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SYNTHESIS AND PROPERTIES OF N-AMINOGUANINES

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Abstract: Syntheses of all positional isomers of ring-nitrogen monoaminated guanines, 1-, 3-, 7-, and 9-aminoguanines, and two N,N'-diaminoguanines, 1,7-, and 3,7-diaminoguanines, were achieved starting with deoxyguanosine or O^6-methylguanine and with hydroxylamine-O-sulfonic acid or 2,4-dinitrophenoxyamine. Physicochemical characteristics of these N-aminoguanines are described.

Among electrophilic modifications of nucleic acid bases, alkylation and oxygenation have been extensively studied, whereas electrophilic amination has yet to be investigated. Although all positional isomers of N-methylguanines[1] and N-hydroxyguanines[2] are known, N-aminoguanines have not been described except for the 7-amino isomer reported in our previous paper.[3] Some N-substituted guanines have been shown to be biologically active; e.g., 7-hydroxyguanine is an anti-viral agent.[4] This paper describes the synthesis of all positional isomers of ring-nitrogen monoaminated guanines, and N,N'-diaminoguanines, starting with deoxyguanosine or O^6-methylguanine and with hydroxylamine-O-sulfonic acid (HAOS) or 2,4-dinitrophenoxyamine (DNPA). Physicochemical data are compared with those of the corresponding N-methyl and N-hydroxy derivatives. Regioselectivity in the amination of guanine derivatives is discussed briefly in connection with those methylated with methyl iodide.

Synthesis of N-Aminoguanines

Deoxyguanosine (dG) and O^6-methylguanine (6Me-G) were employed as starting materials. The strategy for synthesis was to 1) use electrophilic aminating reagents, 2) introduce an amino group at the deionized position-1 of dG, and at the basic position-7 of neutral dG, 3) introduce an amino group at the deionized position-7 or -9 of 6Me-G, and at the basic position-3 of neutral 6Me-G, and 4) remove deoxyribose or the methyl group after the starting compound was aminated. In our previous study, 6Me-G proved to be an effective substrate for selectively introducing a methyl group at positions-3, -7, and -9.[5]

As shown in Chart 1, reaction of dG with HAOS in aqueous 1 N NaOH at 25°C gave 1-amino-dG (**1**), which was converted quantitatively to 1-aminoguanine (**2**) by acid hydrolysis. Reaction of dG with either DNPA in dimethylformamide (DMF) or aqueous HAOS at pH 2 to

