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# Mechanisms for the Solvolytic Decompositions of Nucleoside Analogues. IX. Pathways for the Alkaline Hydrolysis of 6-Substituted 9-(1-Ethoxyethyl)purines

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A few 6-substituted 9-(1-ethoxyethyl)purines have been prepared and the rates of their base-catalyzed hydrolysis were measured by UV spectroscopy. The product mixtures were fractionated by preparative TLC and characterized by NMR and UV spectroscopy. The results obtained suggest that the alkaline cleavage of 9-(1-ethoxyethyl)purines generally proceeds by nucleophilic attack of hydroxide ion on C8 of the purine moiety, resulting in formation of appropriate 4,5-diaminopyrimidine and 8-methylpurine as final products. With 6-methoxy, 6-methylthio, and 6-chloro derivatives nucleophilic attack of hydroxide ion on C6 giving 9-(1-ethoxyethyl)hypoxanthine competes with this reaction.

While there have been numerous mechanistic investigations concerning the acid-catalyzed hydrolysis of purine nucleosides and related compounds,[1-11] the corresponding reactions under alkaline conditions have been much less extensively studied.[12-15] Chromatographic and UV-spectroscopic analyses of the product mixtures have been interpreted to indicate that three different pathways compete in the alkaline cleavage.[14,15] First, nucleophilic attack of hydroxide ion on C8 of the purine ring may lead to opening of the five-membered ring of the base moiety. Second, appropriate substituents on the purine ring, particularly at C6, can be displaced by hydroxide ion. Third, the purine moiety may be intramolecularly displaced by an ionized hydroxyl group of the glycon ring. Which one of the routes prevails undoubtedly depends on both the polar nature of the substrate and the concentration of hydroxide ion. Detailed mechanisms for each of the reactions are unclear. The aim of the present study is to elucidate the competition between the first and second mechanistic possibility and to examine the structures of the intermediates involved. Acyclic nucleoside analogues, 6-substituted 9-(1-ethoxyethyl)purines, have been chosen as model compounds, since with these substrates the intramolecular participation of the carbonyl moiety can be ignored. The substituents at C6 have been selected so that the electron density at C8 exhibits large variations. In other words, the ease of the nucleophilic attack on this site is greatly altered on going from one substrate to another.

## RESULTS AND DISCUSSION

Table 1 records the first-order rate constants for the disappearance of some 6-substituted 9-(1-ethoxyethyl)purines in aqueous alkali. The rate of decomposition is greatly increased with the increasing electron-attracting ability of the 6-substituent, being for each compound proportional to the concentration of hydroxide ion. Both of the findings are consistent with the view that hydroxide ion performs a rate-limiting nucleophilic attack on the substrate. Table 2 summarizes the TLC and spectroscopic data for the products formed in about three half-lives. With the unsubstituted 9-(1-ethoxyethyl)purine the disappearance of the starting material is accompanied with formation of two stable products, having $R_F$ values of 0.72 and 0.32 on Silica gel 60 ($CHCl_3 - CH_3OH$ 2:1). The chromatographic mobilities and the UV and NMR spectroscopic data for these compounds are identical

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*Table 1.* First-order rate constants for the decomposition of 6-substituted 9-(1-ethoxyethyl)purines in aqueous sodium hydroxide.[a]

