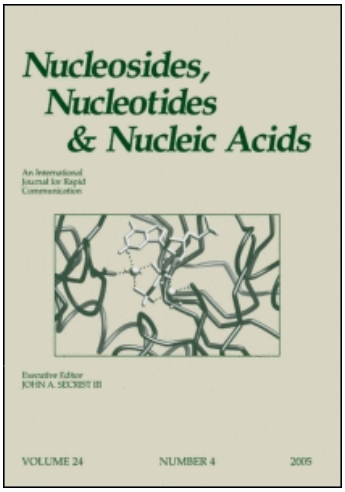

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MECHANISTIC AND SYNTHETIC ASPECTS OF THE C-1' RADICALS IN MODIFIED NUCLEOSIDES

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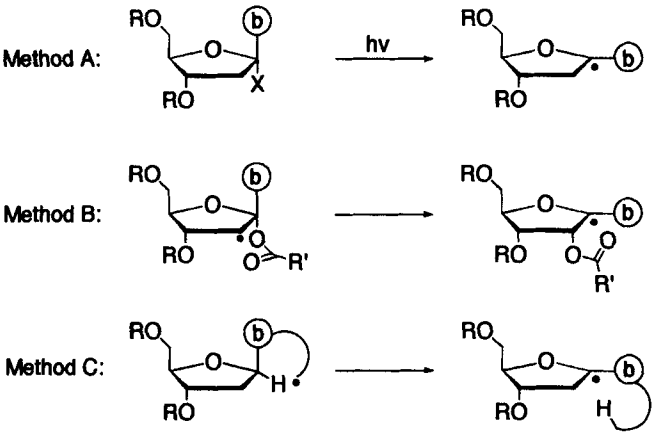
ABSTRACT: The direct and indirect production of C-1' radicals has been achieved through the synthesis of modified nucleosides. Product studies and spectroscopic investigations have been used to study the structure and fate of C-1' radical species under anoxic or aerobic conditions. The results are of fundamental importance in understanding the mechanism of DNA cleavage via C-1' radicals. The mechanistic schemes of some very recent synthetic applications have also been revisited.

A number of agents are able to react with DNA or RNA and generate macromolecular radical species.[1] These processes are of considerable importance since they can lead to base modifications or strand scissions, both important steps in radical-induced DNA damage. As research progresses in the area of the mechanism of attack of oxidative DNA cleavers, it becomes evident that hydrogen abstraction from the C-1' position is involved in many cases. The fate of the C-1' radicals under either anoxic or aerobic conditions are currently in dispute. On the other hand, it is envisaged from the recent literature in the nucleoside area that C-1' radicals may constitute useful intermediates which can generate valuable chemistry currently unexplored but potentially important in medicinal chemistry.[2] In fact, there are a number of natural products reminiscent of nucleosides which contain modifications in the C-1' position.

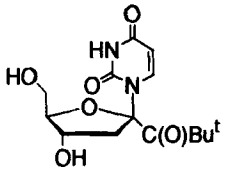
These considerations prompted us to undertake a systematic investigation of the radical chemistry associated with the C-1' position by utilizing modified nucleosides as models. In our synthetic planning, the production of C-1' radicals in model 2'-deoxy- and

Scheme 1



ribonucleosides can be viewed as feasible either through a direct modification of the C-1' position which can function as a precursor of a C-1' radical species (Method A in Scheme 1), or through remote functionalization and utilization of known types of radical migrations (Methods B and C in Scheme 1).

The ketone **1** was first synthesized by Goodman and Greenberg starting from D-fructose (11 steps).[3] These authors reported the efficient generation of C-1' radicals from this substrate *via* Norrish type I photocleavage. Very recently the ketone **1** has been prepared by a new route starting from uridine (7 steps) and with a much higher overall yield.[4] The specific photogeneration of C-1' radicals has been used for spectroscopic studies.[5] Indeed, the electron spin resonance spectrum of the C-1' radical shows hyperfine couplings of the unpaired electron with the two hydrogen atoms in the 2' position (a_H=19.24 and a_H=24.44 G; g=0.00296). Couplings with other nuclei are much smaller and within the linewidth of 2.8 G. Theoretical studies have corroborated these