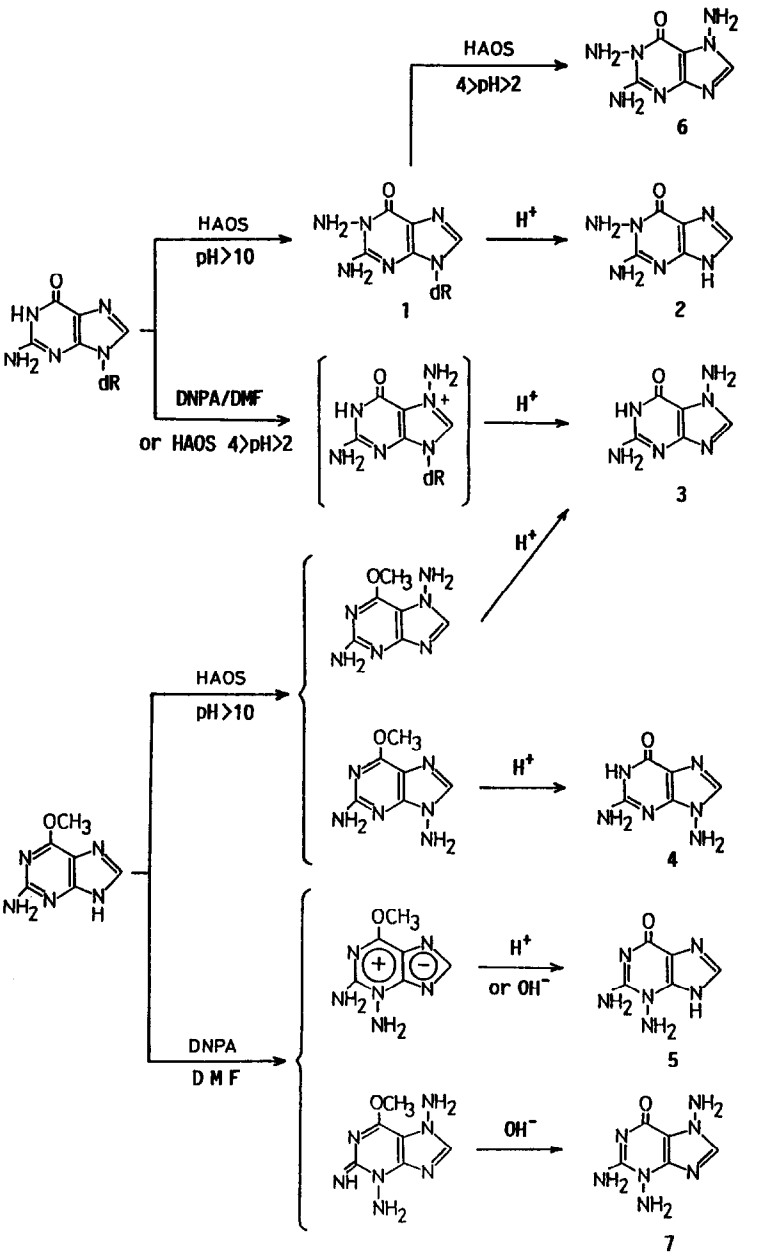
4 yielded 7-aminoguanine (**3**) as we previously reported.[3] Reaction of 6Me-G with HAOS in aqueous 4 N NaOH gave a mixture of the 7- and 9-amino derivatives of 6Me-G in a 1 : 2 ratio. Removal of their O^6-methyl groups by acid hydrolysis gave 7- (**3**) and 9-aminoguanines (**4**), respectively. Reaction of 6Me-G with DNPA in DMF at 45°C gave a mixture of 3-amino- and 3,7-diamino-6Me-G's. The product ratio of 3,7-diamino-6Me-G to 3-amino-6Me-G increased with the amount of DNPA used. Treatment of 3-amino-6Me-G with 0.1 N NaOH yielded 3-aminoguanine (**5**) by replacement of the 6-methoxy group with OH. Acid hydrolysis of 3-amino-6Me-G also gave **5**.

In addition to N-monoaminoguanines, 1,7-diaminoguanine (**6**) was obtained by the reaction of **1** with HAOS at pH 2 to 4 and 70°C; deglycosylation took place immediately in the cationic medium containing 1,7-diamino-dG. 3,7-Diaminoguanine (**7**) was obtained by alkali treatment (0.05 N NaOH, 95°C, 1 h) of 3,7-diamino-6Me-G. The methyl ether of 3,7-diamino-6Me-G was resistant to acid hydrolysis. The structures of these N-amino derivatives were supported by NMR, mass, and UV spectral data as well as elemental analysis. Structural identities of compounds **2**, **3**, and **4** were confirmed by X-ray diffraction analysis as will be mentioned briefly in a subsequent paragraph.

Similarity of Regioselectivity in Aminations and Methylations

The aminations employed in this study proceeded regioselectively in most cases. Amination of dG with HAOS in alkaline media took place exclusively at position-1, whereas those in acidic media took place at position-7, accompanied by ready acid-deglycosylation to give **3**. It may be worth mentioning here that guanosine undergoes amination under acidic conditions to yield 7-aminoguanosine, which is readily rearranged, rather than undergoing deglycosylation, to 8-aminoguanosine *via* a rather complex process as will be reported elsewhere.[6] With regard to amination of dG with DNPA, position-7 was aminated exclusively. In a previous paper, we have shown that 6Me-G is a good substrate for obtaining 3-, 7-, or 9- substituted guanines using electrophilic reagents.[5] Therefore, in order to prepare the 3-, 7-, and 9-amino derivatives, 6Me-G was chosen as the starting material and we successfully obtained the desired derivatives. Thus, amination with HAOS took place at either position-7 or -9 in alkaline media, whereas amination with DNPA in DMF took place at position-3, followed by further amination at position-7 to yield a mixture of the 3-amino and 3,7-diamino derivatives. These aminated 6Me-G's were readily hydrolyzed under acidic or alkaline conditions to give the aminoguanines in question.

