Synthesis of *N*-(1-Nitropyren-6-yl and 8-yl)-2′-deoxyribonucleosides

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Received December 13, 1994[⊗]

A new type of 1-nitropyrene–DNA adduct via addition–elimination reaction was synthesized. Treatment of fluorinated 1-nitropyrene with 3′- and 5′-O-protected 2′-deoxyribonucleoside in dimethyl sulfoxide at 140 °C afforded *N*-(1-nitropyren-6-yl or 8-yl)-2′-deoxyribonucleoside. These DNA adducts resulted from addition of the exocyclic amino group of deoxynucleosides to the fluorinated carbon of the fluoro-1-nitropyrene following elimination of fluoride anion. This is the first report that describes the 1-nitropyrene–DNA adducts in which aromatic ring moiety of 1-nitropyrene is covalently linked to the exocyclic amino group of the deoxyribonucleoside. From our findings, we suggest that the addition–elimination reaction may be responsible for the formation mechanism of the putative 1-nitropyrene–DNA adducts in vivo.

1-Nitropyrene (1-NP)[1] is one of the major nitropolycyclic aromatic hydrocarbons found in diesel engine emissions and ambient air particulates. 1-NP is mutagenic in bacterial (*1*) and mammalian systems (*2*). Recently there are some reports that 1-NP is carcinogenic in rats (*3*). In bacteria, 1-NP is metabolized by bacterial nitroreductase to form a DNA adduct, N-(deoxyguanosin-8-yl)-1-aminopyrene (*4*). However, in mammalian cells, the nitroreduction pathway may not play a major role in the activation of 1-NP in vitro and in vivo (*5*). The major metabolites of 1-NP in rat are ring oxidized products such as 3-, 6-, or 8-hydroxy-1-nitropyrene and 4,5-dihydroxy-4,5-dihydro-1-nitropyrene or 9,10-dihydroxy-9,10-dihydro-1-nitropyrene (*6*). The ^{32}P-fingerprints of DNA adducts of 1-NP from mammary fat pads and livers reveal the presence of multiple putative adducts (*7*). Recently, Roy and co-workers (*8*) characterize the DNA adducts formed from 4,5-epoxy-4,5-dihydro-1-nitropyrene as a metabolite of 1-NP. These adducts result from the addition of the N^2-exocyclic amino group of deoxyguanosine to the benzylic carbon (C5) of the epoxide ring.

Hydroxylated 1-NPs are not able to react directly with DNA. However, in mammalian cells, hydroxylated 1-NPs are metabolized to their conjugates of sulfate, acetate, and gluclonate. Nitro-substituted aromatic compounds are active toward the addition–elimination reaction at the *ortho* and *para* positions of the nitro group when there are leaving groups at that position. Theoretically, the exocyclic amino groups of deoxyribonucleosides can attack the carbon atom substituted with the above acyloxy groups of 1-NP metabolites. This attack induces the elimination of the acyloxy groups. As a result, the aromatic ring moiety of 1-NP ought to be covalently linked to the exocyclic amino group of deoxyribonucleoside. In this paper, a new type of 1-NP–DNA adducts, *N*-(1-nitropyren-6-yl and 8-yl)-2′-deoxyribonucleosides, was synthesized in accordance with the above hypothesis.

Experimental Procedures

Chemicals. Caution: Hazardous Materials: Aminopyrene should be treated as a potential carcinogen and handled accordingly. This and other reagents or solvents should be handled and disposed according to instructions in the respective "Material Safety Data Sheets".

Aminopyrene was purchased from Sigma (St. Louis, MO). Nucleosides and 1-nitropyrene were obtained from Tokyo-Kasei Industry (Tokyo, Japan). *N*-Fluoropyridinium trifluoromethanesulfonate (Onoda-Fluorinate FP-T500) and the reverse-phase HPLC column (Wakosil II 5C18 AR 4.6 × 250 mm) were purchased from Wako Chemicals (Tokyo, Japan). Reagent-grade chemicals and solvents were obtained from commercial suppliers. An HPLC column (LiChrosorb Si60 10 × 250 mm) was purchased from Kanto Chemical (Tokyo, Japan).

