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ALTERNATIVE ROUTES FOR THE GENESIS OF KINETIN: A SYNTHETIC INTRAMOLECULAR ROUTE FROM 2′-DEOXYADENOSINE TO KINETIN

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Abstract—We have tested the possible genesis of kinetin from a 2′-deoxyadenylate unit of DNA by a chemical route involving a head-to-tail transfer of deoxyribose from the 9 to the 3 position of the adenine nucleus *via* a cyclonucleoside, with subsequent elimination of 1′- and 3′-polar groups and $3 \rightarrow N^6$ intramolecular rearrangement leading to kinetin. We have also determined quantitatively the per cent conversions to 3-furfuryladenine and/or kinetin of the following under autoclaving conditions at 120°, pH 4, 2 atm, and 4 hr: (1) adenine/furfuryl alcohol; (2) adenine/2-deoxy-D-ribose; (3) 2′-deoxyadenosine; (4) 3-furfuryladenine; (5) 3,5′-(3′-*O*-diethylphosphoryl-2′-deoxyadenosine)-cyclonucleoside *p*-toluenesulfonate. The sequence of reactions involving cyclonucleoside formation and rearrangement has been shown to be a chemically feasible route by which kinetin can be formed, although it is not the only way this cytokinin can be generated.

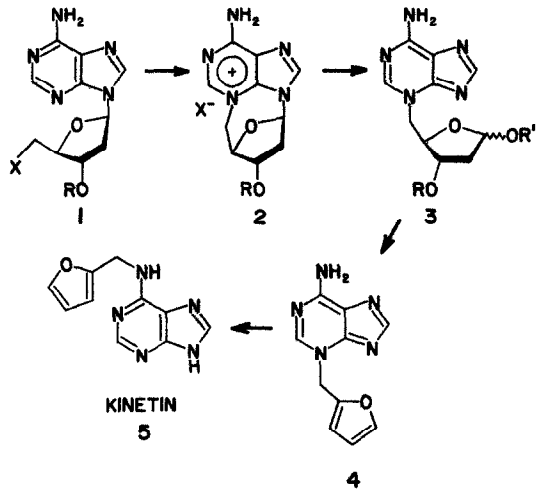
INTRODUCTION

Kinetin (6-furfurylaminopurine) was first isolated and identified at the University of Wisconsin from old preparations of DNA and from freshly prepared DNA that had been autoclaved at pH 4.3 and 120° for 30 min [1–3]. The finding that this compound was a highly active cell division factor for plants marked the beginning of the era of cytokinin research [4–6]. Following autoclaving experiments under similar conditions (pH 4) by Hall and DeRopp [7] of deoxyadenosine or of furfuryl alcohol or deoxyribose with adenine, it was concluded that kinetin was an artefact formed from the natural components of DNA. While these experiments could account for the formation of kinetin in DNA, the presence of kinetin in tissue in trace amounts is considered not unlikely and its presence may be not without functional significance [4]. We felt obliged to test our earlier stated hypothesis [5,8] that kinetin might be formed from a 2′-deoxyadenylate unit of DNA by a chemical route involving a head-to-tail transfer of deoxyribose from the 9 to the 3 position of the adenine nucleus via a cyclonucleoside, with subsequent dehydration and $3 \rightarrow N^6$ intramolecular rearrangement leading to kinetin [5,9]. The feasibility of the final step was indicated by our recent proof that 3-benzyladenine is converted to N^6-benzyladenine even at less acidic pH (5.8) under autoclaving conditions, following a contortional route involving ring opening and ring closing, during which the side chain does not leave its original nitrogen. In this paper we describe a synthetic intramolecular route from 2′-deoxyadenosine to kinetin and a reinvestigation of the experiments on kinetin formation from deoxyribonucleic acid constituents.

