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General Path of *O*-Acyl Migration in D-Glucose Derivatives: Acyl Migration of Methyl Mono-*O*-myristoyl-α- and β-D-Glucopyranosides and Mono-*O*-myristoyl-D-glucopyranoses[1)]

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Although the migration pattern was 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: (1) The well known *O*-1α→ -2 and *O*-4→ -6 migrations take place easily. Evidence for the reverse process (*O*-6→ -4) of the latter migration was obtained for *O*-myristoyl-D-glucosides. (2) For *trans*-migrations, the *O*-2→ -3 process was confirmed. It was apparently reversible for *O*-myristoyl-D-glucosides and also for *O*-myristoyl-D-glucose with pyridine. However, *O*-3→ -4 and *O*-1β→ -2 migrations were not observed. (3) *O*-3→ -6 Migration (through the $^1C_4$(D) conformation) was common for either *O*-myristoyl-D-glucoses or -glucosides. The reverse migration (*O*-6→ -3) was also observed, though to a small extent, for an *O*-myristoyl-α-D-glucoside. However, the *O*-2→-4 migration in an *O*-myristoyl-α-D-glucoside and -D-glucose was not observed, but instead the reverse *O*-4→ -2 process occurred, although only to a small extent. These results suggest that the migrations through the $^1C_4$(D) conformation occur much more readily for the α- than the β-D-anomer. (4) 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. In contrast to the other *O*-myristoyl-D-glucoses, the *O*-myristoyl-1β derivative was solvolyzed to D-glucose and methyl myristate merely when kept in methanol solution.

Keywords——acyl migration; methyl mono-*O*-myristoyl-α-D-glucopyranoside; methyl mono-*O*-myristoyl-β-D-glucopyranoside; mono-*O*-myristoyl-D-glucopyranose; 1-*O*-acyl-β-D-glucopyranose; $^1C_4$(D) conformation; $^4C_1$(D) conformation

The facile migration of acyl groups under acid- and base-catalyzed conditions in partially acylated polyhydric alcohols or carbohydrates is often observed and has been a subject of numerous reports.[2)] It occurs not only upon treatment with acid or base but also during such various reactions as methylation, benzylation, *p*-toluenesulfonylation, thioacetal formation, demercaptalation, and catalytic hydrogenation. It is also observed merely on melting the compound.[3)] The migration is intramolecular in nature and is interpreted as proceeding through a cyclic orthoacid intermediate. The products obtained from the above reactions, however, are frequently complex or of unpredictable structure, due to consecutive migrations; there seems to be no theoretical basis as yet.

In acyl-D-glucoses and -D-glucosides, each oxygen atom of the D-glucose unit is a site of migration origin; an acyl group migrates, in most cases, away from *O*-1 toward *O*-6. Although each migration step is a reversible process, as suggested by a generally accepted orthoacid intermediate, reverse migration is seldom observed.[4)] It has been believed that migration proceeds by the general path *O*-1α,1β→ -2→ -3→ -4→ -6 through a $^4C_1$(D) conformation. One typical example is the methylation of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (I) by methyl iodide and silver oxide (Purdie methylation); this yields the 3,4,6-tri-*O*-acetyl-2-*O*-methyl derivative (II),[5)] which has been considered as the product of consecutive *O*-2→ -3→ -4→ -6[6)] acyl migrations. The path contains several *trans*-migrations,[7)] even though they are hardly expected for cyclohexane-1,2-diols (formation of a five-membered ring orthoacid from

a *trans*- is far more difficult than from a *cis*-disposed glycol).

Of several migration processes, the migrations *O*-4→ -6 and *O*-1α→ -2 have a reasonable stereochemical basis and are well established[8] (they proceed through stable six- and five-membered intermediates, respectively), whereas the others (except *O*-2→ -3) have no direct experimental evidence and are only assumed to have occurred from the structure of the final products.[2] Although *trans*-migration was suggested to occur with almost equal ease to *cis*-migration in some *myo*-inositol derivatives,[9] only the *O*-2→ -3 migration was confirmed for D-glucose derivatives, *i.e.*, base-catalyzed migration of methyl 2-*O*-benzoyl-4,6-benzylidene-α-D-glucopyranoside (III) to give the 3-*O*-benzoyl derivative (IV) (on dissolution of the former in acetone–aqueous sodium hydroxide, the latter almost immediately crystallized out)[10] and Purdie methylation of methyl 2,4,6-tri-*O*-acetyl-β-D-glucopyranoside (V), which gave the 3,4,6-tri-*O*-acetyl-2-*O*-methyl derivative (VI).[11]

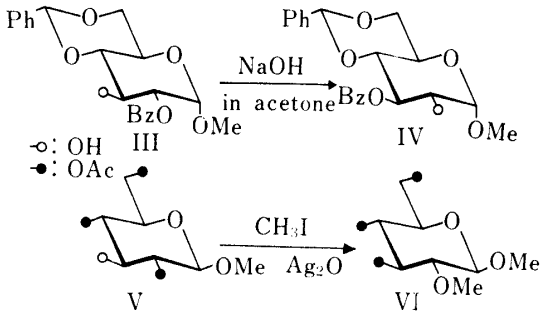

Chart 1. *O*-2→-3 Acyl Migration in D-Glucoside Derivatives[10,11]

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 major paths. *O*-1β→ -6 Migration was once assumed[12] to explain the formation of methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (VIII) from 1,2,3,4-tetra-*O*-acetyl-β-D-glucose (VII) by Purdie methylation, but the possibility of consecutive *O*-1β→ -2→ -3→ -4→ -6 migrations was later suggested since $^4C_1$(D) is the favored conformation for D-glucose.[13] However, the real path is still uncertain if we recall that for cyclohexanediol derivatives a *cis*-1,3-migration generally occurs more readily than a *trans*-1,2-migration, since ring formation between the two groups involved in the reaction is apparently reducing serious 1,3-diaxial interaction created by a ring inversion.

