Table II. ^{31}P NMR Chemical Shifts in Dichloromethane

compd	^{31}P shift,[a] ppm
$(C_6H_5O)_2P(O)OH$ (1)	−12.0
$(C_6H_5O)_2P(O)Cl$ (7)	−6.0
$(C_6H_5O)_2P(O)O(O)P(OC_6H_5)_2$ (6)	−24.8
CEP-OH[b] (2)	11.4[c]
CEP-Cl (4)	18.4
CEP-OCEP (3)	−1.6

[a] From 85% H_3PO_4 at 0 ppm. Positive values are downfield from the reference. [b] CEP = cyclic enediol phosphoryl. [c] 25% dimethyl sulfoxide added.

Experimental Section

Materials. Diphenyl hydrogen phosphate was prepared by a standard procedure. 1,2-Dimethylethenylene hydrogen phosphate (CEP-OH) was prepared as described.[5] *N*-Methylpyridinium diphenyl phosphate was prepared by reaction of pyridine with methyl diphenyl phosphate. *N*-Methylpyridinium 1,2-dimethylethenylene phosphate was prepared as described.[9] Phosgene gas was passed through anhydrous copper sulfate prior to its utilization in the reaction. The dichloromethane was strictly anhydrous.

General Procedure. A solution of the *N*-methylpyridinium salt of the phosphodiester (1.5 mmol) in anhydrous dichloromethane (10 mL) was added dropwise to a stirred solution of phosgene in dichloromethane (10 mL). The phosphate/phosgene molar ratios and the reaction temperatures are given in Table I. After the mixture was stirred for the time indicated, the solvent and excess phosgene were evaporated (30 torr, 15–20 °C). *N*-Methylpyridinium chloride precipitated as evaporation proceeded. The residue from the evaporation was shaken with dichloromethane (1 mL) and the solution separated from the chloride salt by careful decantation. The ^{31}P NMR spectrum of the solution was examined immediately, and the results are given in Table I. The pertinent chemical shifts are listed in Table II.

Care must be exercised to avoid water contamination during the above procedure. Hydrolysis during reaction introduces the following step as an artifact: $(C_6H_5O)_2P(O)Cl + H_2O \rightarrow (C_6H_5O)_2P(O)OH + HCl$ and CEP-Cl + $H_2O \rightarrow$ CEP-OH + HCl.

Acknowledgment. This research was supported by Grant CHE 81-10294 from the National Science Foundation.

Registry No. 2, 20682-72-8; 3, 55894-94-5; 4, 21949-38-2; $(C_6H_5O)_2P(O)O(O)P(OC_6H_5)_2$, 10448-49-4; $(C_6H_5O)_2P(O)Cl$, 2524-64-3; $(C_6H_5O)_2P(O)O^-$, 48168-03-2; $(C_6H_5O)_2P(O)OH$, 838-85-7; $CEPO^-$, 50577-95-2; phosgene, 75-44-5.

Anion Formation and Ring Opening of 9-Substituted Purines in Liquid Ammonia Containing Potassium Amide[1]

Nico J. Kos, Henk C. van der Plas,* and Wouter J. F. Blees

Laboratory of Organic Chemistry, Agricultural University, Wageningen, The Netherlands

Received August 25, 1982

Reaction of 9-methylpurine, 6-chloro-9-methylpurine, and 2′,3′-*O*-isopropylidenenebularine with potassium amide in liquid ammonia leads to opening of the imidazole ring, yielding, after hydrolysis during the workup, 4-(substituted amino)-5-formamidopyrimidines. 6-Chloro-9-methylpurine gives, besides 6-chloro-4-(methylamino)-5-formamidopyrimidine as main product, small amounts of 9-methyladenine and 6-chloro-7,8-dihydro-8-oxo-9-methylpurine. The ring opening will involve adduct formation at position 8. Nebularine, adenosine, and 2′,3′-*O*-isopropylideneadenosine do not react. With a greater excess of potassium amide 2′,3′-*O*-isopropylideneadenosine loses the sugar moiety. The existence of an anion at position 8 can be proved in 9-methylpurine via scavenging with bromobenzene in liquid ammonia containing potassium amide, yielding the 8-phenyl derivative. With 6-chloro-9-(2-tetrahydropyranyl)purine this reaction gives 6-anilino-9-(2-tetrahydropyranyl)purine. Scavenging of 9-methyladenine with bromobenzene gives 6-anilino-9-methylpurine. ^1H and ^{13}C NMR spectroscopy confirm that in this strongly basic medium 7- and 9-methyladenine and 6-(methylamino)-9-methylpurine deprotonate at C-8 and lose a proton from the amino group. Both 8-(methylthio)- and 8-amino-9-methylpurine give with potassium amide in liquid ammonia opening of the imidazole ring, yielding 5-(cyanoamino)-4-(methylamino)pyrimidine, which can react further to give either 8-amino-9-methylpurine or 7,8-dihydro-8-oxo-9-methylpurine.