| Substituent at C6 | $T$/K | $[OH^-]$/mol dm$^{-3}$ | $k/10^{-4}$ s$^{-1}$ |
|---|---|---|---|
| $NH_2$ | 363.2 | 0.50 | 0.342 ± 0.004[b] |
| | 363.2 | 0.30 | 0.207 0.003 |
| | 363.2 | 0.10 | 0.0701 0.0004 |
| $CH_3$ | 363.2 | 0.50 | 14.5 ± 0.2 |
| | 363.2 | 0.30 | 8.12 0.09 |
| | 363.2 | 0.10 | 3.53 0.07 |
| | 353.2 | 0.50 | 6.70 0.09 |
| | 343.2 | 0.50 | 3.22 0.02 |
| $OCH_3$ | 333.2 | 0.50 | 2.35 ± 0.02 |
| | 333.2 | 0.30 | 1.03 0.01 |
| | 333.2 | 0.10 | 0.418 0.07 |
| $SCH_3$ | 353.2 | 0.50 | 11.3 ± 0.1 |
| | 353.2 | 0.30 | 6.43 0.05 |
| | 353.2 | 0.10 | 1.92 0.03 |
| | 343.2 | 0.50 | 5.26 0.06 |
| | 333.2 | 0.50 | 2.31 0.01 |
| H | 333.2 | 0.50 | 9.73 ± 0.08 |
| | 333.2 | 0.30 | 5.66 0.08 |
| | 333.2 | 0.10 | 2.07 0.02 |
| | 323.2 | 0.50 | 4.07 0.04 |
| | 313.2 | 0.50 | 1.37 0.04 |
| Cl | 323.2 | 0.50 | 53.8 ± 0.8 |
| | 323.2 | 0.30 | 36.5 0.7 |
| | 323.2 | 0.10 | 12.7 0.5 |
| | 313.2 | 0.50 | 23.2 0.6 |
| | 303.2 | 0.50 | 10.8 0.1 |

[a] The ionic strength was adjusted to 0.50 mol dm$^{-3}$ with sodium chloride. [b] Standard error of the mean.

with those observed for authentic samples of 8-methylpurine and 4,5-diaminopyrimidine, respectively. In addition, a third product, exhibiting $R_F$ of 0.47, appears soon after the initiation of the reaction and disappears after five half-lives. The $^1H$ and $^{13}C$ NMR chemical shifts for this compound are listed in Table 3. Besides the signals of two aromatic protons, a doublet of three protons at $\delta$ 1.57 and a quartet of one proton at $\delta$ 5.75 is observed in the $^1H$ NMR spectrum in $D_2O$. Most probably the compound contains a group of $CHCH_3$. The $^{13}C$ NMR spectrum lend further support for this conclusion. Signals at $\delta$ 26.0 and 74.8 are observed, in addition to four signals in the region typical to carbons of the pyrimidine ring. The magnitude of the shift of 74.8 ppm strongly suggests that the carbon of the CH group, which with all likelihood is bonded to nitrogen, exhibits $sp^3$ rather than $sp^2$ hybridization. A compound that fulfils the structural requirement indicated above is, for example, intermediate I in Scheme 1. Accordingly, it seems reasonable to assume that rate-limiting nucleophilic attack of hydroxide ion on C8 of the purine moiety leads to opening of the imidazole ring. The pyrimidine derivative, formed possibly as a transient intermediate, then undergoes deformylation, and intramolecular displacement of the ethoxy group by the free amino group yields the observed cyclic intermediate, I. The latter partly decomposes to 4,5-diaminopyrimidine and

*Table 2.* Chromatographic and spectroscopic data for the main products formed in the alkaline decomposition of 6-substituted 9-(1-ethoxyethyl)purines.

