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BASE-CATALYZED RING OPENING AND RECLOSURE OF ADENINE RING: MECHANISM, SUBSTITUENT EFFECT, AND SYNTHETIC UTILITY

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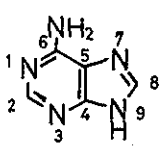
The Dimroth rearrangement in its original scope is an isomerization proceeding by ring fission and subsequent recyclization whereby a heterocyclic nitrogen and its attached substituent exchange places with an α-amino or α-imino group. Since the first observation of Rathke in 1888 on a triazine derivative, the rearrangement has been found to occur in many heterocyclic systems. In the adenine series, 1-alkyl derivatives (type VIII) commonly undergo this type of reaction under alkaline conditions to accomodate the N^1-substituent (R^1) on the exocyclic nitrogen.

Our compelling interest in the Dimroth rearrangement reaction originated from the studies on the N-oxide function as a blocking and/or directing group in the alkylation of the adenine ring (1), which we carried out some ten years ago. We found that the reaction of adenine 1-oxide (II, R^2=H) with alkyl halides in N,N-dimethylacetamide resulted in O-alkylation. The free bases of 1-alkoxyadenines



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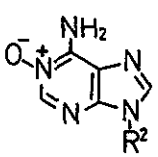

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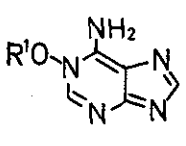

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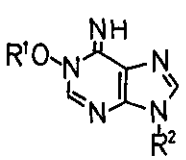

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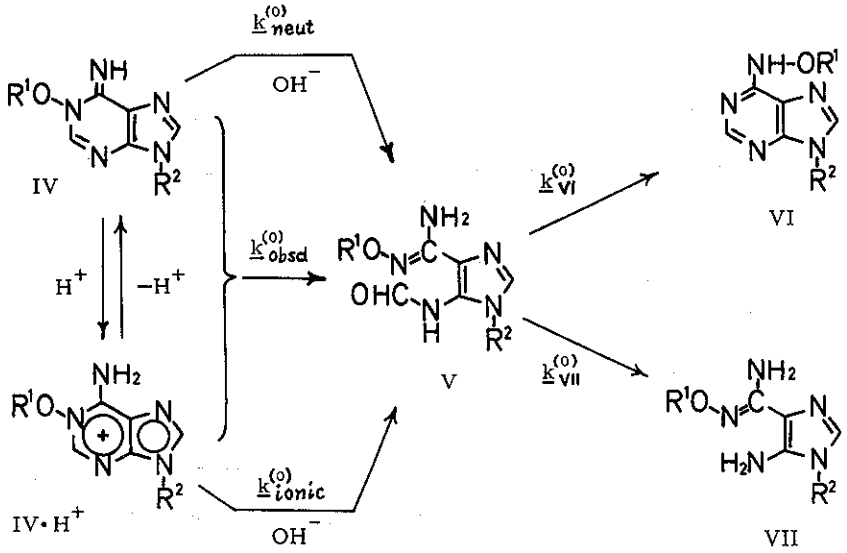
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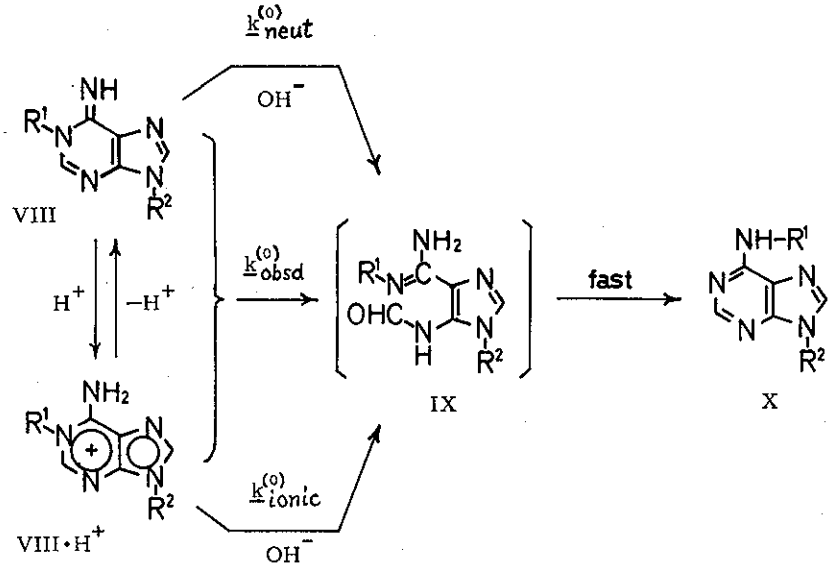
OH^-
IV
H^+
$-H^+$
$k^{(o)}_{obsd}$
V
$k^{(o)}_{VI}$
VI
$k^{(o)}_{VII}$
VII
$IV \cdot H^+$
$k^{(o)}_{ionic}$
OH^-