In an extension of our study of the reactivity of 2-, 6- and 8-substituted purines toward potassium amide in liquid ammonia[2–4] we became interested in the behavior of 9-substituted purines. In this strongly basic medium these compounds cannot be deprotonated at N-9, making them considerably more reactive toward nucleophilic agents than the purines, being unsubstituted at position 9. In anionic purines only position 6 is attacked by the amide ion, and in neutral purines positions 6 and 8 are approximately equally reactive.[5]

The reactivity of purines containing a leaving group is determined not only by its position but also by the position of the substituent on nitrogen.[6] Besides substitution, often ring opening occurs, leading to either an imidazole or a

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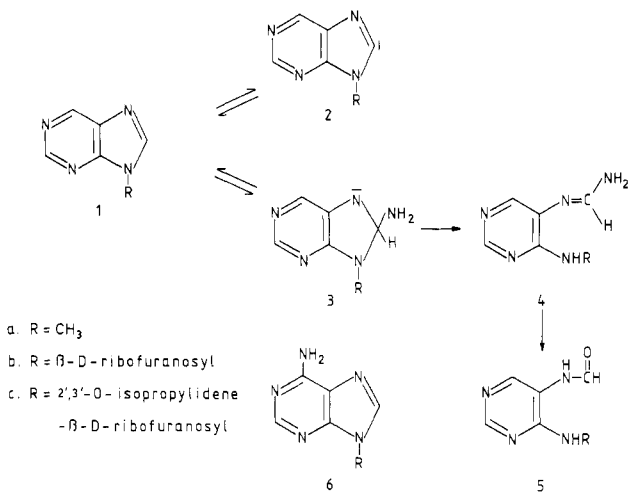
0022-3263/83/1948-0850$01.50/0

Scheme I



pyrimidine derivative. The substitution pattern determines which of the rings will be opened;[7] in 7- or 9-substituted purines it is usually the imidazole ring,[7-11] but it is found that in some cases the pyrimidine ring is opened.[12]

Results and Discussion

(a) 9-Methylpurine, Nebularine, and 2′,3′-*O*-Isopropylidenenebularine. Whereas purine required 20 h at −33 °C to react with 4 equiv of potassium amide in liquid ammonia to form adenine,[2] 9-methylpurine (**1a**) reacts in a few hours at −80 °C with 2.5 equiv of potassium amide, even at a tenfold lower concentration. Not 9-methyladenine but 5-formamido-4-(methylamino)pyrimidine (**5a**) is obtained as the sole product (after 3 h the yield is 25%; a longer reaction time leads to the formation of byproducts). The structure of **5a** was proved by an independent synthesis.[39] These mild conditions show that the reactivity of the purine ring is greatly increased when anion formation at the nitrogen is prevented due to the presence of a substituent at N-9. The 9-methyl compound **1a** has to react at position 8 in order to give **5a**. First the σ-amino *adduct* (**3a**) is formed at position 8, followed by ring opening, giving 5-[(aminomethylene)amino]-4-(methylamino)pyrimidine (**4a**), which is hydrolyzed during workup.[13] It is possible that **4a** is partly reconverted into **1a** during workup (Scheme I).

We also observed that reaction of **1a** with potassium amide in liquid ammonia in the presence of bromobenzene gave 8-phenyl-9-methylpurine. Since bromobenzene reacts very rapidly with potassium amide in liquid ammonia to give benzyne,[16] this result shows that an anion has to be formed at potassium 8 (**2a**), which reacts with benzyne to give the 8-phenyl derivative. Trapping with dimethyl sulfide, methyl iodide, or diphenyliodonium chloride failed. This result is in good agreement with the observation that 9-substituted purines when reacted with electrophiles in the presence of butyllithium involve an *anion* at position 6 or 8.[14,15] Although we could not prove the existence of an adduct by low-temperature NMR spectroscopy, it is possible that an equilibrium exists between the anion and the adduct. The existence of such equilibria has been reported for 2,4,6-trinitrotoluene, 2,4,6-trinitrobenzyl chloride,[18,19] and N-substituted picramides,[17] where the anion formed in the side chain was in equilibrium with an adduct at the aromatic ring.

