analogue **11** did react satisfactorily under standard conditions. The principal mechanism of release was again ethanolysis (>95%), while hydrolysis accounted for the remainder of product turnover. A further attempt to encourage lactonization by substituting acetonitrile for ethanol gave less than 0.1% lactone or free acid; as the acyl enzyme intermediate was detected by ESMS for both substrates **11** and **12** under these conditions, the barrier to release of the products must lie in the deacylation step. The absence of lactone in these experiments shows that in vivo suppression of hydrolysis is not sufficient to ensure macrolactonization, and that additional structural features of the chain in the natural substrate **1** are required to ensure that the TE domain folds correctly.

The results imply that intermediates with 2-methyl, 3-hydroxyl functionality in any stereochemical configuration may be released by lactonization given an appropriately placed and structurally suitable distal hydroxyl group. However, if lactonization is prevented by the absence of a suitable hydroxyl group or other cause, such acyl enzyme intermediates would not be rapidly cleaved by the alternative in vivo mechanism of hydrolysis. The relative inefficiency of hydrolytic release with these substituted analogues is a potentially serious limitation to the range of novel products that are expected to be released in vivo by the erythromycin thioesterase.

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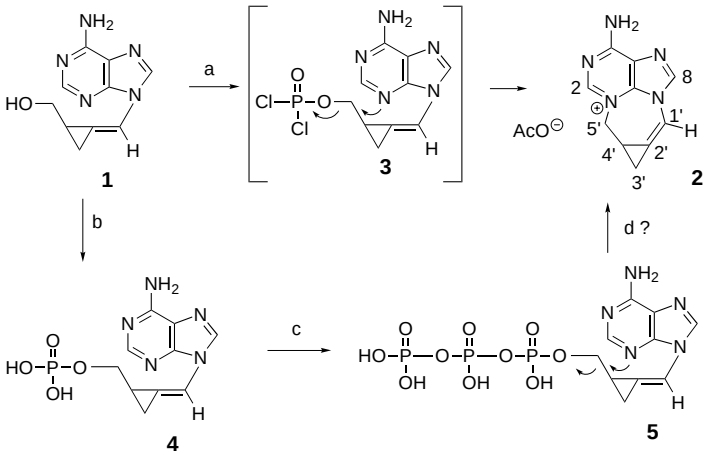
3,5′-Anhydrosynadenol: A Polycyclic Anhydronucleoside Analogue**

Yao-Ling Qiu and Jiri Zemlicka*

Recently we reported new nucleoside analogues that exhibit broad-spectrum antiviral activity and contain a methylenecyclopropane unit.[1, 2] Of these compounds, (*Z*)-9-[(2-hydroxymethyl)cyclopropylidenemethyl]adenine (synadenol; **1**) exhibits potent activity[1] against human and murine cytomegalovirus (HCMV and MCMV), Epstein–Barr virus (EBV), human herpes virus 6 (HHV 6), and hepatitis B virus (HBV), and a moderate effect against human immunodeficiency virus 1 (HIV-1). The ^{1}H NMR spectra and biological activity indicated that **1** and related compounds can be regarded as analogues of nucleosides. Like nucleosides, the base (adenine) can exist in two conformations, *anti* and *syn*.[3] The ^{1}H NMR spectra indicated that the adenine component of **1** has mainly the *anti* conformation in solution, as in nucleosides.[1]

Here we report that the *syn* form of **1** can be converted into the anhydronucleoside analogue **2**; this strengthens the analogy to nucleosides.[4] Reaction of **1** with $POCl_3$/$PO(OMe)_3$ led to a smooth cyclization and gave anhydrosynadenol (**2**), which was isolated as the acetate in 87% yield (Scheme 1). The dichlorophosphate **3** is a likely intermediate in this transformation. In nucleosides this reaction leads only to 5′-*O*-phosphorylation without formation of anhydronucleoside.[5, 6] Trisimidazolylphosphine oxide[7] in pyridine also gave **2** as the sole product. The ease of cyclization is surprising given that methylenecyclopropanes are generally assumed to be destabilized by substantial ring strain.[8] However, according to recent ab initio calculations,[9] the loss of strong



Scheme 1. a) $POCl_3$, $PO(OMe)_3$; b) Dowex 2 (AcO^-); c) intracellular phosphorylation; d) intracellular inactivation.

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cyclopropane C–H bonds associated with the introduction of a trigonal center is largely responsible for destabilization of the molecule. The formation of **2** may be facilitated by an entropic factor (juxtaposition of the 5′-CH_2 group with the heterocyclic base in **1** owing to the presence of a rigid methylenecyclopropane system) and by incorporation of the methylenecyclopropane moiety into a multiring system.

