

1,*N*²-Ethenodeoxyguanosine as a Potential Marker for DNA Adduct Formation by *trans*-4-Hydroxy-2-nonenal¹

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ABSTRACT

The reaction of *trans*-4-hydroxy-2-nonenal, a major α,β -unsaturated aldehyde released during lipid peroxidation, with deoxyguanosine under physiological conditions was investigated in order to assess its DNA damaging potential. This aldehyde was dissolved in tetrahydrofuran (THF) prior to addition to the reaction mixture. The results showed that structurally different adducts were formed in these reactions depending on the THF used. Using THF unprotected from light, reactions yielded adducts 1 to 6. Adduct 1 was characterized as 1,*N*²-ethenodeoxyguanosine (5,9-dihydro-9-oxo-3- β -D-deoxyribofuranosylimidazo[1,2-*a*]purine) by its UV, proton nuclear magnetic resonance, and mass spectrum and by comparison to the corresponding guanosine and guanine adducts reported in the literature. The UV spectrum of adduct 4 was indicative of a substituted 1,*N*²-etheno derivative. Adducts 2, 3, 5, and 6 were essentially identical in UV spectra and appeared to be *N*²-substituted deoxyguanosine diastereomers. At room temperature adducts 2, 3, 5, and 6 were converted quantitatively to a single product at pH 10.5. This product was shown to be identical to 1,*N*²-ethenodeoxyguanosine (adduct 1). Analogous conversions to 1,*N*²-ethenoguanine were also observed for the corresponding guanine adducts. Using THF that had been protected from the light, however, the reactions of *trans*-4-hydroxy-2-nonenal with deoxyguanosine gave three major adducts, 7, 8, and 9. These adducts possessed UV spectra similar to that of 1,*N*²-propanodeoxyguanosine and were not converted to 1,*N*²-ethenodeoxyguanosine upon base treatment. Evidence obtained suggests that adducts 1 to 6 were formed from the reaction of deoxyguanosine with the epoxide of *trans*-4-hydroxy-2-nonenal generated in the presence of hydroperoxide in the light unprotected THF, whereas adducts 7 to 9 were formed by direct Michael addition. Adducts 1 to 6 were formed presumably as a result of nucleophilic addition of the *ex*-amino of deoxyguanosine to the aldehydic group of the epoxide of *trans*-4-hydroxy-2-nonenal. Base treatment of these adducts facilitated subsequent cyclization and eliminations and finally gave 1,*N*²-ethenodeoxyguanosine. These results demonstrated that *trans*-4-hydroxy-2-nonenal readily forms adducts with deoxyguanosine either by direct Michael addition or via its epoxide formation. The facile conversion of some of these adducts to a single adduct suggests that 1,*N*²-ethenodeoxyguanosine may provide a simple and useful marker for assessing potential DNA damage by *trans*-4-hydroxy-2-nonenal and related alkenals associated with lipid peroxidation.

INTRODUCTION

Lipid peroxidation has been associated with liver cell injury (1) and possibly liver carcinogenicity (2, 3). It has been postulated that free radicals generated during this process may be responsible for these adverse effects because of their ability to damage cellular membrane and DNA. Recent studies have shown that aldehydes, in particular 4-hydroxy-2-alkenals, are also produced in stimulated lipid peroxidation *in vitro* and *in vivo* (4-6). Like other α,β -unsaturated aldehydes, 4-hydroxy-alkenals readily form conjugates with thiol groups of cellular proteins (7, 8). These aldehydes exhibit a number of cytopath-

