The 1800–1400 cm^{-1} region FTIR of adduct **2** (Figure 2B, curve **2**) consists of bands due to the mitosene and guanine moieties. The mitosenes exemplified by **5** exhibit a ca. 1722-cm^{-1} band due to the carbamate group (Figure 2B, curve **5**) but this region is completely transparent in guanines. Weighted subtraction of the spectrum of **5** from that of **2** using the 1722-cm^{-1} band as subtraction marker thus produces the difference spectrum Figure 2C which is composed of guanine-related bands. The peaks in curve C of Figure 2 compare most closely with the FTIR 3 N7-(hydroxyethyl)guanine,[11] curve E, Figure 3, but the conclusion is not unambiguous. In contrast, a comparison of differential SEDIR curve in Figure 2c with curves in Figure 3a–f shows clearly that the three asterisked peaks together with a few others in curve c in Figure 2 only match those of Figure 3e.

The above-mentioned examples demonstrate that diff. SEDUV and differential SEDIR offer extremely powerful micromethods for structural studies of molecules containing two (or more) nonconjugated moieties. While the present example is rather specific, we believe that the additional information gained from second derivatization should make it an attractive technique in a broad range of investigations.

Supplementary Material Available: Expanded scale FTIR and SEDIR spectra for all compounds; FTIR and SEDIR spectra of M–guanine B (9 pages). Ordering information is given on any current masthead page.

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Nature of the Destruction of Deoxyguanosine Residues by Mitomycin C Activated by Mild Acid pH

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Received April 16, 1985

Alkylation of genomic deoxyguanosine residues at the 7-position has been implicated as the primary event in the chemically induced carcinogenesis/mutagenesis resulting from exposure to agents such as aflatoxin B$_1$,[1,2] N-mustards, and dimethyl sulfate.[1] The modified deoxyguanosine residues produced by 7-alkylation decompose readily via (i) loss of the ribofuranoside moiety to form apurinic DNA sites or (ii) imidazolium-ring scission to generate N-formamidopyrimidine (NFP) DNA bases (see below). With respect to the latter case, while numerous studies have been conducted on NFP-ribosides, including DNA, their exact structures have continued to elude definition.[1,2]

We wish to report that mitomycin C[3] (MC, **1**), the clinically used antitumor antibiotic, alkylates d(GpC)[4] and DNA in vitro

Figure 1. Products resulting from MC (**1**) and d(GpC) (**3**). Intermediate **17** has not been isolated. *M* in **4–8** denotes the mitosene moiety.

at the guanine 7-position under acidic activation.[5] This finding raises the possibility that MC activation in vivo may well be accomplished by protonation,[6] the other possibility being the well-known (in vitro) reductive activation of MC.[7–9] Furthermore, we report the full structures of the elusive imidazolium-cleaved NFP moieties generated from base-treated 7-ethylguanosine (**9**) (Figure 2). On the basis of the latter model studies, we have also characterized the NFP-deoxyribose–mitosene **6–8** system shown in Figure 1.

An aqueous solution of 18 μmol of d(GpC) (**3**) acidified to pH 3.5–4.0 with Bio-Rad AG 50-W-X-B beads was treated with MC (20 μmol) and the solution adjusted to 2.5 mL with water and maintained at pH 3.5–4.0 by additions of 0.01 N HCl. The solution was neutralized after 3.5 h, room temperature, and chromatographed on Sephadex G-25[9] to give adduct fractions designated M–guanines and M–d(GpC); digestion of M–d(GpC) with snake venom diesterase gave M–dG$_1$ (major) and M–dG$_{11}$ (minor). The latter, the major product under reductive conditions, consists of type **2** mitosene[10] 1α- and 1β-adducts to the O^6 of dG.[9]