Instrumentation. Nuclear magnetic resonance (NMR) spectra were recorded on a Jeol GX-400 spectrometer. The chemical shifts were reported in ppm (δ) downfield from tetramethylsilane. Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were performed with a Jeol DX-300 and Jeol DX-302 spectrometer.

Synthesis. 5′-O-trityl-3′-O-(tetrahydrofuranyl)deoxyribonucleosides **7** and **12** were synthesized according to published procedures (*9*, *10*).

1-Fluoropyrene (3). (A) 1-Aminopyrene (**1**) (435 mg, 2.00 mmol) was dissolved in 20 mL of CH_3CN. HBF_4 (42% solution, 5 mL) was added into the CH_3CN solution. The solution was cooled in ice–water bath. $NaNO_2$ solution was added dropwise to the solution and then a brown precipitate appeared. The precipitate was filtered and washed with cold 5% HBF_4, cold H_2O, and petroleum ether, and then dried *in vacuo*. The precipitate was stood in an Erlenmeyer flask and then heated at 160 °C. After white smoke disappeared, the black residue was partitioned using EtOAc and H_2O. The organic layer was concentrated *in vacuo*. The residue was applied to a silica gel column (20 g). The column was eluted with *n*-hexane–CH_2Cl_2 (10:1). The eluate was concentrated, and the resulting residue was crystallized from *n*-hexane–EtOAc to give **3** as colorless needles in 18% (79 mg) yield.

(B) Pyrene (404 mg, 2.00 mmol) and *N*-fluoropyridinium trifluoromethanesulfonate (Onoda-Fluorinate FP-T500) (1.0 g, 4.0 mmol) were suspended in 15 mL of diglyme. The reaction mixture was heated at 140 °C for 3 days. After addition of H_2O

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⊗ Abstract published in *Advance ACS Abstracts,* May 15, 1995.

[1] Abbreviations: 1-NP, 1-nitropyrene; FD-MS, field desorption mass spectrometry; COSY, correlation spectroscopy; NOESY, nuclear Overhauser enhancement correlation spectroscopy; PAH, polyaromatic hydrocarbon; FP-T500, *N*-fluoropyridinium trifluoromethanesulfonate.

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(0.5 mL), the mixture was dissolved in EtOAc and washed with saturated NaCl. The organic layer was concentrated *in vacuo*. The residue obtained was applied to a silica gel column (50 g). The column was eluted with *n*-hexane−$CHCl_3$ (20:1). The eluate was concentrated, and the resulting residue was crystallized from EtOH to give **3** as colorless needles in 46% (200 mg) yield. MS (*m*/*z*) 220 $(M)^+$.

Nitration of 3. Compound **3** (40 mg, 0.18 mmol) was suspended in 1 mL of AcOH. HNO_3 (0.1 mL) was added into the suspension, and the mixture was stirred at room temperature for 30 min. The reaction mixture was partitioned using CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was concentrated *in vacuo*. The residue was applied to a silica gel column (10 g). The column was eluted with *n*-hexane−CH_2Cl_2 (5:1). The eluate was concentrated to leave the mixture of 3-fluoro-1-nitropyrene (**4**), 6-fluoro-1-nitropyrene (**5**), and 8-fluoro-1-nitropyrene (**6**) in 83% yield as mixture (40 mg). The ratio of **4**:**5**:**6** was about 1:2:2 by the NMR spectrum. The mixture was applied to an HPLC column (LiChrosorb Si60 10 × 250 mm) and eluted with *n*-hexane−EtOAc (20:1). At first, compound **5** was eluted, and then compounds **4** and **6** were eluted as a mixture. The mixture of compounds **4** and **6** was separated with elution of *n*-hexane−$CHCl_3$ (10:1).

