Metal Ion–C(8) Binding in Purine Nucleosides. Ready Formation of Carbon-bound Inosine and Guanosine Complexes of Methylmercury(II)

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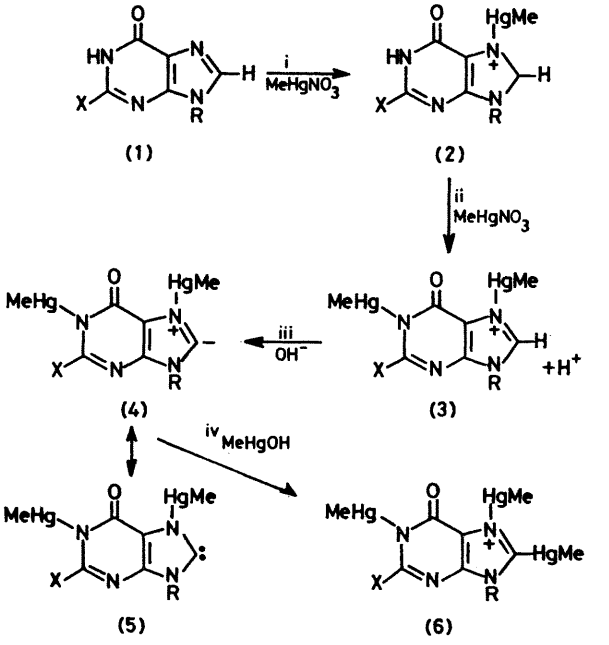
Summary The increased lability of purine nucleoside C(8)–H bonds upon co-ordination of a metal ion to the adjacent N(7) position has been used to explain the observed formation of C(8)-bonded inosine and guanosine methylmercurials, these being the first reported carbon bound species formed from the interaction of nucleosides with organomercurials.

THE binding of heavy metal ions to nucleosides and nucleotides has been the subject of much recent investigation.[1] The $MeHg^{II}$ cation has received particular attention in view of its unifunctionality and readily detected Raman spectroscopic[2] and n.m.r. properties.[3] A knowledge of the mode of binding between $MeHg^{II}$ and nucleic acid constituents takes on added importance in view of the mutagenic nature of some organomercurials.[4]

As a result of u.v. difference spectral studies of the interaction between Hg^{II}, $MeHg^{II}$, and nucleosides, Simpson[5] proposed several specific binding sites, which were subsequently given firmer basis by the Raman difference spectroscopic results of Tobias and his co-workers.[6] The results suggested that in the case of the purine nucleosides inosine (**1**; X = H, R = ribose) and guanosine (**1**; X = NH_2, R = ribose), for r = [$MeHg^{II}$]/[nucleoside] = 1 at low pH, N(7) co-ordination is favoured. Thus formation of the species [MeHg(nucH)]$^+$ (**2**) was postulated (nucH = nucleoside), since N(1) is protonated under these conditions. For r = 1 and higher pH [*ca.* pK_a for ionization of N(1)-H], formation of the corresponding N(1)-bound complex, MeHg(nuc), was favoured. Very recent studies have shown that the 1:1 guanosine[7,8] and inosine[8] complexes, hitherto only postulated to account for results in solution, can be isolated as solids from aqueous solution by mixing equimolar quantities of the nucleoside and $MeHgNO_3$ under appropriate conditions of pH and allowing the complexes to crystallize out. These same studies[7,8] have also shown that at both high and low pH, for r = 2, the 2:1 complexes [$(MeHg)_2$(nuc)]NO_3 can be isolated. The sequence of reactions (i) and (ii) in the Scheme would account for the formation of these species.



