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Essential reactive intermediates in nucleoside chemistry: cyclonucleoside cations†

Anatoly M. Belostotskii,* Elisheva Genizi and Alfred Hassner

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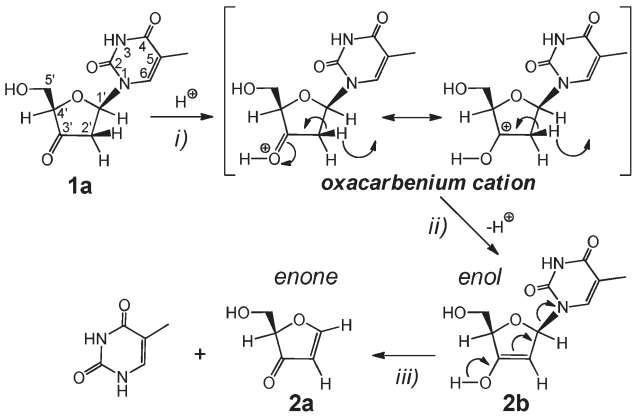
DFT-based modeling as well as experimental examination of model keto nucleosides have revealed that high susceptibility of these compounds to acids is due to formation of intermediate cyclonucleoside cations of low energy. Theoretically established chemical structures of these previously overlooked intermediates explain the reaction courses for a cluster of nucleoside reactions.

Chemical transformations of unnatural nucleoside derivatives can allow us to discern new aspects of the chemistry of naturally occurring nucleosides and, consequently, of key biopolymers – DNA and RNA. In this context, keto nucleosides are interesting. These compounds are often used as synthetic precursors of C-branched,[1] methylene substituted[1,2] and non-ribo[3] nucleosides, many derivatives of which are pharmacologically active.[1a,4] However, synthetic reports often mention an increased lability of keto nucleosides both under basic and acidic conditions[3,5] – these ketones bear a β-positioned hetero substituent (the amino base or alkoxy/ester group) and undergo β-elimination, *e.g.*, **1a**→**2a**.[3,5d–f] Their susceptibility to acids may be extremely high: sometimes, contact with silica is sufficient to cause the nucleobase elimination.[3a]

The reason for the unusual ease of this acid-promoted decomposition of keto nucleosides is not entirely clear. Such an elimination for a β-substituted ketone includes three sequential elementary reactions: protonation of the carbonyl moiety, prototropic rearrangement in triad O=C–C (*i.e.*, enolization) and an anionotropic rearrangement in triad C=C–C (*i.e.*, enone formation) as shown in Scheme 1 for 3′-oxo compound **1a** whose decomposition gives enone **2a**. This general scheme does not disclose molecular structural factors that impart to keto nucleosides the considered distinctive lability. Nevertheless, the nucleoside cation (oxacarbenium ion; Scheme 1) is a remarkable intermediate in this reaction sequence. Strong intramolecular interactions between nucleobases and the sugar ring take place in nucleoside cations as theoretical modeling shows for the



Scheme 1 Acid-catalyzed elimination of the amino base in 3′-oxo-2′-deoxythymidine **1a** [(i) carbonyl protonation, (ii) enolization (α-deprotonation), (iii) eliminative migration of the double bond].

3′-dehydro derivative of thymidine 3′,5′-diphosphate – this cation has a cyclonucleoside backbone.[6] If similar tricyclic cations exist for C=O-protonated keto nucleosides, could they be responsible for the lability of the parent nucleosidic ketones? Herein, we examine this hypothesis by means of theoretical and synthetic models. We establish chemical structures of tricyclic cations of keto and non-keto ("normal") nucleosides in order to understand whether the considered instability reflects a unique chemistry inherent in keto nucleosides or points out some cluster of nucleoside reactions.

