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Substituent Effects on the pH-Independent Hydrolysis of 2′-Substituted Nicotinamide Arabinosides

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Summary: The rates of the pH-independent hydrolysis of a series of 2′-substituted nicotinamide arabinosides have been measured and are used to analyze the direct inductive substituent effect on the stability of oxocarbocationic intermediates.

The effects of 2′ substituents on the acid-catalyzed hydrolysis of glycosides[1,2] and purine nucleosides[3,4] are well established and have been used to support an A1 (dissociative) mechanism, rather than an A2 (associative) mechanism. The A1 mechanism involves two steps (Scheme Ia), protonation of the aglycon followed by scission of the glycosyl linkage. Substituents at the 2′ position can affect both steps. For example, electron-withdrawing substituents will decrease the pK_a of the aglycon (which decreases the concentration of the reactive protonated species in solution) as well as destabilize a cationic activated complex. The 2′ substituent effects have been primarily discussed in terms of their effect on k_2, $\rho_{(k_2)}$, whereas the substituent effect on K_a, $\rho_{(K_a)}$, although mentioned, have not been quantitated[5] (for a recent example, see Withers et al.[6]). The relative contributions from these two factors and their mechanistic implications remain to be explored.

The 2′-substituted nicotinamide arabinosides have two features that make them ideally suited to clarify this ambiguity. First, the quaternary pyridinium leaving group is analogous in charge to protonated aglycons of glycosides or nucleosides; thus, the hydrolysis does not involve preprotonation. Second, intramolecular nucleophilic participation is precluded because the 2′ substituent is cis to the leaving group. In this communication we report rate constants for the pH-independent hydrolysis of six 2′-substituted nicotinamide β-D-arabinofuranosides (Scheme Ib).

The 2′-fluoro, 2′-azido, and 2′-amino nicotinamide arabinosides were prepared from a common synthetic intermediate.[7] Nicotinamide arabinoside was prepared from the 5-tritylarabinosylamine[8] and the nicotinamide 2′-deoxyriboside was prepared by the reaction of nicotinamide[7] with 3′,5′-bis-*O*-(*p*-nitrobenzoyl)-2′-deoxyribosyl chloride.[9] All nucleosides were purified to over 98% anomeric purity by reverse-phase HPLC and analyzed by liquid secondary-ion mass spectrometry, which gave appropriate molecular ion m/z values. Hydrolyses were conducted at 37 °C over the pH-independent region (pH 4–7.5). Hydrolysis of the 2′-fluoroarabinoside was conducted at four temperatures over the range 65–97 °C and the values of the rate constants were extrapolated to 37 °C. Hydrolysis mixtures were 0.8–1.0 mM in nucleoside and contained 200 mM buffer[10] and 1 M KCl. The progress of the cleavage of the nicotinamide–arabinosyl bond was monitored by UV absorbance at the appropriate λ_{max} using a discontinuous cyanide addition assay.[11,12] The first-order rate constants for the hydrolysis of the nicotinamide arabinosides were obtained from plots of log [nicotinamide nucleoside] versus time that were linear to 4 half-lives. Products were analyzed by HPLC;[12] only nicotinamide release was observed.

Scheme I

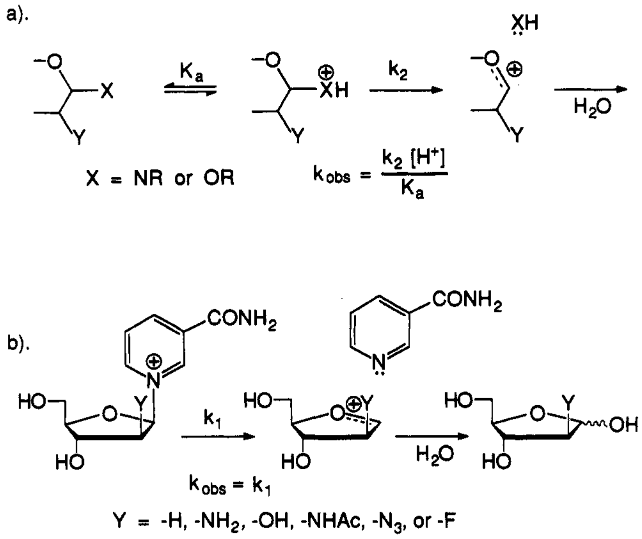

Table I. Rate Constants for Hydrolysis at 37 °C of 2′-Substituted Nicotinamide Arabinosides[a]

Y	$k(s^{-1}) \times 10^8$
H	14500
NH_2	1070
NHAc	99.3
OH	97.1
N_3	20.0
F	4.2

[a] Rate constants were measured at two or three different pH values to establish the pH independence of the reaction and each determination was conducted in duplicate. The values (±3%) represent averages of these experiments.