Table I. ^{1}H NMR Data of the Dianions of Some Adenine Derivatives in Liquid Ammonia Containing Potassium Amide at −50 °C[a]

dianion of	chemical shift H-2	chemical shift NH	chemical shift CH_3	isomer distribution
9-methyladenine	7.52	4.93	3.57	60
	7.70	5.48	3.57	40
7-methyladenine	7.45	4.98	3.95	
6-(methylamino)-9-methylpurine	7.74		3.65	
			2.94	

[a] Chemical shifts in parts per million relative to Me_4Si (δ 0).

It cannot be excluded that **1a** undergoes addition at C-6 (we will show later that 8-(methylthio)-9-methylpurine gives an adduct at position 6), but it can be shown that this adduct does not react further. Since, according to the literature, an anion at position 6 can exist,[15] the conclusion seems justified that four different intermediates can be present (anions and adducts at positions 6 and 8) in the reaction of **1a** with potassium amide (liquid ammonia). However, only the intermediacy of adduct **3a** can explain the formation of **5a**.

Nebularine (**1b**) does not react with potassium amide in liquid ammonia; this is probably due to the loss of protons from the OH groups, deactivating position 8 for nucleophilic attack. However, 2′,3′-*O*-isopropylidenenebularine (**1c**) appeared to be reactive with potassium amide in a mixture of liquid ammonia and ether, yielding 5-formamido-4-[(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine (**5c**), although it reacts much more slowly than **1a**. The β assignment is based on $J_{1,2}$[10,20] (2 Hz for the β isomer) and more reliably on the positions of the methyl signals (occurring at lower field and less close together than for the α isomer[20,21]). When the reaction is carried out under more drastic conditions (without ether or with a higher concentration of potassium amide), we obtained a mixture of the α and β isomers. This mixture can be separated, with difficulty, on TLC. A similar conversion has been observed in aqueous base, but in this medium further reactions take place, involving loss of the formyl group and the sugar moiety.[10] Since the reaction of **1c** was much slower than that of **1a** we attempted to measure intermediates by low-temperature NMR spec-

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Table II. ^{13}C NMR Data of 9-Methyladenine, 8-(Methylthio)-9-methylpurine, and 5-(Cyanoamino)-4-(methylamino)pyrimidine in Liquid Ammonia Containing Potassium Amide at −50 °C[a]

substrate	species	chemical shift C-2	C-4	C-5	C-6	C-8	NCH_3	SCH_3	NCN
9-methyladenine	dianion[b]	152.9	146.8	122.2	164.0	c	29.7		
		154.6	148.7	122.2	166.6	c	30.4		
8-(methylthio)-9-methylpurine	neutral[d]	151.3	153.9	134.4	144.4	157.7	28.3	13.9	
	adduct (14)	154.3	135.6	e	65.4	145.6	28.3	18.6	
5-(cyanoamino)-4-(methylamino)pyrimidine	anion or dianion	150.5	161.7	e	130.1		35.1		118.8
	neutral[f]	146.4	156.4	c	135.3		27.1		126.1

[a] Chemical shifts in parts per million relative to Me_4Si (δ 0). [b] These signals cannot be assigned to the isomers except for C-2, for which selective decoupling shows that the signal at 152.9 ppm belongs to the major isomer. [c] Not observed. [d] Measured in $CDCl_3$. [e] We observed only a signal at 130.1 ppm. [f] After quenching with ammonium chloride.

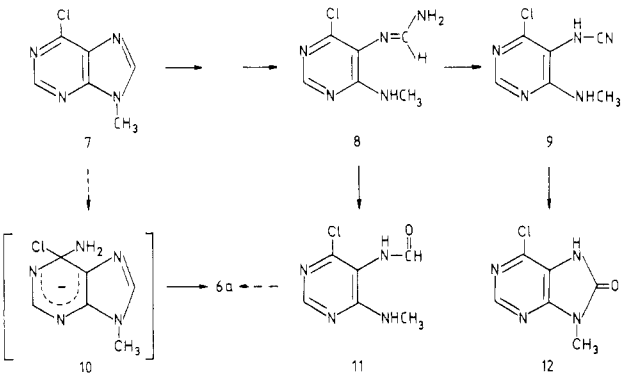
troscopy of **1c** in liquid ammonia containing potassium amide, but without success.