It is worth noting that the regioselectivity demonstrated in the aminations are similar to those in methylation using methyl iodide (MeI).[5] Thus, methylation of 6Me-G with MeI in DMF takes place at position-3, followed by further methylation at position-7, as seen in the amination using the identical reaction medium. Methylation of 6Me-G in DMF in the presence of K_2CO_3 gave the corresponding 7-methyl and 9-methyl derivatives. In our previous paper, we did not describe the formation of 7-methyl-6Me-G, which had passed unnoticed because its Rf value was identical to that of the recovered 6Me-G on a thin-layer chromatogram. However, in the present study, 7-methyl-6Me-G was clearly identified in addition to the 9-methyl



HAOS : NH_2-O-SO_3H DNPA : $NH_2-O-C_6H_3(NO_2)_2$

dR : 2-deoxy-β-D-ribofuranosyl

Chart 1. Syntheses of N-Aminoguanines

derivative, as seen in the amination.[7]

X-ray Diffraction Analysis of 1-, 7-, and 9-Aminoguanines

The structures of 1-, 7-, and 9-aminoguanines were confirmed by X-ray diffraction analysis of their HCl salts. The crystal of 7-aminoguanine HCl salt was a monohydrate whereas others were unhydrated. The protonated positions of 1-, 7-, and 9-aminoguanines were clearly shown to be N-7 or -9, N-9, and N-7, respectively. Single crystals were not available for X-ray analysis of 3-aminoguanine. Details of X-ray diffraction analysis will be reported elsewhere.[8]

UV Spectra and Acid Dissociation Constants (pKa) of N-Aminoguanines

UV absorption maxima of N-aminoguanines are shown in Table I. For comparison, those of N-methyl-[1] and N-hydroxyguanines[2] are also given in the same table. It is worth emphasizing that all N-aminoguanines showed very similar UV spectra to those of the corresponding N-methyl derivatives. In addition, pKa values estimated from UV changes reflecting the pH of the medium are very similar to those of the corresponding N-methyl derivatives. These results indicate that the protonation sites of 1-, 3-, 7-, and 9-aminoguanines are the ring nitrogens of the imidazole moiety. X-ray diffraction analysis of 1-, 7-, and 9-aminoguanine also supports this result. UV absorption maxima and pKa's of N-hydroxyguanines are somewhat different from those of the N-amino derivatives. N-Hydroxyguanines showed lower pKa_2 values and an additional pKa_3 which ranged from 9.5 to 11.5.

EXPERIMENTAL

^1H NMR spectra were recorded with a JEOL FX-100 spectrometer and chemical shifts are expressed in parts per million down field from internal tetramethylsilane. Mass spectra were determined on a JEOL DX-300 spectrometer after samples were trimethylsilylated with N,O-bis(trimethylsilyl)trifluoroacetamide – 1% trimethylsilyl chloride in pyridine. UV spectra were obtained with a Shimadzu UV-2100 spectrophotometer and pKa values were estimated from UV changes reflecting the pH of the medium. Melting points are uncorrected.

1-Aminodeoxyguanine (1). HAOS[9] (1.10 g, 9.91 mmol) in 15 ml of H_2O was added slowly to a solution of deoxyguanosine (1.70 g, 6.36 mmol) in 20 ml of 1 N NaOH, and the mixture was stirred for 20 h at 25°C. The resulting precipitate was collected, washed successively with 1 N NaOH (5 ml x 2), water (5 ml x 2) and acetone (10 ml x 2), and then recrystallized from H_2O to give pure 1-aminodeoxyguanosine (780 mg, 44% yield). mp 221-223°C. ^1H NMR (DMSO-d_6): δ 2.09-2.67 (m, 2H, 2'H), 3.57 (m, 2H, 5'H), 3.80 (m, 1H, 4'H), 4.31 (m, 1H, 3'H), 4.96 (t, 1H, J = 5.7 Hz, 5'-OH), 5.29 (d, 1H, J = 3.7 Hz, 3'-OH), 5.36 (broad s, 2H, 1-NH_2), 6.11 (t, 1H, J = 7.1 Hz, 1'-H), 7.06 (broad s, 2H, 2-NH_2), 7.91 (s, 1H, 8-H). UV λ_{max}nm (ε): pH 1 256.5 (10000) and 278 (7100), H_2O and pH 12 254 (12000) and 270(sh) (8500). Anal. Calcd. for $C_{10}H_{14}N_6O_4$: C, 42.55; H, 4.96; N, 29.79. Found: C, 42.69; H, 4.83; N, 30.42.