The rate constants for the hydrolysis of the nicotinamide arabinosides are summarized in Table I. As shown in Figure 1, the log of the rate constants correlate linearly with the inductive σ constant (σ_I)[13,14] according to the equation $\log(k) = \rho_I \cdot \sigma_I + \log(k_0)$, with a ρ_I of −6.7 (R = 0.99). The log of the rate constants of hydrolysis also correlate linearly with σ_I^Q,[15] (plot not shown), with a ρ_I^Q of −1.4 (R = 0.99). These ρ_I values serve as a direct

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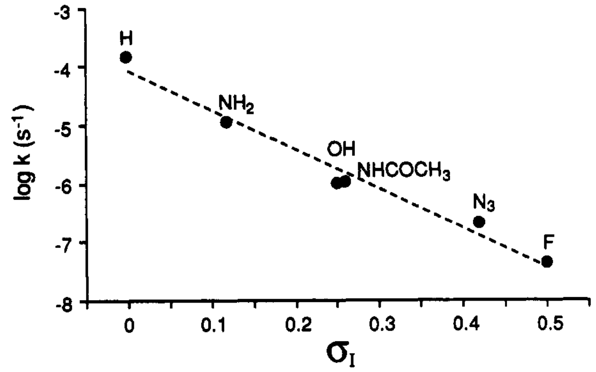

Figure 1. Plot of the log of the first-order rate constants for the pH-independent hydrolysis of the 2′-substituted nicotinamide arabinosides at 37 °C against the inductive σ constant (σ_I).

measure of the change in electron density at the reaction center during bond cleavage and are similar in sign and magnitude to ρ_I values from model reactions involving putative cationic intermediates.[16,17] Therefore, our results are consistent with a dissociative mechanism that involves an intermediate with substantial oxocarbocationic character as outlined in Scheme Ib. A dissociative mechanism is also supported by secondary deuterium kinetic isotope effects[18] and structure–reactivity studies of nucleotides with 3-substituted pyridines as leaving groups.[19]

Because the observed rate constants for the acid-catalyzed hydrolysis of glycosides and nucleosides are a function of both K_a and k_2,[2,20,21] the corresponding ρ_I values are the sum $\rho_{(K_a)} + \rho_{(k_2)}$. In this study, however, ρ_I is a function of only $\rho_{(k_2)}$. Therefore, in the absence of other factors, the observed ρ_I for acid-catalyzed hydrolyses should differ from the ρ_I for the corresponding pH-independent reaction by the value of $\rho_{(K_a)}$. Accurate quantitation of this distinction is not, however, possible at this time based on existing data from the literature.[22] Further structure–reactivity studies with other substituted nicotinamide nucleosides are underway and will be reported in subsequent publications.

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Supplementary Material Available: Experimental procedures for hydrolysis and chromatography of the nicotinamide arabinoses (1 page). Ordering information is given on any current masthead page.

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A Strategy for Synthesis of Conduritols and Related Cyclitols via Stereodivergent Vinylsilane–Aldehyde Cyclizations

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Summary: A novel stereospecific and stereodivergent cyclization of vinylsilane–aldehyde **10**, derived from L-arabinose, has been used to prepare the scalemic protected conduritols **11** and **12**.

The cyclitols[1] are a diverse class of compounds that have in common a polyhydroxylated cycloalkane moiety, with the cyclohexane skeleton being the one most often encountered. Their structural diversity is matched by their range of biological activity. Phosphorylated inositols, for instance, have been shown to be regulators of a number of cellular processes.[2] Aminodeoxyinositols and -conduritols (1,2,3,4-cyclohexenetetrols)[3] make up the aglycons of the aminocyclitol antibiotics.[4] A number of conduritol derivatives have been found to be glycosidase inhibitors,[3,5] as well as to possess antifeedant,[6] antibiotic, antileukemic, tumorostatic, and growth-regulating[3] activity.

The synthesis of both the parent conduritols and O-protected derivatives has been the focus of considerable synthetic effort. Previously, scalemic conduritols have been prepared from carbohydrates[6,7] via the Ferrier reaction,[8] from microbial oxidation products of substituted benzenes,[9] and by deoxygenation of chiral inositols.[10] We now report a novel method of cyclitol synthesis that is both

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