(b) 7- and 9-Methyladenine, 6-(Methylamino)-9-methylpurine, Adenosine, and 2′,3′-*O*-Isopropylidene Adenosine. 9-Methyladenine (**6a**) does not react with potassium amide in liquid ammonia, but low-temperature NMR spectroscopy indicated that **6a** is converted under these conditions into a dianion, formed by abstraction of a proton from both the amino group and C-8. This dianion is present in two geometrical isomers,[22,23] as is apparent from two sets of signals for H-2 and the NH^- group. The signals of the methyl group coincide. The isomeric ratio was 60:40. The syn–anti assignment of the isomers could not be made, since there are no ortho protons present.[24] The ^{13}C NMR spectrum confirmed the occurrence of two geometrical isomers. Evidence that **6a** has lost a proton from C-8 in this strong basic medium was provided by the fact that 8-deuterio-9-methyladenine gave an identical spectrum as **6a** in potassium amide in liquid ammonia (see Table I). This was confirmed by the ^{13}C NMR spectrum, in which the C-8 signal could not be observed. All our attempts to trace the signal for C-8 (that can be expected to be very small) failed[25] (see Table II). Reaction of **6a** with bromobenzene in liquid ammonia containing potassium amide did not give 8-phenyl-9-methyladenine but only 6-anilino-9-methylpurine. ^1H NMR spectroscopy shows that 7-methyladenine and 6-(methylamino)-9-methylpurine also give a dianion, but these dianions are present as only one geometrical isomer.[23] Apparently the influence of the methyl group at N-7 is such that it shifts the syn–anti ratio to one side and shows that this influence is much greater than that of an ortho methyl group as has been observed in the anions of aminopicolines.[24]

Adenosine (**6b**) and 2′,3′-*O*-isopropylideneadenosine (**6c**) do not react with potassium amide in liquid ammonia. Only with a greater excess of potassium amide (8 equiv) does 2′,3′-*O*-isopropylideneadenosine lose the sugar moiety, giving adenine[26] (reaction time 45 min, yield 30%).

(c) 6-Chloro-9-methylpurine. 6-Chloro-9-methylpurine (**7**) does not react with liquid ammonia but gives in the presence of potassium amide three products: 4-chloro-5-formamido-6-(methylamino)pyrimidine (**11**, yield 35%), 9-methyladenine (**6a**, 6%), and 6-chloro-7,8-dihydro-8-oxo-9-methylpurine (**12**, 6%): 50% of starting material is recovered besides 3% of an unidentified dimer (see Scheme II).

Scheme II



The formation of **11** from **7** is similar to the formation of **5a** from **1a** and bears resemblance to the ring opening of 9-substituted 6-chloropurines, except 6-chloro-9-ethylpurine,[27] on treatment with sodium hydroxide.[9,10] The occurrence of ring-opening reactions in these 6-chloro-9-alkylpurines is strongly determined by the basicity of the system, as no ring opening occurs with ammonium hydroxide, but only substitution at C-6 to give 9-substituted adenines.[27-29] 6-(Methylamino)purine is not formed in the reaction of **7** with potassium amide in liquid ammonia, which shows that in the intermediate 4-chloro-5-[(aminomethylene)amino]-6-(methylamino)pyrimidine (**8**), i.e., the precursor of **11**, no intramolecular ring closure occurs by reaction of the chloro atom with the amino group in the (aminomethylene)amino side chain.[11] 9-Methyladenine (**6a**) is a byproduct in the reaction of **7**. It can be formed by an $S_N(AE)^{ipso}$ substitution at position 6.[3,27-29] However, an alternative explanation is possible since we observed that on being allowed to stand in aqueous ammonia, **11** is converted into **6a**, suggesting that the formation of **6a** takes place (partially) from **11**. Support for this possibility comes from the experimental fact that a larger yield of **6a** is obtained when the reaction of **7** with potassium amide/liquid ammonia is quenched with water, giving ammonia, which converts **11** into **6a**.

It is evident that some ring opening, followed by hydrolysis and ring closure, must be involved in the formation of **12**. We postulate (using results given in section d) that 4-chloro-5-(cyanoamino)-6-(methylamino)pyrimidine (**9**) is an intermediate in the formation of **12**. It is not clear