In our theoretical modeling [non-empirical calculations at the B3LYP/6-31+G(d,p) level with approximation of water solution within the limits of the PCM model; see ESI† for details], we located both *anti* and *syn* conformers $\mathbf{3}_{anti}$ and $\mathbf{3}_{syn}$ of a cation of nucleoside **1a** whose chemical structure corresponds to the protonated carbonyl moiety (Fig. 1). These cations are oxacarbenium ions: their C3′···O3′ interatomic distances are longer than the "normal" C=O bond in aliphatic ketones (0.121 nm), but shorter than the C–O bond in aliphatic alcohols (0.143 nm). By converting the East-South geometry (envelope $_1$E) of the furanose ring of *syn* structure $\mathbf{3}_{syn}$ into the North geometry (twist $^3T_2$) and using the resulting structure as the initial one in energy minimization, we succeeded in locating isomeric cation $\mathbf{3}_{iso}$ that has a C3′,2-*O*-cyclonucleoside structure. Similar cyclonucleoside

Department of Chemistry, Bar-Ilan University, Ramat-Gan 52900, Israel. E-mail: belostot@biu.ac.il; Fax: +972 3738 4053

†Electronic supplementary information (ESI) available: Cartesian coordinates, energies, Wiberg indexes and atomic CHELPG charges of optimized structures as well as ^{1}H, ^{13}C NMR and HRMS spectral data of new compounds. See DOI: 10.1039/c2ob25868d

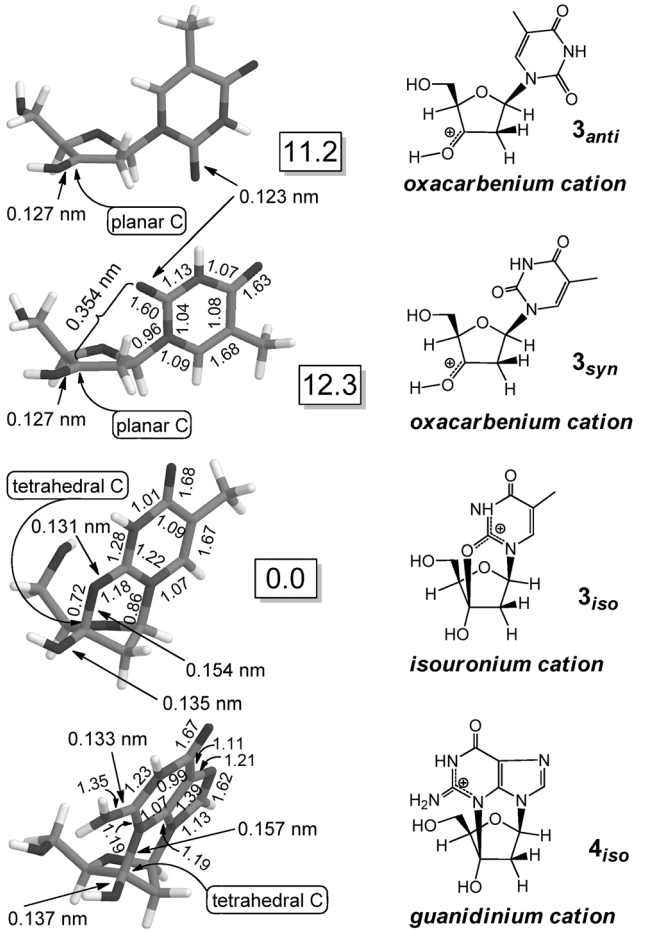


Fig. 1 Optimized geometries and chemical structures of isomeric cations $\mathbf{3}_{anti}$, $\mathbf{3}_{syn}$ and $\mathbf{3}_{iso}$ of protonated keto nucleoside **1a** as well as cyclonucleoside cation $\mathbf{4}_{iso}$ of protonated keto nucleoside **1b**. Arrows show selected bonds whose lengths are indicated. Numbers in rectangles display values of calculated relative energies (kcal mol^{-1}), and small numbers point out calculated orders of the related bonds.

