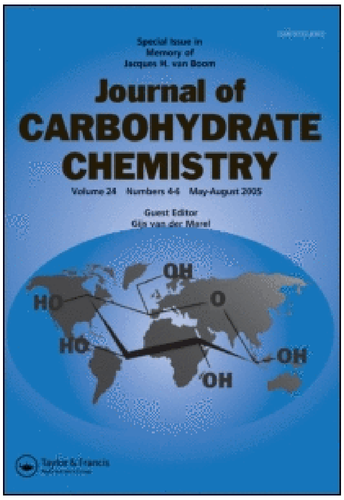

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Radical Anomefhc Chemistry

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REVIEW ARTICLE

RADICAL ANOMERIC CHEMISTRY

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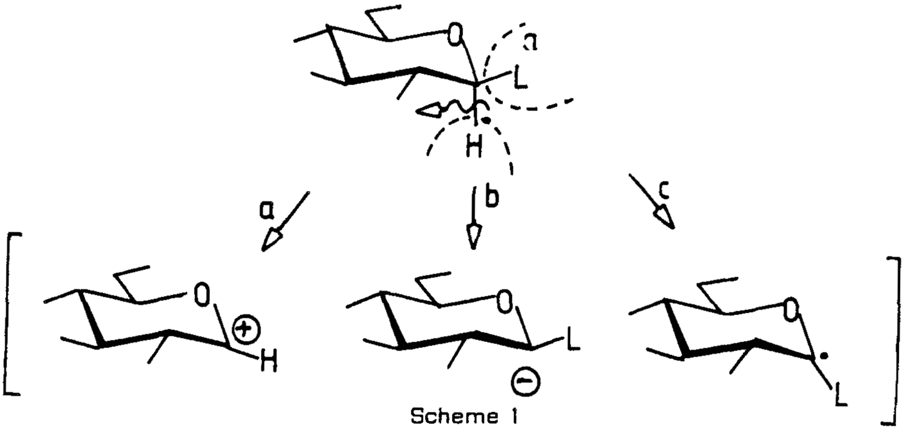
The main synthetic reactions of carbohydrates at the anomeric center involve ionic processes. commonly cationic processes for glycosylations and anionic processes for C-branching reactions. The use of homolytic or radical reactions has emerged in the last decade for the synthesis of complex molecules. These developments are of great interest for synthetic purposes and for the study of stereoelectronic effects at the anomeric center of carbohydrates. This short review summarizes the principal results of radical transformations at C-1 of aldoses.

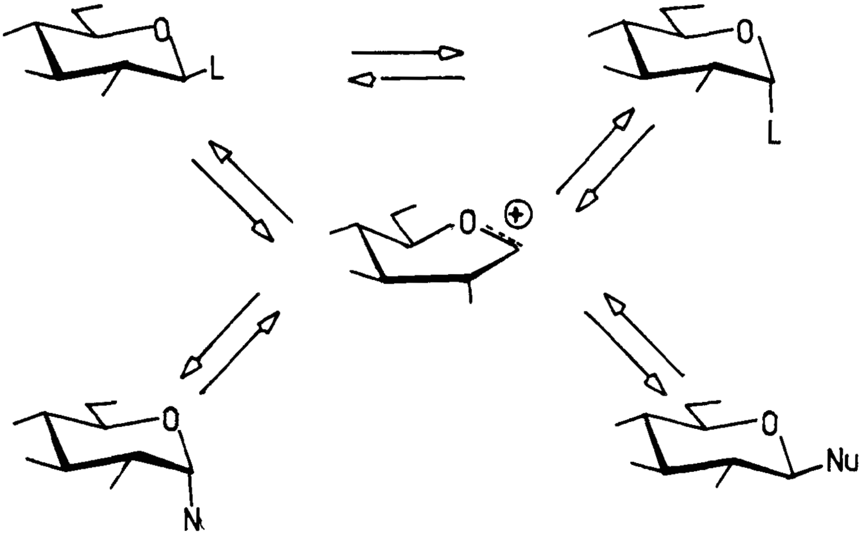
INTRODUCTION

Cleavage at an aldose anomeric carbon atom [Scheme 1] can occur by producing: [a] carbocationic [b], carbanionic or [c] radical species. These intermediates confer electrophilic, nucleophilic, or radical character respectively to the anomeric center:



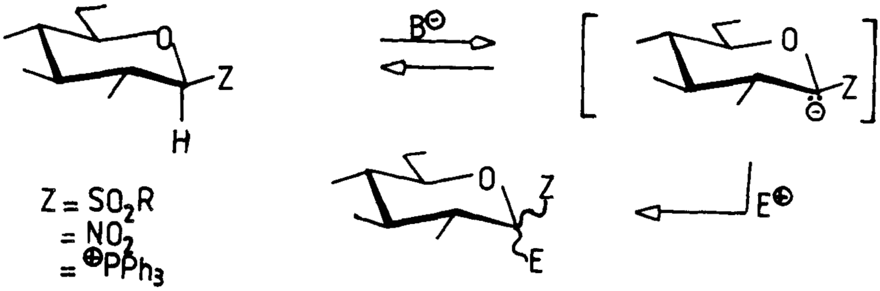
Scheme 1

The electrophilic character of the anomeric center is manifested by glycosylation reactions [Scheme 2]. The carbocation derived from glycopyranosyl derivatives yields mainly α-glycosides due to the anomeric effect, unless participating C-Z substituents [$OCOCH_3$, $NHCOCH_3$, phthalimido, etc...] directs the formation of a β-glycoside.