RESULTS AND DISCUSSION

The alternative route for the genesis of kinetin that we have envisaged [5,8] involves the intramolecular transfer of the 2′-deoxyribose residue of a 2′-deoxyadenylate unit (**1**) at the polynucleotide level, via a cyclonucleotide species **2**, to give the "reversed nucleotide" **3** (R and possibly R′ as phosphate esters), and then elimination of phosphate ester from **3** to give 3-furfuryladenine (**4**), followed by intramolecular rearrangement to furnish kinetin [5,8–10]. In this model sequence which demonstrates the chemical feasibility of this proposal, for the starting 2′-deoxyadenosine derivative a tosyl substituent was chosen in place of a 5′-phosphodiester group to act as an appropriate leaving group in the cyclonucleoside-forming step. A compound of general structure **3** was envisaged as a model for the reversed nucleoside or nucleotide intermediate with RO as an appropriate leaving group such that the conversion of the sugar moiety to a furan system could occur readily in an acid-catalyzed sequence analogous to the degradation of DNA [11].

5′-*O*-*p*-Toluenesulfonyl-2′-deoxyadenosine (**1**, R = H, X = TsO) [12] was converted to the cyclonucleoside **2** (R = H, X = TsO) [13]. Since the methyl acetal derivative of **3** could be expected to be easily accessible and relatively stable [14], it was selected as the initial intermediate. Exposure of the cyclonucleoside **2** to methanolic hydrogen chloride gave the reversed nucleoside **3** (R = H, R′ = Me) as a 65:35 mixture of anomers. Conversion of compound **3** (R = H, R′ = Me) to its 3′-diethylphosphate ester was effected by treatment with diethyl chlorophosphate in pyridine, thereby providing an appropriate leaving group at the 3′ position of the sugar residue. Autoclaving of this derivative (**3**, R = P(O)



$(OEt)_2$, R' = Me) in pH 4 buffer did not result in the formation of 3-furfuryladenine or kinetin, as evidenced by high performance liquid chromatographic (HPLC) analysis of the total reaction mixture [9,15]. Either of these products would have been detected in a conversion of *ca* 0.005%. Conversion of **3** (R = P(O)$(OEt)_2$, R' = Me) to 3-furfuryladenine could be effected to the extent of 40% when a solution of the diethylphosphate derivative and *p*-toluenesulfonic acid in benzene was heated at reflux, but these conditions represented too great a departure from the autoclave conditions applied to DNA. The failure to observe appreciable 3-furfuryladenine or kinetin formation when the same derivative **3** was autoclaved could be associated with pH 4 not being low enough to effect acetal hydrolysis to trigger the remaining steps of the sequence. This result necessitated development of a better model whereby, under pH 4 autoclaving conditions, an intermediate could be generated with the 2-deoxyribose moiety in the hemiacetal form.

To this end, the 3'-diethylphosphoryl derivative of 5'-*O*-*p*-toluene sulfonyl-2'-deoxyadenosine was prepared and converted to the corresponding cyclonucleoside **2** (R = P(O) $(OEt)_2$, X = TsO). The autoclaving of this cyclonucleoside at pH 4 gave conversion to 3-furfuryladenine (**4**) in 2.9% yield. It is reasonable to suppose that this transformation involved initial cleavage of the cyclonucleoside Cl'-N9 linkage to give a hemiacetal derivative **3** (R = P(O) $(OEt)_2$, R' = H) that subsequently underwent elimination of diethyl phosphate and water to provide 3-furfuryladenine. The final rearrangement, the conversion of 3-furfuryladenine to kinetin [5,10] was accomplished under autoclaving conditions (Table 1): 0.50% conversion at pH 4.0 for 4 hr at 120°; 1.4% at pH 5.8 for 24 hr, placing this transformation on a quantitative basis. The results of other autoclaving experiments are also summarized in Table 1. Prior to HPLC analysis, samples of crude reaction product from each of the experiments no. 1–3 were subjected to tobacco callus bioassay; all showed cytokinin activity.