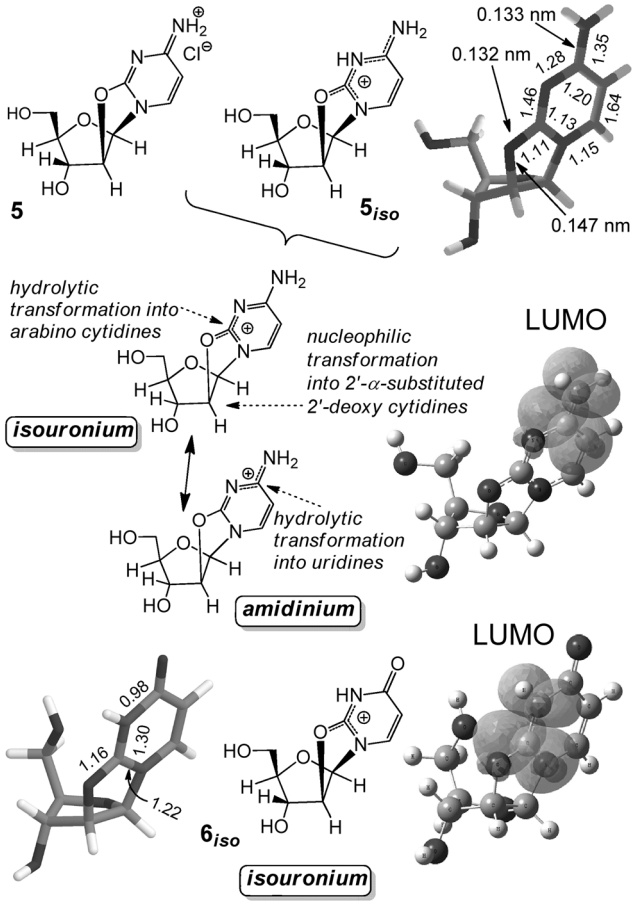


Fig. 2 Optimized geometries, LUMOs and chemical structures of C2′,2-*O*-anhydrocytidine cation $\mathbf{5}_{iso}$ of salt **5** and C2′,2-*O*-anhydrouridine cation $\mathbf{6}_{iso}$. Small numbers show calculated orders of selected bonds. The given Lewis structure of $\mathbf{5}_{iso}$ (top, in the middle) may be represented by two highly-weighted resonance forms shown below.

cations $\mathbf{4}_{iso}$ (Fig. 1), $\mathbf{5}_{iso}$ and $\mathbf{6}_{iso}$ (Fig. 2) also have been located for a model purine keto compound, *viz.* C-3′-oxo-2′-deoxy guanosine (**1b**) with the protonated C3′═O group, and natural pyrimidine nucleosides (cytidine and uridine, respectively). Thus, these calculations show that, in addition to trivial cations of C═O-protonated purine and pyrimidine keto nucleosides (oxacarbenium ions), isomeric cyclonucleoside cations (*e.g.*, $\mathbf{3}_{iso}$), which have the same chemical connectivity *H–heteroatom* as the "normal" cations (*e.g.*, $\mathbf{3}_{anti}$ or $\mathbf{3}_{syn}$) have, do exist.

Similar cations of regular pyrimidine cyclonucleosides (*i.e.*, non-oxo ribosides) are not new in nucleoside chemistry considerations: they are supposed to be intermediates in acid-mediated nucleophilic transformations *cyclonucleoside–*"*normal*" *nucleoside*.[7a–g] In some cases, the corresponding salts are stable and the molecular structure of salt **5** (Fig. 2) was determined by X-ray crystallography.[7g–l] However, their chemical functionalities have only been assumed; *e.g.*, an amidinium structure is merely attributed to compound **5**. In order to describe reliably cyclonucleoside cations in terms of chemical functionality, we calculated bond orders for structures $\mathbf{3}_{syn}$, $\mathbf{3}_{iso}$, $\mathbf{4}_{iso}$, $\mathbf{5}_{iso}$ and $\mathbf{6}_{iso}$ using the NBO (natural bond orbitals) approach[8] to chemical structures.

