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2,6-Diamino-5,8-diaza-7,9-dicarba-purine[1]

Zhijun Wang,[†] Hoan K. Huynh,[†] Bo Han,[‡] Ramanarayanan Krishnamurthy,*[,†,§] and Albert Eschenmoser*[,†,‡,⊥]

The Skaggs Institute for Chemical Biology at the Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Laboratory of Organic Chemistry, Swiss Federal Institute of Technology, Hoenggerberg, HCI-H309, CH-8093 Zürich, Switzerland

eschenmoser@org.chem.ethz.ch

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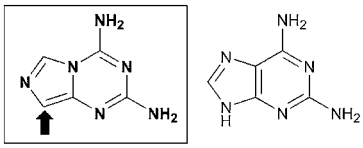
ABSTRACT

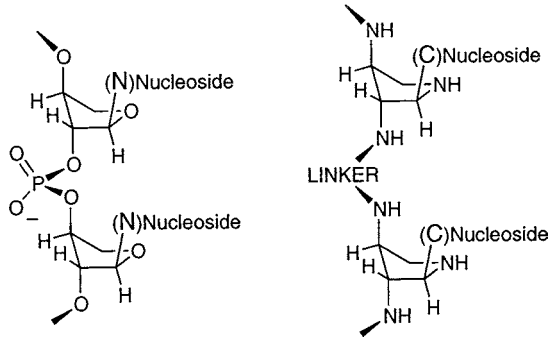


The title compound, a constitutional isomer of the natural nucleobase 2,6-diaminopurine, undergoes regioselective electrophilic substitutions at carbon C-9.

In the wake of the observation that (L)-α-threofuranosyl-(3′ → 2′)-oligonucleotides (TNAs) constitute an efficient Watson−Crick base-pairing system capable of cross-pairing with RNA and DNA,[2] we recently became involved in systematically studying the properties of a family of TNA-related oligomer systems that could, in principle, derive from (C2 + C2 → C4) assembly processes involving nitrogenous intermediates at the oxidation level of glycolaldehyde.[3,4] We had previously argued that TNA could be considered as the limiting case of the fully oxygenous variant within a library of base-pairing systems derived from oxygenous and nitrogenous C4-backbone units joined together by a variety of linker groups.[2] The alternative limiting case would be a four-carbon backbone unit in which all of the oxygens of threose were replaced by nitrogen (Scheme 1). Such considerations raise questions concerning the formation and the stability of corresponding nucleosides, because the nucleosidic C−N bond in (N)-nucleosides becomes labile when the ring oxygen of the furanose sugar unit is replaced by a free NH group;[5] (C)-nucleosides of such systems, on the other hand, can be stable.[6]

In considering heterocycles that could conceivably be formed as alternatives to the natural nucleobases from

Scheme 1[a]



[a] In a TNA-like system in which all oxygens of the threose units were replaced by nitrogen, these units would have to be (C)-nucleosides in order to be stable.

[†] The Scripps Research Institute.
[‡] Swiss Federal Institute of Technology.
[§] Fax: ++1-858-784-9573. Email: rkrishna@scripps.edu
[⊥] Fax: ++41-1-632-1043.

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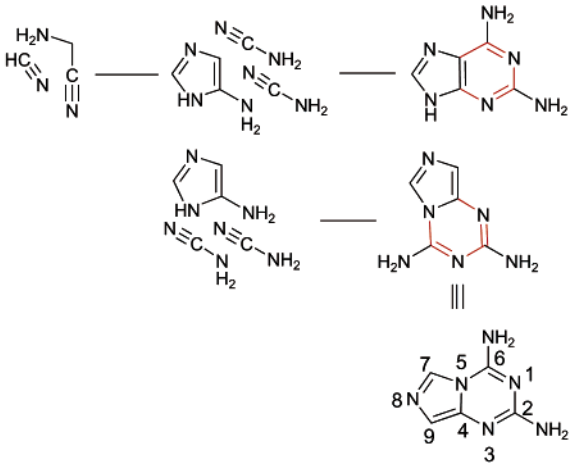
nitrogenous molecules presumed to belong to the prebiotic building blocks of the natural purines,[7] we came across the structural and generational relationship depicted in Scheme 2. The analysis alludes to the existence of the title compound,