In experiments no. 1–3, we showed that both 3-furfuryladenine and kinetin are formed under the pH 4 autoclaving conditions. The reaction of adenine with furfuryl alcohol or 2-deoxy-D-ribose to produce kinetin confirms the findings of Hall and DeRopp [7] although our quantitative data reveal some discrepancy in per cent conversion [17]. Nevertheless, the production of 3-furfuryladenine (experiments no. 1–3) and the known conversion of 3-furfuryladenine to kinetin (experiment no. 4) (Table 1) affirm the possibility, but not the major intermediacy, of compound **4**. The validity of the cyclonucleoside rearrangement hypothesis hinges on the question of the relative percentage conversions to 3-furfuryladenine and kinetin via break-up of intermediates **1**, **2**, and **3** with their subsequent recombination. In the case of the formation of 3-furfuryladenine, the "high" conversion on autoclaving **2** (R = P(O)$(OEt)_2$, X = TsO), a system ideally structured to facilitate the intramolecular process (experiment no. 5), relative to the percent conversions realized in experiments no. 1–3, supports the feasibility of the transformations **2** → **3** → **4** of the hypothesis. The nature of the 3-furfuryladenine (**4**) → kinetin (**5**) transformation may change with pH, since we have observed differences in conversion between pH 4.0 and 5.8. The ^{15}N-labeling studies in the case of the 3-benzyladenine → N^6-benzyladenine rearrangement upon autoclaving at 120° and pH 5.8 established an exclusive intramolecular pathway under these conditions [9]. This pathway is certainly open for the 3-furfuryladenine → kinetin conversion, but a solvolysis-recombination mechanism has not been ruled out. What we have shown is that the steps in the cyclonucleoside formation and rearrangement hypothesis (**1** → **2** → **3** → **4** → **5**) are all chemically feasible. Thus, this sequence of reactions provides a pathway whereby kinetin can be formed from DNA, although it is not the only way kinetin can be generated.

EXPERIMENTAL

Mp's were determined with a Thomas–Hoover apparatus and are corrected. PMR spectra were recorded by Mr. S. Silber on a Varian Associates HA-100 spectrometer using TMS as an internal standard. Microanalyses were performed by Mr. J. Nemeth and his staff. Mass spectra were obtained on a Varian-MAT CH-5 spectrometer by Mr. J. A. Wrona. Field desorption mass spectra were obtained on a Varian MAT 731 mass spectrometer by Mr. J. C. Cook.

Bioassay procedures. The determination of cytokinin activities was based on the tobacco bioassay as described in ref. [18]. The medium contained the mineral salts specified in Table 6, part A, of ref. [18] and the following organic constituents: 30 g/l. sucrose, 10 g/l. Difco agar, 560 μM *myo*-inositol,

Table 1. Percent conversions to 3-furfuryladenine and kinetin in autoclaving experiments

No.	Experiment	3-Furfuryladenine	Kinetin, % This work*	Kinetin, % Ref. [7]†
1	Adenine/Furfuryl alcohol	0 50	0.65‡	2
2	Adenine/2-Deoxy-D-ribose	0.10	0.40	0.54§
3	2'-Deoxyadenosine	0 15	0.15¶	"Biological Activity"
4	3-Furfuryladenine		0.50	—
5	**2**, R = P(O) $(OEt)_2$, X = TsO	2.9		

* Calculated from HPLC, by comparison with standards of 3-furfuryladenine and kinetin. Autoclave conditions: pH 4, 120°, 2 atm, 4 hr (sufficient time for dissolution of reagents in each case). † Autoclave conditions: pH 4, 120°, 2 atm, 30 min. ‡ At pH 5.8 during 4 hr autoclaving, 0.10% conversion to kinetin was realized. § Would be 0.34 from the numbers reported in ref. 7. ¶ At pH 2.5, earlier work in one of our laboratories [16] indicated that kinetin was formed on autoclaving 2'-deoxyadenosine, but its identity was not conclusively established.

11.4 μM IAA, and 1.2 μM thiamine HCl. To facilitate their soln and to avoid possible degradation by heat, the products of autoclaving were dissolved in Me_2SO, appropriate dilutions were made, and aliquots were then added to the cooling, autoclaved agar media. Final concn of Me_2SO did not exceed 0.05% by vol, a concentration which does not affect biological activity in this assay [19].