Keeping these circumstances in mind, the present investigation was undertaken to identify the processes that are favored or disfavored among those just discussed, and also the processes that are reversible or irreversible. Obviously, in addition to the relative configurations at the two centers involved, many other factors, external and internal, are operating on acyl migrations actually observed, such as the solubility of each product, acidity and alkalinity of the medium, and polarity and stereochemical bulk of the migrating acyl group(s) and of substituent(s) already present. In particular, a substituent must markedly influence the relative stability of each migration product. All of these factors complicate the detailed analysis of the migration paths.

We thought that some of these confusing factors might be excluded by studying the migration of mono-*O*-acyl derivatives under simple thermal conditions, such as melting. If enough energy is applied, the ratio of each product obtained in an equilibrated mixture will reflect the relative stability of each component, and if the reaction is stopped at an early stage, the product composition will reflect the relative ease of each migration process.

The difficulty is how to correctly analyze the composition of the product, which is expected to be a mixture of several isomers (positional and anomeric in the cases of D-glucose derivatives); this may be the reason why no report on acyl migration of mono-*O*-acyl-D-

glucose derivatives has appeared. A method of analysis is now available, since we have prepared all positionally and anomerically isomeric mono-*O*-myristoyl-D-glucopyranoses and methyl mono-*O*-myristoyl-D-glucopyranosides, and determined their analytical behavior; gas chromatography (GC) of the per-trimethylsilyl (TMS) derivatives and ^{13}C-nuclear magnetic resonance (^{13}C-NMR) spectra are particularly useful.[14] For this reason we chose myristoyl as an acyl moiety for acyl migration experiments.

We observed that methyl *O*-myristoyl-α- and β-D-glucosides showed considerable extents of acyl migration on heating for 5 min at 200 °C in a glass tube, whereas they were stable at 150 °C. Mono-*O*-myristoyl-D-glucopyranoses were more labile, and extensive migration was observed at 130—150 °C. Therefore, acyl migration of all isomeric mono-*O*-myristoyl derivatives of D-glucopyranose and methyl D-glucopyranosides under various conditions (including thermal, acid- and base-catalyzed, and solvolytic conditions) were investigated. The products were analyzed by GC after converting the mixture to TMS derivatives and also directly by ^{13}C-NMR.

Experimental

Materials——All methyl mono-*O*-myristoyl-α- and β-D-glucopyranosides (Series I) and mono-*O*-myristoyl-D-glucopyranoses (Series II) used for acyl migration were reported previously.[14]

Acyl Migration——The following conditions were employed. Thermal condition: (A) a compound of Series I was heated in an open capillary at 200 °C (bath temp.) for 10 min; (B) a compound of Series II was heated in an open capillary at 150 °C (bath temp.) for 10 min. Solvolytic condition: (C) a sample (0.5—1 mg) was kept in MeOH (2 drops) at room temperature for a week. Base-catalyzed condition: (D) a compound (0.5—1 mg) of Series I in pyridine (2 drops) was heated in a sealed tube at 130 °C for 1 h; (E) a compound (0.5—1 mg) of Series II in pyridine (2 drops) was heated in a sealed tube at 120 °C for 8 h, and (E′) at 120 °C for 1 h. Acid-catalyzed condition: (F) a sample (0.5—1 mg) in dioxane containing 0.5% *p*-TsOH (2—3 drops) was kept in a sealed tube at room temperature for 48 h. The following conditions caused hydrolysis of the myristoyl group for Series II compounds: 1% *p*-TsOH in dioxane, reflux, 2 h; 1% *p*-TsOH in dioxane, room temperature, 48 h; and 0.5% *p*-TsOH in dioxane, reflux, 1 h.

Analysis of the Products——For conditions A and B: the cooled mixture was dissolved in dry pyridine, converted to TMS derivatives according to the method of Sweeley *et al.*,[15] and analyzed by GC. If necessary, the sample was dissolved in pyridine-d_5 (py-d_5) and the ^{13}C-NMR spectrum was measured. For condition C: the mixture was concentrated under reduced pressure (bath temp. <40 °C), converted to TMS derivatives, and analyzed by GC. For conditions D and E: the mixture was directly converted to TMS derivatives, and analyzed by GC. If necessary, for conditions C, D, and E, the acyl migration was carried out on a 20—30 mg scale in an NMR tube with either methanol-d_4 or py-d_5, and ^{13}C-NMR spectra were measured at an appropriate time. For condition F: dry pyridine (*ca.* 0.5 ml) was added to the reaction mixture and the whole was concentrated under reduced pressure (bath temp. <40 °C), converted to TMS derivatives, and analyzed by GC. If necessary, the product was dissolved in py-d_5 and the ^{13}C-NMR spectrum was measured.