$k^{(o)}_{neut}$
OH^-
VIII
H^+
$-H^+$
$k^{(o)}_{obsd}$
fast
IX
X
$VIII \cdot H^+$
$k^{(o)}_{ionic}$
OH^-

(III) were then alkylated in a similar manner to give 1-alkoxy-9-alkyladenine salts (IV·HX). On the other hand, 9-alkyladenines were treated with peracetic acid as in the case of adenosine, and the resulting 9-alkyladenine 1-oxides (II) underwent similar O-alkylation to furnish the same 1-alkoxy-9-alkyladenine salts (IV·HX).

The salts thus obtained were found to be fairly reactive and several characteristic reactions were noted. Probably the most salient feature of their chemical behavior is that the hydrolytic fission of the $N_{(1)}—C_{(2)}$ bond occurs very easily. We have found that 1-alkoxyadenine derivatives (type IV) rearrange to the N^6-alkoxy isomers (type VI) in aqueous solution as do 1-alkyladenine derivatives, but through readily isolable ring-opened intermediates (type V) and the intermediates also suffer the competitive hydrolysis leading to the deformylated derivatives (type VII). In the case of the 1-alkyl derivatives (type VIII), however, no ring-opened intermediates (type IX) have been detected. To our knowledge, therefore, the direct isolation of the intermediate (V) is the first example in the Dimroth rearrangement in the adenine series and gives a positive answer to the earlier question as to the existence of the ring-opened intermediate.

We have also found that the rearrangement of 1,9-dimethyladenine (VIII, $R^1 = R^2 = Me$) to N^6,9-dimethyladenine (X, $R^1 = R^2 = Me$) at 40° and various pH's follows pseudo-first-order kinetics wherein no intermediate is detectable. The results were best interpreted in terms of a mechanism involving a rate-determining initial ring opening, caused by attack of hydroxide ion on both the protonated ($VIII \cdot H^+$) and the neutral species (VIII), and a subsequent ring closure. This is consistent with the mechanism which Macon and Wolfenden proposed for the Dimroth rearrangement of 1-methyladenosine at 25°.

Our kinetic studies further revealed that the initial ring opening of 1-alkoxyadenine derivatives is 7—30 times as fast as that of 1-alkyladenine derivatives and it is also caused by attack of hydroxide ion on both the protonated ($IV \cdot H^+$)

and the neutral species (IV). The attack on the protonated species is much faster than the attack on the neutral species. The rates of the recyclization to the N^6-alkoxy isomers ($\underline{k}_{VI}^{(o)}$) and of the hydrolysis reaction to the deformylated derivatives ($\underline{k}_{VII}^{(o)}$) are comparable to each other and the sum of them does not exceed one eighth of the rate of the ring opening reaction ($\underline{k}_{obsd}^{(o)}$). This feature presents a striking contrast to that of the Dimroth rearrangement of 1-alkyladenine derivatives. Therefore, the acceleration of the ring opening step and the retardation of the recyclization step observed for 1-alkoxyadenine derivatives could be attributed directly to the electron-withdrawing nature of the alkoxyl group.