Autoclaving experiments. Essentially the same procedure was employed in all of the experiments. For example, a soln of adenine (0.50 g, 3.7 mmol) and furfuryl alcohol (0.36 g, 3.7 mmol) in pH 4 buffer (25 ml) was heated in a pressure cooker for 4 hr. at 120° (2 atm). The crude reaction mixture was then assayed as described below.

Determination of yield of kinetin. An aliquot of the reaction mixture was taken up in 1 ml of a buffer soln (25% in diemethylformamide and 0.3 M in formate [ammonium formate–formic acid, pH 4.6]), applied to a 38 × 1.27 cm Aminex A-5 (Bio-Rad) column and then eluted with the same buffer at 0.8 ml/min (300 psi, column temperature 50°). The eluate was monitored quantitatively by absorbance at 254 nm and recorded on a Hewlett–Packard recorder modified as described previously [15]. The yield of 3-furfuryladenine was determined in a similar fashion using a 0.5 M formate buffer (25% in dimethylformamide, pH 4.6) and a column temperature of 70°. To confirm the identity of the kinetin and 3-furfuryladenine obtained in the autoclaving experiments Nos. 1–5, appropriate HPLC column fractions were collected, evaporated to dryness *in vacuo*, and then taken up in 35% aq EtOH and applied to a 95 × 1.27 cm P2 gel column. Elution with 35% aq EtOH provided desalted samples whose UV and MS characteristics were identical with those of authentic samples of kinetin and 3-furfuryladenine.

3,5'-(2'-*Deoxyadenosine*)*cyclonucleoside* p-*toluenesulfonate* **2** (*R = H, X = TsO*). 5'-*O*-*p*-Toluenesulfonyl-2'-deoxyadenosine [12] (0.79 g) was heated at reflux in dry 2-butanone for 10 hr. Solvent was removed *in vacuo* to leave a solid which was thoroughly triturated with hot EtOAc and then filtered and dried to give 0.69 g (87%) of the cyclonucleoside: mp 85–88°; PMR ($(CD_3)_2SO$) δ 9.45–9.15 (*br*, 2), 8.70 (*s*, 1), 8.39 (*s*, 1), 7.50 (*d*, 2, *J* 8Hz), 7.10 (*d* 2, *J* 8Hz), 6.80–6.65 (*m*, 1), 5.60 (*br*, 1), 5.10–4.30 (*m*, 4), 2.45–2.00 (*m*, 2), 2.28 (*s*, 3); $\lambda_{max}^{95\%EtOH}$ 273 nm (ε 14900). FD mass spectrum *m/e* 234 (M^+-$C_7H_7SO_3$). Anhydrous conditions are not, in fact, absolutely necessary for effecting cyclonucleoside formation. For example, on heating 5'-*O*-*p*-toluenesulfonyl-2'-deoxyadenosine at reflux in 10% aq Me_2CO for 18 hr, high conversion to **2** (R = H, X = TsO) is observed.

3,5'-(1'-O-*Methyl*-2',5'-*dideoxy*-D-*ribofuranosyl*)*adenine* **3** (*R = H, R' = Me*). A soln of the cyclonucleoside (**2**, R = H, X = TsO) (0.69 g) in methanolic HCl gas (20 ml, *ca* pH 1) was allowed to stand at room temp for 10 hr. The reaction mixture was neutralized with NH_4OH and then evaporated to dryness. Analysis of the crude product by HPLC revealed that it consisted of a 13:7 mixture of anomers. Purification (as a mixture of anomers) by column chromatography on Si gel, elution with MeOH–$CHCl_3$ (1:19) furnished 240 mg of the "reversed nucleoside" **3** (R = H, R' = Me) (51%). Recrystallization from Me_2CO provided an analytical sample: mp 204–205°; PMR ($(CD_3)_2SO$) [anomeric mixture] δ 8.26 and 8.21 (2*s*, 1), 8.05 (*br*, 2), 7.78 (*s*, 1), 5.25 (*br*, 1), 5.10–4.90 (*m*, 1), 4.70–3.90 (*m*, 4), 3.24 and 3.14 (2*s*, 3), 2.40–2.16, 2.14–1.95, and 1.80–1.55 (*m*, 2); $\lambda_{max}^{95\%EtOH}$ 274 nm (ε 12,200); *m/e* (rel. intensity) 265 (M^+, 4), 205 (20), 178 (28), 149 (77), 136 (71), 135 (100). (Found: C, 49.51; H, 5.85; N, 26.39. $C_{11}H_{15}N_5O_3$ requires: C, 49.80; H, 5.70; N, 26.40%).