1-Aminoguanine (2). Acid hydrolysis of 1 with 1 N HCl at 95°C for 2 h gave quantitative

Table I. Comparison of UV Spectra (λ_{max}nm) and pKa Values of N-NH_2-Guanines, N-CH_3-Guanines[a], and N-OH-Guanines[b]

	1-NH_2-Gua[c]	1-CH_3-Gua	1-OH-Gua
+1[d]	248, 274	251, 272(sh)	248, 275
0	246, 275	250, 272	247, 273
-1	257(sh), 278	261(sh), 276	257, 287
-2			267, 278
pKa	3.6, 10.5	3.1, 10.5	3.5, 6.7, 11.5
	3-NH_2-Gua	**3-CH_3-Gua**	**3-OH-Gua**
+1	245(sh), 267	244(sh), 267	245, 267
0	237, 272	235, 269	270
-1	275	272	254, 292
-2			283
pKa	4.2, 9.8	4.3, 9.8	3.5, 6.0, 10.7
	7-NH_2-Gua	**7-CH_3-Gua**	**7-OH-Gua**
+1	251, 272(sh)	250, 273(sh)	252, 270(sh)
0	245, 282	248, 283	
-1	241(sh), 279	240(sh), 280	234, 290
-2			250(sh), 286
pKa	3.5, 9.6	3.5, 9.9	2.6, 5.8, 9.5
	9-NH_2-Gua	**9-CH_3-Gua**	**9-OH-Gua**
+1	253, 275(sh)	252, 271(sh)	252, 278
0	252, 270(sh)	247, 273	238, 253
-1	257(sh), 267	250(sh), 271	274
-2			272
pKa	2.7, 9.7	2.9, 9.8	2.1, 5.9, 10.7

[a] ref. 1, [b] ref. 2, [c] Gua; Guanine, [d] +1; Cationic, 0; Neutral, -1; Monoanionic, -2; Dianionic.

formation of 1-aminoguanine, which was purified by column chromatography (Sephadex LH20, eluted with H_2O). After the fractions containing 1-aminoguanine were collected and the solvent removed, 1-aminoguanine was recrystallized from 1 N HCl to yield needles. mp 215-218°C (crystal color darkend). ^1H NMR (DMSO-d_6): δ 7.54 (broad s, 2H, NH_2), 8.77 (s, 1H, H-8). Another NH_2 signal was not observed. UV λ_{max}nm (ε): pH 1 248 (9900) and 274 (6700), H_2O 246 (9600) and 275 (7300), pH 12 257(sh) (6300) and 278 (8200). Anal. Calcd. for $C_5H_6N_6O \cdot HCl$: C, 29.62; H, 3.46; N, 41.48. Found: C, 29.85; H, 3.34; N, 41.58.

3-Amino-O^6-methylguanine. O^6-Methylguanine[10] (223 mg, 1.35 mmol) was dissolved in 15 ml of DMF. Then, DNPA[11] (270 mg, 1.36 mmol) was added to the solution, and the mixture was left standing at 45°C for 4 days. After removal of the solvent by evaporation, the residue was dissolved in 30 ml of water, and the pH of the solution was adjusted to 3 with dil. HCl. After this solution was washed with ethyl acetate (30 ml x 3), the aqueous solvent was removed by lyophilization. TLC (silica gel, $CHCl_3$: CH_3OH = 1 : 1) of the residue showed three spots; 3-amino-O^6-methylguanine (Rf 0.38, about 45% yield), 3,7-diamino-O^6-methylguanine (Rf 0.03,

about 10% yield), and O^6-methylguanine (Rf 0.38). 3-Amino-O^6-methylguanine was separated by silica gel column chromatography ($CHCl_3$: CH_3OH = 1 : 1) and further purified on a Sephadex LH20 column eluted with CH_3OH. After removal of the solvent, the residue was recrystallized from EtOH to yield needles. mp 223-225°C (dec.). ^1H NMR (DMSO-d_6): δ 4.06 (s, 3H, CH_3), 6.10 (broad s, 2H, 3-NH_2), 7.56 (s, 1H, 8-H), 7.62 (broad s, 2H, 2-NH_2); HCl salt, δ 4.14 (s, 3H, CH_3), 6.36 (broad s, 2H, NH_2), 8.43 (s, 1H, 8-H), 8.57 (broad s, 2H, NH_2). UV λ_{max}nm: pH 1 and H_2O 234(sh) and 286, pH 12 243(sh) and 287. MS: m/z = 396 (3TMS). Anal. Calcd. for $C_6H_8N_6O$: C, 40.00; H, 4.48; N, 46.65. Found: C, 40.43; H, 4.28; N, 46.83.