Appreciable similarity of calculated orders for bonds N3–C4, C4–C5, C5–C6, N1–C6 and C4–4-O in the furanose-centered cation $\mathbf{3}_{syn}$ and aromatic ring-centered cations $\mathbf{3}_{iso}$ and $\mathbf{6}_{iso}$ (Fig. 1 and 2) shows that cyclonucleoside cations are mainly delocalized in the nitrogen-containing fragments of nucleobases. Orders of the bonds in these fragments show that $\mathbf{3}_{iso}$ and $\mathbf{6}_{iso}$ may be described as isouronium cations, and related cation $\mathbf{4}_{iso}$ may be represented as a guanidinium cation. Disposition of the NBO LUMO for $\mathbf{6}_{iso}$ supports this structural assignment. This vacant orbital is centered on atoms 2-O, C2 and N3, with main localization in the C2–N3 unit.

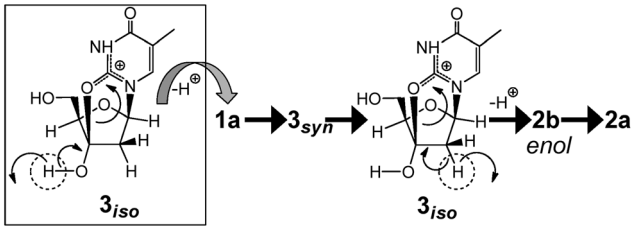
In contrast, according to the calculated bond orders, cation $\mathbf{5}_{iso}$, whose main delocalization domain includes both N1–(C2═O)–N3 and N3–C4–4-N fragments (Fig. 2), cannot be approximated by either amidinium or isouronium functionality. Two resonance forms – amidinium and isouronium cations – display a dual chemical functionality of cyclocytidine cation $\mathbf{5}_{iso}$. Atoms N3, C4, and 4-N are centers of the NBO LUMO (localized mainly in the C4–4-N unit) of $\mathbf{5}_{iso}$ indicating that the amidinium form is the major resonance structure.

Modeled molecular geometries confirm these chemical assignments. For instance, bonds N1–C2 and C2–N3 in tricyclic structure $\mathbf{3}_{iso}$ are shortened with respect to the same bonds in "acyclic" structure $\mathbf{3}_{syn}$ (0.134 and 0.134 nm *vs.* 0.140 and 0.138 nm, respectively). The interatomic distance C3′···2-O in $\mathbf{3}_{iso}$ is longer than the same distance in $\mathbf{3}_{syn}$ (0.131 nm *vs.* 0.123 nm, respectively); however, it is shorter than the length of the C_{arom}–O bond in anisole (0.142 nm[9]). Similar expectable alterations of bond lengths characterize also cations $\mathbf{4}_{syn}$ and $\mathbf{5}_{syn}$.