| Substituent at C6 | Product | $R_F$[a] | NMR chemical shifts[b] | λ (max.)/nm | |
|---|---|---|---|---|---|
| | | | | Acid[c] | Base[d] |
| H | 8-Methylpurine | 0.72[e] | $^1$H NMR:[e] s2.72(3H), s8.73(1H), s8.77(1H) | 265[f] | 276[f] |
| | | | $^{13}$C NMR:[e] 17.2, 131.7, 144.6, 153.5, 158.8, 162.1 | | |
| | 4,5-Diamino-pyrimidine | 0.32[e] | $^1$H NMR:[e] s7.70(1H), s8.23(1H) | 283[f] | 248,288[f] |
| | | | $^{13}$C NMR:[e] 128.8, 135.9, 149.5, 157.7 | | |
| $CH_3$ | 6,8-Dimethylpurine | 0.67 | $^1$H NMR: s2.57(3H), s2.67(3H), s8.37(1H) | | |
| | | | $^{13}$C NMR: 16.8, 21.3, 130.0 152.9 155.5, 156.2, 159.7 | | |
| | 4,5-Diamino-6-methylpyrimidine | 0.47 | $^1$H NMR: s2.30(3H), s7.87(1H) | 286[g] | 250,284[g] |
| | | | $^{13}$C NMR: 19.9, 125.4, 147.2, 149.3, 156.2 | | |
| | 6-Methylpurine | 0.71[e] | $^1$H NMR:[e] s2.67(3H), s8.37(1H), s8.43(1H) | 266[f] | 272[f] |
| | | | $^{13}$C NMR:[e] 21.3, 130.0, 148.3, 153.6, 154.8, 158.3 | | |
| $NH_2$ | 8-Methyladenine | 0.64 | $^1$H NMR:[h] s2.60(3H), s8.10(1H) | 265 | 270 |
| | 4,5,6-Triamino-pyrimidine | 0.34[e] | $^1$H NMR:[e] s7.72(1H) | 287[e] | 277[e] |
| | Adenine | 0.52[e] | $^1$H NMR:[eh] s8.05(1H), s8.13(1H) | 262[f] | 268[f] |
| $OCH_3$ | 9-(1-Ethoxyethyl)-hypoxanthine | 0.80 | $^1$H NMR: t1.20(3H), d1.88(3H), q3.58(2H), q5.95(1H), s8.23(1H), s8.33(1H) | 251 | 255 |
| $SCH_3$ | 9-(1-Ethoxyethyl)-hypoxanthine | | the data given above | | |
| | 8-Methyl-6-methyl-thiopurine | 0.76[i] | $^1$H NMR: s2.67(6H), s8.24(1H) | 227, 298 | 294 |
| | 4,5-Diamino-6-methylthiopyrimidine | 0.65[i] | $^1$H NMR: s2.54(3H), s7.77(1H) | 232, 318 | 298 |
| | 8-Methylpurine | | the data given above | | |
| | 6-Methylthiopurine | 0.72[i] | $^1$H NMR:[eh] s2.78(3H), s8.29(1H), s8.50(1H) | 222, 294[f] | 292[f] |
| Cl | 9-(1-Ethoxyethyl)-hypoxanthine | | the data given above | | |
| | 6-Chloro-4,5-di-aminopyrimidine | 0.52[j] | $^1$H NMR: s7.84(1H) | 268,306[g] | 255,292[g] |

[a] Silica gel 60 F-254, eluent $CHCl_3 - CH_3OH$ 2:1 (v/v) if not otherwise stated. [b] Recorded in $D_2O$ at pD 7 if not otherwise stated. The shifts given are ppm values from DSS. [c] In 0.1 mol dm$^{-3}$ HCl. [d] In 0.1 mol dm$^{-3}$ NaOH. [e] Equal to the data for an authentic sample. [f] Consistent with the data in Ref. 16. [g] Consistent with the data in Ref. 12. [h] Recorded in 0.1 mol dm$^{-3}$ NaOD. [i] Eluent $CHCl_3 - CH_3OH$ 3:1 (v/v). [j] Eluent $CHCl_3 - CH_3OH$ 5:1 (v/v).

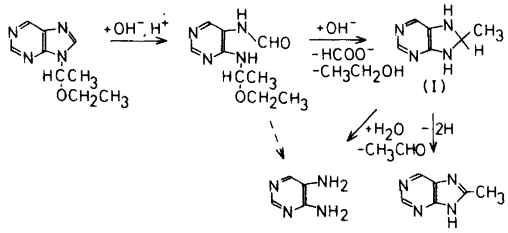
is partly oxidized to 8-methylpurine. However, the possibility that 4,5-diaminopyrimidine is formed directly from the transient intermediate cannot be excluded. 8-Methylpurine doesn't give 4,5-diaminopyrimidine under the present conditions.

The pathway described above can most probably be extended to the hydrolysis of the 6-substituted substrates. Alkaline cleavage of 9-(1-ethoxyethyl)-6-methylpurine, for example, yields both 6,8-dimethylpurine and 4,5-diamino-6-methylpyrimidine. An intermediate analogous to that in Scheme 1 is also observed, though its concentration is considerably smaller than in the hydrolysis of the unsubstituted compound.