3-Aminoguanine (5). 3-Amino-O^6-methylguanine was dissolved in 0.1 N NaOH and the solution was heated at 95°C for 2 h. 3-Aminoguanine which was obtained quantitatively was purified on a Sephadex LH20 column (eluted with CH_3OH). Crystallization of 3-aminoguanine from dil. HCl yielded a powder. Acid hydrolysis of 3-amino-O^6-methylguanine also gave 3-aminoguanine. mp > 250°C. ^1H NMR (DMSO-d_6): δ 6.00 (broad s, 2H, NH_2), 8.11 (broad s, 2H, NH_2), 8.17 (s, 1H, 8-H); free form of **5**, δ 5.57 (broad s, 2H, 3-NH_2), 6.0-6.8 (hump, 2H, 2-NH_2), 7.53 (s, 1H, 8-H). UV λ_{max}nm (ε): pH 1 245(sh) (7500) and 267 (10600), H_2O 237 (7500) and 272 (10500), pH 12 275 (13100). MS: m/z = 382 (3TMS). Anal. Calcd. for $C_5H_6N_6O$·HCl: C, 29.64; H, 3.49; N, 41.48. Found: C, 29.43; H, 3.60; N, 41.05.

9-Amino-O^6-methylguanine, 7-Amino-O^6-methylguanine. O^6-Methylguanine (53.6 mg, 0.32 mmol) was dissolved in 7ml of 4 N NaOH. HAOS (297.3 mg, 2.68 mmol) was then added gradually to the solution and the mixture was left standing at 25°C for 2 days. TLC (silica gel, $CHCl_3$: CH_3OH = 5 : 2 v/v) of the reaction mixture showed two main products, 9-amino-O^6-methylguanine (Rf 0.64) and 7-amino-O^6-methylguanine (Rf 0.57), as well as a trace amount of starting material (Rf = 0.66). The product ratio of 9-amino-O^6-methylguanine and 7-amino-O^6-methylguanine was about 2 to 1 and was determined by ^1H NMR spectroscopy measuring the heights of the 8-H signals of the mixed compounds. After the reaction mixture was neutralized with 1 N HCl, the products were separated by column chromatography (Sephadex LH20, 3.5 x 40 cm, eluted with H_2O). 9-Amino-O^6-methyguanine; ^1H NMR (DMSO-d_6): δ 3.96 (s, 3H, CH_3), 5.80 (broad s, 2H, 9-NH_2), 6.37 (broad s, 2H, 2-NH_2), 7.72 (s, 1H, 8-H). UV λ_{max}nm: pH 1 241 and 286, H_2O and pH 12 248 and 279. 7-Amino-O^6-methylguanine; ^1H NMR (DMSO-d_6): δ 4.00 (s, 3H, CH_3), 6.08 (broad s, 2H, 7-NH_2), 6.16 (broad s, 2H, 2-NH_2), 7.91 (s, 1H, 8-H). UV λ_{max}nm: pH 1 287, H_2O and pH 12 289.

9-Aminoguanine (4). 9-Amino-O^6-methylguanine was heated in 1 N HCl at 95°C for 3 h to yield 9-aminoguanine quantitatively, which was then purified by column chromatography (Sephadex LH20, eluted with H_2O). 9-Aminoguanine was recrystallized from 1 N HCl yielding needles. mp > 250°C. ^1H NMR (DMSO-d_6) of **4** (free form): δ 5.77 (broad s, 2H, 9-NH_2), 6.62 (broad s, 2H, 2-NH_2), 7.55 (s, 1H, 8-H), 10.71 (broad s, 1H, NH). The 8-H signal was shifted to lower magnetic field (δ 9.17) by addition of DCl: UV λ_{max}nm (ε): pH 1 253 (7500) and 275(sh) (5200), H_2O 252 (7400) and 270(sh) (5600), pH 12 257(sh) (7200) and 267 (7700). MS: m/z = 382 (3TMS).