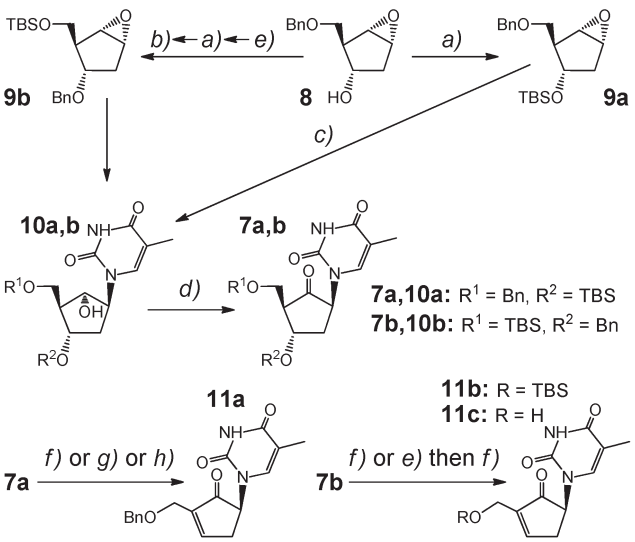
The above established chemical structures of model nucleoside cations permit us to understand the relationship between some known nucleoside transformations, as they reflect versatile reaction ability of the core intermediates (cyclonucleoside cations). For instance, drawing on isouronium chemistry,[10] one can predict that cyclothymidine cations should show "carbodiimide reactivity", *i.e.*, should easily add nucleophiles and release the urea fragment (the leaving group), or, in terms of nucleoside structure, undergo stereospecific α-addition to the furanose fragment accompanied by anhydro ring opening. In contrast, the prediction for cyclocytidine cations is that these species with less isouronium character should be more stable toward nucleophiles. In accordance with these predictions, salts of anhydro cytidines (*e.g.*, anticancer agent **5**) are stable compounds that may be treated in aqueous solutions,[7g,l] while intermediate salts of tricyclic cation structure, *e.g.*, of cation $\mathbf{6}_{iso}$ (Fig. 2), have never been isolated or detected in acid-catalyzed nucleophilic conversions of C2′,2-*O*- or C3′,2-*O*-anhydro pyrimidine nucleosides into the corresponding 2′-α- or 3′-α-substituted "normal" nucleosides.[7a–g] Also, some nucleoside transformations are understandable if formation of cyclonucleoside isouronium cations is taken into account: *e.g.*, nucleophilic substitution of the activated 2′-hydroxy group (and not exclusively elimination) occurred at the *tertiary* 2′-carbon of a 2′-α-Me derivative of cytidine,[11a] configuration retention in nucleophilic conversions of 2′-α-OMes-*N*,*N*-diMe-ψU[11b] and formation of a cyclonucleoside in acidic hydrolysis of a dinucleotide triester.[11c]

For cyclocytidine cations, Fig. 2 shows additional transformations that the dual isouronium–amidinium functionality of these intermediates suggests: they are addition–elimination reactions of isoureas in alkaline solutions that lead to corresponding ureas and amidinium salt hydrolysis that affords amides. Both alkaline hydrolysis of anhydro cytidines to the corresponding "open" *ara*-cytidines and conversion of such cyclonucleoside salts into anhydro uridines do take place,[7g,h,12] in line with this suggestion.

Thus, transformations of *O*-alkylisoureas in the presence of acids mimic chemical behaviour of the anhydro ring fragment of cyclothymidines under acidic conditions. Acid-catalyzed reactions of *O*-alkyl isoureas with nucleophiles include elimination.[13] Acid-associated lability of keto nucleosides becomes clear in this light. Isouronium cation $\mathbf{3}_{iso}$ is a very plausible intermediate in the degradation of the model keto nucleoside **1a** to non-nucleosidic enone **2a**. Indeed, our calculations show that this tricyclic cation is drastically more stable than isomeric "normal" nucleoside cations $\mathbf{3}_{syn}$ and $\mathbf{3}_{anti}$ (Fig. 1). Skeletal rearrangements, which occur not disrupting high energy bonds as well as not altering molecular geometry substantially, are low barrier transformations. These two circumstances make it clear



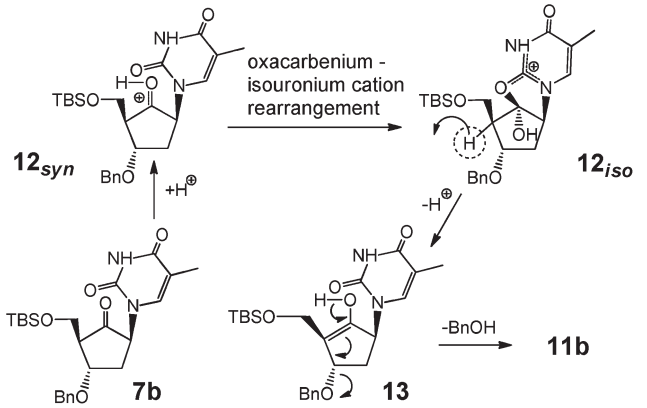
Scheme 2 Stages of eliminative decomposition of 3′-keto nucleosides shown for ketone **1a**. The proposed scheme differs from that in Scheme 1 by introducing a C3′,2-*O*-cyclonucleoside cation (here: $\mathbf{3}_{iso}$) that produces an enol (here: **2b**) *via* the C2′–H-deprotonating 1,2-elimination. "Non-productive" elimination in cation $\mathbf{3}_{iso}$ associated with deprotonation of the 3′-O–H moiety is shown in the frame.



