Reactivity Controlled by Lattice Interactions in Crystal: Intermolecular Acyl Transfer in (±)-2,4-Di-*O*-benzoyl-*myo*-inositol 1,3,5-Orthoformate

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Received September 8, 1997

Abstract: (±)-2,4-Di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate, on heating in the presence of a base, undergoes transesterification to give 2,4,6-tri-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate and 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate in the solid state. The same reaction can also be performed by microwave irradiation instead of heating. The crystal structure of the dibenzoate reveals that the screw-axis-related molecules have the hydroxyl and the carbonyl groups ideally oriented for the reaction and gives a close picture of how such a reaction proceeds in enzymes. The structure of the corresponding acetate, (±)-2-*O*-benzoyl-4-*O*-acetyl-*myo*-inositol 1,3,5-orthoformate, lacks this geometry and hence is unreactive in the solid state. Both the acetate and the benzoate undergo base-catalyzed transesterification in solution.

Introduction

Preorganization of the reacting groups is a factor responsible for the enhanced rate and the stereochemistry of the product obtained by enzyme catalysis.[1] Likewise, zeolites, polymers, and many other hosts provide structured environments for carrying out specific reactions.[2] Some interesting and well-studied examples of geometrically or topochemically controlled reactions are observed in the solid state where the crystal lattice serves to predispose the reactants in a favorable orientation for the reaction and thereby achieves selectivities often not possible in solution.[3] Crystal packing forces can lower the entropy of activation of a reaction by either constraining the molecular conformation leading to a unimolecular reaction or fixing the relative orientation of the sites in the crystal matrix facilitating intermolecular processes. However, most of the intermolecular reactions studied in the solid state involved the dimerization of olefinic bonds, mainly because of the higher chances of observing the proper orientations of the double bonds by stacking of the molecule.[4] Other types of reactions involving different chemical entities are only rarely encountered[5]—weak interactions between the prospective reacting functional groups become overwhelmed by numerous other interactions (like hydrogen bonding) in the crystal lattice positioning them away from each other. Herein, we report on a solid-state reaction that proceeds through the nucleophilic addition of a hydroxyl group to a carbonyl group and show how the proper juxtaposition of the two groups leads to a reaction in one system, whereas the absence of such an orientation prevents the reaction from taking place in another system which, nevertheless, was expected to show a greater reactivity.[6]

Results and Discussion

The dibenzoate[7] **1**, on heating with solid sodium carbonate at 140 °C for 60 h, gave the tribenzoate[8] **3** in excellent yield (Scheme 1). Since this is a disproportionation reaction, the maximum yield of **3** and **5** obtainable is 50% each. The isolated yields of **3** and **5** were 47% and 49%, respectively. These add to a total yield of 96%. There was no reaction when the dibenzoate **1** was heated in the absence of sodium carbonate, and **1** could be recovered quantitatively. This control reaction

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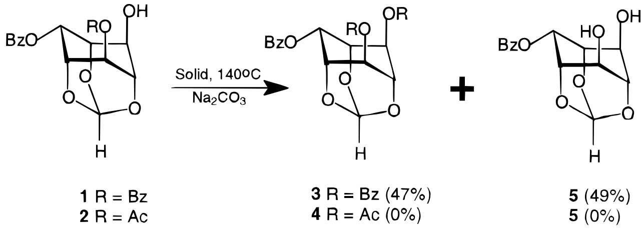
S0002-7863(97)03133-8 CCC: $15.00

Scheme 1



1 R = Bz
2 R = Ac

3 R = Bz (47%)
4 R = Ac (0%)

5 (49%)
5 (0%)

clearly showed that the transesterification of **1** in the solid state is catalyzed by a base. The reaction time for the transesterification of the dibenzoate **1** could be greatly reduced by irradiating the reaction mixture with microwaves.[9] The isolated yield of the tribenzoate **3** after irradiation for 25 min was 46%.

The melting points of the starting dibenzoate **1** and the products **3** and **5** are 163−164, 216−218, and 210−213 °C, respectively. All these melting points are well above the reaction temperature (140 °C), which clearly rules out the reaction under discussion in the molten state. We recorded the X-ray powder pattern for **1** and sodium carbonate as well as for the reaction mixture (see Supporting Information). The diffraction pattern for the reaction mixture is just the superposition of the two reactants recorded separately. These results exclude the possibility of formation of a new solid phase on mixing and grinding the dibenzoate **1** with sodium carbonate.

