Stereoelectronic Control in the Hydrolysis of RNA by Imidazole

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The cleavage of poly(uridylic acid) by imidazole buffer was studied recently by Breslow and Labelle, and a bell-shaped profile was observed for the rate vs. buffer protonation state. The reaction, however, was kinetically first-order in buffer (R. Breslow and M. Labelle, *J. Am. Chem. Soc.*, **108**, 2655 (1986)). The sequential base-acid mechanism proposed by those authors is in agreement with the expectation based on the stereoelectronic effects. In addition, the alternative sequential acid-base mechanism, which could not be excluded on the basis of their kinetic data, may be excluded based on the stereoelectronic considerations.

The hydrolysis of RNA and simpler model compounds has been the subject of much investigation.[1-9] In the hydrolysis of both RNA[1,9] and a simpler phosphate diester, such as methyl 2-hydroxyethyl hydrogenphosphate,[5,6] the mechanistic sequence involves two steps: The formation of a five-membered cyclic phosphate via an intramolecular nucleophilic attack by the vicinal hydroxyl group with concomitant exocyclic cleavage, followed by the hydrolysis of the cyclic diester intermediate. The formation of a 2′,3′-cyclic diester suggests why RNA, which functions as a carrier of genetic information and thus has a high turnover rate, is capable of undergoing rapid degradation. On the other hand, DNA, which serves to store genetic information and from which the requisite 2′-hydroxyl group is absent, is resistant to hydrolysis.

The rate of hydrolysis of five-membered ring cyclic phosphate such as methyl ethylene phosphate (MEP) and ethylene hydrogenphosphate (EP) is 10^6 to 10^8 times faster than that of their acyclic analogues, trimethyl phosphate and dimethyl hydrogenphosphate, respectively. Westheimer and coworkers proposed that this rate acceleration was due to the energy released in going from a strained five-membered cyclic ester to a "strain-free" cyclic phosphorane transition state.[3] However, as pointed out by Gerlt et al.,[10] the amount of ring strain is insufficient to explain the total lowering of activation energy of the five-membered cyclic phosphates. Therefore, Gorenstein et al.[11-14] proposed, based upon molecular orbital calculations on the basic hydrolysis of model phosphate diesters, that a significant fraction of this difference in reactivity between five-membered cyclic phosphates and their acyclic counterparts comes from orbital stereoelectronic effects in the trigonal bipyramid transition state. Gorenstein and coworkers have provided