3-Fluoro-1-nitropyrene (**4**): MS (*m*/*z*) 265 $(M)^+$, 235 $(M - NO)^+$, 219 $(M - NO_2)^+$; HRMS calcd for $C_{16}H_8NO_2F$ $(M)^+$ 265.0539, found 265.0536; NMR (δ, ppm) 8.77 (d, 1H, H-10, $J_{9,10}$ = 9.5 Hz), 8.37 (d, 1H, H-2, $J_{2,F}$ = 10.3 Hz), 8.29−8.25 (m, 2H, H-6,8), 8.21 (bs, 2H, H-4,5), 8.16 (d, 1H, H-9), 8.11 (t, 1H, H-7, J = 7.7 Hz).

6-Fluoro-1-nitropyrene (**5**): MS (*m*/*z*) 265 $(M)^+$, 235 $(M - NO)^+$, 219 $(M - NO_2)^+$; HRMS calcd for $C_{16}H_8NO_2F$ $(M)^+$ 265.0539, found 265.0527; NMR (δ, ppm) 8.65 (d, 1H, H-10, $J_{9,10}$ = 9.2 Hz), 8.55 (d, 1H, H-2, $J_{2,3}$ = 8.8 Hz), 8.29 (d, 1H, H-5, $J_{4,5}$ = 9.0 Hz), 8.12 (dd, 1H, H-8, $J_{7,8}$ = 8.4 Hz, $J_{8,F}$ = 5.5 Hz), 8.08 (d, 1H, H-9), 8.00 (d, 1H, H-3), 7.94 (d, 1H, H-4), 7.73 (dd, 1H, H-7, $J_{7,F}$ = 8.8 Hz).

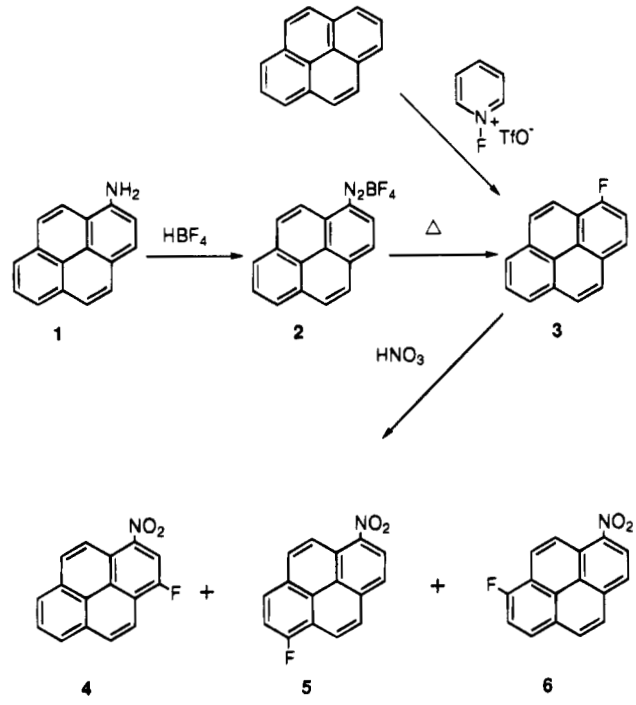
8-Fluoro-1-nitropyrene (**6**): MS (*m*/*z*) 265 $(M)^+$, 235 $(M - NO)^+$, 219 $(M - NO_2)^+$; HRMS calcd for $C_{16}H_8NO_2F$ $(M)^+$ 265.0539, found 265.0530; NMR (δ, ppm) 8.71 (d, 1H, H-10, $J_{9,10}$ = 9.4 Hz), 8.55 (d, 1H, H-2, $J_{2,3}$ = 8.8 Hz), 8.30 (d, 1H, H-9), 8.14 (dd, 1H, H-6, $J_{6,7}$ = 8.4 Hz, $J_{6,F}$ = 5.5 Hz), 8.04 (d, 1H, H-5, $J_{4,5}$ = 8.8 Hz), 8.01 (d, 1H, H-3), 7.88 (d, 1H, H-4), 7.74 (dd, 1H, H-7, $J_{7,F}$ = 9.5 Hz).