The acetate[10] **2** (mp 198 °C) decomposed on heating (at 140 °C) in the presence of sodium carbonate, and no transesterified product **4** could be isolated. Since the expected product, diacetate **4**, has a melting point of 142−143 °C, to rule out the possibility of decomposition of **4** after the reaction, we carried out the transesterification of **1** as well as **2** at lower temperatures. In the case of **1,** the yields of **3** and **5** obtained (after heating for 60 h) respectively were, at 120 °C, 31% and 30% and, at 100 °C, 19% and 19%. The acetate **2**, when allowed to react as above, was unreactive, and neither the diacetate **4** nor the diol **5** could be isolated (90% of **2** could be recovered at 100 °C). These experiments clearly showed that the acetate **2** is unreactive, whereas the benzoate **1** undergoes transesterification under identical conditions in the solid state.

The benzoate **1** as well as the acetate **2** undergoes transesterification in refluxing acetonitrile solution (24 h), in the presence of diisopropylethylamine, to yield 26% and 29% of triesters **3** and **4**, respectively. This reaction in solution is likely to proceed by the intramolecular catalytic assistance provided by the axial hydroxyl group, as has been shown in the base-catalyzed methanolysis of **1**.[7] Despite both **1** and **2** having a free axial hydroxyl group, it is only the benzoate **1** that undergoes the facile reaction in the solid state, suggesting that the proper orientation of the reacting functional moieties (reduction in the entropy of activation), rather than the catalytic assistance by the axial hydroxyl group, is important for the reaction in the solid state. An explanation for the difference in the reactivity in the solid state can be sought in terms of the crystal structures of the two compounds (Figures 1 and 2).

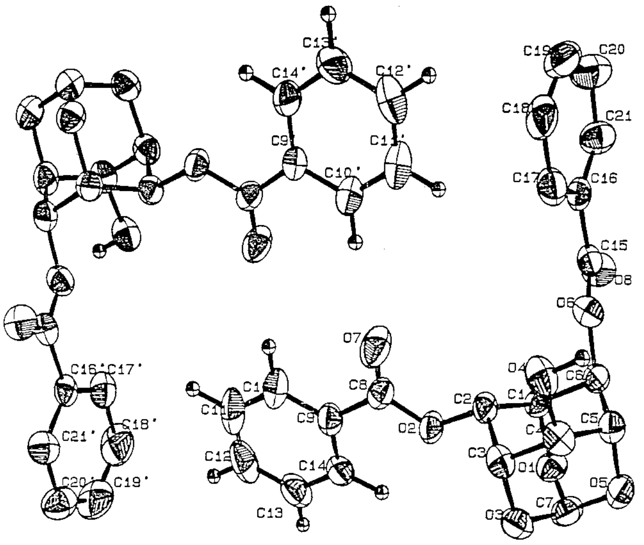


Figure 1. ORTEP[22] diagram of **1**. For clarity all the atoms are not labeled for the primed molecule; H atoms are not shown except for the two central benzene rings and the hydroxyl groups.

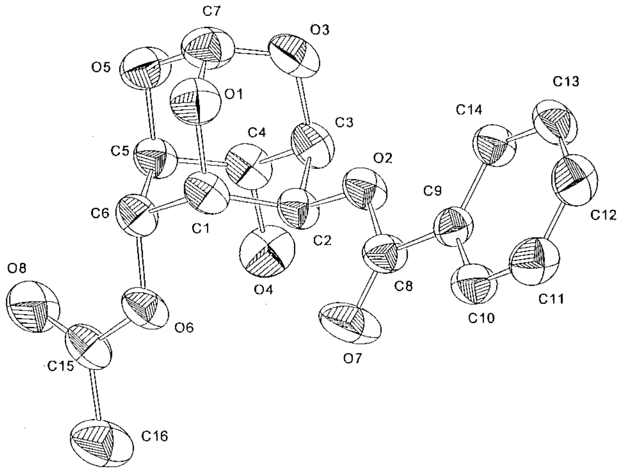


Figure 2. ORTEP[22] diagram of **2**. H atoms are omitted.