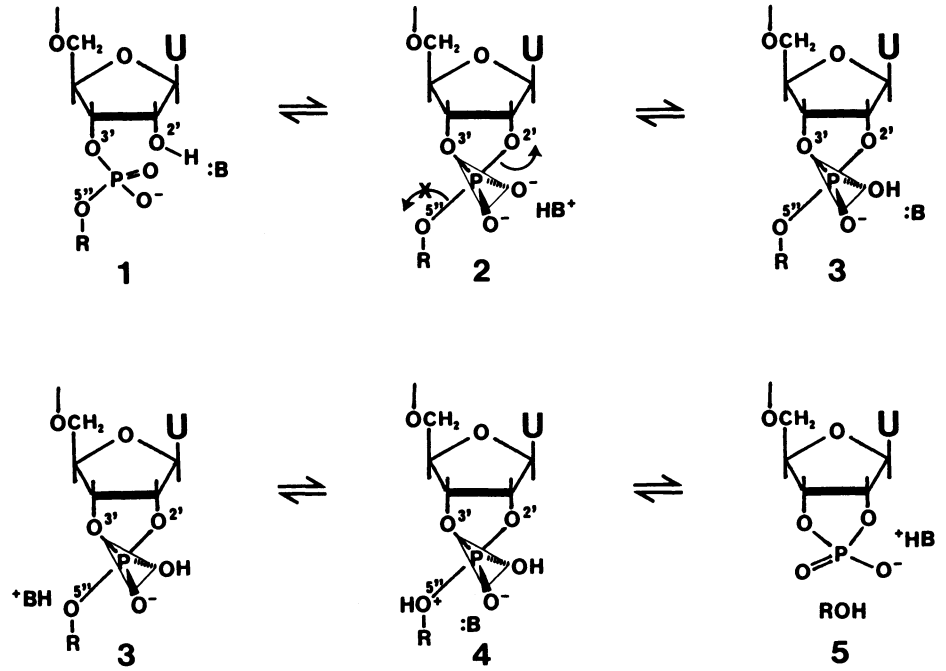

Fig. 1 Breslow and Labelle's mechanism for the hydrolysis of RNA by imidazole.[9] The equatorial positions are indicated by triangle planes.

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theoretical justification[11-19] as well as experimental support[20-28] for these stereoelectronic effects.

Breslow and Labelle[9] recently investigated the hydrolysis of poly(uridylic acid) (poly-U) by imidazole buffers and proposed the sequential general base-acid catalysis mechanism, as shown in Fig. 1. In the first step, nucleophilic attack is catalyzed when the imidazole (:B) removes a proton from the 2′-hydroxyl group of **1**. The resulting more nucleophilic oxygen adds to phosphorus, and the temporarily formed imidazolium ion ($^+$BH) puts a proton back onto one of the equatorial phosphorus oxygens of **2** to generate intermediate **3**. In the reversal of this reaction, the same sequence runs backwards: The endocyclic cleavage of the phosphorane intermediate, **3**, occurs by deprotonation of **3** and eventual protonation of the leaving 2′-oxygen. However, in the forward direction, exocyclic cleavage takes place with the loss of 5′-oxygen of the next nucleotide by a process preferentially catalyzed by imidazolium ion ($^+$BH), but not by imidazole (:B). In the case of the imidazolium ion catalysis, a proton is added presumably to the leaving group first followed by proton removal from the phosphorus oxygen so that the final product monoanion, **5**, is formed.[9]

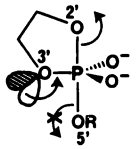
As Breslow and Labelle pointed out,[9] their mechanism is quite curious: The endocyclic cleavage of **3** (backward reaction) is catalyzed by a base (:B), however, the exocyclic cleavage of **3** (forward reaction) is catalyzed by an acid ($^+$HB). Furthermore, due to the well-known kinetic ambiguity, the alternative sequential acid-base mechanism, in which the formation of intermediate **3** is catalyzed by imidazolium ion ($^+$HB) and its forward decomposition is catalyzed by imidazole (:B), cannot be cxcluded on the basis of their kinetic data.

In this paper, we suggest that the mechanism proposed by Breslow and Labelle could be rationalized by the stereoelectronic effect. This explanation not only supports their mechanism, in which an imidazole catalyzes the endocyclic cleavage and an imidazolium ion catalyzes the exocyclic cleavage, but also uniquely excludes the alternative sequential general acid-base mechanism.

Discussion

Stereoelectronic Effects in the Hydrolysis of MEP. The role of orbital orientation in organic and enzymatic reactions has been of considerable interest over the last decade.[11-41] Deslongchamps and coworkers[29] in studying tetracovalent carbon species have demonstrated selective cleavage of bonds which are *trans*-antiperiplanar (app) to lone pairs on directly bonded oxygen and nitrogens. Molecular orbital calculations have provided theoretical justification for these stereoelectronic effects in tetracovalent carbon and phosphorus species and pentacovalent phosphoranes.[11-19,33-38] For example, in the cyclic transition state/intermediate, **8**, which corresponds to Breslow's intermediate, **2**, (the ribose ring portion is omitted) the two lone pairs on the equatorial ring oxygen are oriented partially antiperiplanar (app) to the axial ring ester bond, which corresponds to the phosphorus-(2′-oxygen) bond in **2**.

