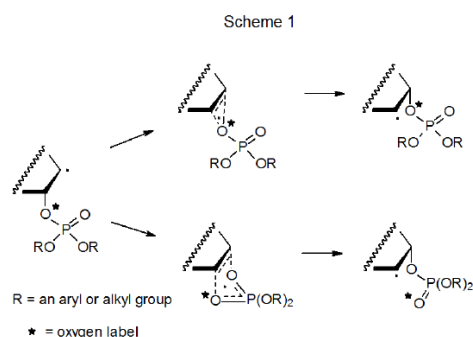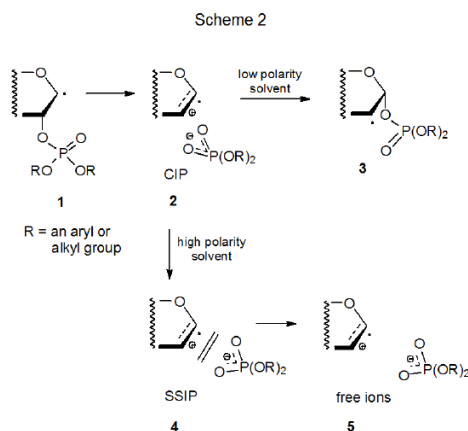# II. Phosphatoxy Group Migration

A. Reaction Mechanism

Initially two mechanisms were considered as possibilities for phosphatoxy group migration of the type shown in ⬚ eq 1. (This same mechanistic choice exists for acyloxy group migration and is discussed in Section V.A of Chapter 8.) The first of these mechanisms consisted of a pair of competing, concerted reactions, each of which passed through a cyclic transition state (Scheme 1).[3–7] A basic difference between this pair was that in one reaction the same oxygen atom was bonded to the carbon-atom framework both before and after migration, but in the other the framework had a different oxygen atom attached after migration. Proposing migration via a combination of these two reactions made it possible to explain experiments with oxygen-labeled substrates in which only a portion of the labeled oxygen was attached to the carbon-atom framework after migration. The results from early studies favored this two-reaction explanation,[3–7] but those from later investigations required it to be changed because the later studies showed that ionic intermediates were involved in the migration process.
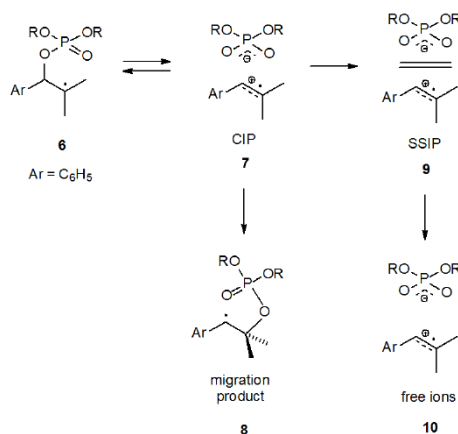

Scheme 1

A mechanism that satisfies the ionic-intermediate requirement is shown in Scheme 2, where the β-phosphatoxy radical **1** fragments heterolytically to give the contact ion pair (CIP) **2**.[8–13] This ion pair recombines in low polarity solvents to form the group-migrated radical **3**, but in more polar solvents the CIP also can separate to become a solvent-separated ion pair (SSIP, **4**) and then free ions **5**.[10]
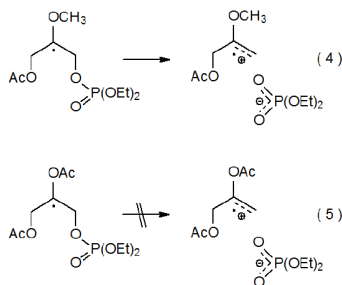

Scheme 2

Critical support for the ion-pair mechanism for phosphatoxy group migration comes from laser-flash-photolysis (LFP) experiments. Both the SSIP **9** and the diffusively free radical cation **10** can be detected in studies where LFP generates the radical **6** (Scheme 3).[12] Evidence for the CIP in this reaction is indirect presumably because its lifetime is too short to permit direct detection. Study of reaction rates in solvents of different polarity supports the idea that the radical **6** is passing through a common intermediate in forming either the migrated radical **8** or the SSIP **9**. A reasonable conclusion is that the common intermediate is the contact ion pair **7** (Scheme 3).[12] Entropies of activation, which are the same for ion-pair formation in high polarity solvents and group migration in solvents of low polarity, also favor a common intermediate for which **7** is the prime candidate.[10,12] Generalizing these results leads to the reaction mechanism proposed in Scheme 2. (The wording in this paragraph also is found in Section V.A.5 of Chapter 8 because the information contained is pertinent to the mechanism of acyloxy group migration.)
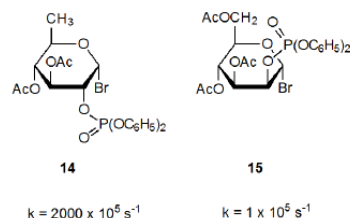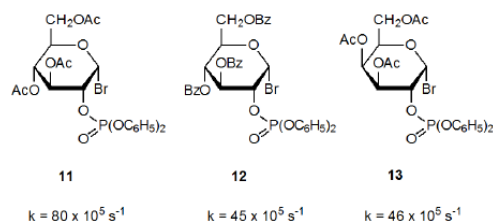
Scheme 3