The principle of structure correlation[11] has been used to map the reaction pathway for the addition of a nucleophile, Nu (amino or hydroxyl), to a carbonyl group.[12] At distances close to or below the sum of the van der Waals radii of Nu and C, the Nu···C=O angle was observed to be nearly constant at 110°. The crystal structure of **1** is interesting enough in itself, as it shows a close association between the two molecules in the asymmetric unit[13] brought about by van der Waals interaction supplemented by the favorable edge-to-face orientation of two pairs of aromatic rings[14] (Figure 1). But more pertinent to our discussion, the hydroxyl group is ~3.2 Å from the carbonyl

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(10) The acetate **2** was prepared by the monobenzylation (K_2CO_3/benzyl bromide in DMF) of the diol **5**, followed by acetylation (acetic anhydride/pyridine) and hydrogenolysis (Pd−C/H_2). Yield obtained in the hydrogenolysis reaction varied depending on the source and batch of the catalyst used. The acetate **2** gave IR, NMR (^{1}H and ^{13}C) spectra, and elemental analysis consistent with its structure (Praveen, T.; Das, T.; Shashidhar, M. S. Submitted for publication).

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(13) The two independent molecules are related by a pseudocenter of symmetry: 0.75, 0.58, 0.25 being the mean of the equivalent atomic positions; i.e., the structure is not too far from *C*2/*c*. This could explain the somewhat surprising fact (Table 1) that the two independent molecules in the unit cell make almost the same interactions with their symmetry-related mates.

Table 1. Distances (Å) and Angles (deg) Involving Intermolecular O···C=O Interactions in the Crystal Structures of **1** (both molecules) and **2**[a]

	1		**2**
O4···C15	3.226(5)	3.249(5)	3.748(3)
O4···C15−O8	88.1(2)	89.9(3)	33.1(1)
C4−O4···C15	117.5(2)	113.1(2)	96.0(1)
H(O4)−O4···C15	113.1(2)	110.0(2)	13.7(1)

[a] The hydroxyl group (O4) is provided by the molecule at *x*, *y*, *z*, and the carbonyl group (>C15=O8) comes from the positions 1 − *x*, 1/2 + *y*, 1/2 − *z* and 2 − *x*, −1/2 + *y*, 1/2 − *z* for the two molecules in the asymmetric unit for **1** and 2 − *x*, 1 − *y*, 2 − *z* for **2**. The standard deviations on various parameters are given in parentheses.

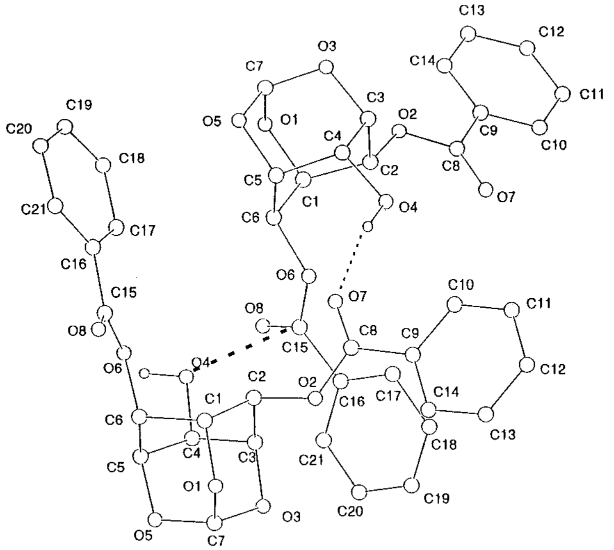

Figure 3. Two crystallographic symmetry-related molecules of **1** held together by hydrogen bonding (thin dashed line) and O···C=O interaction (thick dashed line). The pair corresponding to the second molecule in the asymmetric unit is not shown. For clarity protons other than the ones belonging to the hydroxyl groups have been omitted.

carbon atom of the benzoyl group of a symmetry-related molecule, such that the O···C=O angle is ~90° (Table 1 and Figure 3). Moreover, the X−O···C angles (where X corresponds to the two atoms bonded to O4, viz., C4 and H(O4)) are close to the tetrahedral value indicating that the sp^3 lone pair on the hydroxyl group is oriented approximately perpendicular to the carbonyl group. This relative orientation of the two groups ‘frozen-in’ along the reaction pathway is facilitated by the attractive nature of the nucleophile−electrophile interaction[12] and has also been observed in macromolecular structures.[15] An additional hydrogen bond between the two molecules (Figure 3), again reminiscent of what is observed between the protein and the substrate in the active site of enzymes,[1] helps to maintain the right geometry. As a result, on heating with a base, the reaction is driven to completion along the right pathway. On the contrary, the hydroxyl and the carbonyl groups are involved in intermolecular hydrogen bonding in **2** (Figure 4), and the geometry is not conducive for an electrophile−nucleophile interaction. The large relative movement required to achieve the proper orientation is opposed by various lattice contacts. Indeed, it is known since the pioneering work of Schmidt[16] that a solid-state reaction is facile if it involves a minimum amount of atomic or molecular movement. Consequently, the transesterification reaction in the crystal of **2** cannot proceed.[17]