Thus, the stereoelectronic theory suggests that this app lone pair can significantly facilitate the endocyclic P—O ester bond cleavage. As Deslongchamps argues that a cleavage is stereoelectronically controlled when and only when **two** heteroatoms possess lone pair orbitals app to the departing bond,[29] the exocyclic cleavage (P–OR bond cleavage) can also be stereoelectronically assisted by the lone-pair orbitals on the **two** equatorial anionic oxygens (orbitals not shown in **8**). However, the endocyclic cleavage is still favored over the exocyclic cleavage because the endocyclic breakage is assisted by **all three** equatorial oxygen lone pairs, especially those on the equatorial ring-oxygen. Note that the equatorial ring oxygen lone-pairs (orbitals are shown in Scheme 1) of **8** are app **only** to the apical endocyclic ester bond and **not** to the exocyclic bond. Indeed, as Gorenstein argued earlier, in the five-membered-ring cyclic esters the ring constrained the lone pairs in a stereoelectronically favorable orientation while



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Scheme 1.

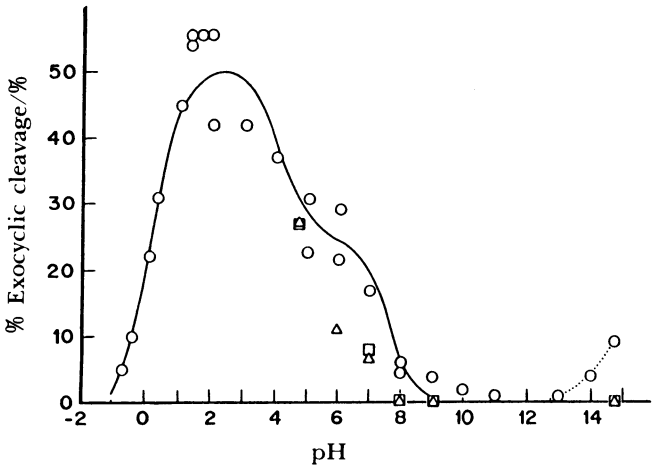


Fig. 2 Percentage exocyclic cleavage of methyl ehylene phosphate (○,△) and ethyl ethylene phosphate (□) vs. pH. Data from Kluger et al.[4] (○) and our own work (△, MEP; □, EEP).[6]

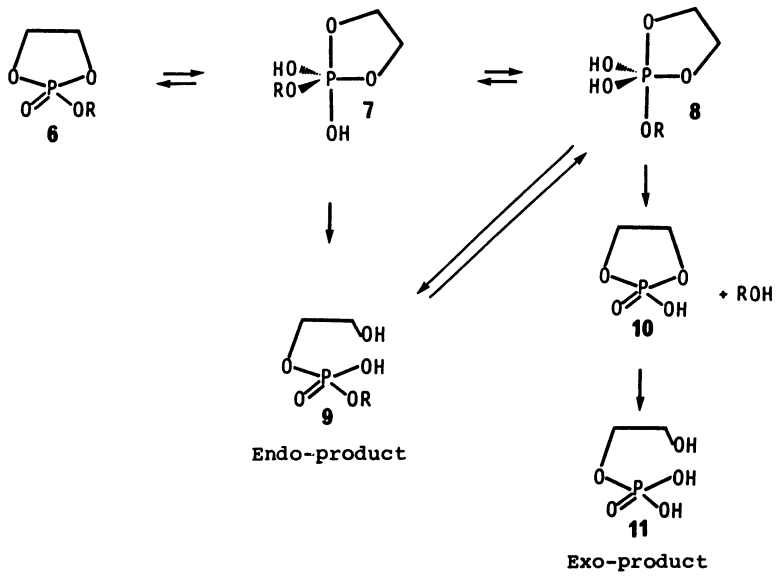


Fig. 3 Reaction paths for the formation of endocyclic and exocyclic cleavage products.

in the acyclic transition state, proper app lone pair overlap would require "freezing" of one or more rotational degrees of freedom about the ester bonds. It is thus significant that a considerable portion of the rate difference between cyclic and acyclic reactions is driven entropically.

