

REVERSIBLE RING OPENING OF 3,9-DISUBSTITUTED ADENINES: EFFECT
OF SUBSTITUENTS[†]

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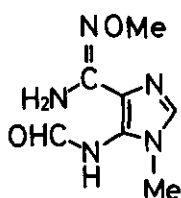
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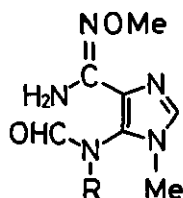
Abstract — The equilibrium constants and the rates of ring opening and cyclization for equilibria between the 3,9-disubstituted adenines IVa-1 and the N-alkylformamidoimidazoles Va-1 in H₂O at pH 8.98 and 25°C have been measured. It has been found that a bulky substituent at the 3-position of IV retards the ring opening to give V, whereas an electron-withdrawing group at the 3- or the 9-position accelerates it. A bulky alkyl group on the formamido nitrogen of V markedly retards the cyclization leading to IV, favoring the ring-opened form in the equilibrated mixture.

3,9-Dimethyladenine hydrochloride (IVa)¹ or perchlorate (IVa: X = ClO₄ for Cl)^{1,2} is the prototype of a number of unstable 3,9-disubstituted adenines prepared as cyclic derivatives,³⁻⁶ N⁶,N⁶-dialkyl derivatives,^{4,7-10} and an N⁶-monomethylated derivative.¹¹ Its nucleoside analogue, 3-methyl-2'-deoxyadenosine, has been assumed to occur as an unstable part structure in DNA's treated with a variety of methylating agents.¹² Compound IVa is duly labile under basic conditions.¹ In 0.1 M aq. NaHCO₃ (pH 8.32) at 25°C, it equilibrates with the ring-opened derivative Va and the reactions in both directions obey pseudo-first-order kinetics.¹ Similar reversible ring openings observed for IVd¹ and IVl¹³ also exemplify the instability of 3,9-disubstituted adenines. We now report the results of our further kinetic study on equilibrium between IV and V, which have revealed the effects of N-3 and N-9 substituents (R¹ and R²) in the adenine ring on the ring opening and cycliza-

[†]Dedicated to Professor Tetsuji Kametani on the occasion of his retirement from Tohoku University.

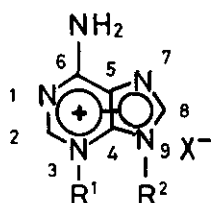


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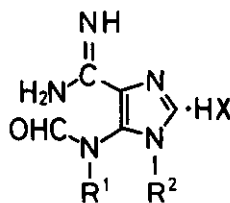
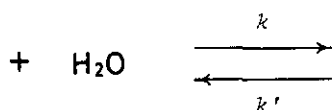


II: R = Me₂CH

III: R = *p*-(MeO)C₆H₄CH₂



IV



V

- a: R¹ = Me; R² = Me; X = Cl
- b: R¹ = Et; R² = Me; X = ClO₄
- c: R¹ = Me₂CH; R² = Me; X = ClO₄
- d: R¹ = PhCH₂; R² = Me; X = ClO₄
- e: R¹ = *p*-(MeO)C₆H₄CH₂; R² = Me; X = ClO₄
- f: R¹ = Me; R² = Et; X = ClO₄
- g: R¹ = Et; R² = Et; X = ClO₄
- h: R¹ = PhCH₂; R² = Et; X = ClO₄
- i: R¹ = Me; R² = PhCH₂; X = ClO₄
- j: R¹ = Et; R² = PhCH₂; X = ClO₄
- k: R¹ = PhCH₂; R² = PhCH₂; X = ClO₄
- l: R¹ = Me; R² = β-D-ribofuranosyl; X = *p*-MeC₆H₄SO₃

tion reactions.

The 3,9-disubstituted adenines selected for the present work were IVa-l,^{1,2,13} which included two new compounds IVc and IVe. The two were synthesized in the following manner by the application of our general method¹ for the synthesis of 3,9-dialkyladenines. Treatment of the formamidoimidazole I¹⁴ with anhydrous K₂CO₃ and isopropyl iodide (48 h) or *p*-methoxybenzyl chloride (3 h) in HCONMe₂ at room temperature furnished the *N*-isopropylformamido derivative II (72% yield; mp 127–128°C)¹⁵ or *N*-(*p*-methoxybenzyl)formamido derivative III (84% yield; mp 90.5–91.5°C). Hydrogenolyses of II and III were separately effected with Raney Ni and H₂ (1 atm,

H_2O + 1 molar equiv. of HCl , room temp., 4–5 h) to give Vc ($X = Cl$ instead of ClO_4) [66% yield; mp 238–239.5°C (dec.)] and Ve ($X = Cl$ for ClO_4) (52% yield; mp 181–182°C). On treatment with a little Et_3N in boiling $EtOH$ for 8 h and addition of 70% aq. $HClO_4$, Vc ($X = Cl$ for ClO_4) cyclized to IVc [mp 250.5–251°C (dec.)] in 56% yield. A similar treatment of Ve ($X = Cl$ for ClO_4) but at 30°C for 7 days produced IVE [mp 166–167°C (dec.)] in 24% yield.