***N*⁶-(1-Nitropyren-6-yl)-3′-*O*-(tetrahydrofuranyl)-5′-*O*-trityldeoxyadenosine (8).** Compound **5** (50.9 mg, 0.192 mmol) was dissolved in 3 mL of dimethyl sulfoxide. K_2CO_3 (110 mg, 0.8 mmol) and 3′-*O*-(tetrahydrofuranyl)-5′-*O*-trityldeoxyadenosine (**7**) (230.4 mg, 0.407 mmol) was added into the dimethyl sulfoxide solution. The mixture was heated at 140 °C for 24 h under N_2 atmosphere. EtOAc and H_2O were added to the reaction mixture. The organic layer was concentrated *in vacuo*. The residue was applied to a silica gel column (30 g). The column was eluted with $CHCl_3$−EtOAc (10:1). The eluate was concentrated to leave **8** in 31% (48 mg) yield. FD-MS (*m*/*z*) $C_{49}H_{40}N_6O_6$ 808 $(M)^+$.

***N*⁶-(1-Nitropyren-6-yl)deoxyadenosine (9).** Compound **8** (30.5 mg, 0.038 mmol) was dissolved in 5 mL of tetrahydrofuran. Trifluoroacetic acid and H_2O were added into the tetrahydrofuran solution. The mixture was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*. The residue was partitioned using *n*-hexane−H_2O. The aqueous layer was concentrated, and the resulting residue was crystallized from H_2O−MeOH to give **9** in 82% (15.5 mg) yield. FD-MS (*m*/*z*) 496 $(M)^+$; HRMS calcd for $C_{26}H_{21}N_6O_5$ $(MH)^+$ 497.1574, found 497.1528; NMR (δ, ppm) 10.62 (bs, 1H, HN), 8.77−8.30 (m, 8H, H-pyrene), 8.56 (s, 1H, H-8), 8.25 (s, 1H, H-2), 6.46 (dd, 1H, H1′, $J_{1',2'}$ = 6.2 and 7.3 Hz), 5.37 (d, 1H, 3′-OH), 5.16 (t, 1H, 5′-OH), 4.47 (m, 1H, H-3′), 3.93 (m, 1H, H-4′), 3.70−3.54 (m, 2H, H-5′a and b), 2.84−2.79 (m, 1H, H-2′a), 2.38−2.32 (m, 1H, H-2′b).

***N*⁶-(1-Nitropyren-8-yl)-3′-*O*-(tetrahydrofuranyl)-5′-*O*-trityldeoxyadenosine (10).** Compound **10** was synthesized by the same way as **8**. FD-MS (*m*/*z*) $C_{49}H_{40}N_6O_6$ 808 $(M)^+$.

Scheme 1. Synthesis of Fluoro-1-nitropyrene



***N*⁶-(1-Nitropyren-8-yl)deoxyadenosine (11).** Compound **10** (30.2 mg, 0.037 mmol) was dissolved in 5 mL of tetrahydrofuran and treated with trifluoroacetic acid and H_2O. The solution was stirred at room temperature for overnight. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between *n*-hexane−H_2O. The aqueous layer was concentrated, and the resulting residue was crystallized from H_2O−MeOH to give **11** in 78% (14.3 mg) yield. FD-MS (*m*/*z*) 496 $(M)^+$; HRMS calcd for $C_{26}H_{21}N_6O_5$ $(MH)^+$ 497.1574, found 497.1607; NMR (δ, ppm) 10.61 (bs, 1H, HN), 8.75−8.31 (m, 8H, H-pyrene), 8.55 (s, 1H, H-8), 8.24 (s, 1H, H-2), 6.45 (t, 1H, H-1′, $J_{1',2'}$ = 7 Hz), 5.36 (d, 1H, 3′-OH), 5.16 (t, 1H, 5′-OH), 4.45 (m, 1H, H-3′), 3.92 (m, 1H, H-4′), 3.68−3.63 (m, 1H, H-5′a), 3.58−3.52 (m, 1H, H-5′b), 2.83−2.76 (m, 1H, H-2′a), 2.36−2.31 (m, 1H, H-2′b).