ological effects including lysis of erythrocytes, inhibition of cytochrome P-450, and inhibition of protein and DNA synthesis (9-11). They are considerably more stable than free radicals and thus appear to be more likely to diffuse into the cellular medium and finally reach nuclear DNA. *trans*-4-Hydroxy-2-pentenal and -nonenal are direct acting mutagens in *Salmonella typhimurium* TA 104 and in V79 Chinese hamster lung cells (12, 13). Among the aldehydes formed from lipid peroxidation, the 9-carbon homologue *trans*-4-hydroxy-2-nonenal is the major one and has been suggested to play a major role in liver toxicity associated with lipid peroxidation (4). In view of its abundance and broad spectrum of biological activities, it is important to assess the DNA damaging potential of this endogenously formed aldehyde. We have previously demonstrated that other mutagenic α,β -unsaturated aldehydes such as acrolein and crotonaldehyde readily form structurally unique cyclic 1,*N*²-propanodeoxyguanosine adducts upon incubation with DNA under physiological conditions (14) and that crotonaldehyde is tumorigenic in F344 rats (15). Since *trans*-4-hydroxy-2-nonenal is a homologue of acrolein and crotonaldehyde, it seems likely that it can interact with DNA forming related adducts. Therefore, in this study we attempted to assess the DNA damaging potential of this important aldehyde by investigating its reaction with deoxyguanosine.

MATERIALS AND METHODS

Instrumentation. HPLC³ analysis was performed with a Waters Associates Model (Water Associates, Milford, MA) equipped with a Model 510 solvent delivery system, a Model 660 solvent programmer, a Model U6K septumless injector, and a Model 440 UV/visible detector at wavelength 254 or 280 nm. The following HPLC systems were used: System 1, 25-cm x 4.6-mm Whatman Partisil octadecylsilane analytical column with a 50-min linear gradient from 0 to 60% methanol in H₂O at a flow rate of 1 ml/min; System 2, 50-cm x 9.4-mm Whatman Partisil ODS-3 Magnum 9 column programmed as follows: 10% methanol in H₂O for 10 min followed by a gradient of 10 to 75% methanol in H₂O in 50 min at a flow rate of 4 ml/min.

UV spectra were recorded on a Hewlett-Packard 8452A diode array spectrophotometer coupled to an IBM XT personal computer. Proton NMR spectra were obtained using a JEOL JNM-GX 400 FT-NMR (Hunter College, City University of New York). Mass spectra were run on a VG-11-250 spectrometer (Rockefeller University).

Chemicals. *trans*-4-hydroxy-2-nonenal was generously provided by Lawrence Marnett and Hermann Esterbauer initially and was later synthesized in gram quantities in our laboratory by published methods (16). It was purified on a silica gel column eluted with CH₂Cl₂:hexane (3:1) initially to remove trace impurities and then followed by CH₂Cl₂:methanol (9:1). 1,*N*²-Ethenodeoxyguanosine was synthesized by published methods (17). Deoxyguanosine was purchased from Pharmacia (Piscataway, NJ). THF was supplied by Fisher Scientific (Fair Lawn, NJ). *tert*-Butyl hydroperoxide was obtained from Aldrich Chemical Co. (Milwaukee, WI).

Reaction of *trans*-4-hydroxy-2-nonenal with Deoxyguanosine. *trans*-4-Hydroxy-2-nonenal (90 mg, 0.58 mmol) was dissolved in THF (1 ml) and added to a solution of deoxyguanosine (32 mg, 0.12 mmol) in 0.1

³ The abbreviations used are: HPLC, high-performance liquid chromatography; NMR, nuclear magnetic resonance; THF, tetrahydrofuran; sh, shoulder.

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M phosphate buffer (pH 7.1, 4 ml) at 37°C. THF used in these reactions had been either protected from or exposed to light. The light unprotected THF was stored in a colorless transparent glass container which had been exposed to the light for 2 to 3 weeks before use. The light protected THF was contained in a brown bottle and stored in a cabinet. After 48 h, the incubation mixture was thoroughly extracted with chloroform. The aqueous phase was evaporated in a vacuum to dryness and redissolved in 1 ml H₂O. The sample was analyzed by reverse-phase HPLC using System 1. Reactions were also carried out at 50°C in order to increase the yield. To collect adducts for proton NMR or mass spectrum, HPLC System 2 was used.

Conversion of Adducts 2, 3, 5, and 6 to 1,N²-Ethenodeoxyguanosine. Adducts collected from HPLC were evaporated to dryness and redissolved in H₂O (1 ml). These samples were reinjected onto the same HPLC system to assure the purity. After dilution with an equal volume of pH 7.0 buffer, UV spectra were recorded. NaOH (1 N) was then added to adjust the pH to 10.5 and UV spectra were measured at 2-min intervals. After 90 min the solutions were neutralized by 1 N HCl and an aliquot was reanalyzed by HPLC using System 1.