3,5'-(1'-O-*Methyl*-3'-O-*diethylphosphoryl*-2',5'-*dideoxy*-D-*ribofuranosyl*)*adenine* **3** (*R = P(O) (OEt)₂, R' = Me*). A soln of 3,5'-(1'-*O*-methyl-2',5'-dideoxy-D-ribofuranosyl)adenine **3** (R = H, R' = Me) (205 mg) in dry C_5H_5N (6 ml) was cooled to *ca* −30° and diethyl chlorophosphate (0.40 ml) was added. The reaction mixture was maintained at −30° for about 3 hr and was then allowed to warm to room temp. Precautions were taken throughout to exclude moisture. After a 16-hr period at room temp, the reaction mixture was cooled to *ca* 0° and 1 ml H_2O was added Evaporation *in vacuo* gave a light brown residue which was partitioned between dil. aq K_2CO_3 (5 ml) and $CHCl_3$ (25 ml). The $CHCl_3$ layer was separated and the aq phase further extracted with (25 ml) $CHCl_3$. The combined $CHCl_3$ extracts were washed and then dried. Removal of the $CHCl_3$ *in vacuo* furnished **3** (R = P(O) $(OEt)_2$, R' = Me) as solid (274 mg, 88%) which was recrystallized from C_6H_6, mp 152–153°; PMR ($(CD_3)_2SO$) (for one anomer) δ 8.26 (*s*, 1), 7.98 (*br*, 2), 7.76 (*s*, 1), 5.15 (*t*, 1, *J* 4 Hz), 5.10–4.84 (*m*, 1), 4.80–4.14 (*m*, 3), 3.89 (*dq*, 4, *J* 8.7 Hz). 3.27 (*s*, 3), 2.40–2.20 (*m*, 2), 1.15 (*dt*, 6, *J* 1,7 Hz); $\lambda_{max}^{95\%,\ EtOH}$ 274 nm (ε 18,300); *m/e* (rel. intensity) 401 (M^+, 1), 215 (18), 189 (17), 187 (17), 149 (27), 135 (20), 127 (19), 99 (47), 81 (100). (Found: C, 44.86; H, 5.83; N, 17.32. $C_{15}H_{24}N_5O_6P$ requires: C, 44.88; H, 6.04; N, 17.45%).

Conversion of 3,5'-(1'-O-*Methyl*-3'-O-*diethylphosphoryl*-2',5'-*dideoxyribofuranosyl*)*adenine to* 3-*furfuryladenine* **4**. The diethylphosphate derivative **3** (R = P(O) $(OEt)_2$, R' = Me) (56 mg) and *p*-toluenesulfonic acid monohydrate (30 mg) were heated at reflux in dry benzene (25 ml) for 4 hr using a Soxhlet with the thimble containing 4A molecular sieves. The cooled reaction mixture was evaporated *in vacuo*, and the residue was dissolved in MeOH and the pH adjusted to *ca* 7 with NH_4OH. This soln was evaporated to dryness and residue partitioned between 2 ml H_2O and $CHCl_3$ (20 ml). After the $CHCl_3$ layer was separated, the aq phase was extracted with a further portion of $CHCl_3$ (15 ml). The combined $CHCl_3$ extracts were dried and the solvent was removed *in vacuo*. Column chromatography of the crude product on Si gel, elution with MeOH–$CHCl_3$ (1:19), gave 3-furfuryladenine (12 mg, 40%) identical with an authentic sample (NMR, UV, MS and R_f).