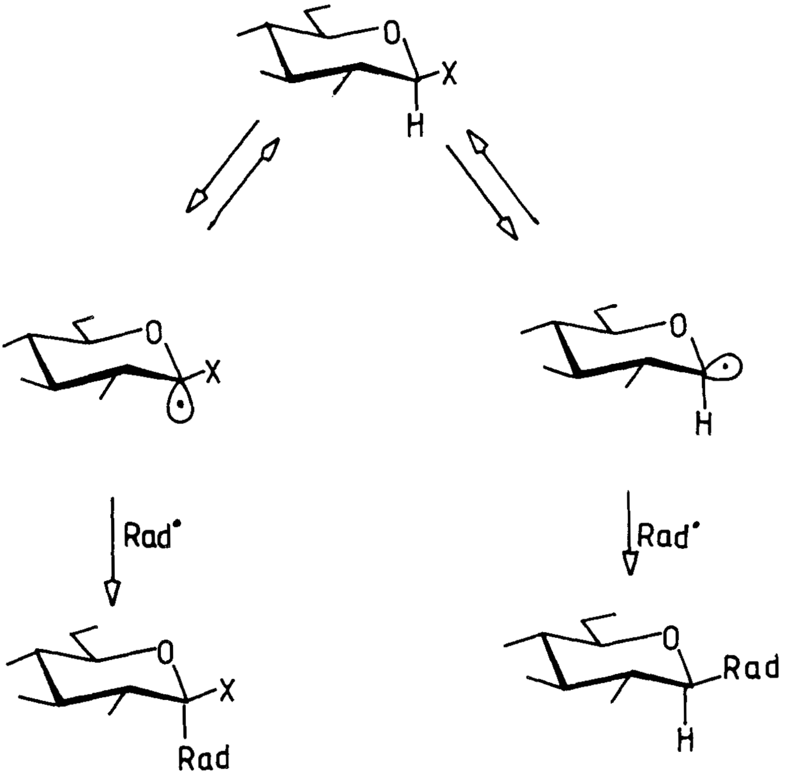
Scheme 2

Recently, an "umpolung" reaction at the anomeric center of carbohydrates has been developed using strong electron-withdrawing groups such as sulfonyl,[2] nitro,[3] and phosphonium.[4] The nucleophilic character produced in these reactions at C-1 was mainly used for the synthesis of C-branched sugars (Scheme 3).



Scheme 3

Radical character can be developed at the anomeric center if the substituents at C-1 are subject to captodative effects. Such substituents stabilize radicals by the simultaneous presence of one "capto" (electron acceptor) and one "dative" (intracyclic oxygen atom) substituent.[5]



Scheme 4

I. FORMATION AND STRUCTURE OF ANOMERIC RADICALS

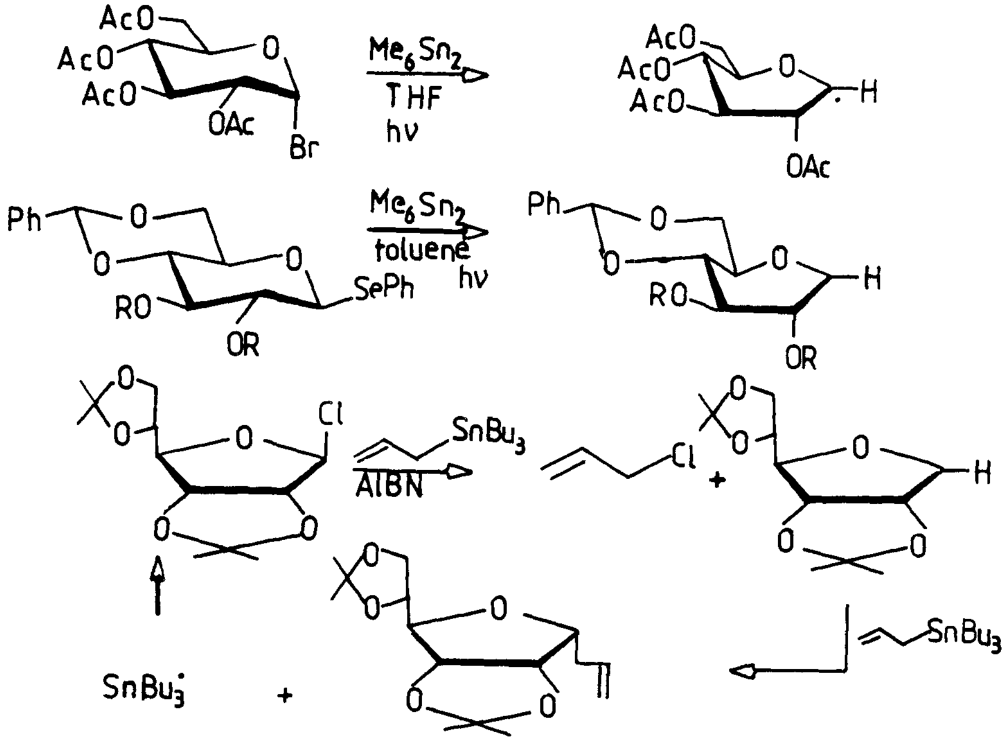
GILBERT et al.[6,7] investigated carbohydrate radicals generated by reaction of unprotected carbohydrates with OH• radicals in aqueous solution and showed a nonselective hydrogen abstraction from all positions of the substrates.

Protected carbohydrates are of special interest from a synthetic point of view. Direct observation (ESR) of anomeric radicals derived from acylated and alkylated furanosyl and pyranosyl derivatives, recently has been reported.[8] These results confirm previous kinetic observations related to formation of anomeric radicals by hydrogen photoabstraction using sensitizers.[9-13]

I.1. Methods of formation of anomeric radicals

The formation of monoradicals is principally obtained by:

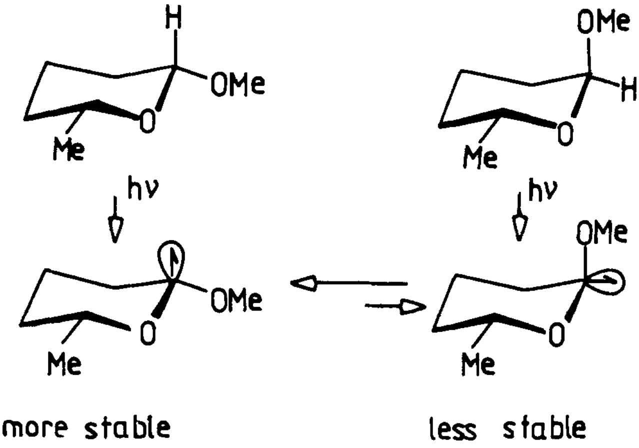
a) cleavage of a C-1 to halogen, selenium, or sulfur bond (Scheme 5) by stannyl radicals under photolytic conditions or using azodiisobutyronitrile (AIBN) as a radical initiator.[14]



Scheme 5

b) cleavage of a C-1 to oxygen or nitrogen bond by a one electron transfer to the anomeric center of the carbohydrate bearing a tertiary nitro[3] or phenoxy group.[16]

c) cleavage of a C-1 to hydrogen bond by photolysis of heterocyclic acetals [8-13] with acetone or benzophenone or in the presence of tert-butoxy radicals (Scheme 6).



