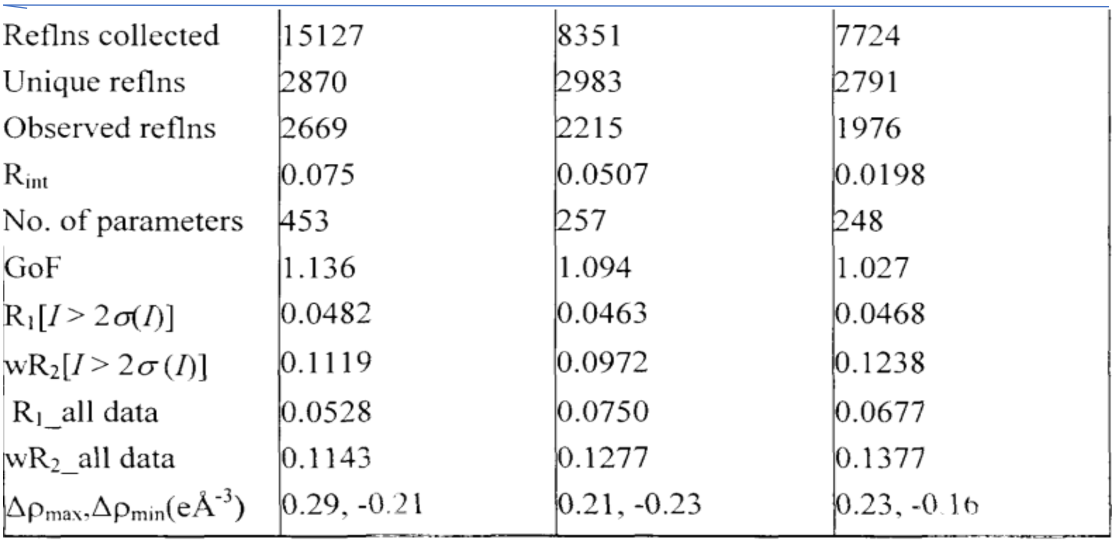
Synthesis, crystallization and X-ray crystallography

Racemic 2,6-di-O-benzoyl 4-O-methyl myo-inositol I,3,5-ortho formate (rac2.2) was synthesised earlier in our laboratory for exploring the solvolysis of benzoyl groups in the presence of the methyl ether at C4. Racemic 2,6-di-O-benzoyl 4-O-methyl myo-inositol I,3,5-ortho formate (rac-2.3) was obtained by silver oxide assisted allylation of rac-1.177.Intensity data for rac-2.2, when collected at low temperature Chapter 3 92 resulted in breakage of the crystal and poor quality diffraction patterns in some trials; hence the data were collected at ambient temperature. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were included in the refinement as per the riding model. The racemic diesters rac-2.10, rac-2.11, rac-2.13, and rac-2.18 were synthesised, characterised and crystallized as described in chapter 2. Diffraction data were collected as reported in Sec. 3.2. Hydroxyl (O H) hydrogen atoms in all the structures were located in difference Fourier maps and refined isotropically. In the case of rac-2.11 and rac-2.18, the 0-H bond length was restrained using the DFIX instruction in SHELXL97. All other H-atoms were placed in geometrically idealized positions and non-hydrogen atoms were refined anisotropically. The experimental details are summarised in Table 3.3 1.

Table 3.3.1 Crystallographic data for tri- and di-substituted myo-inositol 1,3,5 orthoformates.



R_{int}	0.0291	0.0163	0.014
No. of parameters	543	289	230
GoF	1.041	1.046	1.03
$R_1[I > 2\sigma(I)]$	0.0539	0.0344	0.0535
$wR_2[I > 2\sigma(I)]$	0.1170	0.0895	0.1449
R_1_all data	0.0882	0.0367	0.0596
wR_2_all data	0.1327	0.0912	0.1514
$\Delta\rho_{max}, \Delta\rho_{min}(e\mathrm{Å}^{-3})$	0.18, -0.13	0.25, -0.18	0.44, -0.14



Reflns collected	15127	8351	7724
Unique reflns	2870	2983	2791
Observed reflns	2669	2215	1976
R_{int}	0.075	0.0507	0.0198
No. of parameters	453	257	248
GoF	1.136	1.094	1.027
$R_1[I > 2\sigma(I)]$	0.0482	0.0463	0.0468
$wR_2[I > 2\sigma(I)]$	0.1119	0.0972	0.1238
R_1_all data	0.0528	0.0750	0.0677
wR_2_all data	0.1143	0.1277	0.1377
$\Delta\rho_{max},\Delta\rho_{min}(e\text{Å}^{-3})$	0.29, -0.21	0.21, -0.23	0.23, -0.16

