Base-catalysed Acyl Migrations in *myo*-Inositol Dibenzoates

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Base-catalysed isomerizations of readily available I(1,4)Bz_2 and its derivatives efficiently provided all nine regioisomers of IBz_2 and the kinetic behaviour of the benzoyl-migration has been studied.

Since the first report that D-*myo*-inositol-1,4,5-trisphosphate(1,4,5-IP_3) acts as a second messenger through mobilising Ca^{2+} from intracellular stores,[1] the study of the chemistry and biology of the inositol phosphates has seen a rapid progress.[2] Several other *myo*-inositol polyphosphates (IP_ns) including another putative second messenger, 1,3,4,5-IP_4, were also found in living systems and studies to elucidate their functions are in progress. Research on the biological functions of IP_ns would be facilitated by the availability of complete sets of natural and synthetic compounds in quantities. Some of the all possible 63 IP_n isomers,† have been synthesised by independent chemical routes, but the complete preparation of all possible IP_n regioisomers has not yet been achieved.[3]

One of the key problems in the syntheses of inositol phosphates is to prepare suitable, selectively protected inositol intermediates. We have been interested in the syntheses of all possible IP_n isomers, and our synthetic strategy is based on the facile generation of regioisomers of *myo*-inositol benzoates(IBz) as the key intermediates. Recently we have accomplished the total syntheses of all nine regioisomers in the IP_4 set by way of IBz_2 intermediates.[4]

The acyl group migration to its neighbouring hydroxy under acidic or basic conditions has been well known in carbohydrates. The review on the chemistry of *myo*-inositol by Shvets[5] states that acyl migration is almost equally probably in *trans*- and *cis*-directions. But Meek *et al.* reported that the benzoyl migration in I(1,4)Bz_2(**1c**) selectively gave I(2,4)Bz_2(**1f**), the *cis*-migrated compound as the major product in 60% aq. pyridine at 100 °C.[6] We have reexamined these conditions for possible adoption in our synthesis of IP_n regioisomers. The reported conditions did not show much selectivity, instead gave a mixture of all possible nine IBz_2 regioisomers. Therefore, we investigated the kinetic profiles of the benzoyl migrations in IBz_2.

We chose the readily available **1c**, and its monoacetal derivatives **2**, **3** as the starting materials for our study. The nine regioisomers of IBz_2(**1a–i**) generated from **1c** by treatment with aq. pyridine could be nicely analysed by HPLC. The increasing order of the HPLC retention time of these isomers has been found to be I-1,4(**1c**), 2,4(**1f**), 2,5(**1g**), 1,5(**1d**), 1,2(**1a**), 4,6(**1i**), 1,3(**1b**), 4,5(**1h**), 1,6(**1e**)Bz_2 (Fig. 1).[4] when partially protected derivatives of I(1,4)Bz_2, **2** and **3** were subjected to the 60% aq. pyridine conditions and then 80% aqueous acetic acid at reflux, two sets of five isomers of IBz_2 were obtained from the limited benzoyl group migrations (Fig. 2).

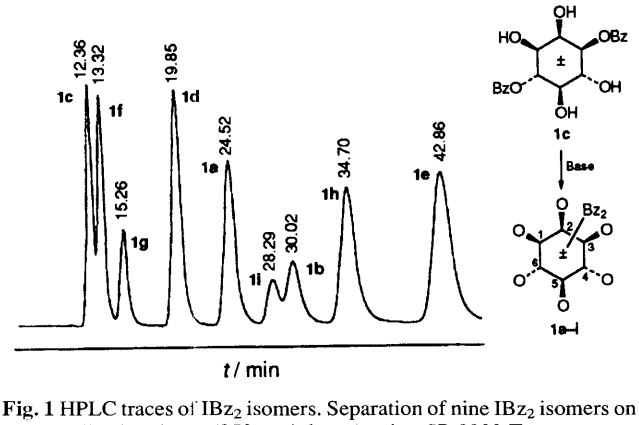

Fig. 1 HPLC traces of IBz_2 isomers. Separation of nine IBz_2 isomers on RP 18 Alltech column (250 × 4.6 mm) using SP 8800 Ternary pump and SP 8450 UV–VIS detector (λ_{max} = 230 nm). Relative peak areas were determined by an SP 4290 integrator. The mobile phase was acetonitrile–water (20:80) at a flow rate of 2 ml min^{-1}. The structural assignments are as follows: **1a**(1,2-IBz_2), **1b**(1,3), **1c**(1,4), **1d**(1,5), **1e**(1,6), **1f**(1,6), **1g**(2,5), **1h**(4,5), **1i**(4,6).