7-Aminoguanine (3). 7-Aminoguanine was obtained from 7-amino-O^6-methylguanine and crystallized using the same procedure as described for the preparation of 9-aminoguanine. mp 200-203°C (the color of the crystal darkened). ^{1}H NMR (DMSO-d_6) of **3** (free form): δ 6.16 (broad, 4H, 2-NH_2 and 9-NH_2), 7.75 (s, 1H, 8-H). UV λ_{max}nm (ε): pH 1 251 (9600) and 272(sh) (7300), H_2O 245 (5900) and 282 (7000), pH 12 241(sh) (6700) and 279 (7200). MS: m/z = 454 (4TMS). Anal. Calcd. for $C_5H_6N_6O \cdot HCl \cdot H_2O$ (dried in vacuo at 50°C for 4 h): C, 27.21; H, 4.08; N, 38.10. Found: C, 27.37; H 3.64; N, 38.40. 7-Aminoguanine was also prepared from the reaction of deoxyguanosine with DNPA in DMF as reported previously.[3]

1,7-Diaminoguanine. 1-Aminodeoxyguanosine (600 mg, 2.13 mmol) was dissolved in H_2O containing 2.7 g of CH_3COOK, and the solution was heated at 70°C. To this warm solution, HAOS (2.4 g, 21.6 mmol) in 25 ml of H_2O was added gradually with stirring, and the reaction mixture was kept at 70°C for 2 h. During the reaction, the pH of the reaction mixture was adjusted to 2 to 4 by addition of 1 N NaOH. After cooling, the precipitate which appeared was removed. TLC (Cellulose; iso-propanol : 1%-ammonium sulfate = 3 : 2 v/v) of the reaction mixture showed spots of 1,7-diaminoguanine (Rf 0.38, about 20% yield), 1-aminoguanine (Rf 0.28) and unreacted 1-aminoguanosine (Rf 0.54). 1,7-Diaminoguanine was separated by paper chromatography (Whatman 3MM and the same solvent used for TLC) and purified on a Sephadex LH20 column eluted with H_2O. ^{1}H NMR (DMSO-d_6): δ 5.34 (broad s, 2H, N-NH_2), 6.10 (broad s, 2H, N-NH_2), 6.70 (broad s, 2H, 2-NH_2), 7.72 (s, 1H, 8-H). UV λ_{max}nm: pH 1 252 and 273(sh), H_2O and pH 12 244(sh) and 283. 1,7-Diaminoguanine was also obtained by the reaction of 1-aminodeoxyguanosine with DNPA in DMF as described for the preparation of 7-aminoguanine from deoxyguanosine and DNPA.

3,7-Diamino-O^6-methylguanine. O^6-Methylguanine (22.7 mg, 0.14 mmol) was dissolved in 15 ml of DMF. DNPA (124.5 mg, 0.63 mmol) was then added to the solution, and the mixture was left at 45°C for 3 days. TLC (Silica gel; $CHCl_3$: CH_3OH = 1 : 1 v/v) revealed the quantitative formation of 3,7-diamino-O^6-methyguanine (Rf 0.03). After the solvent was removed by evaporation, the residue was dissolved in 15 ml of H_2O, and the pH of the solution was adjusted to 3 with dil. HCl. After the solution was washed with ethyl acetate (50 ml x 5), the aqueous solvent was removed by evaporation. 3,7-Diamino-O^6-methylguanine was purified on a Sephadex LH 20 column (eluted with CH_3OH). ^{1}H NMR (DMSO-d_6): δ 4.16 (s, 3H, O-CH_3), 6.30 (broad s, 2H, NH_2), 6.60 (broad s, 2H, NH_2), 6.60 (broad s, 2H, NH_2), 8.38 (s, 1H, 8-H), 8.5-8.7 (broad, 2H, NH_2). UV λ_{max}nm: pH 1 287, H_2O and pH 12 289.

3,7-Diaminoguanine. 3,7-Diamino-O^6-methylguanine was heated in 0.1 N NaOH at 95°C for 1 h. TLC (Silica gel; $CHCl_3$: CH_3OH = 1 : 1 v/v) of the reaction mixture showed quantitative formation of 3,7-diaminoguanine (Rf 0.21). After removing the solvent, 3,7-diaminoguanine was purified on a Sephadex LH20 column (eluted with H_2O). ^{1}H NMR (DMSO-d_6) of the free base: δ 5.67 (broad s, 2H, N-NH_2), 6.25 (broad s, 2H, N-NH_2), 6.87 (broad s, 2H, 2-NH_2), 7.76 (s, 1H, 8-H). UV λ_{max}nm: pH 1 267, H_2O and pH 12 235(sh) and 272. MS: m/z = 541 (5TMS).

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