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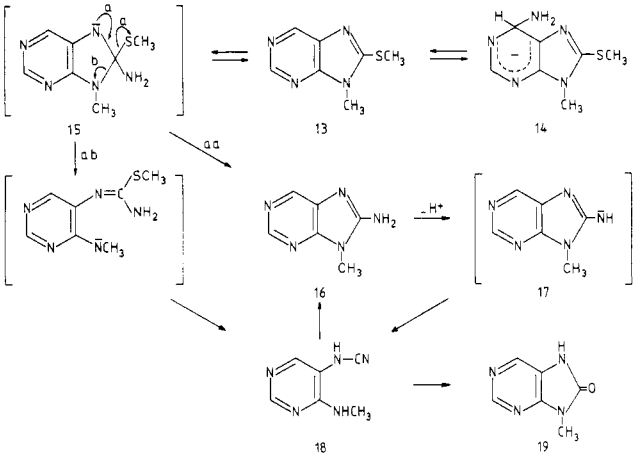
Table III. ^{1}H NMR Data of 8-Substituted 9-Methylpurines in Liquid Ammonia Containing Potassium Amide at −50 °C[a]

compd	species	chemical shift H-2	H-6	NCH_3	SCH_3
8-(methylthio)-9-methylpurine	neutral[b,31]	8.83	8.90	3.71	2.79
	adduct (14)	7.02	5.51	3.39	2.30
5-(cyanoamino)-4-(methylamino)pyrimidine	anion or dianion	7.45[c]	6.95[c]	2.76	

[a] Chemical shifts in parts per million relative to Me_4Si (δ 0). [b] Measured in $CDCl_3$. [c] These assignments can also be interchanged.

Scheme III



how **12** is formed from **9**. The formation of **9** is supported by the observation of absorptions at 2165 and 2174 cm^{-1} (NH–CN) when an IR spectrum of the reaction mixture was made as quickly as possible after evaporation of the ammonia. The cyanamino compound **9** can be formed from **8** which is supposed to be intermediate in the formation of **11**. The conversion of the (aminomethylene)-amino group into a cyanamino group in strong basic medium by a redox-type reaction is not without precedent. Several examples of these reactions have been observed in reactions of halogenoazines with potassium amide in liquid ammonia.[30]

Reaction of 6-chloro-9-(2-tetrahydropyranyl)purine with potassium amide in the presence of bromobenzene gave 6-anilino-9-(2-tetrahydropyranyl)purine instead of the desired 8-phenyl compound. The same product was formed when aniline was used instead of bromobenzene. This reaction involves an $S_N(AE)^{ipso}$ substitution of the anion of aniline at position 6. Taking into consideration all our experiments made in this study, we have to conclude that reaction with potassium amide in liquid ammonia in the presence of bromobenzene gives 8-phenyl derivatives only if position 6 is not substituted by a leaving group or an amino group.

(d) 8-Substituted 9-Methylpurines. Reaction of 8-(methylthio)-9-methylpurine (**13**) with potassium amide in liquid ammonia gives 8-amino-9-methylpurine (**16**, yield 50%) and some 7,8-dihydro-8-oxo-9-methylpurine (**19**), although the last-mentioned compound could never be obtained in a reproducible manner (Scheme III). Compound **16** is probably formed by an $S_N(AE)^{ipso}$ substitution, involving the 8-amino σ adduct **15**. Low-temperature NMR spectroscopy showed, however, that **13**, when dissolved in liquid ammonia containing potassium amide, gives an adduct at position 6, i.e., **14**, as indicated by the large upfield shift for H-6 (3.4 ppm) and C-6 (79 ppm) (Table III). This adduct does not lead to C-6 substituted products but has to be converted into the adduct at position 8 (**15**) in order to account for the formation of both products **16** and **19**. The formation of **15** is not observed, since this adduct will lose the methylthio group immediately, as indicated by the appearance of a signal at 9.5 ppm in the ^{13}C NMR spectrum (characteristic of the methylthio anion). It leads to either **17** (route aa) or to ring-opened product **18** (route ab). Low-temperature NMR spectroscopy shows that **17** is not observed either and undergoes ring opening into **18**. This is evident from the identity of the NMR spectrum of **16** in liquid ammonia, containing potassium amide, with that of **13** after standing, showing that in both solutions 5-(cyanoamino)-4-(methylamino)-pyrimidine (**18**) is present.[32] We were successful in isolating **18** when the amination reaction was quenched very rapidly (not with ammonium sulfate, which dissolves slowly, but with ammonium chloride or methanol).

The IR spectrum of the reaction mixture showed absorptions at 2106 and 2140 cm^{-1}, which confirmed the structural assignment. On being allowed to stand with several reagents (aqueous ammonia, ammonium sulfate in water or methanol, aqueous acid or base), **18** was converted into **16**, not into **19**. The way in which **19** is formed is not quite clear. **16** does not react with potassium hydroxide into **19**, indicating that the conditions necessary for the conversion of **18** into **19** (similar to the conversion of **9** into **12**) are only satisfied during the reaction or workup. Since **18** cannot be isolated when the reaction is quenched with ammonium sulfate (it dissolves too slowly), we have to conclude that **19** is formed during quenching (Table IV).

