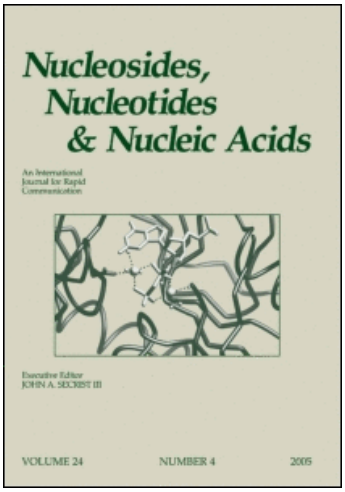

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Kinetics and Mechanism for Acid-Catalyzed Hydrolysis of Regioisomeric 2'-Deoxyribonucleosides of 8-Azaadenine and Substituted Benzotriazoles

Rainer Käppi[a]; Zygmunt Kazimierczuk[a]; Frank Seela[b]; Harri Lönnberg[a]
[a] Department of Che%stry, University of Turku, Turku, Finland [b] Department of Organic and Bioorganic Chemistry, University of Osnabruck, Osnabruck, FRG

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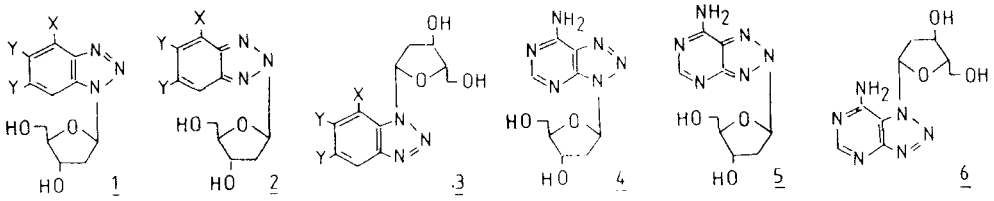
KINETICS AND MECHANISM FOR ACID-CATALYZED HYDROLYSIS OF REGIOISOMERIC 2'-DEOXYRIBONUCLEOSIDES OF 8-AZAADENINE AND SUBSTITUTED BENZOTRIAZOLES

Rainer Käppi,[a] Zygmunt Kazimierczuk,[b] Frank Seela[b] and Harri Lönnberg[a]

[a]Department of Chemistry, University of Turku, SF-20500 Turku, Finland, and [b]Department of Organic and Bioorganic Chemistry, University of Osnabruck, D-4500 Osnabruck, FRG.

Abstract: Kinetics for the acid-catalyzed hydrolysis of regioisomeric 2'-deoxyribonucleosides of 8-azaadenine and various substituted benzotriazoles have been studied.

Regioisomeric 2'-deoxyribonucleosides of benzotriazole (1-3) and 8-azaadenine (4-6) constitute two sets of isosteric analogs of purine nucleosides, both of which exhibit significant biological activity. These nucleoside analogs all undergo acid-catalyzed hydrolysis to free base and sugar at a rate comparable to that of purine 2'-deoxyribosides.



X = H, NH_2, CH_3, NO_2; Y = H
X = H; Y = CH_3, Cl

The following observations suggest that 1-3 are hydrolyzed *via* rate-limiting formation of a cyclic glycosyl oxocarbenium ion, *i. e.* analogously to purine nucleosides. (i) The hydrolysis rate depends on acidity in a manner con-

sistent with rate-limiting departure of the mono- and/or diprotonated base moiety. (ii) Polar substituents on the base moiety exert opposite effects on protonation and heterolysis steps. (iii) The starting materials do not undergo anomerization concurrent with hydrolysis.

N2-Glycosylated benzotriazoles (2) are hydrolyzed considerably faster than their N1 counterparts (1). Their rate profiles remain linear on passing the pK_a value of substrate monocation, indicating that hydrolysis via the dicationic species predominates at $pH < pK_a$. By contrast, this reaction appears to be impeded with N1 nucleosides, since the hydrolysis rates of these compounds (except that of 1b) become pH-independent at $pH < pK_a$.

N3-Glycosylated benzotriazoles (3) are less stable than the N1 nucleosides, as well. For example, the 4-methyl derivative of 3 decomposes 11 times as fast as that of 1. This relatively modest rate-enhancement argues against steric acceleration as the main reason for the well known hydrolytic instability of N3-alkylated purine nucleosides.

The pH-rate profile obtained with 8-aza-2'-deoxyadenosine (4) passes through an inflection point at $pH < pK_a$. The reaction *via* substrate monocation is approximately as rapid as that of 2'-deoxyadenosine, whereas the reaction *via* dicationic species is more than one order of magnitude slower than with the adenine derivative. The N8-glycosylated 8-azaadenine (5) is hydrolyzed 8 times and the corresponding N7-glycosylated derivative (6) 75 times as fast as 4 under conditions where hydrolysis *via* the substrate monocation prevails.