At the inception of the present kinetic study, the reversible ring opening of 3,9-dimethyladenine hydrochloride (IVa) at various pH's was investigated. It may be seen from Table 1 that in the pH range 7.50–10.08 both the ring opening and the cyclization proceeded at rates proportional to hydroxide ion concentration to give an invariable equilibrium constant. The reactions in more alkaline regions were

TABLE 1. Rates and Equilibrium Constant for the Ring Opening of IVa and Cyclization of Va in H_2O at 25°C and Ionic Strength 0.5

pH value	Pseudo-first-order rate constant		Equilibrium constant $K = k/k'$
	k (min^{-1})	k' (min^{-1})	
7.50	5.07×10^{-4}	15.7×10^{-4}	0.32
8.32 ^{a)}	2.88×10^{-3}	9.63×10^{-3}	0.30
8.98	1.20×10^{-2}	3.80×10^{-2}	0.32
9.62	4.57×10^{-2}	15.0×10^{-2}	0.30
10.08	9.76×10^{-2}	32.1×10^{-2}	0.30

a) Data from ref. 1.

found to be complicated by the concomitant deformylation of Va. Although we failed in the determination of the acid dissociation constant of IVa because of its instability under basic conditions, our previous experiment¹ suggested that the basicity of the free base of IVa must be considerably high. Therefore, it is reasonable to assume that in the above ring opening of IVa attack of hydroxide ion on the protonated species at the 2-position is dominant in the pH range determined.

We next measured the rate constants and equilibrium constants for the reversible reactions between IVa-1 and Va-1 in H_2O at pH 8.98 and 25°C. Table 2 summarizes the results. It may be seen that in the ring opening of IV higher alkyl groups at the 3-position retard attack by hydroxide ion at the 2-position. Since there could

TABLE 2. Rate Constants and Equilibrium Constants for the Reversible Reactions between
IVa-1 and Va-1 in H₂O at pH 8.98, 25°C, and Ionic Strength 0.5

Pseudo-first-order rate constant							
Compound			Ring opening		Cyclization		Equilibrium constant $K = k/k'$
No.	R ¹	R ²	$k \text{ (min}^{-1}) \times 10^3$	$k_{\text{rel.}}$	$k' \text{ (min}^{-1}) \times 10^3$	$k'_{\text{rel.}}$	
IVa	Me	Me	12.0	1.0	38.0	1.0	0.32
IVb	Et	Me	3.96	0.33	6.47	0.17	0.61
IVc	Me ₂ CH	Me	1.58	0.13	1.32	0.03	1.20
IVd	PhCH ₂	Me	12.7	1.06	2.78	0.07	4.57
IVe	<i>p</i> -(MeO)C ₆ H ₄ CH ₂	Me	11.1	0.93	1.49	0.04	7.45
IVf	Me	Et	7.63	0.64	15.1	0.40	0.51
IVg	Et	Et	4.24	0.35	3.20	0.08	1.33
IVh	PhCH ₂	Et	12.1	1.01	1.21	0.03	10.0
IVi	Me	PhCH ₂	12.8	1.07	10.7	0.28	1.20
IVj	Et	PhCH ₂	7.69	0.64	2.42	0.06	3.18
IVk	PhCH ₂	PhCH ₂	21.1	1.76	1.24	0.03	17.0
IVl	Me	β-D-ribo- furanosyl	26.8	2.23	21.0	0.55	1.28

be little difference in the electron-donating properties of such alkyl groups,¹⁶ the observed retardation is probably owing to their steric bulk. The rate enhancement observed for IVd and for IVe to a somewhat smaller extent suggests that the electronic property of a 3-substituent affects the hydroxide attack more significantly than its steric bulk. It is also noteworthy that the benzyl group and the β -D-ribofuranosyl group at the 9-position accelerate the ring opening of IV. This may be attributed to the electron-withdrawing nature, relative to an alkyl group, of the benzyl group and of the ribosyl group.¹⁷ On the other hand, a bulky substituent on the formamido nitrogen of V markedly retards the cyclization leading to IV, favoring the ring-opened form (V) in the equilibrated mixture. In conclusion, it is hoped that the above results will be of great help toward our current study on the synthesis of 3-methyl-2'-deoxyadenosine.

ACKNOWLEDGMENT We are pleased to acknowledge the support of this work by a Grant-in-Aid for Cancer Research (to Professor D. Mizuno) from the Ministry of Education, Science and Culture, Japan.

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Received, 31st May, 1980