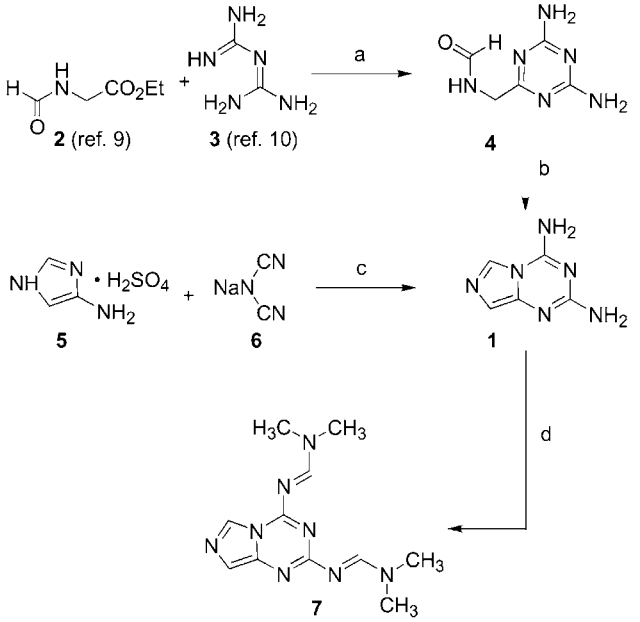
Scheme 2. Structural and Generational Relationship between 2,6-Diaminopurine and a 2,6-Diamino-5,8-diaza-7,9-dicarba-purine



a heterocyclic system isomeric to the 2,6-diamino derivative of the natural purines. The heterocycle caught our attention because it can be expected to have the propensity of reacting with aldosugars or aldosugar-derived iminium ions regioselectively at carbon C-9 to form (C)-nucleosides that would be isosteric to normal (N)-nucleosides of 2,6-diamino-purine. This communication describes the preparation of the title compound and reports exploratory examples of the smooth occurrence of electrophilic substitution at carbon C-9 with iminium ions.

The purinoid **1** was synthesized by two different routes (Scheme 3).[8] One of them, starting from *N*-formyl-glycine ethyl ester **2**[9] and biguanide **3**,[10] represents a preparatively satisfactory and efficient procedure. According to known lines of biguanide chemistry[11] compounds **2** and **3** smoothly condense in methanolic solution to the triazine derivative **4**, which on heating in $POCl_3$ cyclizes to the purinoid **1** in up to 82% yield. The product is obtained as a white solid. Its

Scheme 3. Preparation and Derivatization of Purinoid **1**[a]



[a] Numbers in brackets denote mole equiv referring to starting compound. Numbers before these brackets denote concentrations in M. (a) 0.43 M (1.0 mole equiv) **3**, 0.86 (2.0) **2**, MeOH, rt, 2 h → 45 °C, 3 h, 65%. (b) 0.24 (1.0) **4**, (45) $POCl_3$, 75 °C, 2 h → 110 °C, 3 h, 80%. (c) 1.6 (1.0) **5**, 7.8 (5.0) **6**, H_2O, pH 1.6, rt, 48 h; neutralization followed by chromatography on silica gel, maximally 21%. (d) 0.25 (1.0) **1**, 4.0 (6.0) dimethylformamide dimethylacetal, MeOH, rt, 7 days, 90%.

expected constitution is supported by the ^1H and ^{13}C NMR spectra,[12] mass spectrum,[13] and UV-absorption spectra (Figure 1). For further characterization the purinoid was converted to the bisamidine derivative **7**, an easily soluble crystalline compound (mp 137°, from MeOH) whose X-ray structure analysis[14] (Figure 2) corroborates the structure assignment of the parent purinoid.

The alternative mode of formation for **1** follows more closely the conceptual pattern depicted in Scheme 2 and, therefore, is the one that had been explored first. However, in retrospect, it turned out to be the less satisfactory route from a preparative point of view. The hydrosulfate of the deprotonated form of the (labile and oxygen-sensitive) 4-amino-imidazole[15] **5** reacts with sodium dicyanamide[16] in

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(12) **^1H and ^{13}C NMR Data for 1.** ^1H NMR (600 MHz, DMSO(D_6)): 6.14 ppm (*s*, 2H, NH_2-(C6)), 6.44 ppm (*s*, 1H, H-(C9)), 7.95 ppm(*s*, 2H, NH_2-(C2)), 8.02 ppm(*s*, 1H, H-(C7)). ^{13}C NMR (150.9 MHz, DMSO(D_6)): 109.8 ppm (C9, correlates with signal at 6.44 ppm (H-(C9)) in ^1H NMR), 122.1 (C7, correlates with 8.02 ppm (H-(C7)) in ^1H NMR), 141.8 (C4), 149.3 (C6), 158.1 (C2). Assignments based on NOE, $^1H-^{13}C$, and HMB correlations.