SCHEME

In our own work,[8] the attempted preparation of the 2:1 complex of inosine (**3**; X = H, R = ribose) at pH 7—8, led to the formation of a white precipitate in low yield when the solution was left for 2 days. The ^1H n.m.r. spectrum suggested a 3:1 $MeHg^{II}$–inosine complex. The same observation was made for the guanosine (r = 2) system at pH 7; at pH 3 only the 2:1 complex was pro-

duced. Subsequent experiments with inosine have shown that heating (50 °C; 30 min) an aqueous solution containing the nucleoside and $MeHgNO_3$ ($r = 3$) results in the formation of $[(MeHg)_3(ino)]NO_3$ ($inoH_2$ = inosine).† Similar findings have been observed in the guanosine ($r = 3$) system, although incomplete substitution of H(8) by $MeHg^{II}$ occurs at this stoicheiometry owing to the additional interaction of $MeHg^{II}$ with the 2-amino group. The 60 MHz ^1H n.m.r. spectrum of the inosine complex is shown in the Figure. The low field signal occurring at δ 8·24 is assigned

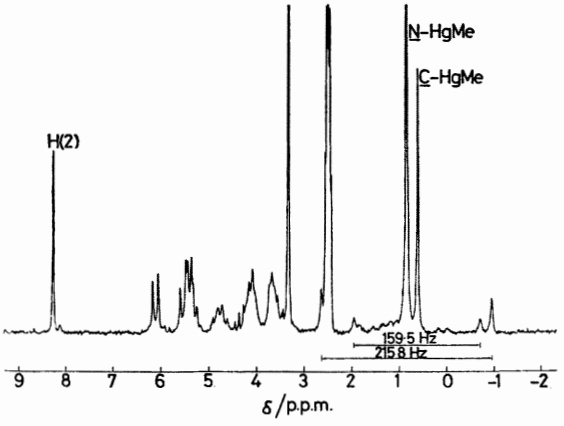


FIGURE. The 60 MHz ^1H n.m.r. spectrum of (**6**; X = H, R = ribose) in $(CD_3)_2SO$. δ Values (p.p.m.) to internal Me_4Si (signal not shown).

to H(2) of (**6**) by comparison with the spectrum of (**3**) in which H(2) is found at δ 8·32 and H(8) at δ 8·93. The absence of a signal attributable to H(8) is readily apparent and is indicative that C(8) is the third co-ordination site. The distinction between *C*- and *N*-bound‡ $MeHg^{II}$ is clearly shown by the two-bond coupling constants, $^2J(^{199}Hg-^1H)$, of 159·5 and 215·8 (±0·5) Hz, respectively, reflecting the greater stability of the *C*-bound $MeHg^{II}$.[1d] Separation of the respective methyl proton chemical shifts, however, is only *ca.* 0·2 p.p.m.

The proposed mechanism of the reaction (Scheme) derives from the increased acidity of the C(8) proton upon co-ordination of a metal ion to N(7) (the metal activation factor).[9] Hydroxide ion abstraction of the C(8) proton (reaction iii) leads to formation of the ylide (**4**). Instead of reprotonation by reaction with the solvent which occurs in the hydrogen exchange process,[9] irreversible formation of the C(8)-bound $MeHg^{II}$ species predominates and (**6**) results.

Metal–carbon bonded structures containing the imidazole function can be considered to be either ylide [involving *e.g.* (**4**)] or carbene [involving *e.g.* (**5**)] complexes. Schönherr and Wanzlick[10] succeeded in preparing a C(2)-bonded Hg^{II} derivative of the 1,3-diphenylimidazolium ion, in the presence of potassium t-butoxide, a reaction which plausibly proceeds *via* the corresponding ylide/carbene species in a manner analogous to steps (iii) and (iv) of the Scheme.

The potential use of mercuriated derivatives of nucleotides has been discussed previously by Dale and his co-workers.[11] Using acetoxymercuriation reactions, these workers were successful in isolating the C(5)-mercuriacetate derivatives of pyrimidines; reactions involving C(8) of purines were not as successful. The generation of purine derivatives such as (**6**) could potentially lead to useful intermediates for the production of C(8)-chloromercuric compounds. Moreover, the present findings of the binding of $MeHg^{II}$ at a carbon centre of purine nucleosides points to possible alternative explanations of the mutagenicity of organomercurials.

We thank the Natural Sciences and Engineering Research Council of Canada for support of this work *via* the Strategic Grants Program.

(*Received, 30th March* 1979; *Com.* 324.)

† Satisfactory analytical data were obtained for this compound.

‡ The resonance for the *N*-bound $MeHg^{II}$ protons (integrates to 6H) is an average value comprising contributions from both N(1)- and N(7)-bound $MeHg^{II}$ as a result of rapid exchange of the metal ion.

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