Scheme 6

The creation of diradicals results from similar intramolecular reactions. In particular, the presence of carbonyl groups on the aglycone chain can generate, after photoexcitation, anomeric diradicals of great reactivity.

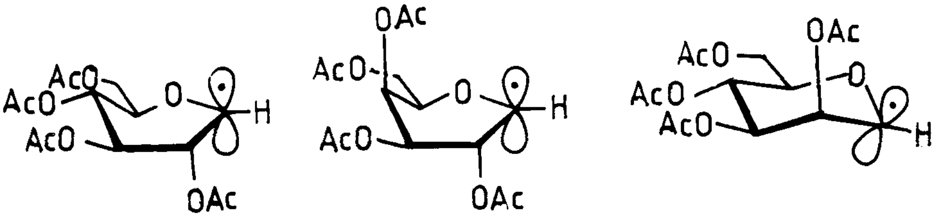
1.2. Kinetics and structural studies of anomeric radicals

The first observation of hydrogen abstraction from an acetal carbon atom in a heterocyclic series was obtained with substituted 2-alkoxy tetrahydropyrans, and showed preferential axial hydrogen abstraction. These experimental observations were confirmed by ESR measurements on acetals, dioxanes, orthoesters[12,13] and carbohydrates.[8]

From the appropriate carbohydrates, ESR spectroscopic data from pyranosyl radicals can be interpreted in terms of an almost planar π -type α -alkoxyalkyl radical.[8] This planar structure at the anomeric center also reveals a dependence of these radicals on the structure of the parent carbohydrate.

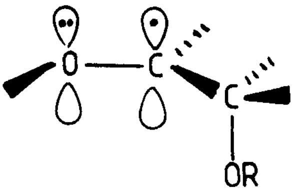
Glucosyl and xylosyl radicals prefer to attain a twisted $B_{2,5}$ boat conformation. With free hydroxyl groups at C-2 and C-3, the resulting conformation is an equilibrium between half-chair forms, this modification probably resulting from hydrogen bonding.

Galactopyranosyl radicals exist in a ^4H half-chair conformation due to the occurence of substituent interactions. Mannopyranosyl and lyxopyranosyl radicals preserve the $^4C_1$ conformation of their precursors by probable interactions between the singly occupied p-orbital and the β-OR bond (Scheme 7).



Scheme 7

All these conformations and their interconversions have been interpreted in terms of a "stabilizing" interaction between the singly occupied p-orbital (SOMO) and the σ^* -LUMO of an axially bonded -C-OR bond[15] (Scheme 8).



Scheme 8

The stabilizing stereoelectronic effects in glucosyl radicals are of the same order as the anomeric effect of glucosyl chlorides.[15c] Electron-donating substituents at the anomeric center destabilize anomeric radicals, while withdrawing groups stabilize these intermediates and makes their formation easier.

These suppositions have been confirmed in studies to be described that involve intra- and intermolecular radical reactivity.

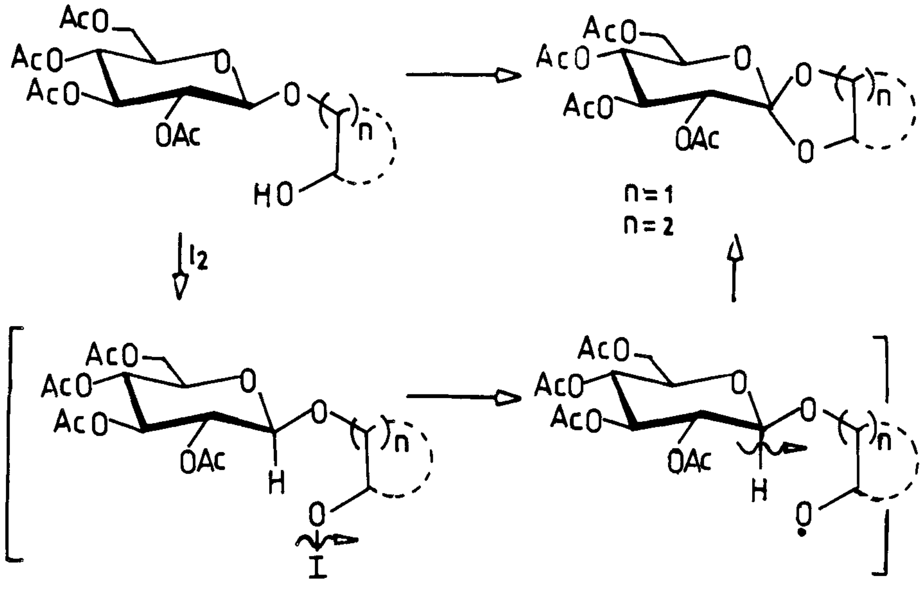
II. INTRAMOLECULAR REACTIVITY OF ANOMERIC RADICALS

The formation of a radical or any excited state on an aglycone chain can induce the abstraction of an anomeric hydrogen and yield new bonds such as C-O or C-C.[1]