(13) **MS Data for 1.** Electrospray-MS (pos.): 151 (100, $[M + H]^+$), 301 (40, $[2M + 1]^+$). Electrospray-MS (neg.): 149 (100, $[M - H]^-$), 185 (100, $[M + Cl]^-$).

(14) Carried out by Raj K. Chadha, TSRI. Crystallographic data for the structure has been deposited with the Cambridge Crystallographic Data Center as deposition no. CCDC 180981. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 union Road, Cambridge CB12 1EZ UK (fax, + 44 (1233) 336 0333; E-mail, deposit@ccdc.cam.ac.uk). Data for **7** in Supporting Information.

(15) Rabinowitz, J. C. *J. Biol Chem.* **1956**, *218*, 175.

(16) Purchased from Aldrich, 96% purity.

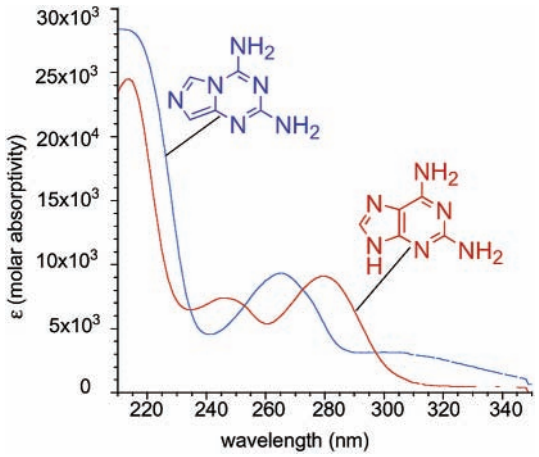


Figure 1. UV-absorption spectrum of purinoid **1** as compared to that of 2,6-diaminopurine ($c = 2.66 \times 10^{-5}$ M in H_2O, rt). Data for **1**: ϵ (220 nm) = 28 400; λ_{max} = 265 nm (ϵ = 9300); ϵ (300−310 nm) = 3100−3000. Data for 2,6-diaminopurine: ϵ (220 nm) = 24500, λ_{max} = 246 nm (ϵ = 7400), λ_{max} = 280 nm (ϵ = 9100).

aqueous solution under argon atmosphere (pH ≈ 1.5) within a day at room temperature to produce a product mixture from which, after neutralization, it is possible to isolate by repeated chromatography on silica gel (CH_2Cl_2/CH_3OH/30% aqueous NH_3, 10:1:0.1, and AcOEt/CH_3OH 4:1) samples of purinoid **1** in yields that range up to 20%. Not only are yields low and fluctuating, but to obtain non-colored and spectroscopically and chromatographically pure samples of **1** is tedious. Nevertheless, all spectral data of pure samples of **1** obtained by this route were identical to those of samples obtained by the other method.

Similar to natural purines, purinoid **1** has little solubility in organic liquids such as methanol, acetonitrile, or DMF. It dissolves well in DMSO on heating and sonicating, remaining in solution at room temperature. It dissolves in (hot) water to an extent of ca. 1.5 mg/mL (after cooling to room temperature) and remains unchanged in 0.01 M NaOH solution (pH ca. 12) or in DMSO/aqueous HCl (1:20, pH ca. 3) at room temperature for (at least) 7 days. In aqueous