CONCLUSION

Organic reactions in the solid-state have been attracting the attention of chemists in recent times because of the product selectivity (due to the fixed orientation and minim movement of molecules in the crystal lattice), which is often different from that observed in the solution state. The reactions in the solid state can be regarded as environment friendly green reactions. Techniques such as X-ray crystallography, solid-state NMR spectroscopy and electron microscopy have emerged as tools that provide information about the reaction centres and mechanism of reactions that proceed in the solid state. Amongst the earliest reported and well-studied solid-state reactions are photochemical addition reactions of olefinic double bonds (C=C)[3]. A variety of other reactions such as pinacol coupling, Beckmann rearrangement. Chapman rearrangement, Michael addition, Grignard, Reformatsky and Luche reactions, Wittig reactions, sodium borohydride reduction, group transfer reactions (methyl, aryl and acyl groups), cis-trans isomerization, and epimerization are known to proceed in the solid-state or under solvent free conditions/ Nucleophilic addition to carbonyl groups is one of the most frequently encountered reactions in organic chemistry. Often, the tetrahedral intermediate generated in such an addition reaction undergoes elimination to regenerate the carbonyl group in a new product, as in reactions of carboxylic acids and their derivatives. Although addition - elimination reactions in solution phase are ubiquitous, documentation of their occurrence in the condensed phases (solvent less) is scarce. Facile benzoyl group migration in the solid-state in di-O-acylated myo-inositol ortho ester derivatives was reported from our laboratory. The subsequent chapters describe our attempt to further probe and understand and broaden the scope of these acyl transfer reactions. In this thesis we investigated the effect of substitution of the hydrogen atom at the bridgehead carbon with methyl and phenyl groups. The effect of substitution of the ester groups at other positions in myo-inositol orthoformate on molecular organization and reactivity in the crystalline state has now been studied by synthesizing esters other than benzoates at C-6 and C-2 position, the synthesis and characterization of derivatives.

The relationship between the structure and solid-state reactivity of di-(9-acylated inositol orthoformate derivatives, was studied by varying the acyl group at the C6(4) position of the diol 1.183. Examination of the crystal structures revealed that acryloyl and the furoyl groups do not induce a helical self-assembly of molecule in the solid-state, as the benzoyl group did. Though rac-2.10 crystallised in two different modifications, none of them possessed the geometry required for acyl transfer reactions. Replacing the benzoyl groups by 4-iodobenzoyl and 4-methylbenzoyl groups resulted in molecular organization in the form of bilayers similar to that observed in the polymorphs of the analogous bromo and chloro derivatives. The hydrogen bonding patterns observed in these compounds seem to arise from the weak interactions due to the ester substitutions at the C6 position and different substituents at the para position in the benzene rings. Evidently, even small perturbations in the chemical structure of a compound can affect the molecular pre-organization in the modified derivatives. Molecules with closely related chemical structures may assemble in radically different fashion in the crystalline-state, which determines their solid-state properties. While reactions in the solid state and single crystals are attractive as 'green reactions', designing molecules which contain reactive groups and growing their crystals wherein the reactive centers are in a favourable orientation for the reaction is still a challenging goal.

The diols 2.16,2.20,2.21 and 1.183 have similar molecular structures, differing only in the substitutions at the para position in the aromatic ring , but the molecular preorganization in the crystals vary greatly. The organization of the molecules of these monoesters in their crystals affects their reactivity to different extent. While 1.183 and 1.185 yielded a mixture of products in the solid-state, the reaction in crystals of 2.16 was more specific attributed to better El- Nu geometry in its crystals. Furthermore, increase in the specificity of the reaction with increase in temperature could be due to the lowering of activation energy required for the acyl transfer and the favourable geometry of the reactive centres. Flow ever, the extent of conversion of 2.16 to products in not high, perhaps due to the lack of reaction channels that allow domino type of reaction in crystals. In contrast the molecules in 2.20 associate in a fashion which does not bring the El and Nu in the required pre-organization for reaction, perhaps due to the interplay of other weak interactions in the crystal. The results presented in this section show that compounds that are inert in solution can display reactivity in the solid-state due to the improved relative geometry of the reacting groups and due to the inflexibility of molecular movement enforced by the packing forces in the crystal lattice. A comparison of the crystal structures and reactivity of the mono acylated and di acylated inositol orthoesters reveal the necessity of reaction channels that allow domino type of reaction in crystals, to achieve specificity and high extent of conversion of reactants to products. A study of molecular pre-organization through weak interactions in structurally related compounds containing electrophilic and nucleophilic groups and their reactivities can aid in designing molecules and growing crystals which react to give specific products in good yield.