II.1. Anomeric C-O bonds formations

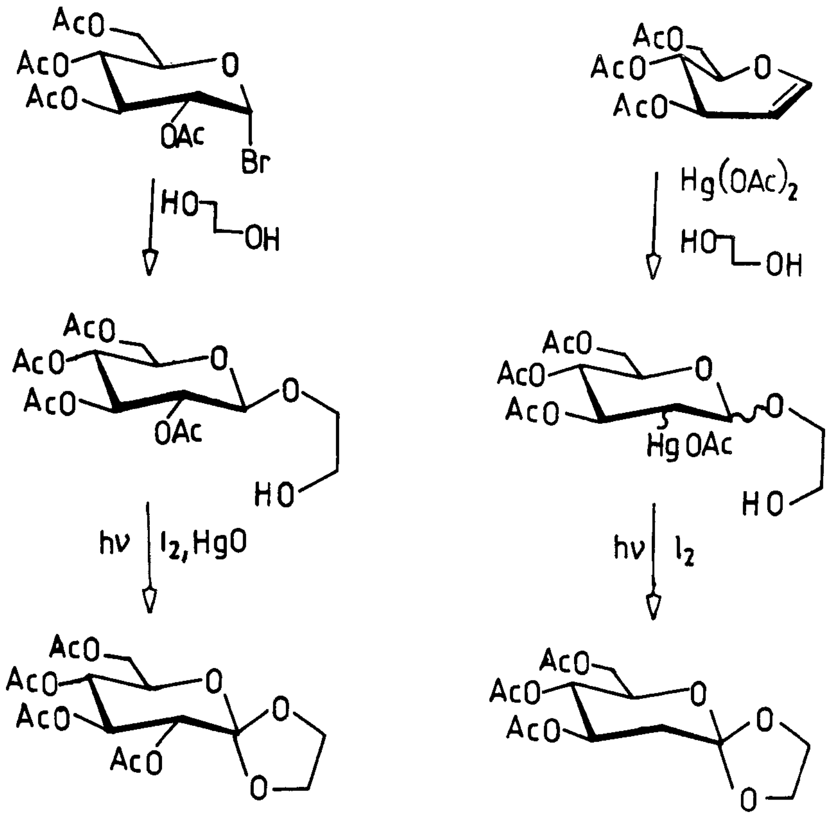
II.1.1. Orthoesterification

The unsusual orthoester linkage between saccharide units is found in a family of antibiotics called orthosomycins.[17] The synthesis of such orthoesters is feasible using radical heterocyclization reactions. Irradiation of hydroxyalkyl glycosides in the presence of iodine and Hg(II) oxide, leads to spiroorthoesters,[18a,b] by preliminary anomeric H-abstraction by the intermediate alkoxy radical (Scheme 9) according to previously described mechanisms.[18c]



Scheme 9

This reaction can be extended to the 2-deoxy anomeric orthoesters[18c] using an addition reaction on tri-O-acetyl-D-glucal according to Scheme 10.



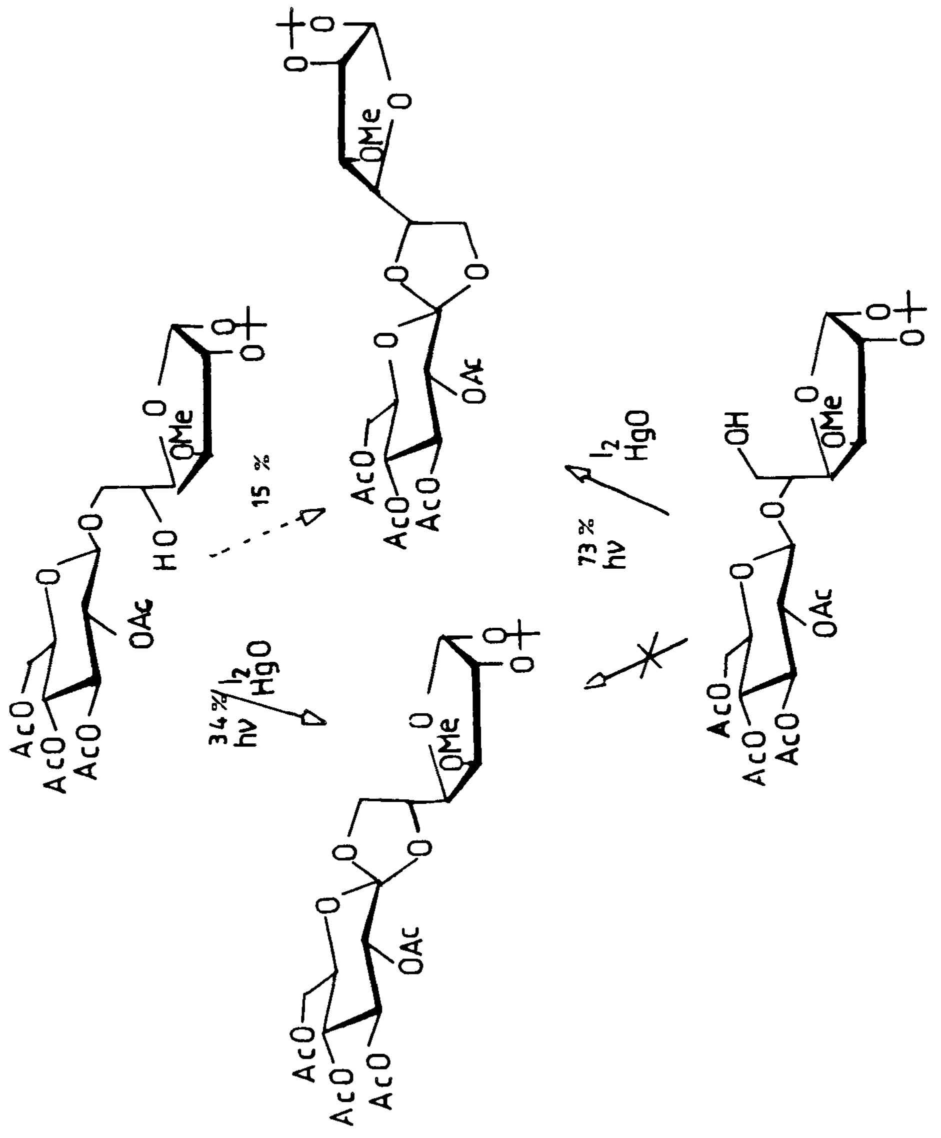
Scheme 10

The stereoselectivity of this radical heterocyclization is observed in the following study [Scheme 11] where retention of configuration of β -hydroxyglycosides is predominant.[18d]

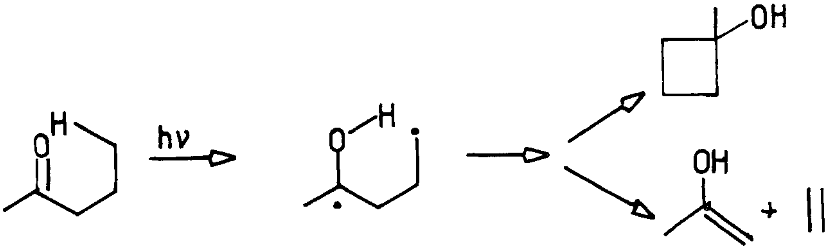
This methodology complements other methods used for the synthesis of anomeric orthoesters.[19,20]

II.1.2. Lactonization

The process of intramolecular abstraction of a hydrogen atom from the γ-carbon atom of an excited carbonyl group is referred to as a "NORRISH type II reaction". The formed diradical can close to a cyclobutanol or cleave to an olefin and an enol [Scheme 12].