GC Analysis——The TMS derivatives were analyzed with a Shimadzu GC-4CMPF gas chromatograph with an FID detector, using a glass column (2 m × 4 mm i.d.); carrier gas, N_2 (80 ml/min). The column packing employed was 1.5% OV-1 on Shimalite W (80—100 mesh). The quantitative composition of each isomer was estimated by comparison of the peak areas.

Measurement of ^{13}C-NMR Spectra——Natural abundance ^{1}H noise-decoupled ^{13}C FT NMR (at 25.0 MHz) spectra were recorded on a JEOL FX-100 FT NMR spectrometer using a 5 mm spinning tube at 24.5 °C. Samples were dissolved, in most cases, in py-d_5. Tetramethylsilane (Me_4Si) served as an internal reference (δ 0). Concentrations were about 0.1—0.3 mmol/ml. FT-NMR measurement conditions were as follows: spectral width, 6024 Hz; pulse flipping angle, 45 °; acquisition time, 0.6799 s; number of data points, 8192. Accuracies of δ values were thus about ±0.1 ppm.

Acyl Migration of 1,6-Di-*O*-myristoyl-α-D-glucopyranose——1α,6-Di-*O*-myristate[14c] (20 mg) in py-d_5 (0.5 ml) was heated at 200 °C for 1 h in a sealed NMR tube to give a 2:1 mixture of 2,6-di-*O*-myristoyl-α- and β-D-glucopyranose (>90%, estimated from the peak ratio of C_1 signals in ^{13}C-NMR). ^{1}H-NMR (py-d_5) δ: 6.02 (0.7H, d, J=3.5 Hz, C_1–H (α-anomer)), 5.40 (0.3H, d, J=6.8 Hz, C_1–H (β-anomer)). ^{13}C-NMR data were presented in ref. 14*c*.

Results and Discussion

GC data for all mono-*O*-myristoyl-D-glucopyranoses and methyl mono-*O*-myristoyl-α-

TABLE I. Relative Retention Times of Methyl Mono-*O*-myristoyl-D-glucosides and Mono-*O*-myristoyl-D-glucose[a)]

	Methyl *O*-myristoyl-D-glucoside (Series I)		*O*-Myristoyl-D-glucose (Series II)	
	α-	β-	α-	β-
6-*O*-	0.90	0.84	0.86	0.89
4-*O*-	0.69	0.72	0.70	
3-*O*-	0.70	0.70	0.70	
2-*O*-	0.80	0.79	0.80	
1-*O*-			0.71	0.79

a) Relative retention time for per-*O*-trimethylsilyl derivatives; internal standard, cholesterol, 1.00.

and β-D-glucopyranosides are shown in Table I.

As already shown,[14a)] most acyl-D-glucoses, except 1-*O*-acyl derivatives, exist as the α-anomer in the crystalline state, and anomerize in solution to give an anomeric mixture. Both the anomers showed the same relative t_R in GC, but can be well characterized by ^{13}C-NMR. Exceptionally, 6-*O*-acyl-D-glucopyranose, which shows a single peak of α-anomer in fresh solution, gives two separated peaks corresponding to the α- and β-anomer (confirmed by ^{1}H- and ^{13}C-NMR) on standing in pyridine. Evaporation of the solvent from the mixture left the crystalline α-anomer only.

Results of acyl migration experiments are collected in Table II. The migration conditions employed include thermal, acid- and base-catalyzed, and solvolytic conditions. Under all the conditions employed, the migration products contained only mono-*O*-acyl derivatives, neither di-*O*-myristate nor D-glucose being found in the mixture; this result indicates that the migration proceeded intramolecularly.

Acyl Migration of Methyl Mono-*O*-myristoyl-α- and β-D-Glucopyranosides

All methyl mono-*O*-acyl-D-glucosides examined were stable on fusion at 150 °C (confirmed by GC and ^{13}C-NMR), but profound acyl migration was observed at 200 °C. 6-*O*-Acyl-D-glucosides were produced from all samples indicating that acyl migration occurs towards *O*-6, but the proportion of 6-*O*-acylate in the product was variable depending on the origin of migration and also on the configuration of the anomeric center.

2-*O*-Acyl derivatives of both α- and β-D-glucoside produced 3-*O*-acylates. The proportions of 3-*O*-acylate and the remaining 2-*O*-acylate in the products were comparable from both anomers (Exp. 7 and 8). Concomitant formation of 6-*O*-acylates was nearly 50% from the α-anomer but less than 30% from the β-anomer.

3-*O*-Acyl-D-glucosides of both the α- and β-anomer produced 2-*O*-acylate, indicating that migration between *O*-2 and *O*-3 is reversible (Exp. 5 and 6). The proportions of 3- and 2-*O*-acylate in the products were again comparable in both anomers, suggesting that the energy levels of the 2- and 3-*O*-acylate are almost equal. Comparison of the proportion of 6-*O*-acylate from each anomer indicated that formation of 6-*O*-acylate from the α-anomers is easier than from the β-anomers. No 4-*O*-acylate was found in the mixture from either source, suggesting that the migration does not proceed through 4-*O*-acylate.