The M–guanines were separated by HPLC, Ultrasphere ODS, MeCN/0.02 M aqueous KH$_2$PO$_4$ (pH 5.0), 8/92, into **4** and **5** (Figure 1). The ^{1}H NMR in Me$_2$SO-d_6 showed three exchangeable 2 H signals assigned as follows by comparison with 2β,7-diamino-1α-hydroxymitosene and guanine: 6.74/6.58 (**4**) and 6.52/6.36 ppm (**5**), 10a-/7-NH$_2$; 6.20 (**4**) and 6.18 ppm (**5**), guanine 2-NH$_2$ (mitosene 2-NH$_2$ signals are broad and rarely observed). The guanine 8-H's were observed at 7.91 (**4**) and 7.46 ppm (**5**). The rest of the spectra showed typical mitosene peaks;[9] **4** and **5** are thus type **2** adducts. The linkage of the mitosene group to N-7 was determined by differential second-derivative UV and FTIR spectroscopy.[11] Finally, the CD of **4**, Δε –0.081 at 525 nm, and **5**, Δε +0.112 at 520 nm show them to be 1α- and 1β-adducts, respectively.[9]

HPLC (conditions same as above) of 200 μg of M–dG$_1$ gave an ill-resolved four-peak pattern which was reproduced upon reinjection of any single peak; M–dG$_1$ is therefore a mixture of interconverting compounds. The ^{1}H NMR showed nonex-

† City University of New York.
‡ Columbia University.
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(4) This dinucleoside phosphate was chosen as the simplest model for a polynucleotide inasmuch as MC binding to DNA increases with increasing G-C base-pair content.
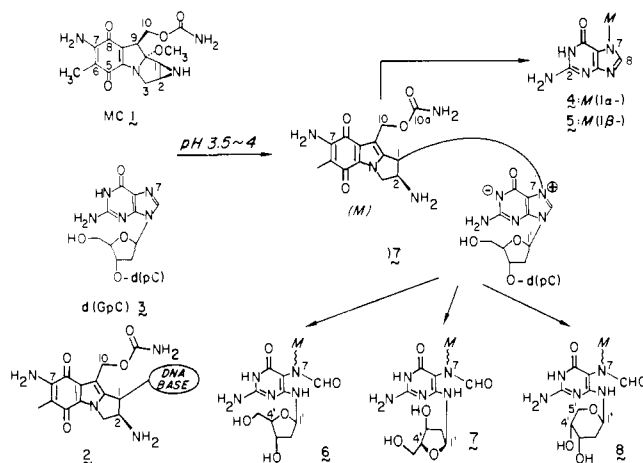(5) Lipman, R.; Tomasz, M. *J. Am. Chem. Soc.* **1979**, *101*, 6063.
(6) The weakly acidic conditions used here for activation may mimic the low pH found inside gastric and solid tumors, for which MC is an effective treatment. Douglass, H. O.; Lavin, P. T.; Goudsmit, A.; Klassen, D. J.; Paul, A. R. *J. Clin. Oncol.* **1984**, *2*, 1372.
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(8) Hashimoto, Y.; Shudo, K.; Okamoto, T. *Tetrahedron Lett.* **1982**, 677; *Chem. Pharm. Bull.* **1983**, *31*, 861; *Acc. Chem. Res.* **1984**, *17*, 403.
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(10) Mitosene derivatives are the end-products of MC activation/alkylation. "Mitosene" refers to the structure as in **2**, without substituents at C-1,-2,-7: Webb, J. S.; Cosulich, D. B.; Mowat, J. H.; Patrick, J. B.; Broschard, R. W.; Meyer, W. E.; Williams, R. P.; Wolf, C. F.; Fulmore, W.; Pidacks, C.; Lancaster, J. E. *J. Am. Chem. Soc.* **1962**, *84*, 3185.
(11) Verdine, G. L.; Nakanishi, K., preceding paper in this issue.
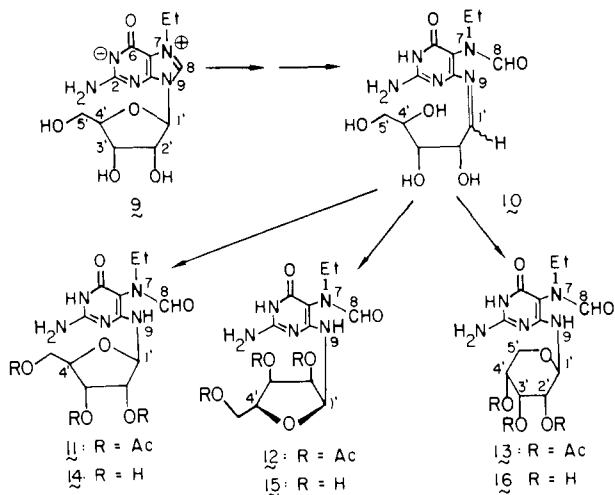
Figure 2. Products resulting from mild base treatment of 7-ethylguanosine (**9**).