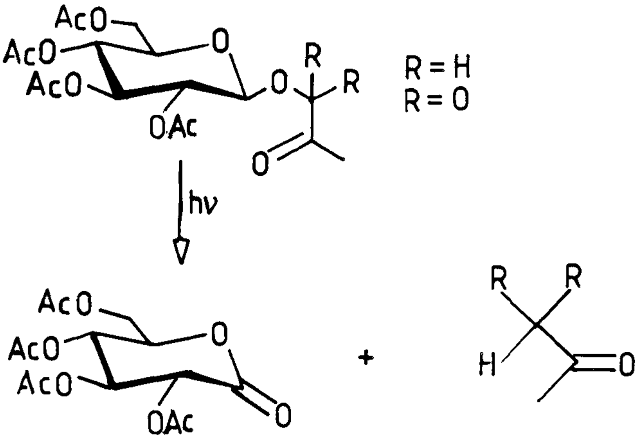

AcO
AcO
AcO
OAc
HO
OMe
34 %
hν
I2
HgO
15 %
73 %
hν
I2
HgO
OH
OMe
OAc
OMe
OAc

Scheme 11



Scheme 12

This NORRISH type II reaction has been applied to carbohydrates for oxidation of the anomeric carbon by irradiation of glycosyl pyruvic ester,[21] or oxo-2 propyl glycoside[11] according to Scheme 13.

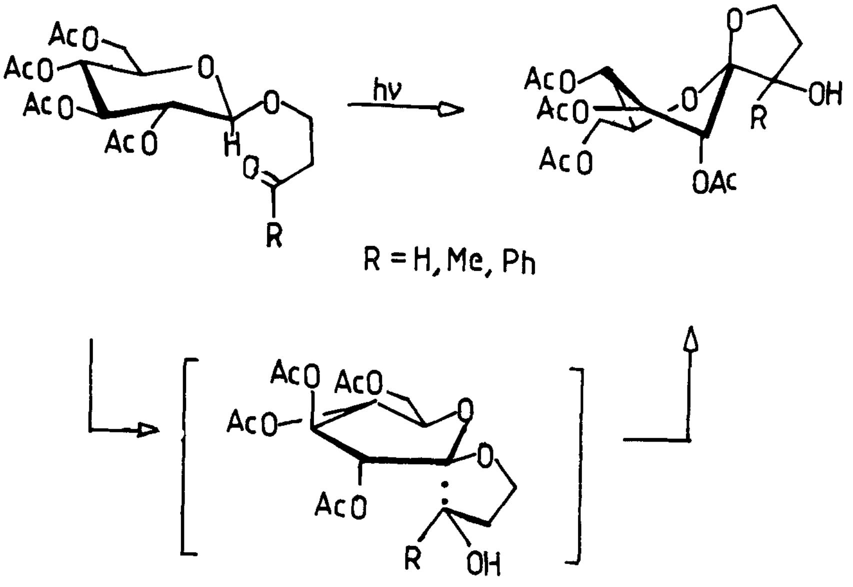


Scheme 13

The oxidation process is possible for both α and β-anomers and has been applied to numerous examples in different carbohydrate series (gluco, 2-deoxy and 2,3-dideoxy, unsaturated sugars etc...).

II.2. Anomeric C-C bond formation

Using the NORRISH type II reaction, anomeric spiro carbohydrates can be synthesized by photocarbocyclization of 3-oxopropyl glycosides after anomeric H-abstraction at the δ -position[22] (Scheme 14).

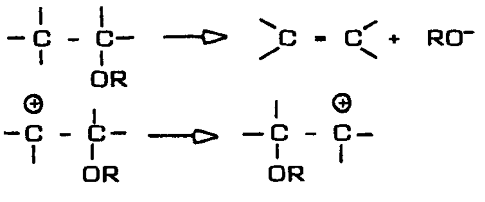


Scheme 14

This regioselective reaction is also stereoselective with preferential photoabstraction of anomeric axial hydrogens. Thus, β -glycosides are much more reactive than the α -glycosides and by freezing the intermediates radicals, cyclization becomes more stereoselective with arylketonic glycosides.[23] This reaction, when applied to the D-manno, D-gluco, L-arabino and 2-deoxy, 2,3-dideoxy series was found to be fastest with D-manno derivatives.[22] The importance of the axial substituent at C-2 is important in the stabilization of the anomeric radical (Scheme 15).

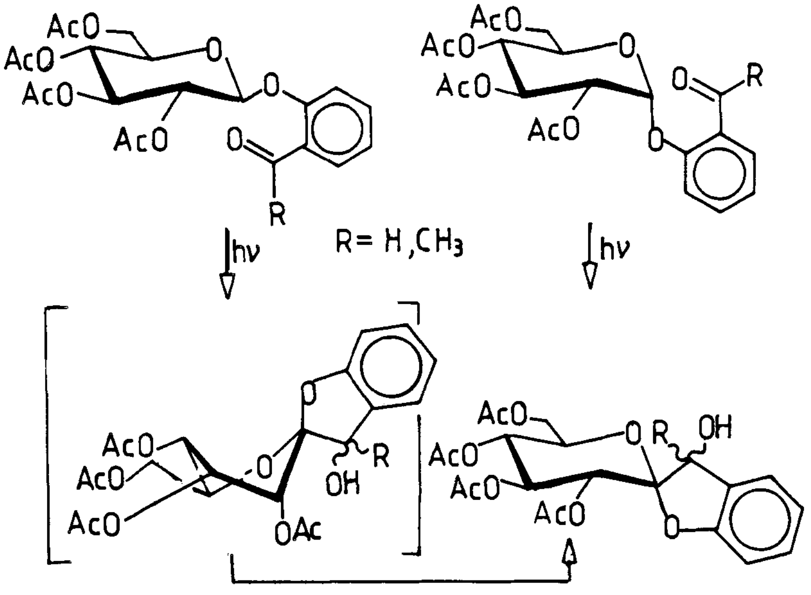
III. INTERMOLECULAR REACTIVITY OF ANOMERIC RADICALS

The preceding intramolecular reactions involved diradicals which were extremely reactive and gave efficient transformations of carbohydrates at the anomeric center. The transformation of radicals by intermolecular pathways must be very fast to avoid racemization reactions or other side reactions observed in ionic precesses e.g elimination, rearrangements, etc...



