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Preliminary communication

General path of *O*-acyl migration in D-glucose derivatives

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Acyl migration that is acid- and base-catalyzed is often observed[1] in partially acylated carbohydrates, and can occur not only upon treatment with base or acid, but also during such various reactions as methylation, benzylation, thioacetal formation, and catalytic hydrogenation. The products obtained from these reactions are frequently complex or of unpredictable structure, due to consecutive migrations. In acyl-D-glucoses and -D-glucosides, each oxygen atom of a D-glucose unit is a site of migration origin; an acyl group migrates, in most cases, away from O-1 towards O-6, although each migration step is a reversible process as suggested by an orthoacid intermediate. One typical example is the Purdie methylation of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside; this yields the 3,4,6-tri-*O*-acetyl-2-*O*-methyl derivative[2], which has been considered as the product of consecutive O-2 → -3 → -4 → -6 acyl migrations.

Of several migration processes possible, the migrations O-4 → -6 and O-1α → -2 have a reasonable stereochemical basis and are well established[3], whereas the others (except O-2 → -3) have no direct experimental evidence. Although *trans*-migration* was suggested to occur with almost equal ease as *cis*-migration in some *myo*-inositol derivatives[4], only the O-2 → -3 migration was observed for D-glucose derivatives, *i.e.*, the base-catalyzed migration of methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside into the 3-*O*-benzoyl derivative[5], and the Purdie methylation of methyl 2,4,6-tri-*O*-acetyl-β-D-glucopyranoside, which gave the 3,4,6-tri-*O*-acetyl-2-*O*-methyl derivative[6]. Acyl migrations in compounds having a $^1C_4$(D) conformation, such as O-3 → -6, O-2 → -4, O-1β → -3, and O-1β → 6, though possible, are not considered as a major path. The present investigation identifies the processes that are favored or unfavored among those just discussed, and also the processes that are reversible or irreversible.

We observed that methyl mono-*O*-myristoyl-α- and -β-D-glucopyranosides showed considerable extent of acyl migration on heating for 5 min at 200° in a glass tube, whereas they were stable at 150°. Mono-*O*-myristoyl-D-glucopyranoses were more labile, and extensive migration was observed at 130–150°. Therefore, acyl migrations of all isomeric mono-*O*-myristoyl derivatives of D-glucopyranose[7] and methyl D-gluco-

*The terms *trans*- and *cis*-migration are used for acyl migration between *trans vic*-glycol and between *cis vic*-glycol groups, respectively.

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pyranosides[8] under various conditions (including thermal, acid- and base-catalyzed, and solvolytic conditions) were investigated (see Table I). The products were analyzed by g.l.c.–c.m.r.[8,9] as per-*O*-trimethylsilyl derivatives (see Table I).

Although the migration patterns were dependent on the conditions of the reaction, a general path of acyl migration for *O*-myristoyl-D-glucoses and -glucosides could be identified as follows:

(a) The well known OH-1α → -2 and OH-4 → -6 migrations take place easily. Evidence for the reverse process (OH-6 → -4) of the latter was confirmed for *O*-myristoyl-D-glucosides (Exp. 1 and 2).

(b) For *trans*-migrations, the OH-2 → -3 process was confirmed (Exp. 7, 8, 26, and 32). It was apparently reversible for *O*-myristoyl-D-glucosides (Exp. 5, 6, and 15), and also for *O*-myristoyl-D-glucose with pyridine (Exp. 31). However, OH-3 → -4 and OH-1β → -2 migrations were not observed.

(c) OH-3 → -6 Migration (through $^1C_4$ conformation) was common for either *O*-myristoyl-D-glucoses or -glucosides. Comparison of the products obtained from 3-*O*- with those from 4-*O*-myristoyl derivatives clearly indicates that this migration did not proceed through a 4-*O*-myristoyl intermediate. The reverse migration (OH-6 → -3) was also observed, though to a small extent, for an *O*-myristoyl-α-D-glucoside (Exp. 10 and 12). However, the OH-2 → -4 migration in an *O*-myristoyl-α-D-glucoside and -D-glucose (Exp. 1, 3, and 30) was not observed, but instead the reverse OH-4 → -2, although it was to a small extent. These results suggest that the migrations through $^1C_4$ (D) conformation occur much more readily for the α- than for the β-D anomer.

(d) The *O*-myristoyl-1β group was rather stable to acyl migration. Upon heating in pyridine, the group migrated to *O*-3, and then to *O*-6 (Exp. 34). The possibility of direct OH-1β → -6 migration is not evident from this experiment and requires further investigation. Contrary to the other *O*-myristoyl-D-glucoses, the *O*-myristoyl-1β derivative was solvolyzed to D-glucose and methyl myristate when merely being kept in methanol solution (Exp. 28).

Interestingly, 6-*O*-myristoyl- produced from 3-*O*-myristoyl-D-glucose by fusion was in the α-D form only (Exp. 19), despite that 6-*O*-myristoyl-α-D-glucopyranose was anomerized on fusion or on being kept in solution to give a 1:1 mixture of α- and β-D anomers (Exp. 17). This result may be explained by postulating a 7-membered ortho-ester intermediate having the α-D configuration only, the formation of the corresponding β-D anomer would require a higher energy. The α-D anomer would be quenched to give 6-*O*-myristoyl-α-D-glucopyranose on being dissolved in pyridine to form the per-*O*-trimethylsilyl derivative, thus providing evidence for a direct OH-3 → -6 migration. The 6-*O*-myristoyl-D glucose produced from the 4-*O*-myristoyl derivative was a mixture of α- and β-D anomer, as expected (Exp. 18).