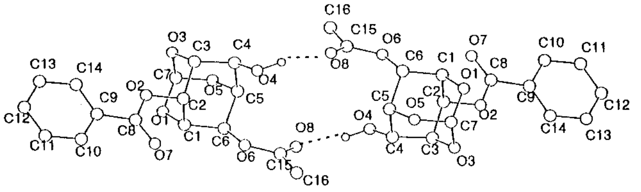

Figure 4. Two molecules of **2** related by a crystallographic inversion center and connected by hydrogen bonding (dashed lines) between the hydroxyl and the carbonyl groups. The closest intermolecular contact between the hydroxyl group and the carbonyl carbon atom also occurs between O4 and C15, shown here.

In most cases, solid-state reactions do not proceed quantitatively, mainly due to the gradual collapse of the lattice as the reaction progresses, which eventually destroys the favorable arrangement of molecules. High yields are only attained if the product is crystallographically isostructural with the starting material (so that the lattice does not collapse) or due to kinetic factors, i.e., if the reaction occurs at a high rate as a domino process in symmetry-related chains. In the present case (**1**), the products have crystal structures[18] quite different from that of the starting material. The high yield of the reaction may be due to the fact that the two molecules of **1** (providing the two reactive groups) are held together tightly (as discussed earlier) by nucleophile−electrophile interaction as well as hydrogen bonding.

Conclusions

There are only a few known examples of intermolecular reaction (usually methyl transfer) brought about in the crystalline state.[5] The reaction reported here involves the substrate **1** and the catalyst (Na_2CO_3) in two solid phases. This indicates that the catalysis occurs at or near the surface of the substrate crystals, and this provides an example showing how the crystal packing (i.e., the interactions in the bulk) can be a controlling factor for a reaction occurring on or near the surface. In the crystal, two screw-axis-related neighbors of **1** are optimally arranged for the nucleophilic attack by a hydroxyl group to a carbonyl center. As the reaction is quite ubiquitous in nature—being used by serine proteases and lipases, as well as many hydrolases and transferases[19]—the geometry of alignment between the reactive groups found here provides a realistic model of what goes on in the enzyme active site.

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(17) It can, however, be added that the intramolecular O4···C15=O8 geometry is quite amenable for an electrophile−nucleophile interaction, values for the four parameters reported in Table 1 being 3.320(3) Å, 98.9(2)°, 96.8(1)°, and 91(1)°, respectively, and the intramolecular migration of the acyl group is a distinct possibility. Nonetheless, since **2** is racemic, this does not lead to a new product.

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Table 2. Summary of Crystal Data, Data Collection, and Structure Solution and Refinement Details

	1	**2**
Crystal Data		
formula	$C_{21}H_{18}O_8$	$C_{16}H_{16}O_8$
molar mass	398.36	336.29
color, habit	colorless, prism	colorless, prism
crystal size, mm	0.30 × 0.30 × 0.70	0.83 × 0.75 × 0.40
crystal system	monoclinic	triclinic
a, Å	16.674(5)	8.370(2)
b, Å	9.822(2)	9.473(2)
c, Å	22.533(5)	9.755(3)
α, deg	90	101.29(2)
β, deg	90.70(2)	102.87(2)
γ, deg	90	90.46(2)
V, Å^3	3690(2)	738.4(3)
space group	$P2_1/c$	$P\bar{1}$
Z	8	2
$F(000)$	1664	352
d_{calc}, g cm^{-3}	1.434	1.513
μ, mm^{-1}	0.111	0.123
Data Acquisition		
T, K	293(2)	293(2)
unit-cell reflcns (θ range, deg)	25 (16.5−23)	25 (14.3−21.8)
max θ (deg) for reflcns	23.42	23.46
hkl range of reflcns	−18 18, 0 10, 0 25	−9 9, 0 10, −10 10
variation in three standard reflcns	<1%	0.0%
reflcns measd	5432	2187
unique reflcns	5432	2187
reflcns with $I > 2\sigma(I)$	3423	1977
Structure Solution and Refinement		
refinement on	F^2	F^2
solution method	SHELXS86	SHELXS86
H atom treatment	from Δ-map, not refined	from Δ-map, not refined
no. variables in LS	523	217
k in $w = 1/(\sigma^2 F_o^2 + k)$ $[P = (F_o^2 + 2F_c^2)/3]$	$(0.0914P)^2 + 4.3008P$	$(0.0728P)^2 + 0.5070P$
R, R_w, gof	0.060, 0.177, 1.068	0.047, 0.1296, 1.057
density range in final Δ-map, e Å^{-3}	−0.373, 0.327	−0.335, 0.225
final shift, error ratio	−0.001	−0.001
sec extnct type	none	none