$$-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{\underset{OR}{|}}{C}}- \longrightarrow \;>C=C<\; + \; RO^-$$

$$-\overset{\oplus}{\underset{|}{C}}-\overset{|}{\underset{\underset{OR}{|}}{C}}- \longrightarrow -\overset{|}{\underset{\underset{OR}{|}}{C}}-\overset{\oplus}{\underset{|}{C}}-$$



Scheme 15

In radicals with β -heteroatoms, these reactions do not compete with chain reactions and other substitution and addition reactions can occur to yield C-H or C-D, C-halogen, C-O and C-C bonds.

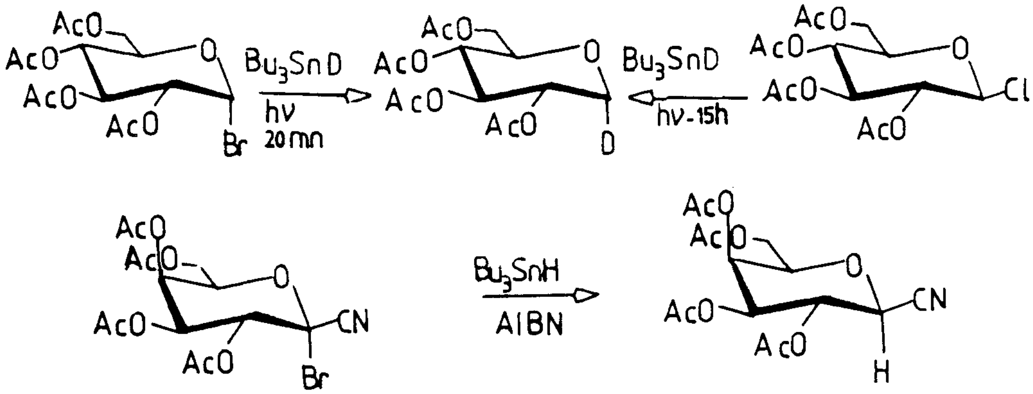
III.1. C-H or C-D bond formation

The radical cleavage of an anomeric C-halogen, C-N or C-S bond is possible under radical initiation conditions [24] (hν or AIBN) or reductive lithiation by SET (lithium naphtalenide).[2]

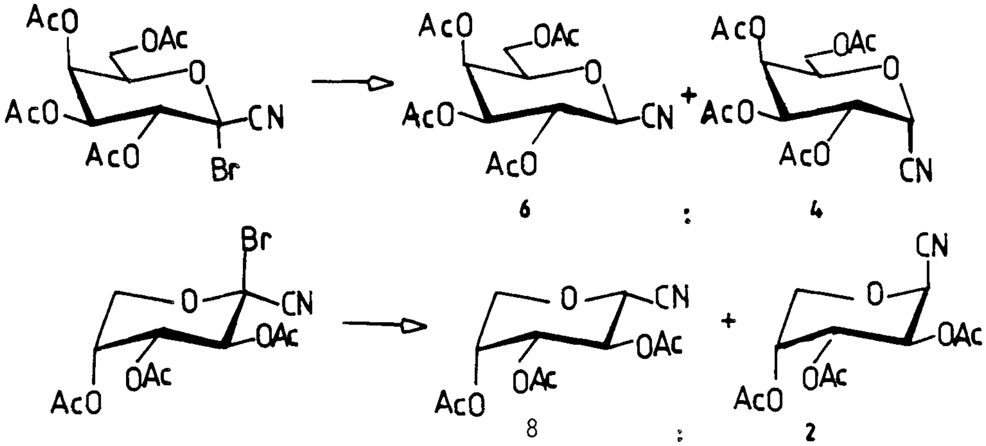
These highly stereoselective reductions are observed with retention of configuration starting from α -glycosyl derivatives. In contrast, β -glycosyl derivatives are reduced more slowly into α -compounds with inversion of configuration. Examples of such reductions are given in Scheme 16.

Stabilized anomeric radicals in pyranose or furanose systems were also evoked to explain reduction reaction[25] or decarboxylation[26] (Scheme 17) that proceeded with lower stereoselectivity.

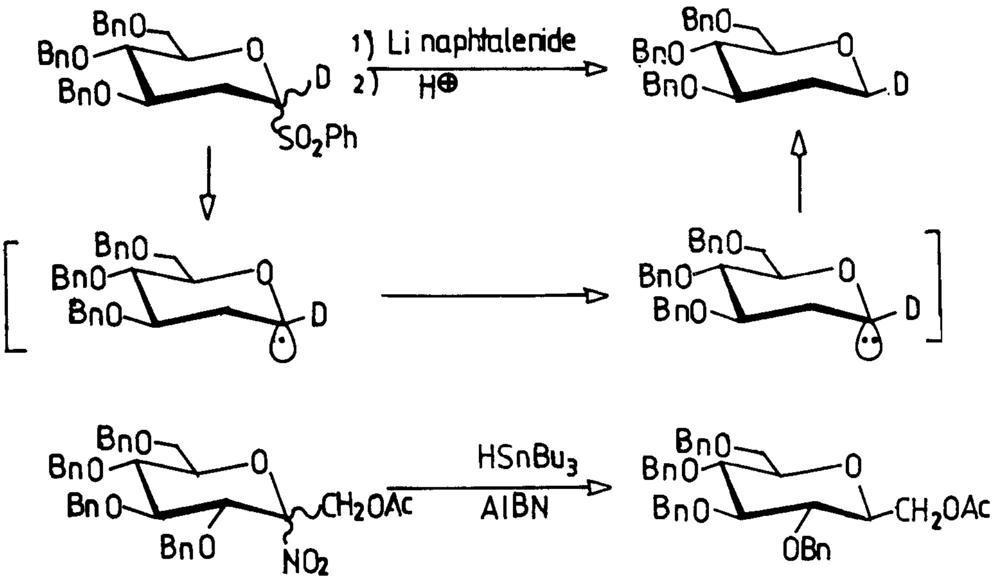
Similar reactions result during reductions by non anomeric stabilized radicals[27] (Scheme 18).