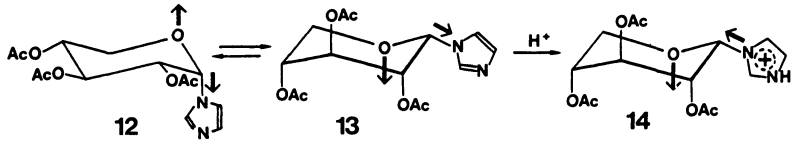
However, a major difficulty with the stereoelectronic effect explanation for a portion of the rate acceleration was the observation of significant exocyclic cleavage (Fig. 2) in the hydrolysis of methyl ethylene phosphate (MEP) (Fig. 3).[3,4] As shown in Figures 2 and 3, hydrolysis of **6** (MEP) yielded not only the endocyclic cleavage product **9** but also as much as 1—50% of the exocyclic cleavage product **11**, formed by rapid hydrolysis of the initially formed ethylene hydrogenphosphate (EP), **10**. While the exocyclic cleavage in acid could be reconciled with the "reverse anomeric effect"[30] (see below), the 9 and 15% exocyclic cleavage in 5 and 10 M† alkali, respectively, was at odds with the stereoelectronic effect: Recall that the lone pairs on the ring oxygen are app only to the endocyclic bond (**8** in Scheme 1).

We carried out the hydrolysis of ethyl ethylene phosphate (EEP)[5] as well as MEP[24] at **low** concentration of ester in 5 M NaOH and analyzed the reaction products by phosphorus NMR instead of the earlier proton NMR and GC methodology.[4] We found that, compared with Kluger et al.'s earlier results,[4] there was much less (0±3% vs. the reported 9%) exocyclic cleavage product produced in the hydrolysis of MEP in 5 M NaOH. These results were consistent with the prediction of the stereoelectronic effect. However, recently Kluger and Thatcher[7,8] rechecked Kluger et al.'s earlier results[4] by proton NMR (and to a lesser extent by phosphorus NMR), employing **much higher** concentration of the starting ester. By monitoring the appearance of the methanol peak, they found that at strong alkaline conditions the fraction of "methanol" (which they equate with the exocyclic cleavage product) in fact appeared to increase to as much as 24% exocyclic cleavage in saturated NaOH (18.5 M) and 9.2% in 5.6 M NaOH.

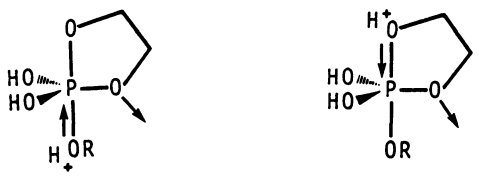
However, Gorenstein et al. now report[41] that, in contrast to the claims of Kluger and Thatcher,[7,8] the increase in exocyclic cleavage product with increasing strong base is shown to arise from an artifactual sidereaction in the base-catalyzed hydrolysis of MEP. The initial product of endocyclic cleavage, methyl 2-hydroxyethyl hydrogenphosphate **9**, reacts with a second molecule of MEP **6**, when the reaction is carried out at **high** concentration of MEP, to yield a reactive "triester dimer" which subsequently releases methanol to yield a relatively stable "diester dimer": note that Kluger and Thatcher equate the amount of "methanol" with the exocyclic cleavage product. Although a small amount of exocyclic cleavage product is observed in strong alkali (<0.5%±1.5% for EEP and 2—4%±1.5% for MEP), these results are still completely consistent with arguments regarding stereoelectronic control in these reactions.[41]

In conclusion, a base-catalyzed hydrolysis of five-membered-ring cyclic phosphates, such as EEP and MEP, preferencially undergoes endocyclic cleavage. It is important to notice that, in Fig. 1, the endocyclic cleavage of **3** (backward reaction) occurs by a prior deprotonation of an equatorial oxygen (base catalysis).

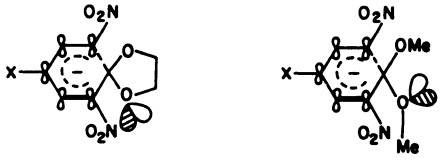
† 1 M=1 mol dm^{-3}.