4-*O*-Acyl derivative migrated to 6-*O*-acylate, but simultaneous formation of 2-*O*-acylate from the α-anomer, though small in extent, was observed (Exp. 3 and 4).

6-*O*-Acyl derivatives were stable, as expected, but they showed some tendency to migrate to *O*-4 (Exp. 1 and 2). In the case of the α-anomer, the product was accompanied by 2-*O*-

TABLE II. Migration of *O*-Myristoyl Group in Methyl Mono-*O*-myristoyl-D-glucosides and Mono-*O*-myristoyl-D-glucose

Exp.	Methyl *O*-myristoyl-D-glucoside (Series I)[a]	Condition[b]	Product composition (%)[c]
1	6α	A	2α (10), 4α (17), s.m. (73)[d]
2	6β	A	4β (18), s.m. (82)
3	4α	A	2α (10), s.m. (35), 6α (55)
4	4β	A	s.m. (50), 6β (50)
5	3α	A	2α (28), s.m. (28), 4α (trace), 6α (44)
6	3β	A	2β (36), s.m. (30), 6β (34)
7	2α	A	s.m. (26), 3α (28), 6α (46)[e]
8	2β	A	s.m. (44), 3β (28), 6β (28)[e]
9	All samples	C	Unchanged
10	6α	D	3α (10), s.m. (90)
11	Other samples	D	Unchanged
12	6α	F	2α (trace), 3α (16), s.m. (84)
13	4α	F	s.m. (35), 6α (65)
14	4β	F	s.m. (22), 6β (78)
15	3α	F	2α (28), s.m. (30), 6α (24)
16	Other samples	F	Unchanged

Exp.	*O*-Myristoyl-D-glucose (Series II)[a]	Condition[b]	Product composition (%)[c]
17	6(α)	B	6(α) (49), 6(β) (51)
18	4(α, β)	B	s.m. (49), 6(α, β) (51)
19	3(α, β)	B	s.m. (55), 6(α) (45)
20	2(α, β)	B	Unchanged
21	1α	B	s.m. (52), 2(α, β) (48)
22	1β	B	Unchanged
23	6(α)	C	3(α, β) (14), 6(α) (42), 6(β) (44)
24	4(α, β)	C	s.m. (13), 6(α) (39), 6(β) (48)
25	3(α, β)	C	s.m. (18), 6(α) (36), 6(β) (46)
26	2(α, β)	C	3(α, β) (14), 6(α) (43), 6(β) (43)
27	1α	C	s.m. (15), 2(α, β) (23), 6(α, β) (62)
28	1β	C	D-Glucose, methyl myristate
29	6(α)	E	6(α) (46), 6(β) (54)
30	4(α, β)	E	2(α, β) (23), s.m. (21), 6(α, β) (56)
31	3(α, β)	E′	2(α, β) (30), s.m. (29), 6(α, β) (41)
32	3(α, β)	E	2(α, β) (25), s.m. (21), 6(α, β) (54)
33	2(α, β)	E	s.m. (21), 3(α, β) (35), 6(α, β) (44)
34	1α	E	s.m. (21), 2(α, β) (35), 6(α, β) (44)
35	1β	E′	s.m. (39), 3(α, β) (23), 6(α, β) (38)
36	1β	E	s.m. (39), 3(α, β) (19), 6(α, β) (42)
37	6(α)	F	6(α) (52), 6(β) (48)
38	4(α, β)	F	s.m. (7), 6(α) (39), 6(β) (54)
39	3(α, β)	F	s.m. (51), 6(α) (49)
40	Other samples	F	Unchanged

a) The numbers indicate the position of the acyl group, and α and β indicate the configuration of the anomeric position (those in parentheses are compounds that are easily anomerizable). For example: 3(α, β), 3-*O*-myristoyl-α- and β-D-glucopyranoses; 2α, methyl 2-*O*-myristoyl-α-D-glucopyranoside; 1β, 1-*O*-myristoyl-β-D-glucopyranose; 6(α), 6-*O*-myristoyl-α-D-glucopyranose.

b) A: Fusion at 200 °C (bath temp.), 10 min.
B: Fusion at 150 °C (bath temp.), 10 min.
C: MeOH, on standing at room temp., for a week.
D: Pyridine, 130 °C (bath temp.), 1 h.
E: Pyridine, 120 °C (bath temp.), 8 h.
E′: Pyridine, 120 °C (bath temp.), 1 h.
F: 0.5% *p*-TsOH in dioxane, room temp., 48 h.

c) The composition was analyzed by GC of the TMS derivative, and was confirmed by ^{13}C-NMR spectral analysis.

d) s.m.: starting material.

e) The data given in a preliminary communication [Y. Tsuda and K. Yoshimoto, *Carbohydr. Res.*, **87**, C1 (1981)] should be revised to these values.

acylate, which must be formed through 4-*O*-acylate, since no 3-*O*-acylate was found in the mixture (Exp. 1).

All mono-*O*-acyl-D-glucosides were stable in MeOH at room temperature and were recovered unchanged after storage for a week (Exp. 9).

In pyridine (condition D), most of the samples were stable and were recovered unchanged (Exp. 11). Interestingly 6-*O*-acyl-α-D-glucoside showed a tendency for migration towards *O*-3, confirming the presence of direct *O*-6→ -3 reverse migration (Exp. 10). The β-anomer was stable as expected from the relative instability of the $^1C_4$(D) conformation (see below). However, there is still a question as to why 3-*O*-acyl-α-D-glucoside did not rearrange to 6-*O*-acylates under this condition.