***N*⁴-(1-Nitropyren-6-yl)deoxycytidine (13).** Compound **13** was synthesized by the same way as **9**. FD-MS (*m*/*z*) 472 $(M)^+$; HRMS calcd for $C_{25}H_{21}N_4O_6$ $(MH)^+$ 473.1461, found 473.1455; NMR (δ, ppm) 10.35 (bs, 1H, HN), 8.78−8.38 (m, 8H, H-pyrene), 8.1 (bs, 1H, H-5), 6.2 (bs, 1H, H-6), 6.20 (t, 1H, H-1′, $J_{1',2'}$ = 6.6 Hz), 5.14 (d, 1H, 3′-OH), 5.04 (t, 1H, 5′-OH), 4.24 (m, 1H, H-3′), 3.83 (m, 1H, H-4′), 3.6 (m, 2H, H-5′a and b), 2.2 (m, 1H, H-2′a), 2.05 (m, 1H, H-2′b).

***N*⁴-(1-Nitropyren-8-yl)deoxycytidine (14).** Compound **14** was synthesized by the same way as **11**. FD-MS (*m*/*z*) 472 $(M)^+$; HRMS calcd for $C_{25}H_{21}N_4O_6$ $(MH)^+$ 473.1461, found 473.1430; NMR (δ, ppm) 9.10−8.60 (m, 8H, H-pyrene), 8.34 (bs, 1H, H-5), 6.5 (bs, 1H, H-6), 6.50 (t, 1H, H-1′), 6.56 (d, 1H, 3′-OH), 5.34 (bs, 1H, 5′-OH), 4.55 (m, 1H, H-3′), 4.13 (m, 1H, H-4′), 3.89 (m, 2H, H-5′), 2.51 (m, 1H, H-2′a), 2.34 (m, 1H, H-2′b).

Reaction of 5 with Calf Thymus DNA. Calf thymus DNA (280 mg) was dissolved in 20 mL of 10 mM phosphate buffered saline, pH 7.3. To the solution was added compound **5** (50 mg) in 60 mL of dimethyl sulfoxide. The mixture was incubated for 1 week at 37 °C. Then calf thymus DNA was hydrolyzed according to published procedures (*8*). After 1-butanol extraction, the adducts were analyzed with reverse-phase HPLC (column, Wakosil II 5C18 AR (4.6 × 250 mm); solvent, MeOH−water (8:2 v/v); flow rate, 0.7 mL/min; detection, 420 nm).

Results and Discussion

Halogenated 1-NP had only one reactable site for nucleophilic attack of the amino group. 1-Fluoropyrene