Scheme 16



Scheme 17



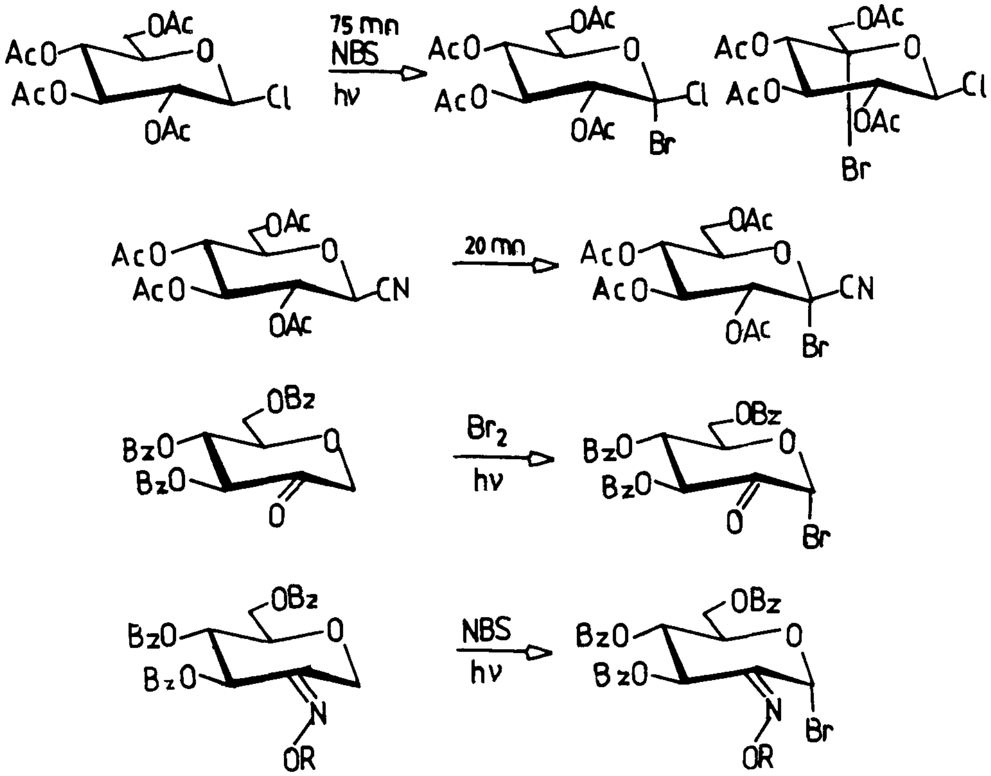
Scheme 18

III.2. C-halogen bond formation

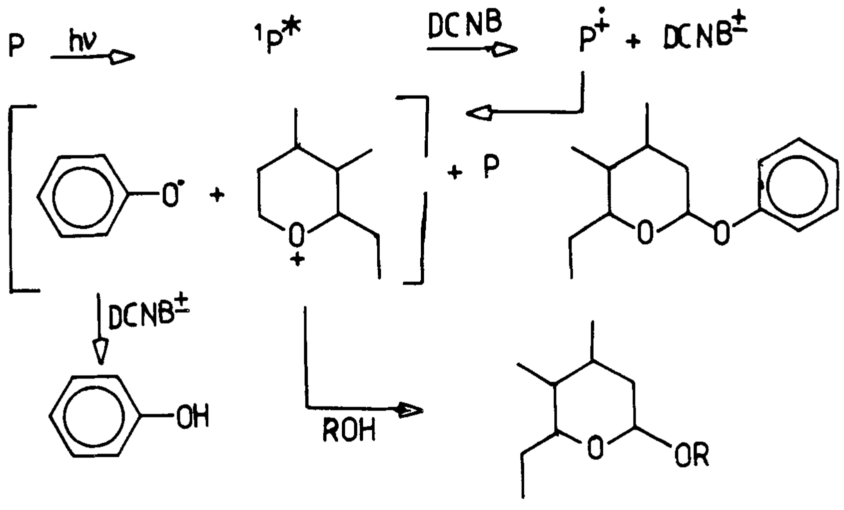
Radical brominations of a range of aldopyranosyl compounds have been described by R. J. FERRIER et al.,[28] by which the halogen can be introduced into sugar rings at positions adjacent to the ring oxygen atom (C-4, C-5). The presence of electron withdrawing groups such as halogens (Cl, F, Br), keto functions or their O-substituted oximes at C-2, C-nitrile groups at proanomeric carbons, activate this position towards homolytic bromination.[29,30] (Scheme 19).

The regio and α -stereoselectivity of photobromination results from the captodative radicals which are formed with considerably greater ease in quantitative conversions.