Reaction of *trans*-4-Hydroxy-2-nonenal with Deoxyguanosine in the Presence of *tert*-Butyl Hydroperoxide. *trans*-4-Hydroxy-2-nonenal (90 mg, 0.58 mmol) dissolved in 0.5 ml of light protected THF was added to a phosphate buffer (4 ml, pH 7.2) containing deoxyguanosine (32 mg, 0.12 mmol). To this reaction mixture was added 0.1 ml of *tert*-butyl hydroperoxide. The reaction was carried out at 50°C in an incubator with shaking for 64 h. The reaction mixture was extracted thoroughly with chloroform and the aqueous phase was evaporated to dryness and redissolved in 1 ml of H₂O. The final sample was analyzed by HPLC using System 1.

RESULTS

Depending on the THF used to dissolve the aldehyde, different adducts were formed in the reactions with deoxyguanosine. Using THF unprotected from light, 6 major adducts were formed (Fig. 1A). These adducts were designated as 1 to 6. Adduct 1 appeared to be considerably more polar than the other adducts and was eluted at 22 ml. Adduct 1 showed a bathochromic shift in its UV spectra comparing to the cyclic 1,N²-propanodeoxyguanosine adducts formed from acrolein or crotonaldehyde (14). The UV spectra of adduct 1 were similar to

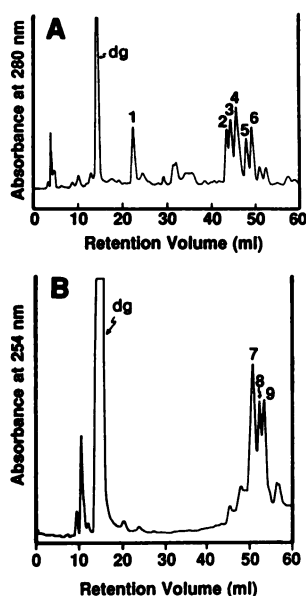


Fig. 1. HPLC chromatograms obtained upon analysis of reaction mixtures of *trans*-4-hydroxy-2-nonenal and deoxyguanosine (dg). *trans*-4-Hydroxy-2-nonenal was dissolved in THF prior to reacting with deoxyguanosine. (A) THF used had been exposed to light; (B) THF used had been protected from light. The reaction was carried out at pH 7.0 and 50°C and HPLC System 1 was used.

those of 1,N²-ethenodeoxyguanosine with λ_{\max} at 223, 272, and 291 (sh) nm (pH 1); 228 and 283 nm (pH 7); and 232, 277, and 306 nm (pH 13) (Fig. 2) (17). The proton NMR spectrum of this product showed, aside from deoxyguanosine protons, two aromatic protons that appeared as doublets at 7.33 and 7.56 ppm (Fig. 3). The spectroscopic data support the structure of this product as 1,N²-ethenodeoxyguanosine. This structural assignment of adduct 1 was further confirmed by desorption chemical ionization mass spectrum which showed m/e 292 ($M^+ + 1$) indicating the addition of $-C=C-$ to deoxyguanosine. Adducts 2, 3, 4, 5, and 6 which eluted at 43, 44, 46, 48, and 49 ml appeared to be much less polar than adduct 1. Adduct 4 showed UV spectra resembling that of 1,N²-ethenodeoxyguanosine suggesting that it is a substituted 1,N²-ethenodeoxyguanosine derivative. The UV spectra of adducts 2, 3, 5, and 6 were essentially identical. They were closely related to those of N²-substituted guanosine with λ_{\max} at 254, 277 (sh) nm (pH 1.0); 251, 277 (sh) nm (pH 7.0); and 250, 272 (sh) nm (pH 11.0) (18). At 50°C, the combined yield of adducts 2, 3, 5, and 6 was approximately 2–3% based on deoxyguanosine. This represents 65–75% of the total adduct yield. Interestingly, at room temperature and pH 10.5 these four adducts converted quantitatively to a single product. This product possessed spectroscopic and chromatographic properties identical to that of 1,N²-ethenodeoxyguanosine (adduct 1). Contrary to the results just described, adducts 1 to 6 were not formed in reactions in which light protected THF was used. Instead, these reactions resulted in the formation of 3 major products which eluted at 50, 52,