Experimental Section

^{1}H NMR spectra were obtained with a Varian XL-100-15 or a Varian EM 390. For measurement in $CDCl_3$ internal Me_4Si was used as the standard. For measurement in liquid ammonia the sample temperature was ca. −50 °C, and NH_3 was used as the standard. The spectra were converted to the Me_4Si scale by adding 0.95 ppm. ^{13}C NMR spectra were obtained by means of a Varian XL-100-15 equipped with a Varian 620/L16K computer. Me_3N was used as the internal standard. By addition of 47.5 ppm these spectra were converted to the Me_4Si scale. Typical ^{13}C NMR spectral parameters were as follows: spectral width, 5120 or 7500 Hz: pulse delay, 0–1.2 s; pulse width, 10 μs. Mass spectra were determined on an AEI MS-902 mass spectrometer. IR spectra were obtained with a Perkin-Elmer 237 and a Hitachi EPI-G3 and UV spectra with a Beckman Acta CIII and a Perkin-Elmer 550.

Preparation of Starting Materials. Adenosine (**6b**) was purchased from Aldrich. The following compounds were synthesized according to common procedures: 9-methyladenine (**6a**),[33] 8-deuterio-9-methyladenine,[34] 7-methyladenine,[35] 6-(methylamino)-9-methylpurine,[29] 6-chloro-9-(2-tetrahydropyranyl)purine,[28] 8-(methylthio)-9-methylpurine (**13**),[36] nebularine (**1b**),[37] 2′,3′-*O*-

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(31) Brown, D. J.; Ford, P. W. *J. Chem. Soc. C* **1969**, 2620.
(32) Compare with the signals of the anions of (methylamino)pyridines in liquid ammonia containing potassium amide (**18** is present as only one geometrical isomer): Kos, N. J.; Breuker, J.; van der Plas, H. C.; van Veldhuizen, A. *J. Org. Chem.* **1981**, *46*, 3509.
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Table IV. Reaction Procedures and Yields for the Reactions with Potassium Amide in Liquid Ammonia

starting compd	concn, mL/mmol	equiv of KNH_2	equiv of C_6H_5Br	reaction time, min	temp, °C	product	yield, %
9-methylpurine (1a)	150	2.5		180	−80	5-formamido-4-(methylamino)pyrimidine (5a)	25
	15	3	1.5	60	−80	8-phenyl-9-methylpurine	15
2′,3′-*O*-isopropylidenenebularine (1c)	45[a]	4		45	−33	5-formamido-4-[(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine (5c)	50
9-methyladenine (6a)	15	4	2.5	120	−33	6-anilino-9-methylpurine	20
6-chloro-9-methylpurine (7)	150	2.5		20	−80	4-chloro-5-formamido-6-(methylamino)pyrimidine (11)[b]	50
6-chloro-9-(2-tetrahydropyranyl)purine	15	3	1.5	60	−80	6-anilino-9-(2-tetrahydropyranyl)purine	45
8-methylthio-9-methylpurine (13)	15	2.5		45	−33	8-amino-9-methylpurine (16)[c]	50

[a] In a mixture of 50% diethyl ether and 50% liquid ammonia. [b] Besides some 9-methyladenine (6a) and 6-chloro-7,8-dihydro-8-oxo-9-methylpurine (12). [c] Sometimes also 7,8-dihydro-8-oxo-9-methylpurine (19).

isopropylideneadenosine (6c),[38] 5-formamido-4-(methylamino)-pyrimidine (5a),[39] and 4-chloro-5-formamido-6-(methylamino)-pyrimidine (11).[40] 9-Methylpurine (1a) was synthesized by reduction of 6-chloro-9-methylpurine (7) (yield 65%).[41] 6-Chloro-9-methylpurine (7) was synthesized by reaction of 5-amino-4-chloro-6-(methylamino)pyrimidine with methyl diethoxyacetate[42] (yield 80%).[41]

6-Chloro-7,8-dihydro-8-oxo-9-methylpurine (12). 5-Amino-4-chloro-6-(methylamino)pyrimidine (500 mg) was fused with urea (800 mg) at 180 °C for 30 min.[43] Recrystallization from ethanol gave 6-chloro-7,8-dihydro-8-oxo-9-methylpurine: yield 10%; mp 278–281 °C. Anal. Calcd for $C_6H_5ClN_4O$: C, 39.04; H, 2.73. Found: C, 39.34; H, 2.86.