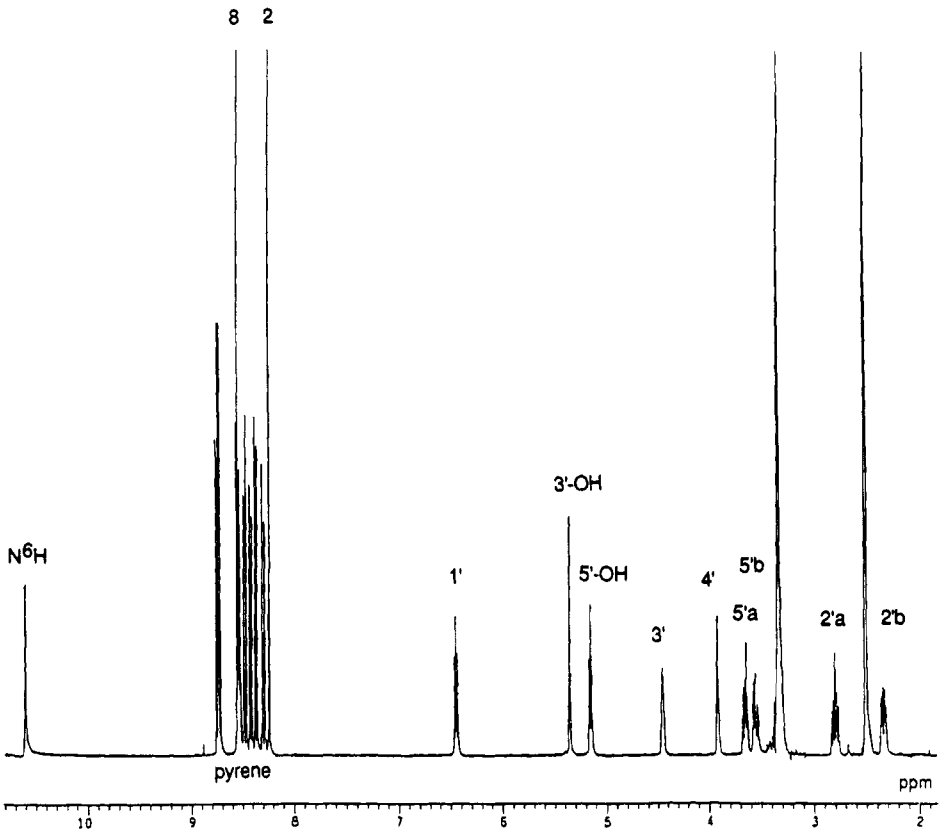
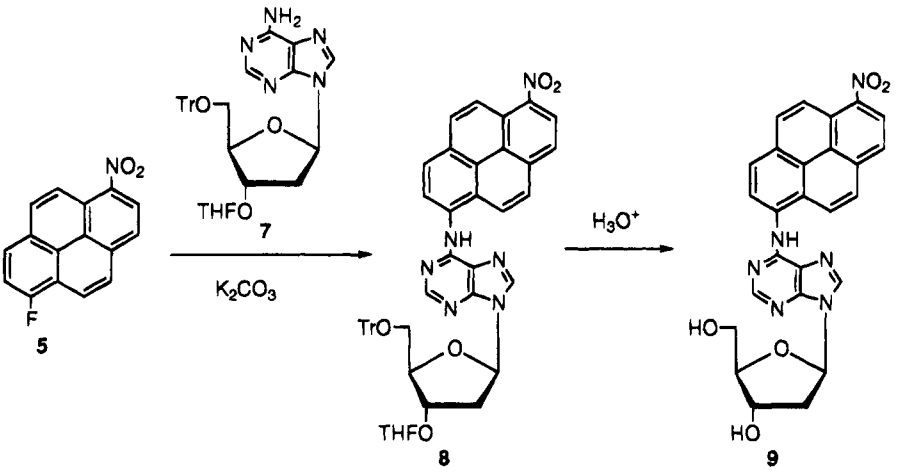
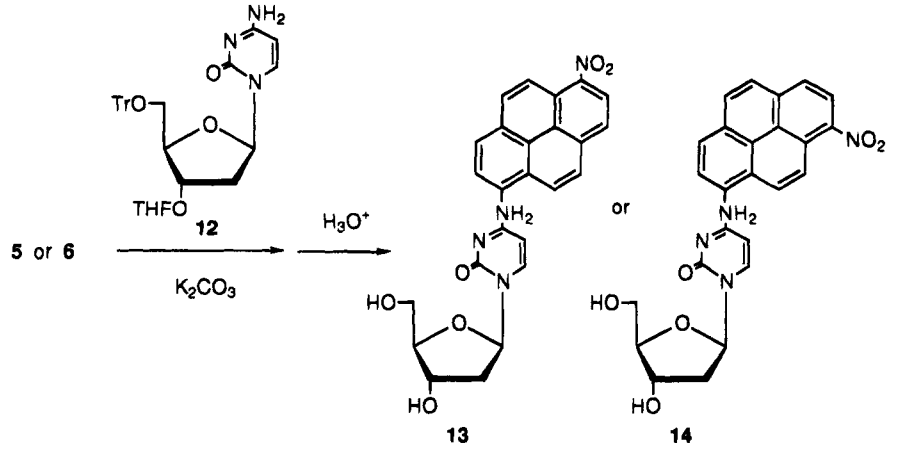


Figure 1. ^{1}H-NMR spectrum of N^6-(1-nitropyren-6-yl)-2′-deoxyadenosine at 400 MHz in dimethyl sulfoxide-d_6.