*Table 3.* NMR chemical shifts for the intermediates (structure I in Scheme 1) formed in the alkaline hydrolysis of 6-substituted 9-(1-ethoxyethyl)purines in 0.10 mol $dm^{-3}$ sodium hydroxide.

| Substituent at C6 | NMR chemical shifts[a] | $x$(I)[b] |
|---|---|---|
| H | $^1$H NMR: d1.57(3H), q5.75(1H), s7.07(1H), s8.10(1H)<br>$^{13}$C NMR: 26.0, 74.8, 116.4, 135.0, 148.6, 162.8 | 0.6 |
| $CH_3$ | $^1$H NMR: d1.58(3H), s2.13(3H), q5.47(1H), s7.63(1H)<br>$^{13}$C NMR: 18.2, 26.0, 73.7, 131.8, 134.4, 150.2, 161.1 | 0.3 |
| $NH_2$ | not detected | |
| $OCH_3$ | not detected | |
| $SCH_3$ | $^1$H NMR: d1.55(3H), s2.67(3H), q5.50(1H), s7.62(1H) | 0.1 |
| Cl | $^1$H NMR: d1.64(3H), q5.75(1H), s7.64(1H) | <0.1 |

[a] See footnote *b* in Table 2. [b] Approximative proportion of the intermediate of the total amount of substrate decomposed in one half-life.




*Scheme 1.*

Some 6-methylpurine is also formed in the reaction. Analogously, 9-(1-ethoxyethyl)adenine is decomposed to 8-methyladenine and 4,5,6-triaminopyrimidine, the expected products of the reaction described above, and free adenine. The mechanism for the production of the latter compound is unclear. Possibly intermolecular displacement of the purine base by hydroxide ion takes place, or the substrate is spontaneously decomposed to purine base and an oxocarbenium ion derived from the 1-ethoxyethyl group. The fact that 9-(1-ethoxyethyl)adenine appears to yield free purine base to a larger extent than the other nucleoside analogues studied makes the former alternative more attractive. The electropositive amino substituent increases the electron density at N9 retarding the rupture of the C – N-bond. Accordingly, it would be somewhat surprising if with this compound spontaneous decomposition of the substrate could compete with nucleophilic reactions more effectively than with those nucleoside analogues having better leaving groups. Most probably the susceptibility to polar effects is in spontaneous decomposition at least as great as in nucleophilic displacement reactions. Moreover, marked spontaneous decomposition would change the reaction order with respect to the hydroxide ion from unity at low base concentrations.

In the alkaline cleavage of the 6-methoxy, 6-methylthio, and 6-chloro compounds nucleophilic attack of hydroxide ion on C6 competes with the nucleophilic attack on C8. 9-(1-Ethoxyethyl)-6-methoxypurine is completely converted to 9-(1-ethoxyethyl)hypoxanthine. With the 6-chloro derivative this reaction represents about 60 % of the total decomposition and with the 6-methylthio derivative about 20 %. 9-(1-Ethoxyethyl)-hypoxanthine is quite stable under alkaline conditions, since it is present as N1 anion and hence not susceptible to nucleophilic attack of hydroxide ion. 6-Chloro-9-(1-ethoxyethyl)purine also yields 6-chloro-4,5-diaminopyrimidine, the product of Scheme 1, and traces of several other products. The concentration of the intermediate, I, is, however, so low that it can hardly be detected by NMR. The product mixture of the alkaline hydrolysis of 9-(1-ethoxyethyl)-6-methylthiopurine is most diverse. Besides the hypoxanthine derivative, it contains 4,5-diamino-6-methylthiopyrimidine, 8-methyl-6-methylthiopurine, 8-methylpurine and traces of 6-methylthiopurine. Possibly 8-methylpurine is formed as an oxidation product of the intermediate, I, along with 8-methyl-6-methylthiopurine.