Experimental Section

Transesterification in the Solid State. The dibenzoate **1** (0.100 g, 0.25 mmol) and sodium carbonate (0.212 g, 2.0 mmol) were ground together using a pestle and mortar, and the resulting mixture was heated at 140 °C in an atmosphere of argon for 60 h. The solid obtained after the reaction was cooled to ambient temperature and extracted with chloroform followed by methanol. The combined organic extract was evaporated to dryness; the products **3** (0.06 g, 47%) and **5** (0.036 g, 49%) were isolated by column chromatography over silica gel (eluant: ethyl acetate−light petroleum, gradient elution) and characterized by comparison (TLC, mp, IR, and NMR spectra) with authentic samples.[8] Transesterification of **1** was also carried out at 100 and 120 °C as above. The yields of **3** and **5** obtained (after heating for 60 h) respectively were, at 120 °C, 31% and 30% and, at 100 °C, 19% and 19%.

Transesterification of 1 in the Solid State by Microwave Irradiation. Transesterification of **1** was also carried out (as above) using **1** (0.100 g, 0.25 mmol) and sodium carbonate (0.212 g, 2.0 mmol) by irradiating the reaction mixture in a microwave oven (make, BPL-Sanyo; power, 400 W). Yield of the tribenzoate **3** obtained after irradiation for 25 min was 46%.

Transesterification in Solution. The dibenzoate **1** (0.100 g, 0.25 mmol) was dissolved in 1 M diisopropylethylamine solution (2 mL) in dry acetonitrile and refluxed for 24 h. The solvent was evaporated, and the residue was chromatographed as above to obtain the tribenzoate **3** (0.033 g, 26%) and the diol **5** (0.019 g, 26%).

Transesterification of the acetate **2** (0.129 g, 0.37 mmol) in the presence of diisopropylethylamine was carried out as above (in 3 mL of solution) to obtain the diacetate **4** (0.040 g, 29%) and the diol **5** (0.032 g, 29%). The diacetate **4** was characterized by comparison (TLC, mp, IR, and NMR spectra) with an authentic sample.[8]

X-ray Crystallography. Crystals in the form of colorless prisms were grown by dissolving **1** in a minimum volume of chloroform and slowly diffusing into it petroleum ether (60−80 °C). The acetate **2** was crystallized from chloroform. Intensities of reflections to 2θ (Mo) = 47° were measured by $\omega/2\theta$ scan technique on a CAD-4 diffractometer. Structures were solved using the program *SHELXS*86,[20] and least-squares refinement on $|F^2|$ was carried out with *SHELXL*93.[21] All the H atoms were located from the difference Fourier map, and their isotropic temperature factors were kept fixed. Crystal data for **1** and **2** are given in Table 2.

Acknowledgment. We thank Dr. V. Ramaswamy for recording the powder diffraction pattern and Dr. B. M. Bhawal for suggestions in carrying out transesterification by microwave irradiation. Financial support from the Department of Science and Technology is gratefully acknowledged. T.P., U.S., and T.D. were supported by fellowships from the Council of Scientific and Industrial Research and the University Grant Commission, New Delhi, India.

Supporting Information Available: X-ray powder diffraction patterns for the dibenzoate **1**, sodium carbonate, and the reaction mixture (**1** + sodium carbonate) (3 pages, print/PDF). See any current masthead page for ordering and Web access instructions.

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