Using this photobromination methodology, many di- and trisaccharides have been obtained in good yield.[29]



Scheme 19

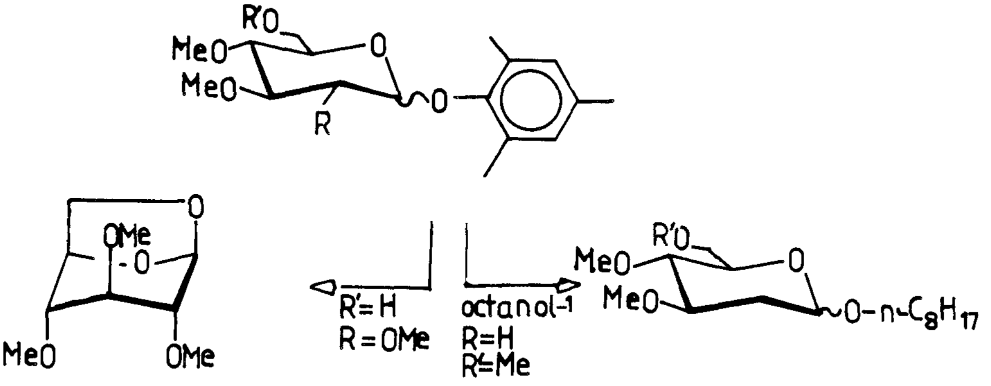


Scheme 20

III.3. C–O bond formation

Photosensitized transacetalizations are possible using a binary sensitizing system consisting of a high absorbing aromatic hydrocarbon (P: phenanthrene) and a non-light absorbing cyanoaromatic compound (p-dicyanobenzene: DCNB). This reaction involves a photostimulated one electron transfer process (Scheme 20).

Photolysis of glucosides with a free hydroxyl at C-6 yields an intramolecular cyclization product. If the C-6 hydroxyl group is protected, intramolecular acetalization occurs in the presence of n-octane (Scheme 21).

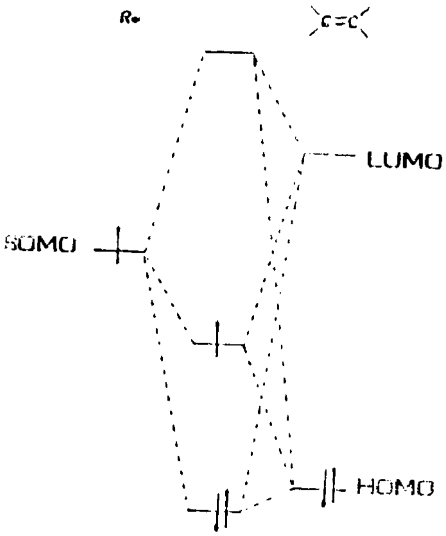


Scheme 21

III.4. C–C bond formation

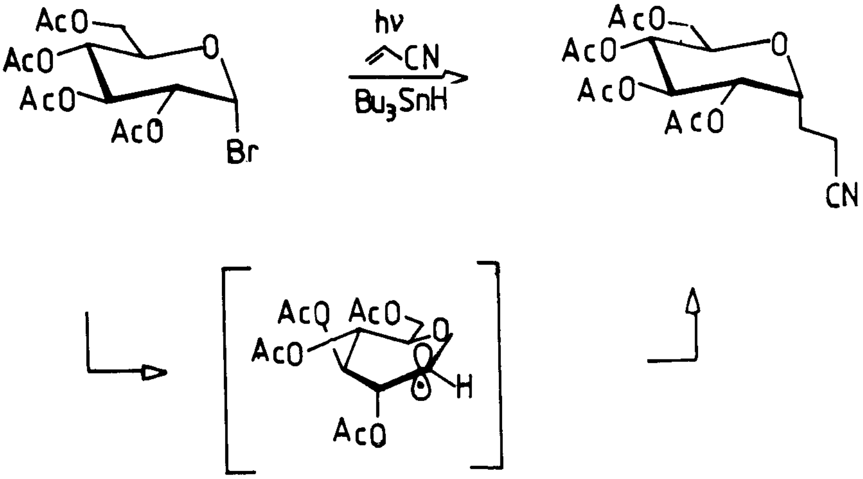
The addition of anomeric radicals to alkenes is one of the most interesting methods for the synthesis of C-glycosides.[1] These reactions are carried out, using sugar halides or selenides, either photolytically at room temperature or thermally with radical initiation (e.g. AIBN).

The anomeric radical is nucleophilic and interacts by its high lying SOMO with the LUMO of an electron-poor alkene such as acrylonitrile or methyl acrylate. The presence of such electron-withdrawing substituents in the alkene lowers the LOMO energy and increases the addition rate by reducing the SOMO-LUMO difference (Scheme 22).



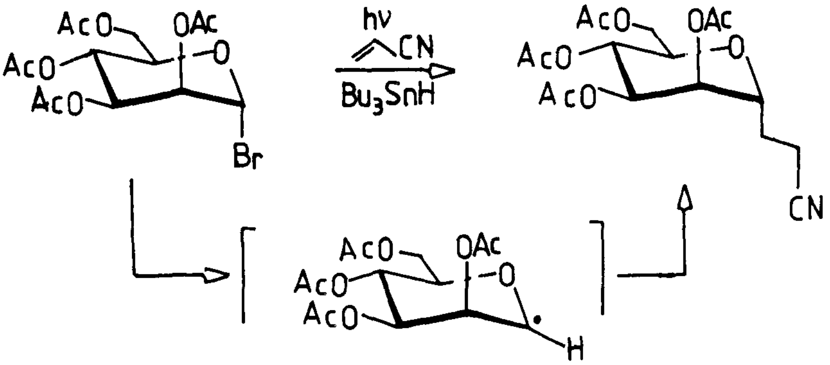
Scheme 22

This addition reaction forms predominantly the C-glucosides by equatorial attack at the previously described boat conformation of the glucosyl anomeric radical[31,32] [Scheme 23].



Scheme 23

In contrast, the α-attack in the manno series results from the shielding effect of the axial C-2 substituent in the chair conformation of the intermediate radical[15] [Scheme 24].



Scheme 24

The high stereoselectivity for synthesizing α-C-glycosides is particularly interesting and C-disaccharides have been obtained using this methodology.[33]

CONCLUSIONS

The radical chemistry at the anomeric center of carbohydrates, because of its regio- and stereoselectivity, has been increasingly employed in organic synthesis. Many substitution, addition, oxidation and reduction reactions between radicals and between radicals and nonradicals by intra- and intermolecular routes have been reported. The development of single electron transfer processes should be observed in the future by the systematic use of "umpolung" reactions at the anomeric position of sugars substituted by electron-withdrawing groups.

With the high regioselectivity and stereoselectivity of radical transformations at anomeric carbons the accompanying mild reaction conditions are particularly useful for the synthesis of complex carbohydrates.

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