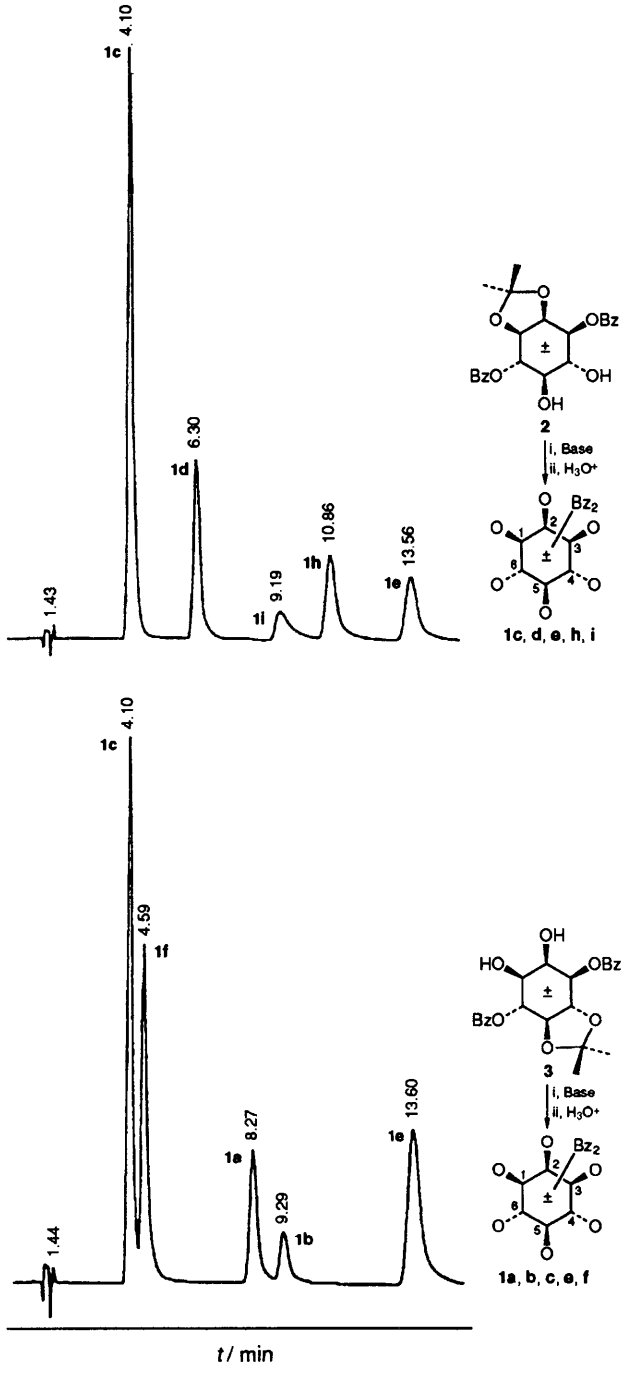

Fig. 2 Separation of five inositol dibenzoate isomers. The HPLC conditions were the same as Fig. 1 except that the mobile phase was acetonitrile–water (22:78).

From the kinetic profiles of **1c**, **2**, **3** at various temperatures (Fig. 3), it is quite clear that the *cis*-1,2-benzoyl migration is generally faster than the *trans* migration as expected, and that the initial product distributions are largely due to one migrations and then slowly followed up by two migrations to reach the equilibrium mixture [Fig. 3, (*a*), (*c*)]. The temperature variation showed substantial effects on the overall migration rate to the equilibrium, but not much on the *cis*/*trans* selectivity. With compound **2**, no discernible selectivity was observed under all conditions examined, suggesting that the energy barriers in the available *trans* migrations in **2** are similar.

In order to understand the nature of the migratory behavior we have also subjected compounds **1c** and **3** to various other

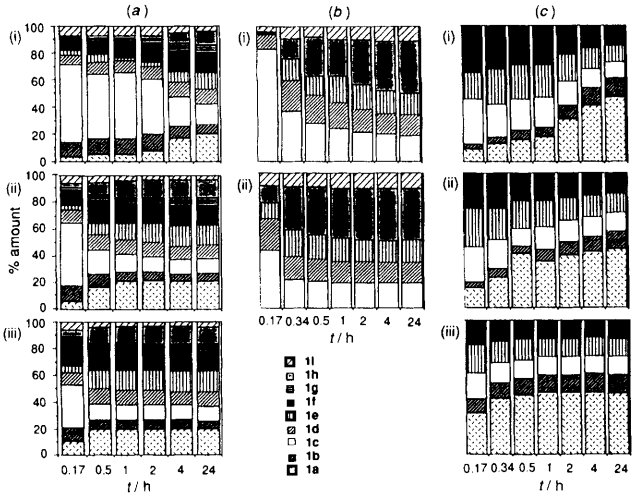

Fig. 3 Kinetic profiles of IBz_2 isomerisation. (*a*) Aq. pyridine-catalysed isomerisation of **1c** was measured at 60 (i), 80 (ii) and 100 °C (iii). (*b*) Aq. pyridine-catalysed isomerisation of **2** at 80 (i) and 100 °C (ii) followed by hydrolysis. (*c*) Aq. pyridine-catalysed isomerisation of **3** at 60 (i), 80 (ii) and 100 °C (iii) followed by hydrolysis.