The experimental results, database surveys and analysis of solid-state reactions reported in literature in volving the carbonyl group and an electrophile indicates that the presence of favorable electrophile-nucleophile geometry is apprerequisite for a facile reaction. Additionally in an intermolecular reaction, the presence of a reaction tunnel for propagation of the reaction through the crystals is also essential for a clean reaction and to achieve complete conversion of reactants to products. An understanding of poly morphism , solvatomorphism and phase changes in a system can be utilized to control the re activity in the solid-state. It appears that prior assessment of the electrophile-nucleophile geometry in crystals can be used as a criterion for the prediction and explanation of their solid state re activity and as corollary, reactions that are facile in the crystalline state can often be explained based on the geometry of the reactive centers. Solid-state reactions have not been utilized to a large extent in synthetic organic chemistry with the exception being photo chemical reactions in organic crystals. The reason for this could be the difficulty associated in predicting crystal structures and obtaining crystals that contain the reactive centers in the right orientation and the existence of polymorphic modifications and their phase transitions. Even with such limitations, it is still meaningful to explore reactions in the condensed phases as an alternative to solution state reactions, for the unique product selectivity, high yield, and more often than not simplicity in workup and handling that a facile solid-state reaction can exhibit.

REFFERENCES:

1. (a) G. R. Desiraju, Crystal Engineering. The D esign of Organic Solids. Elsevier, Amsterdam, 1989; {b) G. R. Desiraju, Angew. Chem. Int. Ed. Engl.. 2007. 46, 8342-8356.

2. (a) P. Metrangolo, G. Resnati, T. Pilati and S. Biella, Struct. Bond, 2008, 126. 105-136; (b) M. Fourmigue, Curr. Opin. Solid State Mater. S c i. 2009. 13. 36 45. 3. M.Nishio,Y.Umezawa. K.Honda, S.Tsuboyama and H.Suezawa, CrystEngCom m , 2009, I I . 1757-1788.

4. G. Cavallo, P. Metrangolo. T. Pilati, G. Resnati. M. Sansotera and G. Terraneo, Chem. Soc. Rev.. 2010, 39, 3772-3783.

5. (a) D. L. Reger, J. D. Elgin, R. F. Semeniuc, P. J. Pellechia and M. D. Smith. Chem. Commun., 2005, 4068-4070; {b) Y. Chang, Y. Chen, C, Chen. Y. Wen. J. T. Lin, H. Chen, M. Kuo and I. Chao, J. Org. Chem., 2008, 71 4608-4614.

6. (a) R. Bishop, M. L. Scudder, D. C. Craig, A. Noman, M. M, Rahman and S. F. Alshahateet, Mol. Cryst. Liq. Cryst., 2005, 440, 173 186; {b) M. C. Aragoni, M. Area, F. Demartin, F. A. Devillanova, T. Gelbnch, A. Garau. M. B. Flursthouse and F. Isaia and V. Lippolis, Cryst. Growth Des., 2007, 7. 1284-1290. 7. C. Murali, M. S. Shashidhar, R. G. Gonnade and M. M. Bhadbhade. Chem Eiir. , /..2009. /5. 261-269. Chapter 3 114

8. Bruker 2003, SADABS (Version 2.05). SM ART (Version 5.631) and SAINT (Version 6.45). Bruker AXS Inc., Madison, Wisconsin. USA.

9. G. M. Sheldrick. ActaCrystallogr., Sect. A: Found. CrystaUogr. 2008. 64. 112- 122.

10. L. J. Farrugia. J. Appl. Crystallogr., 1997, 30, 565.

11. C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler and J. van de Streek, J. Appl. Crystallogr., 2006, 39, 453 457. 12. A. L. Spek, J. Appl. Crystallogr., 2003, 36, 7-13.

13. T. Das and M. S. Shashidhar, Carbohydr. Res., 1997, 297, 243-^249.

14. T. Praveen, T. Das, K. M. Sureshan, M. S. Shashidhar, U. Samanta. D. Pal and P. Chakrabarti, J. Chem. Soc. Perkin Trans. 2, 2002, 358-365.