Scheme 3 Synthesis of nucleoside analogs **7a,b** and examination of their stability towards acids. (a) TBSCl, Im, DMF, −10°, 18 h; (b) NaH, BnBr, Bu_4NI, THF, rt, 12 h; (c) thymine, LiH, DMF, Ar, 120°, 1 h, then **9a** or **9b** in DMF, 140°, 20 h; (d) $(PyH^+)_2{\cdot}Cr_2O_7^{-2}$, $CHCl_2$, molecular sieves, Ar, rt, 5 h; (e) $Pd(OH)_2$/C, cyclohexene, EtOH, Ar, reflux, 6 h; (f) silica gel, 30 min; (g) AcOH–THF–H_2O (3 : 1 : 1), rt, 24 h; (h) $Zn(BF_4)_2$–THF–H_2O, rt, 48 h.

that "normal" cation $\mathbf{3}_{syn}$ is converted into tricyclic cation $\mathbf{3}_{iso}$ rapidly and completely. As an isouronium cation, the resulting intermediate $\mathbf{3}_{iso}$ is associated with 1,2-elimination. This elementary reaction leads to formation of enol **2b** that is the precursor of the final compound **2a** in decomposition of **1a** (Scheme 2). The concurrent 1,2-elimination that arises from deprotonation of the C3′-positioned OH group leads to the starting ketone **1a**, and, therefore, does not affect the thermodynamically dictated conversion of **1a** into **2a**.

An alternative hypothesis suggests that the acid-mediated lability of keto nucleosides is due to protonation of the amino base. In order to inspect it and evaluate involvement of isouronium cations, we have prepared new keto carbonucleosides **7a,b** with a 1,2-positioned keto group and an amino base using a known route to such compounds[14] (see Scheme 3 and ESI† as well), and examined their susceptibility towards acids.



Scheme 4 Chemical structures of isomeric cations $\mathbf{12}_{syn}$ and $\mathbf{12}_{iso}$ and acid-promoted β-elimination in ketone **7b**.

Ether protected β-hydroxy groups of keto carboanalogs of hexopyranoses and pentofuranoses (including benzyl, silyl, isopropylidene and *tert*-Bu ethers) but lacking an amino base are generally stable upon action of both weak bases and weak acids.[15] Neither has β-elimination been detected for the corresponding OH derivatives (aldols) for these conditions. By contrast, 2-thymino cyclopentanones **7a,b** show different behavior. Both 3′-*O*-silyl **7a** and 3′-*O*-benzyl **7b** ethers are completely transformed into elimination products **11a** and **11b**, respectively, when in contact with silica gel. Also AcOH converts **7a** into enone **11a**. A weak Lewis acid, $Zn(BF_4)_2$, causes the same decomposition in the presence of water. Furthermore, transfer hydrogenolysis of **7b** leads to a mixture of nucleoside compounds which, as expected, bear neither a benzyl nor a silyl group. NMR shows no presence of compound **11c**. However, **11c** is obtained in 63% yield when this mixture is subjected to chromatography on silica gel. Thus, secondary β-ether or hydroxy ring substituents of carbocyclic keto nucleosides **7a,b** are eliminated under very mild conditions. This lability, which does involve nucleobase elimination, demonstrates that it is unnecessary to postulate amino base protonation.

Our calculations for oxacarbenium cations $\mathbf{12}_{syn}$ and $\mathbf{12}_{anti}$ as well as isouronium cation $\mathbf{12}_{iso}$ of the C=O-protonated model ketone **10b** (Scheme 4; see ESI† for $\mathbf{12}_{anti}$) support the above conclusion that high stability of cyclonucleoside isouronium cations is the driving force of nucleobase elimination reactions in keto nucleosides.