Table 1

Run	Substrate	Conditions[a]	Product distribution								
			1a	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**	**1i**
1	**3**	py–toluene (1 : 1) 100 °C, 1 h	—	—	89	—	—	11	—	—	—
2	**3**	py, 100 °C, 1 h	—	—	80	—	—	20	—	—	—
3	**3**	py–DMF (1 : 1) 100 °C, 1 h	—	—	74	—	—	26	—	—	—
4	**3**	Py–H_2O (9 : 1) 100 °C, 1 h	—	2	64	—	7	27	—	—	—
5	**3**	py–H_2O (8 : 2) 80 °C, 1 h	1	—	48	—	15	36	—	—	—
6	**3**	py–H_2O (8 : 2) 100 °C, 10 min	36	12	24	—	17	11	—	—	—
7	**3**	THF (Na_2CO_3) room temp., 1 d	—	—	74	—	9	17	—	—	—
8	**3**	DMF (Na_2CO_3) room temp., 2 h	—	—	29	—	24	47	—	—	—
9	**3**	DMF (Na_2CO_3) room temp., 4 h	6	2	27	—	20	45	—	—	—
10	**1c**	py–H_2O (9 : 1) 60 °C, 1 h	12	4	33	12	8	16	7	3	5
11	**1c**	DMF (Na_2CO_3) room temp., 2 h	—	—	92	—	—	8	—	—	—
12	**1c**	DMF (Na_2CO_3) room temp., 40 h	2	4	48	5	6	26	3	—	6

[a] The benzoyl migrations were carried out under the indicated conditions by using the substrate (2 mg) and the solvent (2 ml). All reactions were homogeneous except those employing Na_2CO_3 (100 mg). In the case of **3**, the acetonide protecting group was hydrolysed in boiling aq. acetic acid before analysis.

reaction conditions and the results are shown in Table 1. Several trends are clearly discernible. From the data in entries 1–3, the *cis*-migration rate in **3** increases with the increasing solvent polarity.‡ The entries 4–6 show that an increasing amount of water facilitates the migration, but the initially observed *cis*/*trans* selectivity slowly disappears with the increasing reaction time under these conditions. The product distribution in entry 6 was found to represent essentially the equilibrium mixture. The same solvent polarity effect on the migration rate and the loss of the *cis*/*trans* selectivity could be seen with sodium carbonate base at room temperature (entries 7–9). The benzoyl migration in **1c** showed similar trends (entries 10–13). With sodium carbonate base in DMF, the migration in **1c** took place more slowly than in **3** (entries 8–9 *vs.* 11–12). The *cis*/*trans* selectivity of the migration in **1c** in aq. pyridine could not be improved by lowering the reaction temperature (entry 10).

These results might be explained on the basis of the following. (*i*) The *cis*-migrations generally involve lower activation energies than the competing *trans*-migrations because of the apparent geometric advantages.§ (*ii*) The benzoyl migration involves a tetrahedral intermediate, which is more polar than the starting material and thus better stabilized by more polar solvent environment, and proceeds at a faster rate in polar solvents such as aq. pyridine and DMF. The effect of water on the reaction rate appears to be primarily due to its polarity rather than its protic nature. (iii), The reasonably high *cis*/*trans* selectivity observed in **3** as opposed to **1c** is most likely due to its rigid conformation which is more conducive to the *cis*-migration. In order to obtain a good *cis*/*trans* selectivity in compounds such as **1c** with flexible conformations, one needs to find conditions which allow reasonably fast migrations while conformational rigidity is maintained. Our mechanistic and synthetic studies on the acyl migrations are in progress with the aids of X-ray crystallography, spectroscopy and computational methods.

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Footnotes

† No. of isomers. IP:4(6), IP_2:9(15), IP_3:12(20), IP_4:9(15), IP_5:4(6), IP_6:1. Total 39 regioisomers (enantiomerically 63).

‡ Solvent polarity is defined as polarity index, *P'*, which is a measure of the ability of the solvent to interact with various polar test solutes. *P'* for pyridine = 5.3, pyridine–toluene (1 : 1) = 3.9, pyridine–DMF (1 : 1) = 5.9, pyridine–water (9 : 1) = 5.8, pyridine–water(8 : 2) = 6.3, THF = 4.0, DMF = 6.4 (see ref. 7).

§ From the X-ray crystal structure of **3**, the distances of O(1)···O(2) for *cis*-migration and O(3)···O(4) for *trans*-migration are found to be 2.800 Å and the somewhat longer 2.875 Å, respectively.

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