Acid-catalyzed migration under condition F was found to occur readily. Under this condition most of the β-anomers were stable; 2-, 3-, and 6-*O*-acyl-β-D-glucosides were unchanged (Exp. 16), but the 4-*O*-acyl group readily migrated to *O*-6 (Exp. 14). In contrast to the β-anomers, the α-anomers were far more labile under this condition. Although the 2-*O*-acyl derivative was unchanged (Exp. 16), 3-*O*-acyl-α-D-glucoside rearranged readily to give 2- and 6-*O*-acylate (Exp. 15), and 6-*O*-acyl-D-glucoside gave 3-*O*-acylate (16%) with concomitant formation of 2-*O*-acylate (trace) (Exp. 12). Of course, 4-*O*-acyl-D-glucoside rearranged to 6-*O*-acylate (65%) (Exp. 13).

The above results are schematically summarized in Chart 2. The experiments confirmed the presence of reversible *O*-2⇄ -3 *trans*-migration, and *O*-4→ -2 and *O*-3⇄ -6 migrations through a $^1C_4$(D) conformation, together with the well known *O*-4→ -6 migration. It must be emphasized that there was no indication of *O*-3→ -4 or the reverse migration. The above results indicate that each step is more or less reversible. Interestingly, reversible *O*-2→ -3 migration (which must proceed through the $^4C_1$(D) conformation) took place readily, although it is *trans*-migration. For *O*-4→ -2 and *O*-3→ -6 migrations the ring must adopt the $^1C_4$(D) conformation. This ring inversion is energetically less favored in the β- than in the α-anomers, since in the β-anomers all substituents must have an axial orientation. Therefore the migrations through the $^1C_4$(D) conformation occur much more readily for the α- than β-D-anomer (*cf.* Exp. 5 and 6, and 15 and 16). This explains why the α-anomer is, in general, more labile to acyl migration than the corresponding β-anomer.

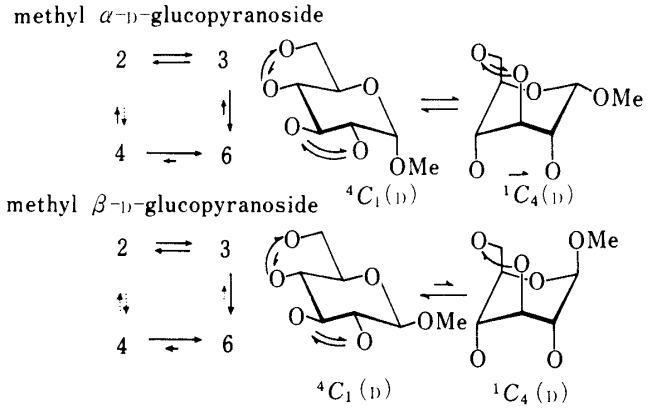

Chart 2. General Path of Acyl Migration in Methyl α- and β-D-Glucopyranosides

Solid arrow: migration observed.
Broken arrow: migration possible but not observed.
Horizontal arrow: migration through $^4C_1$(D) conformation.
Vertical arrow: migration through $^1C_4$(D) conformation.

Preference for taking $^1C_4$(D)-form for α- rather than for β-anomers is also illustrated by the following examples: Purdie methylation of methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside

(IX) gives the 2,3,6-tri-*O*-acetyl-4-*O*-methyl ether (X),[16] while the corresponding α-anomer (I) gives 3,4,6-tri-*O*-acetyl-2-*O*-methyl ether (II) as a major product.[5]

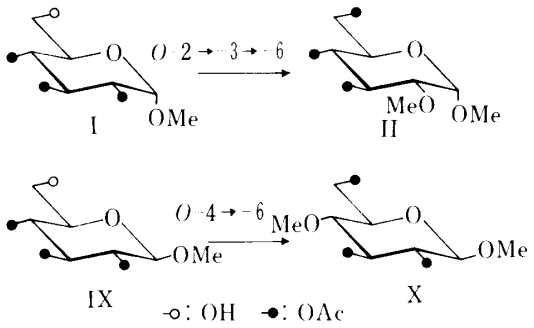

Chart 3. Product Dependency on Methylation Due to the Configurational Difference at the Anomeric Center[5,16]

If *O*-3→ -6 acyl migration were equally easy for both anomers, the result could not be explained. Formation of the 2-*O*-methyl ether (II) from the α-anomer (I) must be the result of *O*-2→ -3→ -6 acyl migrations, whereas the $^1C_4$(D) form for the β-anomer (IX) is less favored (increase of bulkiness of OH groups by acetylation is also a factor in decreasing the stability of the $^1C_4$(D) form) and *O*-4→ -6 migration predominates, thus yielding the 4-*O*-methyl ether (X). The result is in accord with our finding that acid-catalyzed *O*-4→ -6 acyl migration is preferred for the β- rather than for the α-anomer (*cf.* Exp. 13 and 14).