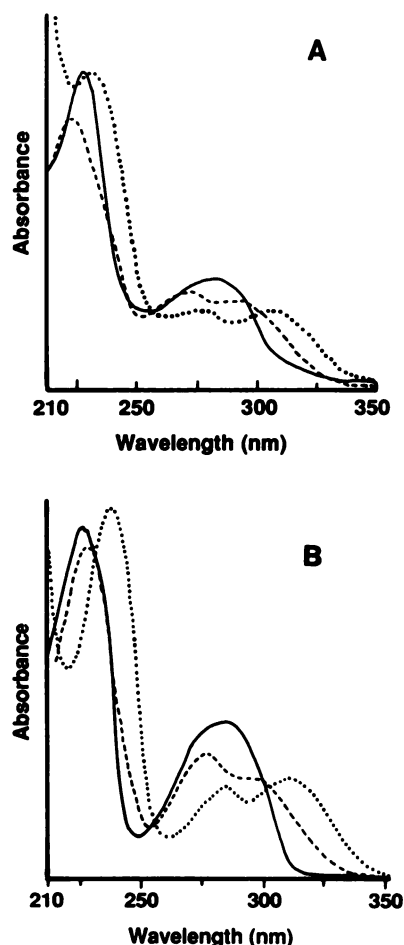
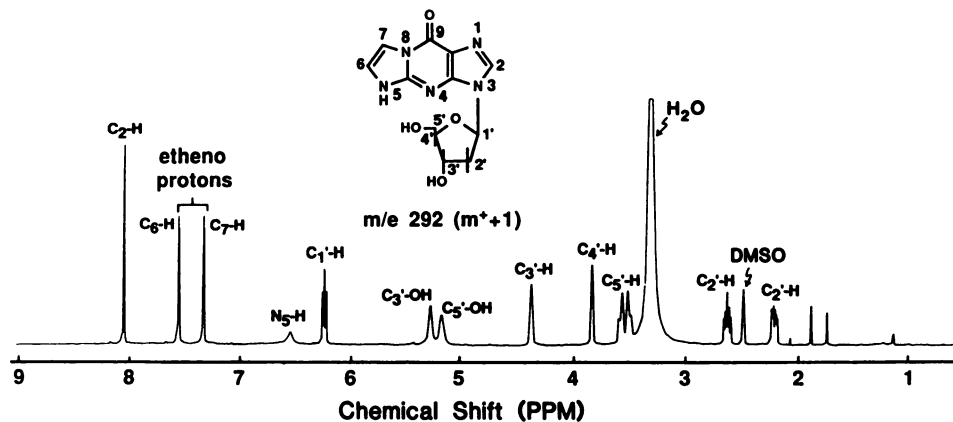


Fig. 2. UV spectra at pH 1 (—), pH 7 (---), and pH 13 (····) of (A) adduct 1 versus (B) reference 1,N²-ethenodeoxyguanosine.

Fig. 3. Proton NMR spectra (400 MHz) of adduct 1 in dimethyl sulfoxide-*d*₆ (DMSO).



and 53 ml on HPLC System 1. These adducts are designated as 7, 8, and 9 (Fig. 1B). These adducts, unlike adducts 2, 3, 5, and 6, were not converted to 1,N²-ethenodeoxyguanosine in base. They possessed UV spectra characteristic of the 1,N²-propanodeoxyguanosine adducts obtained from acrolein or crotonaldehyde (14) and similar to that reported recently by Winter *et al.* (19) from reaction of *trans*-4-hydroxy-2-hexenal and -nonenal.