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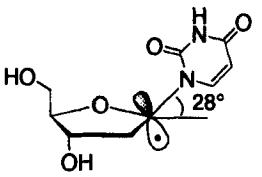
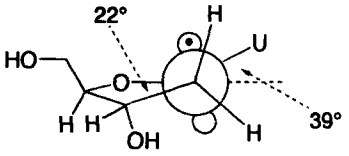
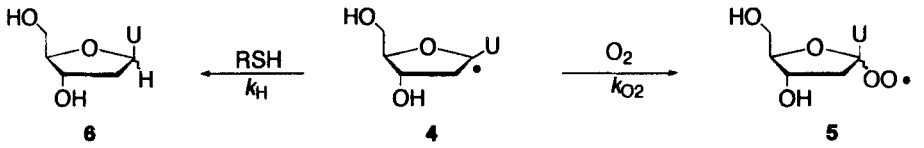


2



3

Scheme 2



6 **4** **5**

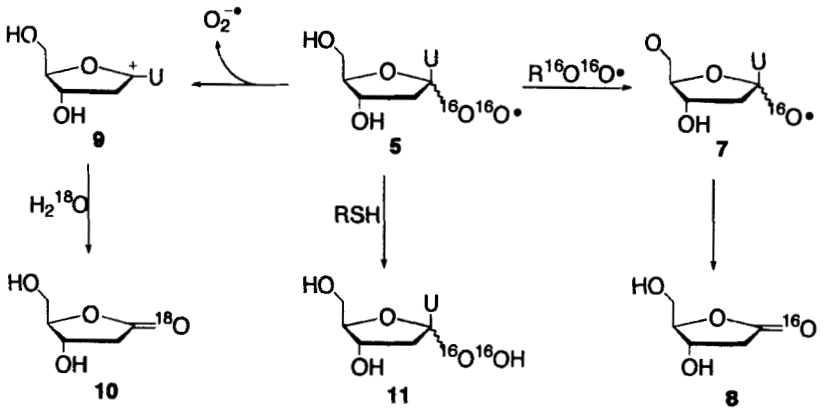
assignments and have indicated that the configuration of the C-1' radical is strongly bent (structure **2**) and there is no appreciable delocalization on the uracil moiety. The preferred conformation around the radical center is shown in structure **3**. These data are in sharp contrast with the general assumption that C-1' radicals are planar or nearly so, due to the delocalization of the unpaired electron on the base ring.

The UV-visible spectrum of the C-1' radical has also been recorded by using laser flash photolysis and shows a broad band between 280 and 360 nm with a λ_{max} at 320 nm.[5] In these studies, the rate constant (k_{O2}) for the reaction of C-1' radical **4** with molecular oxygen to form the peroxyl radical **5** (Scheme 2) was also measured to be about 1 x 10^9 M^{-1} s^{-1}. On the other hand, the reaction of C-1' radical **4** with a thiol, generated a mixture of α,β-2'-deoxyuridine **6** (Scheme 2). In order to obtain relative rate constants for the two processes, Goodman and Greenberg studied the reaction in the presence of O_2 and $HOCH_2CH_2SH$.[3] By assuming that the uracil formation derived exclusively from the reaction of C-1' radical **4** with O_2 (*vide infra*) and plotting [**6**]/[Uracil] versus $[HOCH_2CH_2SH]/[O_2]$ they obtained $k_H/k_{O2} = 1.9 \times 10^{-3}$. Combination of these kinetic data gave $k_H = 1.9 \times 10^6$ M^{-1} s^{-1} for the reaction of C-1' radical **4** with β -mercaptoethanol.

Under aerobic conditions, however, C-1' radical **4** affords 2-deoxyribonolactone through a number of currently disputed pathways. Very recently Greenberg's[6] and our[4] groups have independently reported mechanistic studies for the formation of 2-deoxyribonolactone using ^{16}O–^{16}O and $H_2{}^{18}O$.