Considering the actual or potential utility of the Dimroth rearrangement in synthetic operations and chemical modification of adenine derivatives as well as nucleic acids, we planned to learn more about the effect of substituents at the 1- and the 9-position on the reaction rate. The kinetic results with a series of 1-alkyl-9-methyladenines (type VIII, R^2=Me), 1-alkyladenosines (type VIII, R^2=β-$\underline{\underline{D}}$-ribofuranosyl), 1-alkoxy-9-methyladenines (type IV, R^2=Me), 1-benzyloxyadenosine (IV, R^1=$PhCH_2$; R^2=β-$\underline{\underline{D}}$-ribofuranosyl), and 1-($\underline{p}$-substituted benzyloxy)-9-methyladenines (type IV, R^2=Me) revealed that the rate of the hydroxide attack on the protonated species is much faster than the attack on the neutral species and that the former is influenced by an electronic factor of the 1-substituent, whereas the latter, by both a steric and an electronic factor. It may be of particular interest to point out that the β-$\underline{\underline{D}}$-ribofuranosyl group at the 9-position accelerates the ring opening of both the neutral and the protonated species, but to a somewhat further extent for the latter. We are as yet uncertain whether this is attributed purely to the electron-withdrawing effect of the ribosyl group and/or intramolecular participation of the hydroxyl group at the 5′-position. In both the reclosure (V $\rightarrow$ VI) and the deformylation step (V $\rightarrow$ VII), the β-$\underline{\underline{D}}$-ribofuranosyl group on the imidazole-ring nitrogen of V exerts a rate-promoting effect, whereas the ben-

zyl group on the O-atom of the amidoxime moiety of V seems to have a rate-retarding effect. At present, however, we wish to refrain from discussing the detailed mechanisms for these two reaction steps because of the lack of theoretical pH—rate profiles which correspond closely with the observed ones.

Since the discovery of kinetin (X, R^1=furfuryl; R^2=H), a cell-division promoting factor, in 1955, many synthetic routes to N^6-substituted adenines (type X) have been reported. Among these, one may find a route through the Dimroth rearrangement of 1-substituted adenines (type VIII). The synthetic value of this route has been enhanced by the ready availability of the 1-substituted derivatives, which has grown out of the intensive studies on alkylation of adenine derivatives by Robins et al., Leonard et al., and others. Thus, there are ample examples in the literature of the synthesis of N^6-substituted adenines (type X) through the use of the Dimroth rearrangement.

Ueda and his co-workers utilized the ring-opening reaction of 1-methoxy-N^6-cyanoadenosine in their chemical conversion of adenosine into guanosine. Our ring-opening and deformylation reactions have been adopted by Montgomery and Thomas in their synthesis of 2-aza-adenosine and related derivatives. Similarly, the ICN Nucleic Acid Research Institute group (U. S. A.) utilized the deformylated derivatives (type VII) for introducing a variety of substituents into the adenine ring at the 2-position. Our syntheses of 3,9-dimethyl- and 3-methyl-9-ethyladenine from N′-alkoxy-1-alkyl-5-formamidoimidazole-4-carboxamidine (type V, $R^1=R^2$=Me, Et) and of 7,9-dimethyladenine or 7-methyladenosine from N^6-methoxy-9-methyladenine (VI, $R^1=R^2$=Me) or N^6-methoxyadenosine (VI, R^1=Me; $R^2=\beta$-D-ribofuranosyl) made it possible to multiply the number of known N^X, N^Y-disubstituted adenines. Furthermore, we have demonstrated that the conversion of N^6,9-dimethyladenine (X, $R^1=R^2$=Me) into the 1,9-dimethyl isomer (VIII, $R^1=R^2$=Me) is feasible when the methoxyl group is used at the 1-position as an

easily removable directing group. This structural transformation is reverse to what occurs in the usual Dimroth rearrangement.

In conclusion, it is of interest to note that all of the four possible N^9,N^X-dialkyladenines can now be synthesized from 1-alkoxyadenine (III) by combination of alkylation, ring opening, recyclization, hydrogenolysis, and so on, and the alkoxyl group plays a very important role in these transformations.

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