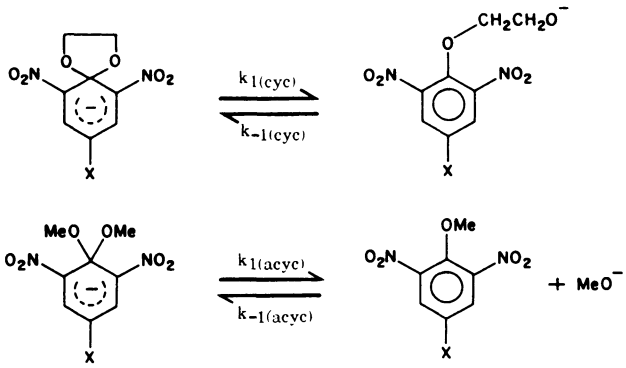
Scheme 2.



Scheme 3.



Scheme 5.



Scheme 4.

The Reverse Anomeric Effect. Electron-withdrawing substituents show a powerful preference for the axial position in 2-substituted tetrahydropyrans (ground state stereoelectronic effect or anomeric effect). However, groups such as *N*-alkylpyridinium appear to show a preference for the equatorial position, and there is evidence to suggest that this preference is stronger than the usual steric preferences found in cyclohexanes.[30] This reversed equatorial preference by protonated or positively charged substituents, which are even stronger electron-withdrawing groups, is called "the reverse anomeric effact." Although, to date, the origin of the reverse anomeric effect is not well understood, dipole moment interaction appears to operate, since the preference of imidazole for the equatorial position (**13**) in the equilibrium (**12**⇄**13**) of Scheme 2 is greater in more polar solvent and, when sufficient trifluoroacetic acid is added to the solvent ($CDCl_3$), only the isomer **14** with the imidazolium group equatorial exists.[30]

In the acid-catalyzed hydrolysis of MEP, the above-mentioned dipole moment arguments suggest that protonation on the exocyclic ester oxygen is favored over the endocyclic oxygen. This would thus favor exocyclic cleavage in acidic media (Scheme 3).

In strong acid, protonation of both exo- and endo-oxygens may be possible, in which case the mode of cleavage is again governed by the stereoelectronic effect (see Fig. 2).

In related systems, Bernasconi and Howard[42] thoroughly investigated the breakdown of spiro cyclic and acyclic Meisenheimer complexes derived from 1-(2-hydroxyethoxy)-2,6-dinitro-4-X-benzenes and 2,6-dinitro-4-X-anisoles, respectively, where X was Cl, CF_3, NO_2, or SO_2CF_3.

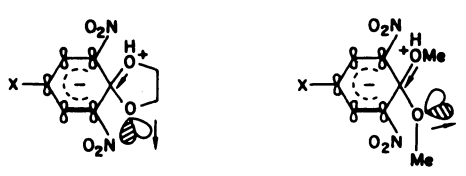
They concluded that the difference in intrinsic reactivity between the two families was quite large ($\Delta\Delta G^{\ddagger}=\Delta G^{\ddagger}[k_{1(acyc)}]-\Delta G^{\ddagger}[k_{1(cyc)}]=3.80$ to 5.34 kcal mol^{-1} (1 cal=4.184 J)) and this difference increased as the X substituent became more electron-withdrawing. The most likely cause for the difference in reactivity is of stereoelectronic origin. As described in the above-mentioned endocyclic cleavage of **8**, the orientation of the lone-pair orbitals on oxygen in the spiro cyclic complexes is such as to lead to n–σ^* overlap (app orientation) in the transition state. On the other hand, in the acyclic (1,1-dimethoxy-) complexes the orientation of the lone-pair orbitals does not lead to such overlap unless the complex first undergoes an unfavorable conformational change (Scheme 5).

The fact that $\Delta\Delta G^{\ddagger}$ increases with the electron-withdrawing strength of the X substituent supports this interpretation because the n–σ^* overlap leading to a transfer of electron density from the nonreacting oxygen into the antibonding orbital of the scissile bond becomes more important when a transfer of electron density from the benzene ring (p–σ^* type interaction) is less available because of an electron-withdrawing X group.