15. M. P. Sarmah, R. G. Gonnade, M. S. Shashidhar and M. M. Bhadbhade, Chem. Eur. J. 2005, I I , 2103-2110.

16. (a) T. Steiner, W. Hinrichs, W. Saenger, and R. Gigg, Acta Cryst. Sect. B. 1993, 49, 708-718; [b) R. G. Gonnade, M. S. Shashidhar, M. M. Bhadbhade, and A. K. Sanki, Chem. Commun., 2005, 5870-5872; (c) R. G, Gonnade, M. S. Shashidhar, and M. M. Bhadbhade, CrystEngCom m , 2008, 10, 288-296.

17. (a) S. D. Cosgrove. G. Steele, T. K. Austin, A. P. Plumb, B. Stensland, E, Ferrari and K. J. Roberts. J. Pharm. Sci., 2005, 94, 2403-2415; {b) S. Wishkerman and J. Bernstein, CrystEngCom m , 2006, 8, 245-.M-9; (c) D. Vega, A. Petragalli, D. Fernandez and J. A. Ellena, J. Pharm. Sci., 2006, 95. 1075 1083; (d) S. Roy, P. M. Bhatt, A. Nangia and G. J. Kruger, C'ryst. Growth

18.Purification of Laboratory Chemicals, Perrin, D. D. and Arrnarego, W, L. F. 2nd edition, Pergamon Press, Oxford, UK, 1988.

19. BeiLstein, 2, IV, I47I. 3. Vogel's Textbook of Practical Organic Chemistry, 5th edition. UK 1989

20. P, Uhlrnann and A. Vasella, flelv. Chim. Acta. 1992, 75, 1979 1994

21. T. Das and M. S. Shashidhar, Carhohydr. Res., 1997, 297. 243-249.

22. U. Samanta, V. G. Puranik. P. Chakrabarti. P. Thoniyot and M. S. Shashidhar. Acta Cryst. Sect. C 1998, 54. 1289-1291.

23. G. Bhosekar, C. Murali, R. G. Gonnade, M. S. Shashidhar, and M. M. Bhadbhade, Cryst. Growth Des., 2005, 5, 1977-1982.

24. C. Murali, M. S. Shashidhar, R. G. Gonnade and M. M. Bhadbhade. Eur. J. Org. Chem., 2007, 1153-1159.

25. R. G. Gonnade, M. M. Bhadbhade and M. S. Shashidhar, CryslEngComm. 2008, 70,288-296.

26. R. G. Gonnade, M. M. Bhadbhade, M. S. Shashidhar and A. K. Sanki, Chem. Com mim., 2005. 5870-5872. U.K.M.Sureshan and M.S.Shashidhar, Tetrahedron Lett., 2000, 41. 4185 4188.

27.J. D. Dunitz, Acta Crystallogr. Sect. B: Struct. Sci., 1995, 57, 619-631;

28.G. R. Desiraju, Science, 1996, 278, 404-405;

29. J. A, R. P. Sarma and (i. R. Desiraju, Crystal Engineering: Polym orphism and Pseudopolym orphism in Organic Crystals: A Cam bridge Structural D atabase Study, ed. S. R. Seddon and M. Zaworotko, Kluwer, Norwell, MA, USA, 1999;

30. T. Threlfall, Org. Process Res. Dev., 2000, 384-390;

31. J. Bernstein, Polymorphism in M olecular Crystals, Oxford University Press, Oxford, UK, 2002;

32. R. K. R. Jetti, R. Boese, J. A. R. P. Sarma, L. S. Reddy, P. Vishweshwar and (1. R. Desiraju,/Ingeiv. Chem., Int. Ed. E n g l, 2003, 42, 1963-1967;

33. A. Kalman. A cta Crystallogr. Sect. B: Struct. Sci., 2005, 61, 536-547;

34. K. Manoj, R. G. Gonnade, M. M. Bhadbhade and M. S. Shashidhar,Cryst. Growth Des., 2006, 6, 1485-1492; (/) A. Kalman and L. Fabian, Acta Crystallogr. Sect. B: Struct. Sci., 2007, 63, 411-417;

35. K. Manoj, R. G. Gonnade, M. M. Bhadbhade and M. S. Shashidhar, CrystEngCom m , 2009, IJ, 1022-1029; (A) R. G. Gonnade. M. M. Bhadbhade and M. S. Shashidhar, CrystEngCom m , 2010, 12, 478-484. 2. (a) M. D. Cohen and G. M. J. Schmidt, J. Chem. Soc., 1964, 1996 2000;