5'-O-p-*Toluenesulfonyl*-3'-O-*diethylphosphoryl*-2'-*deoxyadenosine* **1** (*R = P(O) (OEt)₂, X = TsO*). A soln of 5'-*O*-*p*-toluenesulfonyl-2'-deoxyadenosine (1.01 g) in dry C_5H_5N (25 ml) was cooled to *ca* −30° and diethyl chlorophosphate was added (1.70 ml). The reaction mixture was maintained at *ca* −30° for 2 hr and then at 0° for 3 hr. Precautions were taken throughout to exclude moisture. The work-up procedure was similar to that described for **3** (R = P(O) $(OEt)_2$, R' = Me) and furnished 490 mg (36%) of the 3'-phosphoryl derivative as a glass; PMR ($CDCl_3$) δ 8.25 (*s*, 1), 7.96 (*s*, 1), 7.71 (*d*, 2, *J* 8 Hz), 7.24 (*d*, 2, *J* 8 Hz), 6.40 (*dd*, 1, *J* 8,6 Hz), 6.20 (*br*, 2), 5.18 (*m*, 1), 4.42 (*m*, 1), 4.32 (*m*, 2), 4.15 (*dq*, 4, *J* 8,7 Hz), 3.30–2.50 (*m*, 2), 2.40 (*s*, 3*H*), 1.36 (*dt*, 6H, *J* 1,7 Hz); $\lambda_{max}^{95\%EtOH}$ 261 nm (ε 12900); FD mass spectrum *m/e* 541 (M^+). This compound very readily underwent cyclization to the cyclonucleoside **2** (R = P(O) $(OEt)_2$, X = TsO), during crystallization. The analysis for the cyclonucleoside is recorded below.

3,5'-(3'-O-*Diethylphosphoryl*-2'-*deoxyadenosine*)*cyclonucleoside* p-*toluene sulfonate* **2** (*R = P(O)(OEt)₂ X = TsO*). 5'-*O*-*p*-Toluenesulfonyl-3'-diethylphosphoryl-2'-deoxyadenosine **1** (R = P(O) $(OEt)_2$, X = TsO) (415 mg) was heated at reflux in dry butanone for 14 hr. The precipitated cyclonucleoside salt was collected by filtration and dried, giving 294 mg (71%) of analytically pure material: mp 161–164°; PMR ($(CD_3)_2SO$) δ 9.38 (*br*, *s*, 1), 9.28 (*br*, *s*, 1), 8.76 (*s*, 1) 8.38 (*s*, 1). 7.48 (*d*, 2, *J* 8 Hz), 7.08 (*d*, 2, *J* 8 Hz), 6.84 (*m*, 1), 5.30–4.50 (*m*, 4), 4.06 (*dq*, 2, *J* 8,7 Hz), 4.02 (*dq*, 2, *J* 8,7 Hz), 2.65–2.40 (*m*, 2), 2.26 (*s*, 3), 1.24 (*dt*, 3, *J* 1,7 Hz), 1.22 (*dt*, 3, *J* 1,7 Hz); $\lambda_{max}^{95\%EtOH}$ 274 nm (ε 13400); FD mass spectrum *m/e* 370 (M^+-$C_7H_7SO_3$). (Found: C, 46.29; H, 5.14; N, 12.87. $C_{21}H_{28}N_5O_8PS$ requires: C, 46.58; H, 5.21; N, 12.93%).

3,5'-(3'-O-*Diethylphosphhoryl*-2'-*deoxyadenosine*)*cyclonucleoside* p-*toluenesulfonate* **2** (*R = P(O)(OEt)₂, X = TsO*) was subjected to the autoclaving conditions described earlier in this Section, and the yield of 3-furfuryladenine was determined by HPLC [See Table in Results and Discussion].

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