Accelerative Effect of N^6-Acyl Groups on the C(8)-Hydrogen Exchange of 9-Substituted Adenines

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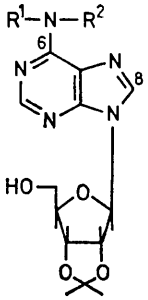
Summary N^6-Acyl-9-substituted adenines undergo C(8)-hydrogen exchange much faster than the parent 9-substituted adenines.

HYDROGEN exchange at the C(8)-position of purines of nucleic acids, nucleotides, and nucleosides has received much attention recently. Kinetic studies[1,2] have suggested that the mechanism of the exchange reaction involves OH^--catalysed abstraction of the C(8)-hydrogen from the 7-protonated form of the purines giving rise to an ylide-type intermediate which is then protonated at C(8) by the medium.

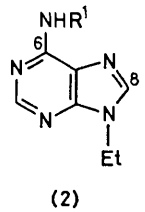
We found that introduction of electron-withdrawing acyl groups into the amino-group of 9-substituted adenines results in significant acceleration of their C(8)-hydrogen exchange. The present results show that the long ignored substituent effect of the N^6-acyl group may be used to promote a new type of chemical modification at the N^7- and C(8)-positions of 9-substituted adenines.

The hydrogen exchange rates were measured for various 9-substituted adenine derivatives (**1a**—**d**) and (**2a**—**c**)† in CD_3OD–$(CD_3)_2SO$. The reactions were carried out in sealed n.m.r. tubes at 75 °C and followed by n.m.r. spectroscopy.



(1)

a; $R^1 = R^2 = H$
b; R^1 = Me, $R^2 = H$
c; $R^1 = R^2$ = Me
d; R^1 = COPh, $R^2 = H$



(2)

a; $R^1 = H$
b; R^1 = COPh
c; R^1 = COMe

† All the compounds described herein gave satisfactory microanalytical results and spectral data consistent with their structures.

During the reaction the n.m.r. integral value of the C(8)-hydrogen of the substrates was reduced while that of the C(2)-hydrogen was almost constant. This fact indicates that the hydrogen exchange of the substrates employed occurs exclusively at C(8). All the substrates were unchanged even upon prolonged heating in the solvent.

TABLE. Effect of N^6-acyl groups on the C(8)-hydrogen exchange of 9-substituted adenines.

Substrate[a]	Pseudo-first-order rate constant k' ($\times 10^6/s^{-1}$)	Half-life/h
(**1a**)	8·68	22·18
(**1b**)	6·18	21·14
(**1c**)	3·38	57·02
(**1d**)	104·2	1·85
(**2a**)	11·0	17·50
(**2b**)	175·9	1·06
(**2c**)	187·5	1·03

[a] Substrate concentration 0·2 M; solvent: CD_3OD–$(CD_3)_2SO$ (7 : 3 v/v); 75 °C.

The effects of the N^6-substituents on the C(8)-hydrogen exchange of the 9-substituted adenines are shown in the Table as pseudo-first-order rate constants ($k' \times 10^6/s^{-1}$) and half-lives (h), which clearly demonstrate that the N^6-acetyl and -benzoyl groups significantly accelerate C(8)-hydrogen exchange in both the 9-ribofuranosyl and 9-ethyl series.‡ A plot of log k' *vs.* the Brown–Okamoto σ_P^+ values[3] for the 9-ribofuranosyl series (**1a**—**d**) shows an approximately linear relationship (Figure).§

It is generally accepted that the predominant site of protonation of 9-substituted adenines is not N^7 but rather N^1.[4]

The n.m.r. spectroscopic study showed that protonation of the N^6-benzoyl and -acetyl derivatives (**2b**) and (**2c**) occurred preferentially at N^7 rather than at N^1: $\Delta H(8)/\Delta H(2)$ values {$\Delta H(8)$ or $\Delta H(2)$ = [chemical shift of C(8)-H or C(2)-H] − [chemical shift of C(8)-H or C(2)-H on the addition of trifluoroacetic acid]} in $(CD_3)_2SO$ were 4·37 for (**2b**) and 4·50 for (**2c**), whereas the value was 0·93 for (**2a**). Thus the change of the preferential protonation site ($N^1 \rightarrow N^7$) in 9-substituted adenines by the introduction of an N^6-acyl group leads to a significant acceleration of C(8)-hydrogen exchange.

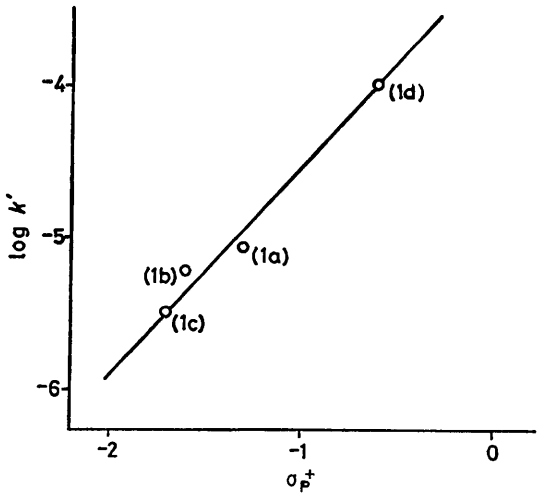


FIGURE. Correlation between pseudo-first-order rate constants (log k') and Brown–Okamoto σ_P^+ values in the C(8)-hydrogen exchange of N^6-substituted 2′,3′-*O*-isopropylideneadenosines (**1a**—**d**).

The remarkable substituent effect of the N^6-acyl group in the 9-substituted adenines may be explained qualitatively in terms of suppression of the amidine resonance which contributes most significantly in the adenine molecule, resulting in acceleration of C(8)-hydrogen exchange.

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‡ The nature of the 9-substituent also influences to some degree the C(8)-hydrogen exchange. In general, the C(8)-hydrogen exchange of the 9-ethyl and 9-benzyl derivatives was faster in comparison with that of 9-ribofuranosyl derivatives. In the ribofuranosyl derivatives, the isopropylidene protecting group and the presence of the free 5′-hydroxy-group tend to accelerate the exchange.

§ Kawazoe *et al.* have observed that N^6-methyl and especially N^6N^6-dimethyladenosine undergo slower C(8)-hydrogen exchange in comparison with the parent adenosine (ref. 1).

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