Phosphatoxy group migrations are not wide-spread in carbohydrate chemistry; in fact, all reported reactions involve migration from C-2 to C-1 in a pyranoid or furanoid ring. This situation exists because the stabilization afforded by the ring oxygen atom is critical at the transition state leading to radical-cation formation. Examining the reactivity of the noncarbohydrate radicals shown in equations 4 and 5 is instructive. An oxygen atom must be fully able to participate in radical-cation stabilization for heterolytic bond breaking to occur (eq 4).[14] Replacing the methoxy group in the substrate in the reaction shown in eq 4 with an acetyl group, as is done in the reaction shown in eq 5, prevents radical-cation formation because an oxygen atom with an electron-withdrawing group attached is unable to stabilize sufficiently the transition state leading to the radical-cation intermediate.[14]
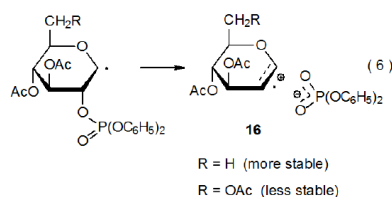

B. Relative Reaction Rates

Relative rate constants for phosphatoxy group migration in the reactions of the five hexopyranosyl bromides **11-15** are given in Table 1.[15] The rate constant for reaction of the 6-deoxy bromide **14** is substantially larger than those for the other bromides. Replacing the electron-withdrawing acyloxy group at C-6 with a hydrogen atom makes the radical cation **16** more stable and, in so doing, stabilizes the transition state leading to it (eq 6).

CH_2OAc

CH_2OBz

CH_2OAc

AcO OAc Br $P(OC_6H_5)_2$

BzO OBz Br $P(OC_6H_5)_2$

AcO OAc Br $P(OC_6H_5)_2$

11

12

13

$k = 80 \times 10^5 \text{ s}^{-1}$

$k = 45 \times 10^5 \text{ s}^{-1}$

$k = 46 \times 10^5 \text{ s}^{-1}$

CH_3 OAc AcO Br $P(OC_6H_5)_2$

AcOCH$_2$ $P(OC_6H_5)_2$ OAc AcO Br

14

15

$k = 2000 \times 10^5 \text{ s}^{-1}$

$k = 1 \times 10^5 \text{ s}^{-1}$

All reactions were conducted at 27 °C.

Table 1. Relative rates of phosphatoxy group migration.

CH_2R OAc AcO $P(OC_6H_5)_2$ $\longrightarrow$ CH_2R OAc AcO $P(OC_6H_5)_2$ (6)

16

R = H (more stable)

R = OAc (less stable)

The rate constant for reaction of the D-mannopyranosyl bromide **15** is decidedly smaller than those for reactions of the bromides **11-14**. One factor that contributes to this reduced reactivity is the enhanced stability of the radical **17** when compared to the corresponding radicals derived from the other bromides (**11-14**). Only **17** remains in a relatively strain-free, $^4C_1$ conformation while taking advantage of the stabilizing interaction of parallel p_o, p_c, and σ^* orbitals (Table 2).[15] To benefit from parallel-orbital stabilization, the radicals derived from bromides **11-14** must assume less stable conformations; for example, the radical derived from **11** adopts the $B_{2,5}$ boat conformation **18**.[15] As migration takes place in each of the radicals **17-19**, p_o, p_c, σ^* orbital stabilization is lost, but for radicals **18** and **19** this loss is compensated for, at least in part, by movement toward a more stable, $^4C_1$ conformation. Such compensation means that the transition states for radical-cation formation from **18** and **19** are not as high in energy as that for reaction of **17**; consequently, group migration for the radical **17** is slower than for **18** and **19**.