6-Anilino-9-methylpurine. Methylation of 6-anilinopurine[44] with tetramethylammonium hydroxide via sublimation at 160 °C and 0.1 mm[33] gave, after recrystallization from benzene, 6-anilino-9-methylpurine: yield 40%; mp 156–159 °C; exact mass calcd for $C_{12}H_{11}N_5$ 225.1014, found 225.1007. Anal. Calcd for $C_{12}H_{11}N_5 \cdot 2.5H_2O$: C, 53.32; H, 5.97. Found: C, 53.33; H, 5.79.

8-Phenyl-9-methylpurine was prepared by fusion of 4-amino-5-(methylamino)pyrimidine with benzamidine:[45] yield 30%; mp 167–168.5 °C. Anal. Calcd for $C_{12}H_{10}N_4$: C, 68.55; H, 4.79. Found: C, 68.76; H, 4.81.

8-Amino-9-methylpurine (16). A 200-mg sample of 8-(methylthio)-9-methylpurine (13) was heated with 10 mL of ethanolic ammonia in a sealed tube for 24 h at 180 °C. Evaporation of the solvent and column chromatography on silica gel with 15% methanol/chloroform as the eluent gave 8-amino-9-methylpurine (yield 20%). Anal. Calcd for $C_6H_7N_5$: C, 48.31; H, 4.73. Found: C, 48.09; H, 4.74.

Amination Procedure. The potassium amide was prepared in dry liquid ammonia, and when necessary dry diethyl ether was added. After the mixture cooled, the starting material was added at the reaction temperature; in cases where scavenging experiments were carried out the bromobenzene was also added immediately. After the reaction the mixture was quenched with ammonium sulfate, the ammonia was evaporated, and the residue was extracted with chloroform and methanol. Separation of the products was achieved by column chromatography or preparative TLC with mixtures of chloroform and methanol as the eluents. All reaction products being formed and isolated were familiar compounds or were synthesized independently except for 6-anilino-9-(2-tetrahydropyranyl)purine [^{1}H NMR ($CDCl_3$) δ 1.3–2.2 (m, CH_2's), 3.5–4.2 (m, OCH_2), 5.67 (dd, J = 4, 8 Hz, OCH), 6.9–7.8 (m, phenyl), 7.98, 8.48 (s, H-2 and H-8), 8.30 (br s, NH); exact mass calcd for $C_{16}H_{17}N_5O$ 295.1433, found 295.1432] and 5-formamido-4-[(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine: mp 161–165 °C, (reconverts to 2′,3′-*O*-isopropylidenenebularine on longer heating); UV λ_{max} 265 nm (pH 1), 238 and 274 (pH 7), 265 (pH 12); ^{1}N NMR (Me_2SO-d_6) δ 1.27 and 1.43 (2 s, CH_3's), 3.4 (m, C_5' H), 4.7 (m, C_2' H and C_3' H), 5.87 (d, J = 2 Hz, C_1' H), 8.25, 8.31 and 8.36 (s, H-2, H-6, and CHO).

Acknowledgment. We are indebted to Mr. A. van Veldhuizen for measuring some NMR spectra, to Dr. C. A. Landheer and Mr. W. P. Combé for the mass spectroscopic data, to Mr. H. Jongejan for carrying out the microanalyses, and to Mr. A. Koudijs for the synthesis of nebularine.

Registry No. **1a**, 20427-22-9; **1b**, 550-33-4; **1c**, 67604-85-7; **5a**, 84602-76-6; **5c**, 84602-77-7; **6a**, 700-00-5; **6b**, 58-61-7; **6c**, 362-75-4; **7**, 2346-74-9; **11**, 84602-78-8; **12**, 84602-79-9; **13**, 24851-51-2; **16**,

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84602-80-2; **18**, 84602-81-3; **19**, 39188-96-0; 6-chloro-9-(2-tetrahydropyranyl)purine, 7306-68-5; 8-phenyl-9-methylpurine, 33833-45-3; 6-anilino-9-methylpurine, 84602-82-4; 6-anilino-9-(2-tetrahydropyranyl)purine, 84002-83-5; 5-amino-4-chloro-6-(methylamino)pyrimidine, 52602-68-3; 6-anilinopurine, 1210-66-8; 4-amino-5-(methylamino)pyrimidine, 3059-67-4; benzamidine, 618-39-3; 9-methyladenine (dianion), 84623-11-0; 7-methyladenine (dianion), 84623-12-1; 6-(methylamino)-9-methylpurine (dianion), 84602-84-6; methyl diethoxyacetate, 16326-34-4; potassium amide, 17242-52-3; bromobenzene, 108-86-1.