Scheme 2. Synthesis of N^6-(1-Nitropyren-6-yl)-2′-deoxyadenosine



Scheme 3. Synthesis of N^4-(1-Nitropyren-6-yl and 8-yl)-2′-deoxycytidine



(**3**) was obtained by two methods. One was Shieman reaction of aminopyrene (Scheme 1), and another was direct fluoridation of pyrene with *N*-fluoropyridinium trifluoromethanesulfonate (FP-T500). Treatment of **3** with $NaNO_2$ gave the mixture of 3-, 6-, or 8-fluoro-1-nitropyrene. After separation with HPLC, the position of halogen was determined by the 2D-NMR spectrum of COSY and NOESY.

Treatment of 3′-*O*-(tetrahydrofuranyl)-5′-*O*-trityldeoxyadenosine (**7**) with 6-fluoro-1-nitropyrene (**5**) in dimethyl sulfoxide in the presence of K_2CO_3 at 140 °C afforded N^6-(1-nitropyren-6-yl)-3′-*O*-(tetrahydrofuranyl)-5′-*O*-trityldeoxyadenosine (**8**) in 31% yield. On the FD-MS spectrum of **8**, the molecular ion (*m*/*z* 808) appeared. Because compound **8** was a mixture of stereoisomers of the 3′-*O*-tetrahydrofuranyl group, the ^{1}H-NMR spectrum of **8** was very complex. The deprotection reaction was done to simplify the ^{1}H-NMR spectrum. Acid treatment of **8** gave the deprotected compound, N^6-(1-nitropyren-6-yl)deoxyadenosine (**9**), in 82% yield (Scheme 2). On the FD-MS spectrum of **9**, the molecular ion (*m*/*z* 496) was observed. On the ^{1}H-NMR spectrum of **9**, the signals of pyrene ring protons gave eight couples of doublet from 8.77 to 8.30 ppm. At 8.56 and 8.25 ppm, the signals of adenine ring protons appeared as each singlet (Figure 1). The amino proton appeared as one proton at 10.62 ppm as a broad singlet. The signals of the sugar portion were almost as same as the normal deoxyribonucleoside. The 2D-NMR spectrum of NOESY of **9** indicated the substituted position of pyrene ring was the 6-carbon atom of 1-NP. Accordingly, this addition−elimination reaction occurred at the fluorinated carbon of fluoro-1-nitropyrene. These spectrum data indicated that the structure of **9** was N^6-(1-nitropyren-6-yl)deoxyadenosine. In the same manner, the treatment of 8-fluoro-1-nitropyrene (**6**) with **7** gave N^6-(1-nitropyren-8-yl)deoxyadenosine (**11**) after deprotection.

Deoxycytidine derivatives also reacted with compound **5** and **6**, and then N^4-(1-nitropyren-6-yl)deoxycytidine (**13**) and N^4-(1-nitropyren-8-yl)deoxycytidine (**14**) were obtained (Scheme 3). The structures of **13** and **14** were confirmed with their MS and NMR spectrum in the same manner.

In the case of deoxyguanosine derivative, treatment of O^6-ethyl-3′-*O*-tetrahydrofuranyl-5′-*O*-trityl-2′-deoxyguanosine (*11*) with **5** or **6** afforded the corresponding adducts in the same way of **8**. Zoltewicz and co-workers (*12*) reported that the glycosyl bonds of deoxyguanosine derivatives were more unstable than other deoxynucleoside derivatives. We also observed depurination of deoxyguanosine derivatives under the deprotection procedures, treatment with trimethylsilyl iodide following acid hydrolysis. So the deprotected deoxyguanosine−1-nitropyrene adducts could not be obtained.

After incubation of calf thymus DNA with compound **5**, some adducts were detected with HPLC analysis, but the yields were very low (<0.01%). Because of the poor yield, these structures could not be confirmed. There may be good conditions in which the adducts are formed in better yield.

In this paper we demonstrated the possibility that 1-nitropyrene derivatives could form the new type of DNA adducts via an addition−elimination reaction. This mechanism of the DNA adduct formation will be able to be also applied to the other nitroarene derivatives.

Acknowledgment. The authors wish to thank to Drs. H. Ito and S. Serizawa (NIES) for MS analyses.

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