$(ArO)_2PO$ AcOCH$_2$ AcO AcO = $(ArO)_2P$—O p_o σ^* p_c

17

AcO CH$_2$OAc AcO OP(OAr)$_2$ = p_o p_c —P(OAr)$_2$ σ^*

18

AcO CH$_2$OAc AcO OP(OAr)$_2$ = p_o p_c —P(OAr)$_2$ σ^*
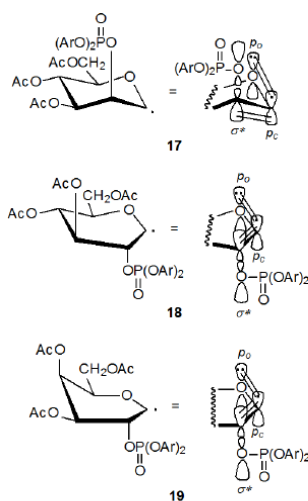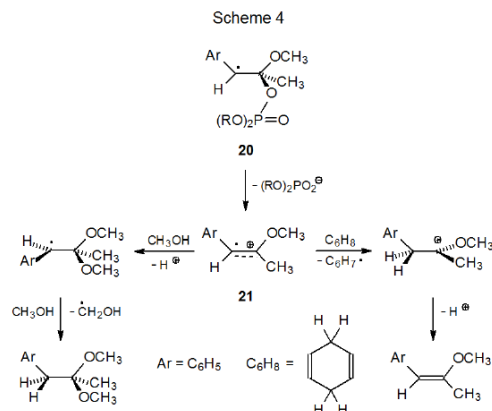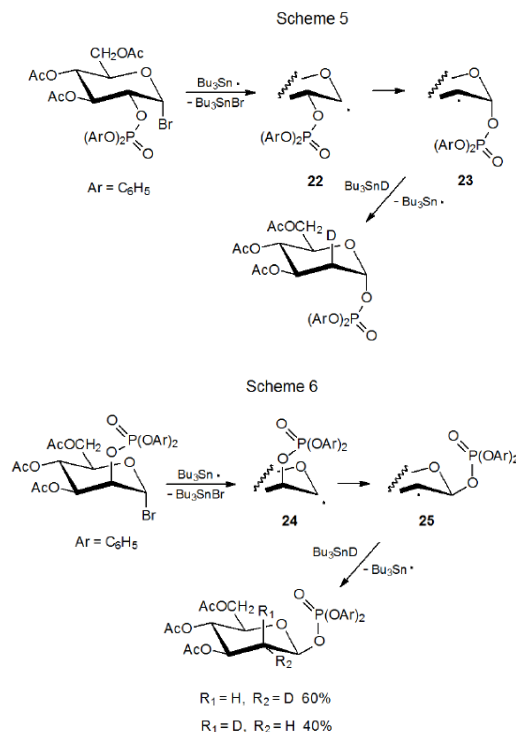
19

Table 2. Conformations of pyranos-1-yl radicals

Pertinent information about formation and reactivity of radical cations comes from the study of noncarbohydrate systems.[16,17] Nucleophilic trapping of the radical cation **21** by methanol (k< 1 x 10^3 $M^{-1}s^{-1}$) is slow compared to hydrogen-atom abstraction from 1,4-cyclohexadiene (k = 6 x 10^5 $M^{-1}s^{-1}$) (Scheme 4).[17] To the extent that this observation is a general one, radical cations can be expected to have greater radical reactivity than cationic reactivity.
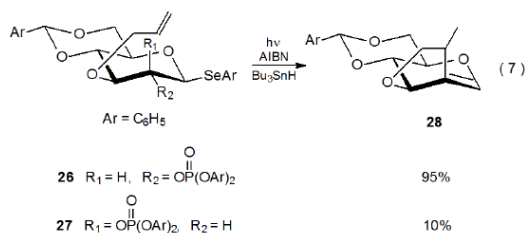

Scheme 4

C. Stereoselectivity

The reactions pictured in Schemes 5 and 6 show that phosphatoxy group migration is a stereospecific process; thus, the epimeric radicals **22** and **24** give the product radicals **23** and **25**, respectively.[1,15] Once migration has taken place, stereoselective deuterium abstraction completes the reaction. For the radical **23** abstraction is highly stereoselective, but it is much less so for the radical **25**. Shielding of the α face of **23** by the axial phosphatoxy group causes deuterium to be abstracted from the β face of this radical (Scheme 5). The equatorial phosphatoxy group in **25** is not nearly as effective at forcing Bu₃SnD to the opposite face of the pyranoid ring (Scheme 6).
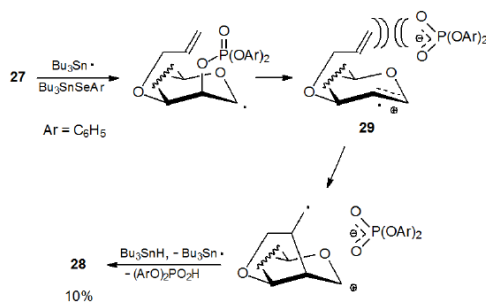

Scheme 5

Scheme 6

Differential shielding of the faces of a pyranoid ring affects the ability of the phosphates **26** and **27** to undergo new ring formation (eq 7). The phosphate **26** gives a decidedly higher yield of the glycal **28** than does its epimer **27**.[18] The substantially lower product yield from reaction of **27** is attributed to steric hindrance by the nearby phosphate counter ion during cyclization of the radical
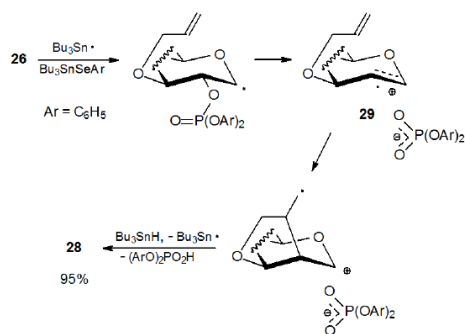
cation **29** (Scheme 7). When **29** is generated from **26**, however, the counter ion is on the opposite face of the ring and does not impede cyclization (Scheme 8).

Scheme 7

Scheme 8