The conversion of adducts 2, 3, 5, and 6 in base to 1,N²-ethenodeoxyguanosine was unexpected. This process can be monitored by UV at λ_{\max} 306 nm. Fig. 4 shows the conversion of adduct 2 in a pH 10.5 solution to 1,N²-ethenodeoxyguanosine at 25°C. This conversion appeared to follow first-order kinetics with $t_{1/2}$ = 9 min. The isobestic points at 246 and 281 nm indicates the conversion is quantitative. Entirely analogous results were obtained with adducts 3, 5, and 6. Depurination of adducts 2, 3, 5, and 6 in 0.1 N HCl at 37°C resulted in two guanine adducts eluting at 44 and 48 min using HPLC System 1. These two guanine adducts had identical UV spectra with λ_{\max} at 249 nm, 276 nm (pH 1) and 247 nm, 275 nm (pH 7.0). However, at pH 10.5 both guanine adducts converted to a product that eluted at 19 min using the same HPLC system. This product also coeluted with the depurinated product obtained from adduct 1 and showed UV spectra identical to that of 1,N²-ethenoguanine (17). These results indicate that adducts 2, 3, 5, and 6 are diastereomers. Consistent with these findings,

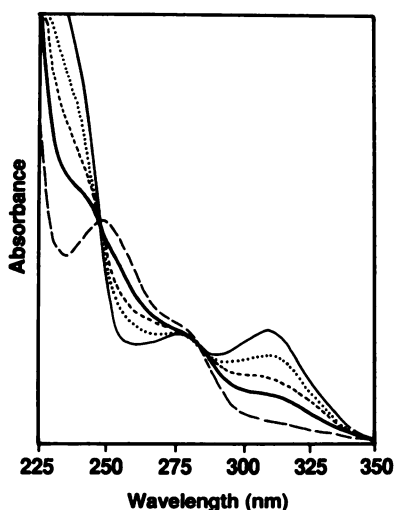


Fig. 4. Conversion of adduct 2 in a pH 10.5 medium to 1,N²-ethenodeoxyguanosine as monitored by UV. Spectra were taken at 2-min intervals. For clarity, spectra were taken at 1 min (—); 5 min (---); 9 min (····); 15 min (- · - ·), and 27 min (— — —).

reactions of deoxyguanosine and *trans*-4-hydroxy-2-nonenal carried out at room temperature and pH 10 resulted in the formation of 1,N²-ethenodeoxyguanosine as the major product.

This conversion of adducts to 1,N²-ethenodeoxyguanosine under mild conditions represents a possible approach to develop a simple marker for measuring potential DNA damage by *trans*-4-hydroxy-2-nonenal and related aldehydes. Therefore, we studied the conversion in the presence of other unmodified nucleosides. Adducts 2, 3, 5, and 6 were added to calf thymus DNA hydrolysates and the conversion was carried out at pH 10.5 as described in "Materials and Methods." The results showed that these adducts also converted quantitatively to 1,N²-ethenodeoxyguanosine in the presence of DNA hydrolysates.

DISCUSSION

The formation of 1,N²-ethenoguanosine was first reported as a product in the reaction of guanosine with chloroacetaldehyde, a metabolite of vinyl chloride (17). Alternatively, 1,N²-ethenoguanosine can be obtained from reactions of epoxides of α,β -unsaturated aldehydes with guanosine. Reaction of epoxide of crotonaldehyde with guanosine in base gave 1,N²-ethenoguanosine in 40% yield (20). Glycidaldehyde, the epoxide of acrolein, yielded a substituted 1,N²-etheno adduct upon reaction with guanosine in base (21). By adopting the mechanism by Nair and Offerman (20), we proposed a mechanism for the formation of 1,N²-ethenodeoxyguanosine adduct from *trans*-4-hydroxy-2-nonenal. This mechanism is illustrated in Fig. 5. Epoxidation of *trans*-4-hydroxy-2-nonenal by a hydroperoxide of THF could