We investigated the reaction without exogenous hydrogen donors and under continous photolysis with a 500 W high pressure mercury lamp.[4] We showed that under these conditions, the peroxyl radical **5** reaches such a concentration that decays either via a bimolecular reaction with another peroxyl radical to give an instable tetroxide which decomposes to alkoxyl radical **7**, or via a unimolecular path (heterolytic cleavage) to

Scheme 3

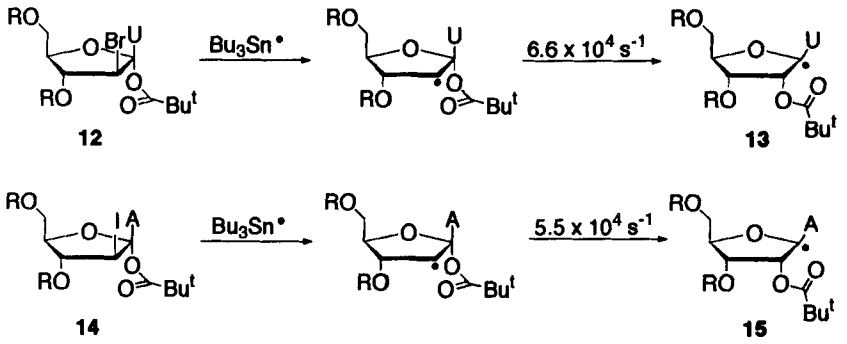


generate the carbocation **9** and superoxide radical anion. The cationic intermediate **7** was trapped by $H_2{}^{18}O$, thus demonstrating the partition between the two channels.

On the other hand, Greenberg and coworkers gave evidence of the superoxide formation in a more complex system,[6] i.e. in the presence of β-mercaptoethanol as the hydrogen donor and under photolytic conditions where the peroxyl radical **5** reaches a much lower concentration. They assumed that the hydroperoxide **11** is quantitatively transformed into 2-deoxyribonolactone containing ^{16}O. As a result of several simplifications and assumptions, they estimated a rate constant of ca. 1.2 s^{-1} for the formation of the superoxide radical anion. In our opinion, more experiments are needed in order to give reliable kinetic data on this intriguing mechanism, meanwhile we suggest taking Greenberg's values with extreme caution.

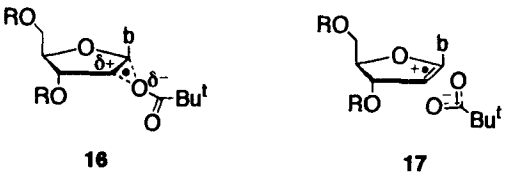
The halopivaloates **12** and **14** have been obtained by electrophilic halopivaloyloxylation of the corresponding 1',2'-didehydro-2'-deoxynucleosides.[7,8] Tanaka's and our group have independently shown that the reaction of halopivaloates **12** and **14** with tributyltin hydride generates indirectly the radicals **13** and **15**, respectively, through a β-(acyloxy)alkyl radical rearrangement (Scheme 4).[7,8] Rate constants for these rearrangements have been measured by us using free-radical clock methodology and found to be the same within experimental errors upon substitution of uracil with adenine in the same diastereotopic configuration (Scheme 4).[7]