Acetolysis of Permethylated *O*-Alkyl Glycopyranosides: Kinetics and Mechanism[1-4]

Momčilo Miljković* and Margaret Habash-Marino

Department of Biological Chemistry, The Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, Pennsylvania 17033

Received July 13, 1982

Acetolysis of permethylated methyl α- and β-glycopyranosides of D-glucose, D-galactose, and D-mannose was studied. It was found that α-glycosides of D-glucose and D-galactose acetolyze at a greater rate than the corresponding β anomers, contrary to the behavior of these substrates toward acid-catalyzed hydrolysis and contrary to previous findings on the acetolysis of peracetylated disaccharides. The results were rationalized as a consequence of the coplanar and trans-diaxial orientation of the C(1) to glycosidic oxygen bond and the axially oriented nonbonding electrons of the ring oxygen in α anomers, resulting not only in orbital mixing of the axial lone-pair electrons of the ring oxygen with the C(1) to the glycosidic oxygen antibonding orbital but also in a highly favorable geometry for an E1 elimination. The reversed behavior of permethylated methyl α- and β-D-mannopyranoside as compared to permethylated α- and β-D-gluco- and -galactopyranosides was explained to be the consequence of a much higher conformational energy of the β anomer.

In connection with other work, we wanted to hydrolyze the *O*-glycosidic bond of selected permethylated methyl glycopyranosides. Since the glycosidic bond of these sugars was remarkably resistant even at elevated temperatures to acid-catalyzed hydrolysis, we became interested in acetolysis[5] as an acceptable alternative.

Preliminary experiments with methyl 2,3,4,6-tetra-*O*-methyl-α- and -β-D-glucopyranosides indicated that at +2 and/or −20 °C, acetolysis of the glycosidic bond with acetic anhydride containing 1% (v/v) of concentrated sulfuric acid was very fast, giving an equilibrium mixture of α- and β-1-acetates as the only reaction products. The observation that the α-glycosidic bond was cleaved faster than the β-glycosidic bond was contrary to reported rates for glycosidic bond cleavage by acetolysis of several peracetylated disaccharides[6] as well as the reported rates for acid-catalyzed hydrolysis of the glycosidic bond in anomeric methyl D-glycopyranosides[7] and their permethylated derivatives.[8] This unexpected finding, together with a lack of available data on the influence of stereoelectronic factors other than neighboring group participation upon the acetolysis rates of alkyl α- and β-glycopyranosides, prompted us to undertake a detailed study of the acetolysis of permethylated methyl α-and β-glycopyranosides of D-glucose, D-galactose, and D-mannose. The chosen substrates are the only ones which do not have the O–O or C–O 1,3 nonbonding interactions in either α or β anomer of a given hexopyranoside. This is very important for the interpretation of the kinetic data since the presence of such interaction would enormously complicate the situation.

Because of its complexity, the progress of acetolysis of a glycosidic bond is difficult to follow by observing the

Table I. Experimental Conditions for Separation of Permethylated Methyl α- and β-Glycopyranosides 1-6 and the Corresponding 1-α- and 1-β-Acetates (7-11) by Reverse Phase HPLC

sugar	solvent CH_3CN/H_2O	flow rate, mL/min	retention time, min
Methyl 2,3,4,6-tetra-*O*-methyl			
α-D-glucopyranoside (1)	1:3	1.0	5.60
β-D-glucopyranoside (2)	1:3	1.0	7.40
α-D-galactopyranoside (3)	1:5	1.2	4.80
β-D-galactopyranoside (4)	1:5	1.2	5.45
α-D-mannopyranoside (5)	1:4	1.2	6.55
β-D-mannopyranoside (6)	1:4	1.2	4.86
1-*O*-Acetyl-2,3,4,6-tetra-*O*-methyl			
α-D-glucopyranose (7)	1:3	1.0	8.10
β-D-glucopyranose (8)	1:3	1.0	11.80
α-D-galactopyranose (9)	1:5	1.2	6.90
β-D-galactopyranose (10)	1:5	1.2	9.45
α-D-mannopyranose (11)	1:4	1.2	7.70

(1) Taken in part form the Ph.D. thesis of M.H.-M.
(2) Supported in part by Public Health Service Grant CA15483.
(3) Dedicated to the memory of Prof. Milivoje S. Lozanić.
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