The partial rate constants, $k(1)$, for the reaction depicted in Scheme 1 can be estimated by eqn. (1) from the rate constants observed for the decomposition of the substrates. Here [P(1)] stands for the sum concentration of the intermediates and products

$$k(1)=\frac{[\mathrm{P}(1)]}{[\mathrm{P}(\mathrm{tot.})]}k \qquad (1)$$

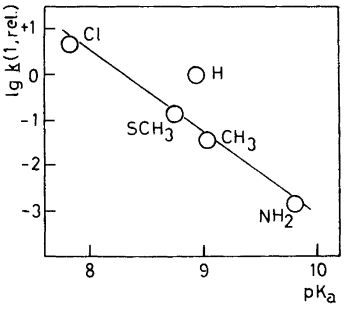



*Fig. 1.* The effect of the 6-substituent on the alkaline hydrolysis of 6-substituted 9-(1-ethoxyethyl)purines. The partial rate constants for the reaction depicted in Scheme 1 plotted against the $pK_a$-values of the correspondingly substituted purines.[17] The values of $k(1,\text{rel.})$ for the 6-$CH_3$ and 6-$NH_2$ derivatives were obtained by extrapolating $k(1)$ for the unsubstituted compound to higher temperatures *via* the Arrhenius equation.

formed by this pathway, and [P(tot.)] is the decrease in the total substrate concentration at the same moment. Estimation of the ratio [P(1)]/P(tot.)] from the $^1$H NMR data referring to about one half-life enables the calculation of $k(1)$. As seen from Fig. 1, an approximate linear relationship exists between the logarithmic rate constants and the $pK_a$ values of the corresponding purines. In other words, the rate of the reaction described by Scheme 1 increases with the decreasing electron density of the imidazole ring of the substrate. The value of about 2 for the slope of the straight line obtained indicates that polar effects of 6-substituents play an even more decisive role in this reaction (at C8) than in the deprotonation of the purine system (at N9). The entropy of activation, $-48\ \text{J K}^{-1}\ \text{mol}^{-1}$, for the hydrolysis of the unsubstituted compound is in the expected range for an intermolecular nucleophilic displacement reaction. The detailed mechanism cannot be deduced on the basis of the present data.

## EXPERIMENTAL

*Materials.* 6-Substituted 9-(1-ethoxyethyl)purines were prepared from 1-chloro-diethyl ether and appropriately 6-substituted purines by the method described earlier.[18] Table 4 records the chromatographic and spectroscopic data for the compounds synthesized. The $^{13}$C NMR chemical shifts observed closely resemble those reported for corresponding 9-(β-D-ribofuranosyl)derivatives, indicating that the compounds are N9 isomers. If the ethoxyethyl substituent were attached to N7, the signals for C4 and C5 would be expected to occur at about 10 ppm lower and higher field, respectively.[20]

4,5-Diaminopyrimidine and 4,5,6-triaminopyrimidine employed as reference materials were commercial products of Sigma Chemical Company. 8-Methylpurine was synthesized as described elsewhere.[17]

*Table 4.* Chromatographic and spectroscopic data for the 6-substituted 9-(1-ethoxyethyl)purines prepared.

| Substituent at C6 | $R_F$[a] | NMR chemical shifts[b] $\delta(2)$ | $\delta(4)$ | $\delta(5)$ | $\delta(6)$ | $\delta(8)$ | $\delta$(6-X) | $\delta(CHCH_3)$ | $\delta(CH_2CH_3)$ | $\lambda$(max.)/ nm[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| H | 0.84 | for the $^1$H and $^{13}$C NMR chemical shifts see Ref. 18. | | | | | | | | 264 |
| $CH_3$ | 0.86 | $^1$H: s8.57 | | | | s8.13 | s2.70 | d1.68,q5.92 | t1.07,q3.33 | 262 |
| | | $^{13}$C: 154.1 | 152.2 | 134.8 | 162.1 | 146.7 | 21.1 | 23.6,84.8 | 16.7,67.8 | |
| $NH_2$ | 0.84 | for the $^1$H and $^{13}$C NMR chemical shifts see Ref. 19. | | | | | | | | 262 |
| $OCH_3$ | 0.90 | $^1$H: s8.33 | | | | s8.17 | s4.14 | d1.85,q5.98 | t1.16,q3.39 | 253 |
| | | $^{13}$C: 152.3 | 151.9 | 121.4 | 161.1 | 139.7 | 54.3 | 22.6,81.1 | 14.8,64.7 | |
| | | (151.7)[d] | (151.8) | (121.2) | (160.5) | (142.4) | | | | |
| $SCH_3$ | 0.92 | $^1$H: s8.51 | | | | s8.00 | s2.70 | d1.78,q5.95 | t1.18,q3.41 | 284 |
| | | $^{13}$C: 152.0 | 148.1 | 131.3 | 161.7 | 140.0 | 11.7 | 22.5,80.9 | 14.8,64.7 | |
| | | (151.5)[d] | (148.0) | (131.3) | (160.5) | (143.1) | | | | |
| Cl | 0.90 | $^1$H: s8.49 | | | | s8.38 | | d1.86,q6.01 | t1.19,q3.42 | 267 |
| | | $^{13}$C: 152.1 | 151.0 | 131.6 | 151.6 | 142.9 | | 22.5,81.7 | 14.8,65.0 | |
| | | (150.3)[d] | (152.4) | (132.2) | (152.4) | (146.4) | | | | |