More importantly, the study of Bernasconi and Howard[42] further indicates that the difference in intrinsic reactivity is smaller for the acid-catalyzed compared to the noncatalyzed pathway, and this difference diminishes with increasing acidity of the catalyst. For the specific acid-catalyzed pathway the reactivity difference between the two families nearly disappears ($\Delta\Delta G^{\ddagger}$ spans a range ca. 0.09 to 0.2 kcal mol^{-1}). This means that in acidic media one does not observe much of a stereoelectronic effect. This indicates that for the acid-catalyzed lower activation-energy pathway a further lowering of the activation energy by the stereoelectronic effect becomes less important, compared to the noncatalyzed pathway. The breakdown behavior of these Meisenheimer complexes is very similar to that of the hydrolysis of EEP, MEP, and as well as RNA by imidazole: Under basic conditions the cyclic C(P)-O bond breaks (endocyclic cleavage) much faster than the acyclic C(P)-O bond (exocyclic cleavage), however, the exocyclic bond cleavage $k_{1(acyc)}$ starts to compete with the endocyclic bond cleavage $k_{1(cyc)}$ upon an increase in acidity of the medium, as shown by the percentage of exocyclic cleavage in Fig. 2.

Favored Protonation on 5′ Oxygen. If we use the above-mentioned dipole moment analysis in the protonation of the Meisenheimer complexes, it can easily be shown (Scheme 6) that protonation of the acyclic complexes is favored. This interpretation is consistent with Bernasconi and Howard's observation[42] of less negative ρ values and smaller Bronsted α values in the cyclic Meisenheimer complexes, indicating that less positive charge (H^+) has been transferred to the cyclic system than to the acyclic counterpart from the catalyst in the transition state.

The favorable protonation of the acyclic complexes is also consistent with the Hammond Postulate. In case of the breakdown of the cyclic complexes, one might expect an early transition state due to the intrinsically high reactivity of these compounds.[43] Because of the early transition state, the pK_{app} of the departing oxygen for the cyclic complexes would be low, and hence would not be subject to appreciable protonation. The acyclic complexes, on the other hand, would be less reactive than the cyclic counterparts, and in turn would have their transition states further along the reaction coordinate. Because of this later position on the reaction coordinate, one might expect the pK_{app} of the oxygens of the acyclic complexes to be higher than that of the cyclic counterparts and in turn more susceptible to transition state protonation. These predictions would lead to more positive ρ values and larger Bronsted α values in the acyclic families.



Scheme 6.

Similar argument would support our earlier analysis in that the exocyclic 5′ oxygen, in **3** (Fig. 1) or **8** (Scheme 1), is more susceptible to transition state protonation. In case of the exocyclic cleavage of the strain-free[3] intermediates, **3**, or **8**, one might expect a later transition state due to an increase in ring strain in the transition state in forming the five-membered cyclic diesters, **5** or **10**. The endocyclic cleavage, on the other hand, would not experience any increase in ring stain and therefore would have an earlier transition state, resulting in a less favorable protonation for the endocyclic 2′ oxygen.

Hydrolysis of RNA by Imidazole. The elegant work by Breslow and Labelle[9] has given us insight into a sequential catalytic mechanism for the hydrolysis of RNA by imidazole buffer. As they pointed out, their preferred mechanism (Fig. 1) is quite curious since, for the cleavage of the phosphorus-(2′-oxygen) bond (endocyclic cleavage) in **3**, the basic form of imidazole is utilized, whereas for the cleavage of the phosphorus-(5″-oxygen) bond (exocyclic cleavage) the conjugate acid form of imidazole acts as a catalyst. They pose the question: "*Why is it that loss of the C-5″ oxygen from intermediate* **3** *occurs by a prior protonation of the leaving group oxygen, while loss of the C-2′ oxygen from* **3** *occurs by a prior deprotonation of an oxygen on the phosphorus? If in the alternative slower path the loss of the 5″ oxygen can also occur with imidazole catalysis, and thus with a prior deprotonation, why is it that the prior protonation mechanism is not the best for the loss of C-2′ oxygen? It is hard to see a good reason for this mechanistic distinction* ...."