Acyl Migration in Mono-*O*-myristoyl-D-glucopyranoses

In contrast to *O*-acyl-D-glucosides, *O*-acyl-D-glucoses were unstable and all conditions employed induced more or less acyl migration. On fusion at 150 °C, the 1α-*O*-acyl group migrated to *O*-2 (Exp. 21), but the 1β-*O*-acyl group was stable under the same condition (Exp. 22). The 2-*O*-acyl group was also stable (Exp. 20). The 3-*O*-acyl group migrated to *O*-6 producing, interestingly, only the α-anomer, 6-*O*-acyl-α-D-glucopyranose (Exp. 19). This result is curious when compared to the fact that 6-*O*-acyl-D-glucoses give almost a 1 : 1 anomeric mixture on the same treatment (Exp. 17). This result could be explained by supposing that the stable orthoacid of structure (XI) is formed as an intermediate, and is quenched to XII on being dissolved in pyridine and transformed to the TMS derivative. The 4-*O*-acyl group rearranged to the 6-*O*-acylate which was a mixture of α- and β-anomer, as expected (Exp. 18). Neither *O*-3→ -4 nor the reverse migration was observed.

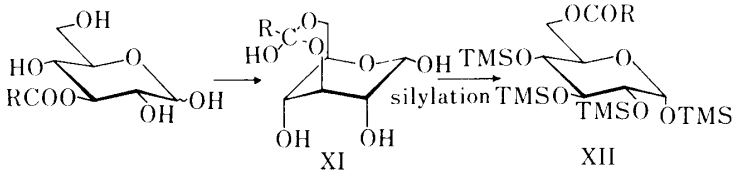

Chart 4. Acyl Migration of 3-*O*-Acyl-D-glucopyranose on Fusion

In pyridine (condition E), all *O*-acyl-D-glucoses except 6-*O*-acylate migrated. 4-*O*-Acyl-D-glucoses rearranged to 6-*O*-acylate, interestingly, together with the formation of 2-*O*-acylate (23%), which is the product of a reverse rearrangement (Exp. 30). The 3-*O*-acylate migrated to 2-*O*- and 6-*O*-acylate (Exp. 31 and 32). The ratio of 6-*O*- *vs.* 2-*O*-acylate (41 : 30) after 1 h at 120 °C (Exp. 31) increased to 54 : 25 on prolongation of the reaction time (8 h) (Exp. 32). Formation of the 2-*O*-acylate from 3-*O*-acyl-D-glucose, observed in this condition only, indicated that reverse rearrangement between *O*-3 and *O*-2 is possible. 2-*O*-Acyl-D-glucose

gave the 3-*O*-acylate (35%) and 6-*O*-acylate (44%) (Exp. 33). *cis*-Migration of 1α-*O*-acyl-D-glucose to 2-*O*-acylate was easy, and resulted in the formation of 2-*O*-acylate and 6-*O*-acylate (Exp. 34). Acyl migration from 1β-*O*-acyl-D-glucose was also observed, the products being 6-*O*- and 3-*O*-acylates (Exp. 35 and 36).

In acidic medium (condition F), *O*-acyl-D-glucoses were rather stable. 1α-*O*-, 1β-*O*-, 2-*O*-, and 6-*O*-Acyl derivatives were unchanged (Exp. 37 and 40). 3-*O*-Acyl- and 4-*O*-acyl-D-glucoses migrated to 6-*O*-acylates, confirming the *O*-3→ -6 and *O*-4→ -6 migrations (Exp. 38 and 39). The 6-*O*-acylate produced from the 3-*O*-acylate in this reaction was again only found as the α-anomer.

Under a solvolytic condition (condition C), all samples, except 1-*O*-acyl-β-D-glucopyranose, showed acyl migration towards *O*-6. The 1α-*O*-acyl group migrated to *O*-2 and *O*-6 (Exp. 27). 2-*O*-Acyl-D-glucose gave 3-*O*- and 6-*O*-acylate (Exp. 26). 3-*O*-Acyl-D-glucose yielded only 6-*O*-acylate (Exp. 25). The 6-*O*-acylate produced under this condition was always a mixture of the α- and β-anomer. The 4-*O*-acyl group migrated only to *O*-6 (Exp. 24). Interestingly, a reverse migration of the 6-*O*-acyl group to *O*-3 (Exp. 23) was observed. The 1β-*O*-acyl derivative did not give any migrated products under this condition, but instead solvolysis took place producing D-glucose and methyl myristate (Exp. 28). During the reaction, formation of no other *O*-acyl-D-glucose was detected. Obviously the products indicate that this solvolysis proceeds through path A of the two alternative paths, A and B.

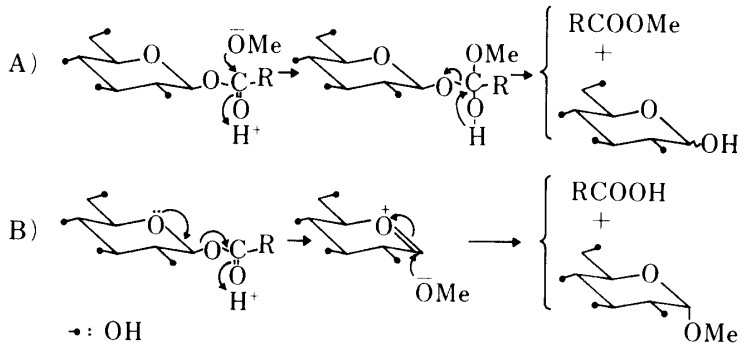

Chart 5. Solvolysis of 1-*O*-Acyl-β-D-glucopyranose (Path A is Preferred)

This easy solvolysis of the 1β-*O*-acyl group must depend on the nature of the acyl group, since 1-*O*-acyl-β-D-glucopyranoses bearing a bulky terpenoidal acid have been isolated from plants by extraction with boiling methanol.