The reaction of **1** with less reactive phosphorylating agents, such as chlorophosphoramidates,[10] leads to 5′-*O*-phosphorylation products without formation of **2**. There is also evidence[11] that intracellular phosphorylation of **1** forms the phosphates **4** and **5** necessary for antiviral activity (Scheme 1). Like other nucleoside analogues, **1** is thus a prodrug of the corresponding triphosphate **5**, which is the final product of the phosphorylation cascade. Anhydrosynadenol (**2**) lacks two features important for the biological activity per se: 1) the 5′-hydroxyl group necessary for phosphorylation and 2) the *anti* conformation of the base as in **1**. The triphosphate group of **5** is a better leaving group than the monophosphate residue of **4**. Nucleophilic displacement of this functional group in ATP is an important feature of some enzyme-catalyzed transformations.[12] Whether a similar intramolecular reaction (Scheme 1) can play a role in the inactivation of **5** remains to be established.

The ^{1}H NMR spectrum of **2** exhibits a strong downfield shift of the signals of all cyclopropane protons. The H-5′ protons are nonequivalent; one of them is strongly shielded. Models indicate that this shielding is possibly due to the double bond of the methylenecyclopropane unit in an *exo* conformer[13] of **2**. The formation of **2** is unambiguous proof of the *Z* configuration of **1**. This configuration is important for the antiviral activity of **1** and its analogues.[1, 2] In addition, the structure of **2** is a novel polycyclic system containing a methylenecyclopropane moiety.

Experimental Section

2: $POCl_3$ (86 μL, 0.92 mmol) was added to a suspension of **1** (100 mg, 0.46 mmol) in $PO(OMe)_3$ (16 mL) with stirring at 0°C. The clear solution was allowed to stand for 19 h at room temperature, and the solvent was then removed in vacuo (bath temperature <47°C). The sirupy residue solidified after addition of THF (20 mL) and sonication. The solvent was decanted to leave a hygroscopic solid, which was washed with THF (5 mL) and dissolved in water (50 mL). The aqueous phase was washed with CH_2Cl_2 (5 × 20 mL) and then lyophilized. The residue was stirred with Dowex 2 (X-8, 100–200 mesh, acetate, 7 g) in water (20 mL) for 0.5 h. Filtration and lyophilization of the filtrate gave **2** (112 mg, 87 %), m.p. > 300°C. Paper electrophoresis (Whatman No. 1 paper, 0.02 M Na_2HPO_4, pH 7.0, 40 V cm^{-1}, 1 h): Mobility −1.33 of AMP, identical with that of 2′,3′-*O*-isopropylidene-3,5′-anhydroadenosine.[14] UV (ethanol): λ_{max} (ε) = 274 (16700), 238 (14100); (H_2O, pH 7): 272 (16400), 240 (13400). ^{1}H NMR (D_2O): δ = 8.47, 8.37 (2 s, 2 H, H-2, H-8), 7.47 (s, 1 H, H-1′), 5.05 (dd, 1 H) and 3.60 (dd, 1 H, H-5′), 2.50 (q, 1 H), 2.38–2.50 (m, 1 H) and 1.82 (dd, 1 H, H-3′, H-4′); ^{13}C NMR: δ = 181.05 (CO), 157.16, 148.88, 141.86, 138.74, 124.30, 120.22, 115.22 (adenine, C-1′ and C-2′), 58.05 (C-5′), 23.16 (CH_3), 15.89 (C-4′), 14.24 (C-3′). FAB-MS (thioglycerol matrix): *m*/*z* (%): 308 [*M*+H − AcOH+thioglycerol] (100), 260 [*M*+H] (22), 200 [*M*+H − AcOH] (41.0), 136 [adenine+H] (59.5); elemental analysis calcd for $C_{10}H_9N_5 \cdot 0.95\,CH_3CO_2H \cdot 1.35\,H_2O$: C 50.94, H 5.57, N 24.96; found: C 50.67, H 5.37, N 25.24.

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Perchloropolysilane: X-Ray Structure, Solid-State ^{29}Si NMR Spectroscopy, and Reactions of $[SiCl_2]_n$**

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We have succeeded in the preparation of perchloropolysilane, $[SiCl_2]_n$ (**1**) as very pale yellow, highly moisture-sensitive single crystals and obtained the X-ray structure. This is the first example of a single crystal X-ray structure analysis of a polysilane. We also report solid-state ^{29}Si NMR data.[1]

Since the investigations by Schwarz and co-workers[2a, b] of the higher silicon halides (described as viscous liquids or

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