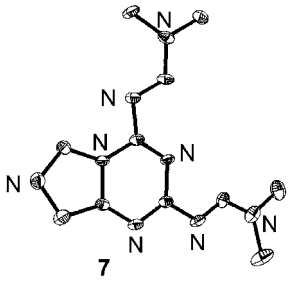
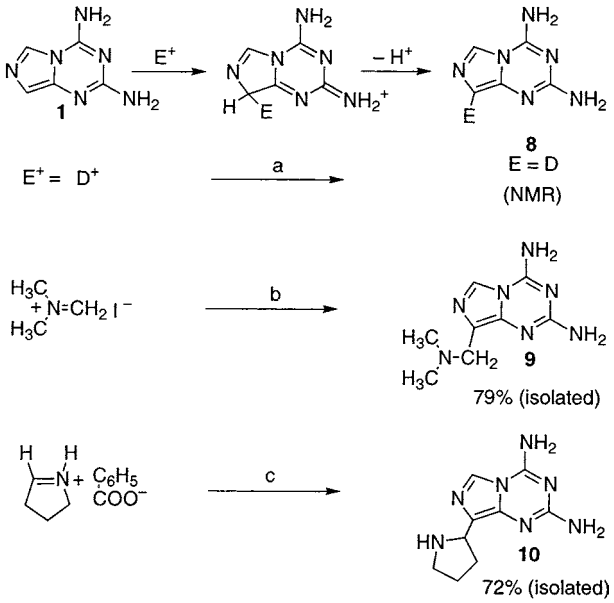


Figure 2. X-ray structure analysis of the derivative **7**.[14] UV data of **7** in H_2O, rt: λ_{max} = 291 nm (ϵ = 47 600); ϵ (355 nm) = 5900.

Scheme 4. Regioselective Electrophilic Substitution Reactions at Position C-9 of Purinoid **1**[a]



[a] (a) 0.05 mM (1.0 mole equiv) **1**, 0.7 μM (0.03) CD_3CO_2D, D_2O/DMSO(D_6) 4:1, pH 4.7, rt, (deuteration at C-9 within minutes). (b) 0.1 M (1.0) **1**, 0.1 (1.0) *N*,*N*-dimethyl-*N*-methylidene iminium iodide, DMSO, rt, 5 min, 79%. (c) 0.13 (1.0) **1**, 0.2 (1.5) pyrroline, 0.2 (1.5) BzOH, DMSO, rt, 1 h, 72%.

solution at pH 1 (HCl) it undergoes hydrolytic ring opening to a mixture of the triazine **4** and its deformylated derivative within 3 days (see Supporting Information). In the solid state (sealed under N_2) the purinoid is thermally stable at 200 °C (for at least 8 h); in solution it is moderately sensitive to oxygen.

In a solution of **1** in D_2O/DMSO(D_6) 4:1, at pH 4.0 (acetic acid(D_4)) at room temperature, the vinylic proton H−(C9) (δ = 6.44 ppm) undergoes exchange, within minutes, to afford **8** (^{1}H NMR); corresponding exchange of the H−(C7) proton (δ = 8.02 ppm) is much slower (less than 10% after 5 h and still incomplete after 3 days). In accordance with expectation (for its rationale see Scheme 4) as well as the observed ease of proton → deuterium exchange in acidic solution, purinoid **1** undergoes (C9)-regioselective electrophilic substitution with *N*,*N*-dimethyl-*N*-methylidene iminium iodide[17] within minutes in 0.1 M DMSO solution at room temperature to give the dimethylaminomethyl purinoid-derivative **9** in high (isolated) yields (Scheme 4).[18] Assignment of constitution rests on ^{1}H and ^{13}C NMR spectroscopic data (in addition to UV and mass spectra). An analogously smooth condensation was observed with pyrroline[19] in 0.2 M DMSO solution in the presence of 1 mole equiv of benzoic acid as catalyst affording **10**[20] (Scheme 4). These encouraging observations led to an extended study on the capacity of

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(18) Data for **9** in Supporting Information.
(19) Poisel, H. *Monatsh. Chem.* **1978**, *109*, 925.
(20) Data for **10** in Supporting Information.

purinoid **1** to act as nucleobase partner in nucleophilic coupling reactions with aldosugar- and azasugar-derived iminium ions to form directly corresponding C-nucleosides. Results of these studies are reported in the following communication.[21]

Acknowledgment. This work was supported by the Skaggs Research Foundation and Novartis A.G. (Basel). H.K.H and Z.W. have been Skaggs Postdoctoral Fellows.

Supporting Information Available: Experimental procedure for the synthesis of 2,6-diamino-purinoid **1** and data for derivatives **7**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL030044N

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