The following examples, methanolysis of 1-*O*-mesitoates (XIII and XV), illustrate the difference of reactivity of 1α- and 1β-*O*-acyl derivatives.[8b] On treatment with sodium methoxide the α-anomer (XV) gives the migrated product (XVI), whereas the β-anomer (XIII) gives only the solvolyzed product (XIV) without acyl migration. The presence of the bulky 1β-substituent again inhibits the compound (XIV) from taking a $^1C_4$(D) conformation, thus preventing *O*-1β→ -3 migration.

The above results are schematically summarized in Chart 7 which illustrates that the migration proceeds through the paths *O*-1α→ -2→ -3→ -6, *O*-4→ -6, and *O*-1β→ -3→ -6. *O*-1α→ -2 *cis*-Migration and *O*-4→ -6 migration (through a six-membered ring intermediate) take place very readily. The very easy *O*-4→ -6 acyl migration is also illustrated by the following example: 4-*O*-acyl-D-glucopyranoses produced by debenzylation upon hydrogenolysis under neutral conditions were always accompanied by 20—30% of 6-*O*-acyl derivatives.[14a] *trans* *O*-2→ -3 Migration is again possible in mono-*O*-acyl-D-glucose. However, *O*-3→ -4 *trans*-migration was again not observed. *O*-3→ -6 Migration through the $^1C_4$(D) conformation also takes place, and occurs more readily than *trans* *O*-2→ -3 migration

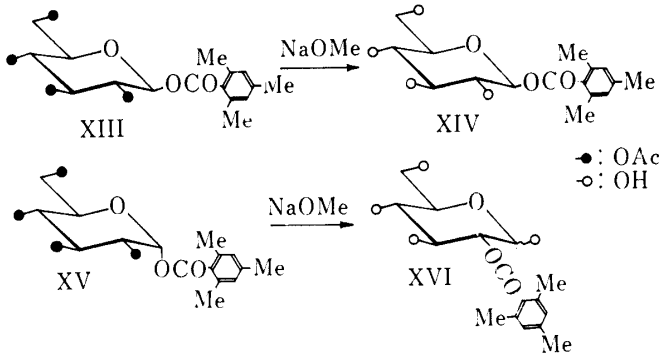

Chart 6. Product Dependency on Solvolysis Due to the Configurational Difference at the Anomeric Center[8b]

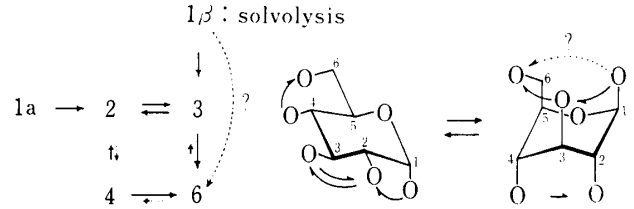

Chart 7. General Path of Acyl Migration in D-Glucose Derivatives

Solid arrow: migration observed.
Broken arrow: migration possible but not observed.
Horizontal arrow: migration through $^4C_1$(D) conformation.
Vertical arrow: migration through $^1C_4$(D) conformation.

(*cf.* Exp. 19 and 20, 39 and 40). As suggested above, taking the $^1C_4$(D) conformation becomes more difficult when the bulkiness of a substituent (and also of an acyl group) is increased; therefore substitution of hydroxyl groups reduced the ease of *O*-3→ -6 migration. Thus 1,6-di-*O*-myristoyl-α-D-glucopyranose gave, on heating in pyridine, 2,6-di-*O*-myristoyl-D-glucopyranose in good yield.

Based on the above findings, some puzzling results in earlier reports can now be clarified. Purdie methylation of either 1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (XVII)[2d] or 1,2,3,6-tetra-*O*-acetyl-β-D-glucopyranose (XVIII)[17] gave the same methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (VIII), which was also obtained from 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (XIX).[2d] Previously, the reactions of XVII to VIII and XVIII to VIII were suggested to involve *O*-1β→ -2 acyl migration: the former is *O*-1β→ -2 and the latter *O*-1β→ -2→ -3→ -4.[2d] However, we found that *O*-3→ -4 and *O*-1β→ -2 never occur, and we can now understand that the former case is *O*-1β→ -3→ -2 and the latter case is *O*-1β→ -3→ -6→ -4 acyl migrations. Formation of the same product (VIII) from 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (VII) by Purdie methylation[12] is, contrary to the previous suggestion of *O*-1β→ -2→ -3→ -4→ -6,[2d,13a] also the result of *O*-1β→ -3→ -6 acyl migration (the possibility of direct *O*-1β→ -6 migration will be discussed in the accompanying paper).