As in the case of cations $\mathbf{3}_{syn}$, $\mathbf{3}_{anti}$ and $\mathbf{3}_{syn}$ (Fig. 1), the isouronium cation (*i.e.*, $\mathbf{12}_{iso}$) is much more stable than the isomeric oxacarbenium cations. Both cations $\mathbf{12}_{syn}$ and $\mathbf{12}_{anti}$ of opposite rotational orientation of the nucleobase, which are primary intermediates in the acid-promoted elimination *via* enol **13** (Scheme 4), are higher in energy than $\mathbf{12}_{iso}$ by 11.5 and 9.7 kcal mol^{-1}, respectively (Fig. 3).

This high relative stability of cyclonucleosidium cations also is consequential for other reactions of nucleosides. Cyclizations of some nucleoside derivatives into anhydronucleosides is thought to occur *via* generation of a carbocation that is localized in the sugar ring.[16a,b] It is obvious that, when bringing the carbocationic ring carbon and the 2-positioned oxygen of the pyrimidine base closer, the molecule is rearranged into the

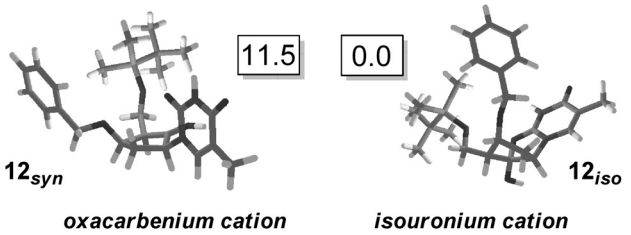


Fig. 3 Optimized structures of isomeric cations $\mathbf{12}_{syn}$ and $\mathbf{12}_{iso}$ of protonated ketone **7b**. Numbers in rectangles indicate calculated relative energies (kcal mol^{-1}) of $\mathbf{12}_{syn}$ and $\mathbf{12}_{iso}$.

corresponding cyclonucleoside isouronium cation. Indeed, this molecular geometry is intermediate in the path of minimal geometrical changes, and this energy minimum lies significantly lower than the minimum that corresponds to the initial cation. Thus, these cyclizations occur in three stages: (i) carbonium ion generation, (ii) cyclonucleoside cation formation and (iii) transformation into the product. Formation of these cyclic reactive intermediates explains why nucleophilic addition that sometimes takes place instead of cyclization is stereospecific (from the α-stereoface).[16c]

Thus, by establishing chemical structures of cyclonucleoside cations, we introduce these reactive intermediates in reasoned considerations of a cluster of related transformations of nucleosides/nucleotides. Such transformations are not limited by now explained elimination reactions of keto nucleosides or by nucleophilic additions to anhydronucleosides under acidic conditions. Cyclonucleoside cations certainly are components of the equilibrium of interconverting chemically isomeric nucleoside or nucleotide cations localized at any fragment of the furanose–nucleobase backbone. The finding that cations of sugar–nucleobase-bonded nucleosides are much more stable than the corresponding "normal" cations may provide new, valuable insight into the chemistry of oxidative[17] or hydrodynamically induced[18] breaks of DNA and RNA chains. For instance, cyclonucleoside carbocations may assist in keeping the integrity of translocated ssDNA (*e.g.*, transposons, unpacked viral ssDNA in the cell). If the 3′-C–O bond of a pyrimidine nucleotide unit of the moving strand is heterolytically ruptured due to stretching, the ultimately formed C3′,2-*O*-cyclonucleoside isouronium cation may be captured in the solvent cage by the 5′-phosphate of the 5′ → 3′ scrap, restoring the strand in the original chemical connectivity and stereochemistry as well.

Acknowledgements

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Notes and references

‡ In Ref. 6, an incorrect chemical structure has been assigned to the modeled cation of a 3′-dehydro nucleotide derivative. Our analysis of molecular structure of nucleotide cations that includes the correct chemical structure of such "3′-cations" will be published elsewhere.

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