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Hydrolysis of 2'-Deoxypurine Nucleosides. The Effect of Substitution at the C-8 Position.

Ali Laayoun, Jean-Luc Décout, and Jean Lhomme*

L.E.D.S.S., URA CNRS 332, Université Joseph Fourier, BP 53, 38041 GRENOBLE Cedex 9, France
FAX : 76.51.43.82

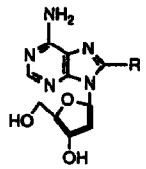
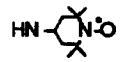
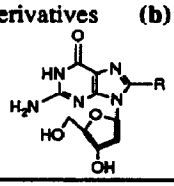
Abstract : The hydrolytic stability of 2'-deoxypurine nucleosides is decreased by introduction of electron-withdrawing substituents at the C-8 position in the series of compounds 2-8, 10-14. The sulfone group causes a 2.9 x 10^4 rate acceleration for glycosidic bond cleavage in compound 14.

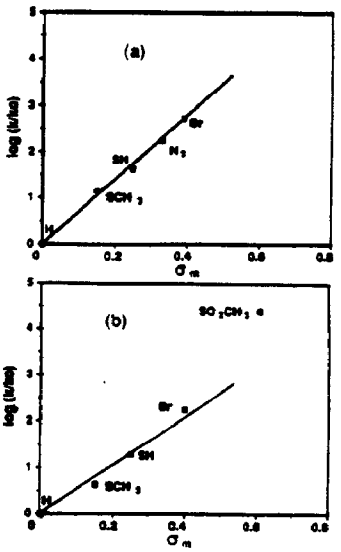
Modification of purine nucleosides at C-8 has been thoroughly studied in the search for anticancer and antiviral agents, and for introducing labels.[1] Substitution at C-8 modifies the hydrolytic stability of the nucleoside, a property that has been studied for some ribonucleosides[2] and 2'-3'-dideoxyderivatives.[3] The purine 2'-deoxyribonucleosides, however, have received less attention.[2a] We report some new nucleosides designed as probes (7, 8) or for linking active agents (3-6, 11-14), and describe their hydrolytic stability.

Introduction of the thio group in the 2'-deoxyadenosine and 2'-deoxyguanosine systems 1 and 9 to give 3 and 11 was accomplished by treating the bromides 2[4] and 10[5] with hydrogen sulfide in DMF.[6] The thioethers 4-6, 12-13 were obtained by alkylation of the thiolates generated with potassium carbonate in DMF with the corresponding 1-halogenoalkanes. Oxidation of the thioether 12 using *m*-CPBA in ethanol led to cleavage of the glycosidic bond, releasing 8-methylsulfonylguanine. However, slow portionwise addition of the reagent at 0°C in buffered solution allowed the quantitative isolation of the unstable sulfone nucleoside 14. The intermediate sulfoxides could not be isolated, but transient appearance of two peaks in the HPLC was observed in the course of the oxidation. The same oxidation was performed starting from 5 in an effort to prepare 8-propylsulfonyl-2'-deoxyadenosine. Under all conditions used, however, cleavage of the glycosidic bond occurred to give 8-propylsulfonyl adenine, which was isolated in good yield (83 %). The azido derivative 7 was obtained (67 % yield) by treatment of the bromide 2 with sodium azide in DMF.[7] Refluxing 2 in ethanol with a 10-fold excess of 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl in the presence of triethylamine afforded the labelled nucleoside 8 (40 % yield).

Studies of the glycosidic bond hydrolysis in 1-14 were carried out at 80°C in water (pH 5.2) at 10^{-4} M concentrations. The reactions were followed by measuring the disappearance of the reacting nucleosides by reverse-phase HPLC and showed good pseudo-first-order kinetics (Table). Analysis of the reaction products indicated that the release of the corresponding base (characterized by mass spectrometry and/or ^{1}H and ^{13}C NMR spectroscopy) occurred cleanly for all nucleosides. All compounds were found to undergo hydrolysis more rapidly than the parent nucleosides 1 and 9. The trend was the same in both the deoxyadenosine and deoxyguanosine series, although the adenine leaving group was more sensitive than guanine to the effect of the substituent. The most dramatic effect was observed for the sulfone substituent, which caused a 2.9 x 10^4-fold acceleration in 14. The substituents listed in the Table exert a withdrawing effect and there is an apparent correspondence between the inductive electron-withdrawing character of the substituents and the rates of hydrolysis. Indeed, good linear correlations were found on plotting the Hammett σ_m coefficients[8] ($\rho \approx 6.8$ and 5.8 in the 2'-deoxyadenosine and 2'-deoxyguanosine series, respectively) when the sulfone derivative 14 was excluded from the plot. This can be viewed as reflecting the inductive contribution of the substituent to the leaving group capacity of the nucleobase. Product 14 has been excluded from the σ_m correlation, as the effect of the sulfone undoubtedly includes mesomeric stabilization of a partial negative charge in the hydrolysis transition state.[9]

Table : Rates of Hydrolysis of C-8 Substituted 2'-Deoxyadenosine and 2'-Deoxyguanosine Derivatives in H_2O, pH 5.2, 80°C and Correlation with σ_m[8] Hammett Coefficients : $Log_{k_R/k_O} = \rho\,\sigma_m$

Compound		R	k_{s-1}	k_{rel}	σ_m
2'-Deoxyadenosine derivatives (a)	1	H	1.20×10^{-7}	1	
	2	Br	6.36×10^{-5}	530	0.39
	3	SH	5.11×10^{-5}	42	0.25
	4	SCH_3	1.75×10^{-6}	14	0.15
	5	S-Propyl	1.64×10^{-6}	13	
	6	S-Pentyl	1.46×10^{-6}	12	
	7	N_3	2.18×10^{-5}	180	0.33
	8		7.72×10^{-7}	6	
2'-Deoxyguanosine derivatives (b)	9	H	1.92×10^{-7}	1	
	10	Br	3.50×10^{-5}	182	0.39
	11	SH	3.97×10^{-6}	20	0.25
	12	SCH_3	8.25×10^{-7}	4	0.15
	13	S-Propyl	7.92×10^{-7}	4	
	14	SO_2CH_3	5.57×10^{-3}	29 000	0.60



In conclusion, it has been demonstrated that substitution at C-8 can modify dramatically the hydrolytic stability of the nucleoside. Introduction of the EPR label in **8** has relatively little effect, and sulfides can be used safely to link substituents at C-8. Oxidation to the sulfone, however, converts the base moiety into a highly powerful leaving group. This property has been used to prepare oligonucleotides containing abasic sites.[10]

References and notes

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9. Some studies have appeared in the literature concerning the effect of substituents at C-8 upon the hydrolytic rates, mainly for ribonucleosides[2], but also for 2'-deoxy and 2',3'-dideoxynucleosides.[3] These studies were conducted in acidic conditions, a situation in which the hydrolysis proceeds by rate-limiting departure of the protonated base with formation of a glycosyl oxocarbocation.[11] In this situation electron-withdrawing groups decrease the concentration of protonated substrate, but simultaneously the purine moiety becomes a better leaving group. The influence on the initial protonation and on the rate-limiting hydrolysis are opposite, and largely cancel each other.[2c] In the present study, carried at pH 5.2, the electron-withdrawing substituents exert their effect essentially by increasing the leaving capacity of the nucleobase.
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