[a] See footnote *a* in Table 2. [b] Taken as ppm from TMS. $^1$H NMR spectra were recorded in $CCl_4$ and $^{13}$C NMR spectra in $CDCl_3$. [c] In $CH_2Cl_2$. [d] The data for the corresponding 9-(β-D-ribofuranosyl) derivative.[20,21]

*Kinetic measurements.* The hydrolyses were carried out in stoppered bottles immersed in a thermostatted water bath. Reactions were initiated by adding the substrate in the pre-thermostatted reaction medium to give the concentration of $2 \times 10^{-4}$ mol $dm^{-3}$ and 10–12 aliquots of 2 $cm^3$ were withdrawn at suitable time intervals during 2–3 half-lives. The reaction was usually stopped with $NaH_2PO_4$ solution, the concentration of which was suitable to make the final pH 7. The unreacted starting material was extracted into methylene dichloride and the UV-absorption spectra of the organic phases were recorded. The spectra obtained at different intervals with the 6-H, 6-$CH_3$ and 6-$NH_2$ derivatives were identical with those of the starting materials and the final samples, taken at ten half-lives, exhibited no marked absorption. Accordingly, only the unreacted substrates appeared to be transferred into methylene dichloride. With the 6-$OCH_3$ and 6-$SCH_3$ derivatives the extractions were carried out directly from the cooled base solutions to keep the reaction products as their anions in the aqueous phase. The rate constants were calculated from the integrated first-order rate-equation.

Hydrolysis of 6-chloro-9-(1-ethoxyethyl)purine was too rapid to be followed by the technique described above. With this compound the determination of the rate constants was performed by continuous monitoring of the UV-spectrum of the reaction solution in the cuvette thermostatted to the temperature wanted. The rate constants were calculated by the method of Guggenheim from the absorbances at the absorption maximum of the starting material. No curvature in the Guggenheim plots was observed, suggesting that the progress of a single reaction was followed.

*Product analyses.* Progress of the hydrolysis reactions was also followed by TLC on Silica gel 60 using mixtures of chloroform and methanol as eluent. With these experiments the initial substrate concentration was of the order of $5 \times 10^{-2}$ mol $dm^{-3}$.

Product mixtures at one and three half-lives were prepared by hydrolyzing the substrates as $5 \times 10^{-2}$ mol $dm^{-3}$ solutions in 0.1 mol $dm^{-3}$ aqueous sodium hydroxide. The unreacted starting material was removed by extraction with methylene dichloride and the aqueous phase was neutralized with aqueous hydrogen chloride. Evaporation to dryness under reduced pressure afforded the product mixture that was then fractionated by preparative TLC on Silica gel 60. The products were eluted from the silica gel by methanol. About 200 mg of the mixture was applicated on one plate. UV-spectra were recorded on Unicam SP 1700 spectrophotometer, $^1H$ NMR spectra on Jeol JNM-PMX 60 and $^{13}C$ NMR spectra on Jeol FX60 spectrometers. Internal standards (DSS or TMS) were employed.

The NMR spectra of the intermediates were obtained by comparing the spectra of the product mixtures at various time intervals with the spectra of the products isolated.

UV- and NMR-spectroscopic characterization of the methylene dichloride phases evaporated to dryness indicated that only the starting material was extracted from the aqueous solution under basic conditions.

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