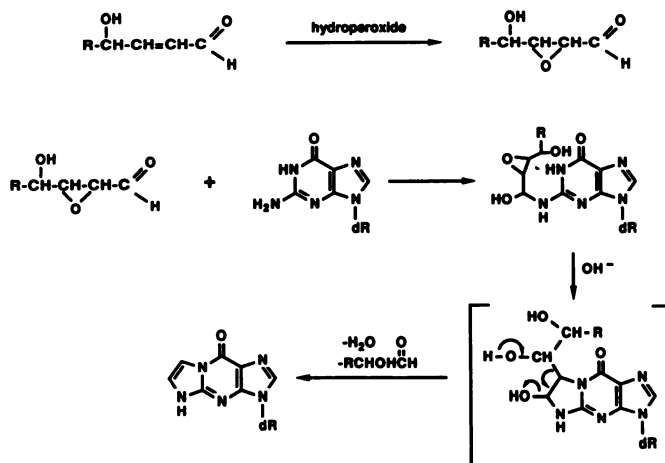


Fig. 5. Mechanism for the formation of 1,N²-ethenodeoxyguanosine from *trans*-4-hydroxy-2-nonenal in THF.

give the corresponding epoxy nonanal. Nucleophilic addition of the exocyclic amino of guanine to the epoxy aldehyde could form N²-substituted deoxyguanosine adducts. These adducts, upon base treatment, could cyclize via nucleophilic attack at the epoxy group by N-1, followed by eliminations of α -hydroxy aldehyde and H₂O to yield the 1,N²-ethenodeoxyguanosine adduct. The involvement of the epoxide in this reaction was initially suggested by the observations that light unprotected THF contains a considerably higher concentration of peroxide than light protected THF⁴ and by replacing light unprotected THF with ethanol which resulted in the formation of adducts that were not converted. Additional support was provided by carrying out parallel reactions in which either light protected THF or light protected THF containing *tert*-butyl hydroperoxide was used. Contrary to the adducts formed in light protected THF, the addition of *tert*-butyl hydroperoxide resulted in the formation of adducts which were converted to 1,N²-ethenodeoxyguanosine and these adducts were identical both spectroscopically and chromatographically to those formed in the reactions using light unprotected THF. The complete structural characterization of adducts 2 to 6 and their stereochemical properties are currently under investigation.

Like other α,β -unsaturated carbonyl compounds, *trans*-4-hydroxy-2-nonenal or its epoxide readily forms adducts under physiological conditions with deoxyguanosine. Direct Michael addition yields 1,N²-propanodeoxyguanosine adducts as reported by Winter, *et al.* (19), whereas reactions via the epoxide give adducts which can be quantitatively converted to 1,N²-ethenodeoxyguanosine in mild base. *In vitro* studies have shown that acrolein or crotonaldehyde are converted to the corresponding epoxides by microsomal enzymes (22). While the formation of the epoxide of *trans*-4-hydroxy-2-nonenal has yet to be demonstrated, it is quite possible that epoxy nonanal could be formed in a cellular microsomal system or in a lipid peroxidation system in which hydroperoxides are generated. In addition, it is conceivable that reactions with the epoxides of other homologous alkenals could form structurally related adducts which are also converted to 1,N²-etheno adducts. These results suggest that 1,N²-ethenodeoxyguanosine could provide a simple marker for assessing possible DNA damage by the epoxide of endogenously formed *trans*-4-hydroxy-2-nonenal generated in lipid peroxidation or by other related aldehydes. To detect 1,N²-etheno adduct after base conversion in a modified DNA, it is required to develop a ³²P-postlabeling method using synthetic 1,N²-ethenodeoxyguanosine 3'-monophosphate or a monoclonal antibody based immunoassay using 1,N²-ethenodeoxyguanosine coupled to a carrier. These detection methods have been applied to 1,N²-propanodeoxyguanosine adducts in acrolein or crotonaldehyde modified DNA (23). The relative levels of 1,N²-etheno and 1,N²-propanodeoxyguanosine adducts in DNA could serve as an index in assessing the role of epoxidation and direct Michael addition in DNA damage by *trans*-4-hydroxy-2-nonenal and related aldehydes.

⁴ Determined by KI test as follows. Add 1 ml of freshly prepared 10% aqueous KI to 2 ml of the solution to be tested, shake, and let it stand for 1 min. Appearance of a yellow color indicates peroxide.

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