However, taken together with the observation, in the hydrolysis of MEP, that an endocyclic cleavage is preferred in basic media due to the stereoelectronic effect and an exocyclic cleavage becomes competitive in acidic media because protonation is more favorable on the exocyclic oxygen (the reverse anomeric effect), a similar analysis to the hydrolysis of RNA provides a capability for uniquely supporting the mechanism of Breslow and Labelle. The deprotonation of **3** by imidazole leads to **2**, which is equivalent to **8** in Scheme 1, resulting in stereoelectronically favorable P-(2′-O) bond cleavage. For the forward reaction, protonation is preferred on the exocyclic 5″-oxygen, leading to the loss of 5″ oxygen of the next nucleotide. Apparently, this analysis disfavors the kinetically equivalent alternative mechanism, a sequential general acid-base catalysis, since protonation is never favored on an endocyclic 2′-

oxygen and at the same time the stereoelectronic effect disfavors an exocyclic cleavage.

This mechanism may indeed be significant for the action of Ribonuclease.[9] At the active site of Ribonuclease, the basic imidazole of the enzyme (His-12) acts to remove the proton from the attacking 2′-hydroxyl group which then adds to phosphorus from the opposite side of the leaving 5″-OR group, leading to the in-line mechanism[44-46] intermediate, **2**. In order to shift the equilibrium toward the exocyclic cleavage, via the monoanion intermediate, **3**, the temporarily formed imidazolium ion (His-12) transfers its proton to one of the equatorial oxygens (the equatorial positions are indicated by a triangle plane in Fig. 1). Recall that without this proton transfer, the dianion intermediate, **2**, stereoelectronically favors the decomposition to the starting diester, **1**. The imidazolium ion of the enzyme (His-119) then acts to put a proton on the leaving 5″-oxygen atom, and indeed this is the preferred protonation site, as discussed in terms of the reverse anomeric effect as well as the Hammond Postulate.

It is important to realize that all the reaction steps discussed in the previous paragraph are also the chemically favored lower energy pathways (i.e., in-line over adjacent, endo- over exo-cleavage of the basic form of the intermediate, and 5′- over 2′-protonation). For the first transesterification step, the more electron-withdrawing 2′-oxygen and 5′-OR groups occupy the apical positions, as required by the preference rule,[3] leading to the in-line mechanism. The first stereochemical study of an enzymatic P–O bond cleavage was that of Usher, Eckstein, and their associates on pancreatic ribonuclease A.[44,45] They showed that each of the two P–O bond cleavage steps catalyzed by this enzyme proceeded with inversion of configuration at phosphorus (in-line mechanism). Presently, over thirty stereochemical studies of enzymatic substitution at phosphorus have been carried out.[46] There is as yet no indication of an adjacent mechanism which involves pseudorotatory rearrangements in pentavalent intermediates of enzymatic substitutions at phosphorus. All reactions studied to date are stereospecific, and the available data strongly supports the hypothesis that each enzymatic substitution at phosphorus proceeds by an in-line mechanism with inversion of configuration at phosphorus. Together with the probable involvement of the stereoelectronic and reverse anomeric effects in the action of Ribonuclease, this enzyme appears to take advantage of any energy lowering effects at each reaction steps (in-line over adjacent, endo-over exo-cleavage, 5′- over 2′-protonation, etc.), in accord with the "evolutionary perfection."[47]

In conclusion, as can be seen in Fig. 2, the mode of cleavage of MEP and EEP is pH-dependent: The exo- and endocyclic cleavages are preferred in acidic and basic media, respectively. Similarly, the exo- and endocyclic cleavages of the RNA intermediate, **3**, are catalyzed by the acidic and basic forms of imidazole, respectively. These observations are consistent with the arguments regarding the stereoelectronic effect and the reverse anomeric effect.

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