The preference for OH-2 → -3 migration and the lack of OH-3 → -4 and -1β → -2 migrations may be rationalized by considering the changes of torsion angles in a pyranose ring. The easily reversible migration OH-2 → -3 in glucosides suggests that the dihedral angle between O-2 and O-3 decreases to a value lower than that expected for

TABLE I

MIGRATIONS OF *O*-MYRISTOYL GROUP IN METHYL MONO-*O*-MYRISTOYL-D-GLUCOSIDES AND MONO-*O*-MYRISTOYL-D-GLUCOSE

Exp.	*Methyl O-myristoyl glucoside*	*G.l.c.* [a]	*Conditions* [b]	*Product composition (%)* [c]
1	6-α-	0.90	A	2-α- (10), 4-α- (17), s.m. (73)
2	6-β-	0.84	A	4-β- (18), s.m. (82)
3	4-α-	0.69	A	2-α- (10), s.m. (35), 6-α- (55)
4	4-β-	0.72	A	s.m. (50), 6-β- (50)
5	3-α-	0.70	A	2-α- (28), s.m. (28), 4-α- (trace), 6-α- (44)
6	3-β-	0.70	A	2-β- (36), s.m. (30), 6-β- (34)
7	2-α-	0.80	A	s.m. (20), 3-α- (23), 6-α- (57)
8	2-β-	0.79	A	s.m. (40), 3-β- (60), 6-β- (trace)
9	All samples		C	Unchanged
10	6-α-		D	3-α- (10), s.m. (90)
11	Other samples		D	Unchanged
12	6-α-		F	2-α- (trace), 3-α- (16), s.m. (84)
13	4-α-		F	s.m. (35), 6-α- (65)
14	4-β-		F	s.m. (22), 6-β- (78)
15	3-α-		F	2-α- (28), s.m. (30), 6-α- (24)
16	Other samples		F	Unchanged
	O-Myristoyl-D-glucose			
17	6-α- [d]	0.86(α), 0.89(β)	B	6-α- [d] (49), 6-β- [d] (51)
18	4-α,β- [d]	0.70	B	s.m. (49), 6-α,β- [d] (51)
19	3-α,β- [d]	0.70	B	s.m. (55), 6-α- [d] (45)
20	2-α,β- [d]	0.80	B	Unchanged
21	1-α-	0.71	B	s.m. (52), 2-α,β- [d] (48)
22	1-β-	0.79	B	Unchanged
23	6-α- [d]		C	3-α,β- [d] (14), 6-α- [d] (42), 6-β- [d] (44)
24	4-α,β- [d]		C	s.m. (13), 6-α- [d] (39), 6-β- [d] (48)
25	3-α,β- [d]		C	s.m. (18), 6-α- [d] (36), 6-β- [d] (46)
26	2-α,β- [d]		C	3-α,β- [d] (14), 6-α- [d] (43), 6-β- [d] (43)
27	1-α-		C	s.m. (15), 2-α,β- [d] (23), 6-α,β- [d] (62)
28	1-β-		C	Glucose, methyl myristate
29	6-α- [d]		E	6-α- [d] (46), 6-β- [d] (54)
30	4-α,β- [d]		E	2-α,β- [d] (23), s.m. (21), 6-α,β- [d] (56)
31	3-α,β- [d]		E	2-α,β- [d] (25), s.m. (21), 6-α,β- [d] (54)
32	2-α,β- [d]		E	s.m. (21), 3-α,β- [d] (35), 6-α,β- [d] (44)
33	1-α-		E	s.m. (21), 2-α,β- [d] (35), 6-α,β- [d] (44)
34	1-β-		E	s.m. (39), 3-α,β- [d] (19), 6-α,β- [d] (42)
35	6-α- [d]		F	6-α- (52), 6-β- [d] (48)
36	4-α,β- [d]		F	s.m. (7), 6-α- [d] (39), 6-β- [d] (54)
37	3-α,β- [d]		F	s.m. (51), 6-α- [d] (49)
38	Other samples		F	Unchanged

[a] Relative retention time for per-*O*-trimethylsilyl derivatives; internal standard, cholesterol. Column: 1.5% of OV-1 on Shimalite W (80–100 mesh). Temp. for methyl *O*-myristoyl-D-glucosides, 250°; and for *O*-myristoyl-D-glucose, 270°. [b] (A) Fusion at 200° (bath temp.), 10 min; (B) fusion at 150° (bath temp.), 10 min; (C) In methanol solution, being kept at room temp. for one week. (D) in pyridine solution at 130° (bath temp.) for 1 h; (E) in pyridine solution at 120° (bath temp.) for 8 h, and (F) in 0.5% *p*-toluenesulfonic acid solution in 1,4-dioxane at room temp. for 48 h. [c] The composition was analyzed by g.l.c. of the per-*O*-trimethylsilyl derivative and confirmed by c.m.r. spectral analysis; abbrev.: s.m., starting material. [d] Easy anomerization.

normal *trans*-diequatorial substituents. This decrease produces an increase of the dihedral angles between O-3 and O-4, and between O-1 and O-2. Consequently, the formation of a 5-membered ring orthoacid intermediate between these groups requires a higher energy and is destabilized, thus inhibiting the OH-3 → -4, and -1β → -2 migrations. Calculations of these angles from the reported X-ray analysis data[10] support this conclusion. For crystalline methyl α-D-glucopyranoside having $^4C_1$ (D) conformation, the angles between O-2 and O-3, and between O-3 and O-4 are 58.7° and 67.7°, respectively, showing a marked difference. The angle for the *cis*-relationship O-1α and O-2 is 61.5°. These data suggest that the pyranose ring may be distorted during the reaction in order to decrease the angle between O-2 and O-3 without a great increase of the torsion energy. Details of the experiments reported in this communication and a more detailed discussion will be given in a full publication.

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