Scheme 4

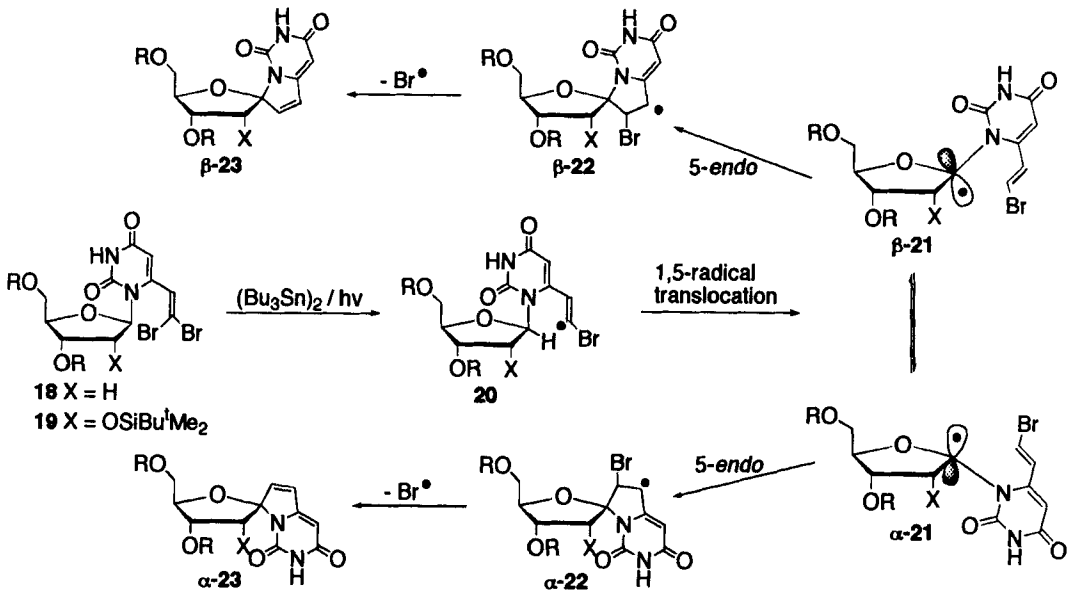


It was shown that in the absence of a significant driving force (thermodynamic control), the (β-acyloxy)alkyl rearrangement does not occur readily.[9] As shown in 2'-deoxyuridin-1'-yl (**4**) the radical center has a pyramidal shape in which the delocalization of the unpaired electron on the base ring is unimportant. Therefore, we suggest (at least for the uracil derivative) that the unpaired electron is delocalized on the α-oxygen and it does not alter substantially the anomeric stabilization involving the glycosidic bond. On the other hand, comparing our results with the large number of kinetic data available in the literature for such rearrangements,[9] we further suggest that the charge separation during the reactions is an important issue for the pivaloate shift in these nucleosides (kinetic control). The transition state for these rearrangements is expected to be either like **16** or **17**, the three-center-five-electron mechanism (**16**) being less polarized than that of the five-center-five electron shift (**17**).[9]

Recently, Tanaka's and our group have also generated C-1' radicals through 1,5-radical translocation (Method C in Scheme 1) for synthetic purposes.[10,11] Two examples from our work are shown in Scheme 5.[10] That is, reaction of 2'-deoxy nucleoside **18** with photogenerated $Bu_3Sn^•$ radical provided the spiro nucleosides **23** as the sole products in a 78 % yield and in an anomeric β:α ratio of 2:1 whereas the protected ribo **19** gave only the β-anomer **23** in a 37% yield. The factors controlling the stereoselection in these cyclizations deserve some comments in light of the C-1' radical structure. The



Scheme 5



mechanism that we conceived for these reactions is outlined in Scheme 5. It is comprised of a cascade of free radical reactions involving bromine abstraction from C-8 by a stannyl radical to generate the vinyl radical species **20**, followed by a 1,5-radical translocation to the anomeric position, then a rare 5-*endo* cyclization of the anomeric radical **21** onto the proximal double bond and finally product formation by bromine atom ejection from **22**. Since the C-1' radicals are shown to be bent, the inversion of configuration at the C-1' radical is expected to be the main factor controlling the stereochemical outcome. Thus, when a bulky substituent is present in the C-2' position (X = $OSiBu^tMe_2$) the equilibrium between β-**21** and α-**21** is expected to lie on the β-anomer, where the two substituents in the C-1' and C-2' positions have a *trans* arrangement. This is most probably the reason why a single stereoisomer is observed in the reaction of the ribo series. In the 2'-deoxyribo series (X = H), presumably the intermediate C-1' radical is rapidly inverting and the product distribution is controlled only by the difference between the total free energy of activation for each pathway (Curtin-Hammett principle).

In conclusion, C-1' radicals are no longer elusive intermediates and can be generated by a variety of methods. The detailed chemistry involving the C-1' position has not been clarified and, therefore, in the near future we will see more work in the

following main areas: (i) C-1' radicals as useful synthetic intermediates in medicinal chemistry, (ii) the specific generation of C-1' radicals and the investigation of their chemistry in DNA and related systems.

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