changeable signals at 6.7-8.2 ppm corresponding to *N*-formyl, thus suggesting imidazole ring opening. Because 7-substituted purine nucleosides are also known to undergo an important but unclarified imidazole ring fission,[12,13] a model system was first investigated. Namely, 7-ethylguanosine (**9**)[14] was treated with 2N NH$_4$OH (room temperature, 2 lyophilized, lyophilized, and passed through Sephadex G-25. HPLC of the product gave an ill-resolved multiple peak pattern, the components of which also interconvert at room temperature. Since the UV resulting from subtraction of 2β,7-diamino-1α-hydroxymitosene from M-dG$_I$ was almost identical with that of base-treated **9**, the latter was studied as a model for the M-dG$_1$ constituents.

Thus the NH$_4$OH-treated 7-ethylguanosine (**9**) was acetylated and submitted to HPLC (IBM-ODS, MeCN/H$_2$O 15/85) to give triacetates (90% yield) **11**, **12**, and **13** (Figure 2) in 1:2:2 ratio: CI-MS *m/z* 456 (identical for **11-13**); UV (in CH$_3$CN) for all three with peaks at 211, 238 (sh), and 272 nm are typical for ring-opened 7-alkylguanosines. the ^{1}H NMR of **11**[15] and **12**[16] show them to be the C-1' β- and α-anomers, respectively, of D-ribofuranose triacetate linked to N-9 of the imidazole-cleaved guanine moiety (Figure 2); similarly, **13**[16] is the β-anomer of ribopyranose triacetate linked to N-9. The C-1' configurations of **11-13** were determined by NOE experiments. The furanoses and pyranose result from addition of 4'- and 5'-OH in **10** to the imine bond (Figure 2).[17]

The unacetylated mixture from **9** was separated by HPLC, (IBM-ODS, MeCN/H$_2$O 1.5/98.5) to yield pure **14**, **15**, and **16** upon collection at -78 °C; acetylation gave respective acetates **11**, **12**, and **13**.

We thus conclude that MdG$_1$ also consists of interconverting ribosides **6-8** (Figure 1). Substitution of calf thymus DNA for d(GpC) (**3**) in the reaction with acid-activated MC was also found to yield M-guanines **4/5** and the MdG$_I$ mixture.[18]

Although many carcinogens alkylate guanosine residues at N-7, the imidazolium fission products had to date not been adequately characterized. Apurination or rearrangement of the riboside

moiety as shown in Figure 1 could lead to destruction of the secondary structure of DNA at the alkylation site. The nature of such ring-cleaved moieties resulting from interaction of MC with double-stranded DNA, as well as their relationship to excision-repair mechanisms, remains to be clarified.