Theoretical Considerations

Now, let us consider the reason why *O*-2⇄ -3 migration is so easy, in spite of the finding that *O*-3→ -4 and *O*-1β→ -2 migrations are prohibited. This result may be rationalized by considering the changes of torsion angles in a pyranose ring. The easily reversible acyl migration *O*-2⇄ -3 in glycosides suggests that the dihedral angle between *O*-2 and *O*-3 decreases to a value lower than that expected for normal *trans*-diequatorial substituents. This decrease produces an increase of the dihedral angle between *O*-3 and *O*-4, and between *O*-

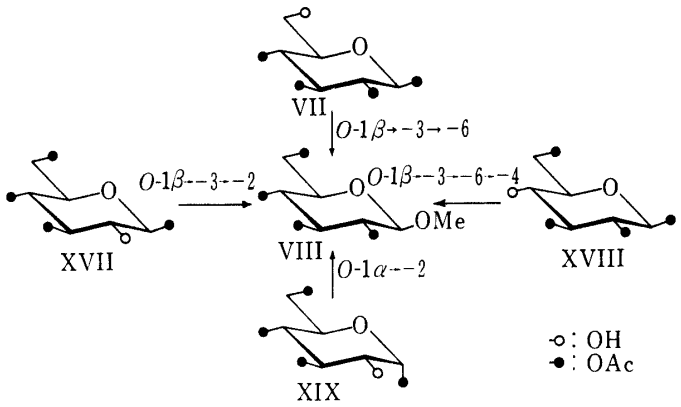

Chart 8. Acyl Migration during Purdie Methylation[2d,12,17]

2 and *O*-1β. Consequently the formation of a five-membered ring orthoacid intermediate between these groups requires a higher energy, inhibiting the *O*-3→ -4, and *O*-1β→ -2 migrations. Calculation of these angles from the reported X-ray analysis data[18] support this conclusion. For crystalline methyl α-D-glucopyranoside having the $^4C_1$(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 of *O*-1α and *O*-2 is 61.5°. These data suggested that the pyranose ring may be distorted in the reaction in order to decrease the angle between *O*-2 and *O*-3 without a great increase of torsion energy. As for the origin of the above distortion of the pyranose ring, we attribute it to an anomeric effect which produces a double bond character between *O*-5 and *C*-1. This causes a movement of substituents as shown in Chart 9, thus decreasing the dihedral angle between *O*-2 and *O*-3 (see Chart 9).

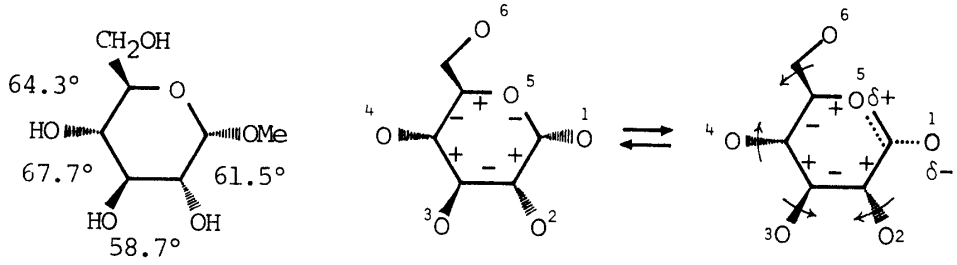

Chart 9. Endocyclic Torsion Angle Changes and Dihedral Angles in Methyl α-D-Glucopyranoside

The next question is that, if migrations through the $^1C_4$(D) conformation are common, why is *O*-2→ -4 migration not observed equally to *O*-3→ -6 migration, instead of only the reverse *O*-4→ -2 migration (though only to a small extent) being observed? This can be understood by assuming that the 4-*O*-acyl derivative is at a higher energy level than the 2-*O*-acyl derivative. The cyclic orthoacid intermediate formed between *O*-2 and *O*-4 has a non-bonded 1,3-diaxial interaction between OH-3 and $-C^6H_2OH$, which is diminished in the orthoacid formed between *O*-3 and *O*-6 (due to ring formation), where the non-bonded interaction between OH-2 and OH-4 is apparently smaller than that between OH-3 and $-C^6H_2OH$. Therefore the activation energy of *O*-2→ -4 migration is obviously greater than that of *O*-3→ -6. We have already seen that *O*-1β→ -3 is not as easy as *O*-3→ -6 migration. This may be due to similar reasons. Relative potential and activation energies among these mono-*O*-acyl derivatives are shown schematically in Fig. 1.

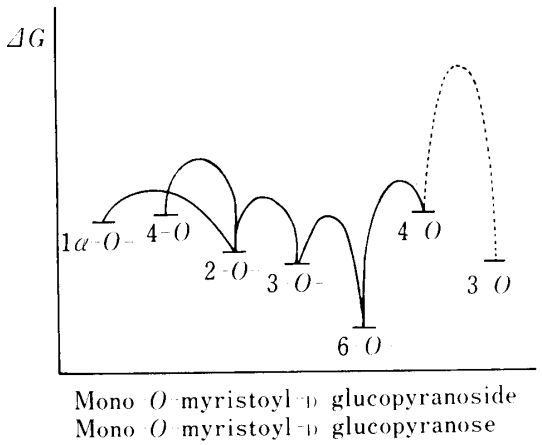

Fig. 1. Relative Potential and Activation Energy Levels (Schematic) of Mono-*O*-acyl-D-glucose Derivatives

The possibility of direct *O*-1$\beta\rightarrow$ -6 migration is not evident from our present experiments and requires further investigation. The following paper treats this subject.

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