Supplementary Material Available: Difference UV of MdG$_1$ minus 2β,7-diamino-1α-hydroxymitosene, ^{1}H NMR of **11-16**, ^{1}H NMR of MdG$_1$ mixture (downfield region), ^{1}H NMR of crude hydrolysis mixture from base treatment of 7-ethylguanosine, and ^{1}H NMR of M-guanine A (**4**) and M-guanine B (**5**) (11 pages). Ordering information is given on any current masthead page.
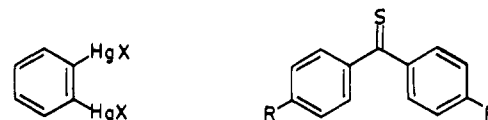
Multidentate Lewis Acids. Reduction of Thioketones in the Presence of Organomercury Trifluoroacetates

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Recently we described the unusual coordination chemistry of three bidentate Lewis acids, the 1,2-phenylenedimercury dihalides **1-3**.[1] Unlike simple monodentate organomercuric halides, bi-

1 (X = Cl)
2 (X = Br)
3 (X = I)
4 (X = OOCCF$_3$)

5 (R = OCH$_3$)
6 (R = N(CH$_3$)$_2$)
7 (R = H)

dentate acids **1** and **2** form isolable complexes with added halides. We have now discovered that related bidentate Lewis acids bind and activate thioketones, facilitating their reduction by formal donors of hydride.

Deep blue solutions of bis(4-methoxyphenyl)methanethione (**5**)[2] in CH$_3$CN turned yellow-green when equimolar amounts of bis(trifluoroacetato)-1,2-phenylenedimercury (**4**)[3,4] were added. At the same time, singlets at δ -1595 (CD$_3$CN)[5a] in the ^{199}Hg

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(2) Scheeren, J. W.; Ooms, P. H. J.; Nivard, R. J. F. *Synthesis* **1973**, 149-151.

(3) Prepared in 87% yield from chloride **1** by treatment with aqueous NaOH, followed by neutralization with CF$_3$COOH.

(4) The structure assigned to this new compound is consistent with its elemental analysis and its IR, NMR, and mass spectra. These data are included in the supplementary material.

(5) (a) All δ (^{199}Hg) are reported in parts per million relative to external neat dimethylmercury. Negative values indicate upfield shifts. (b) The direction of this shift is persuasive evidence of additional coordination to mercury. Kidd, R. G.; Goodfellow, R. J. In "NMR and the Periodic Table"; Harris, R. K., Mann, B. E., Eds.; Academic Press: London, 1978; pp 195-278. (c) Small upfield shifts in the ^{13}C NMR spectra of complexed thioketones are also reported by: Bret, J.-M.; Castan, P.; Commenges, G.; Laurent, J.-P.; Muller, D. *J. Chem. Soc., Chem. Commun.* **1983**, 1273-1275. Burman, S.; Sathyanarayana, D. N. *J. Inorg. Nucl. Chem.* **1981**, *43*, 1189-1192. Olah, G. A.; Nakajima, T.; Prakash, G. K. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 811-812.

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(14) Cf. 7-methylguanosine: Jones, J. W.; Robins, R. K. *J. Am. Chem. Soc.* **1963**, *85*, 193.

(15) **11-16** are each present as a set of inseparable rotameric formyl isomers; thus, many protons give rise to more than one signal. ^{1}H NMR of **11** (Me$_2$SO-d_6) δ 10.78 (br s, exchangeable, N^1-H); 8.11/7.71 (s, 8-CHO), 7.38/7.23 (d, exchangeable, N^9-H), 6.77/6.65 (br s, exchangeable, 2-NH$_2$), 5.93/5.82 (dd, 1'-H), 5.42/5.34 (dd, 2'-H), 5.25/5.20 (dd, 3'-H), 4.30-3.95 (m, 4'-H/5'-H), 3.52-3.12 (m, 7-CH$_2$), 0.96/0.92 (t, 7-CH$_2$CH$_3$).

(16) Supplementary material.

(17) Cf.: Lönnberg, H.; Lehikoinen, P. *J. Org. Chem.* **1984**, *49*, 4964.

(18) Tomasz, M.; Lipman, R.; Verdine, G.; Nakanishi, K., manuscript in preparation.