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Direct detection of the mercury–nitrogen bond in the thymine–Hg^{II}–thymine base-pair with ¹⁹⁹Hg NMR spectroscopy†

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We have observed the 1-bond ¹⁹⁹Hg–¹⁵N J-coupling (¹J(¹⁹⁹Hg, ¹⁵N) = 1050 Hz) within the Hg^{II}-mediated thymine–thymine base pair (T–Hg^{II}–T). This strikingly large ¹J(¹⁹⁹Hg, ¹⁵N) is the first one for canonical sp²-nitrogen atoms, which can be a sensitive structure-probe of N-mercured compounds and a direct evidence for N-mercuration.

Mercury-199 NMR spectroscopy is used to probe coordination modes, coordinating elements, and the nature of metals in biomolecules.¹ Within the ¹⁹⁹Hg NMR data, those for N–Hg bonds are of particular importance as metals in proteins and in DNA/RNA molecules frequently interact with nitrogen atoms. Moreover, the N–Hg^{II} bond formation in the Hg^{II}-mediated thymine–thymine base pair (T–Hg^{II}–T) corresponds to an irregular “deprotonative” N-mercuration in water of a bulk proton source.^{2–7} In addition, extraordinary thermal stability with a positive reaction entropy was observed for N–Hg^{II}–N bonding in a DNA duplex.^{8–12}

The stability of the Hg–DNA complex can be explained partly owing to the metallophilic attraction between Hg atoms in consecutive T–Hg^{II}–T base pairs, and the metallophilic attraction itself is a recent hot topic of inorganic chemistry.^{13–17}

Despite such biological/chemical importance, N–Hg^{II} bonds remained uncharacterized. Particularly, the measurements of ¹J(¹⁹⁹Hg, ¹⁵N) is challenging, owing to the large chemical shift anisotropy (CSA) of ¹⁹⁹Hg and low natural abundance of ¹⁵N.¹⁸ The only ¹J(¹⁹⁹Hg, ¹⁵N) value of a linear two-coordinate complex was recorded for (Me₃Si)₂N–Hg^{II}–N(SiMe₃)₂.¹⁹ The ¹J(¹⁹⁹Hg, ¹⁵N) values for other coordination modes of ¹⁹⁹Hg are also limited to Hg^{II}–CyDTA (*trans*-1,2-diaminocyclohexane-*NNN'*-tetraacetate)²⁰ and Hg^{II}–(NHMe₂)₂Cl₂²¹ complexes (Tables S1 and S2 in ESI†). However, in all cases, some of important parameters such as structure, ¹⁵N or ¹⁹⁹Hg NMR chemical shifts ($\delta(^{15}\text{N})$ or $\delta(^{199}\text{Hg})$), 2-bond ¹⁵N–¹⁵N J-couplings across Hg^{II}, (²J(¹⁵N, ¹⁵N)) or hybridization state of nitrogen atoms always remained unknown. Therefore, a complete ¹⁹⁹Hg/¹⁵N NMR J/ δ dataset for a structurally well-defined compound has never been recorded so far.

In this sense, the T–Hg^{II}–T base pair (Fig. 1) provides an excellent platform for studying ¹J(¹⁹⁹Hg, ¹⁵N), as its chemical and 3-dimensional (3D) structures have been solidly determined^{3,6,7,12,22} and historically accumulated data^{2–4,23,24} are available. Regarding the NMR parameters of the T–Hg^{II}–T base pair, the ¹⁹⁹Hg chemical shift $\delta(^{199}\text{Hg})$,²³ the 2-bond ¹⁵N–¹⁵N J-coupling across Hg^{II}, ²J(¹⁵N, ¹⁵N)⁶ and $\delta(^{15}\text{N})$ ⁶ were previously determined. Hence, the only missing NMR parameter for characterizing the unique physicochemical properties of the N–Hg^{II} bond is ¹J(¹⁹⁹Hg, ¹⁵N). Once it is measured for T–Hg^{II}–T, the T–Hg^{II}–T system will provide a complete J/ δ dataset for ¹⁹⁹Hg/¹⁵N with a reliable structure, and the ¹J(¹⁹⁹Hg, ¹⁵N) value may provide a key concept for constructing molecular devices^{8,25–44} from Hg^{II}–DNA complexes.

To measure ¹J(¹⁹⁹Hg, ¹⁵N) in T–Hg^{II}–T, its highly soluble ¹⁵N-labeled complex is crucial for ¹⁹⁹Hg/¹⁵N signal detection. In addition, Hg^{II}–ligand exchanges must be suppressed to avoid the disappearance of ¹J(¹⁹⁹Hg, ¹⁵N) owing to exchange broadening. Considering these facts, we determined the ¹J(¹⁹⁹Hg, ¹⁵N) value by using a thymidine–Hg^{II}–thymidine complex (T–Hg^{II}–T).

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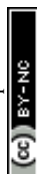
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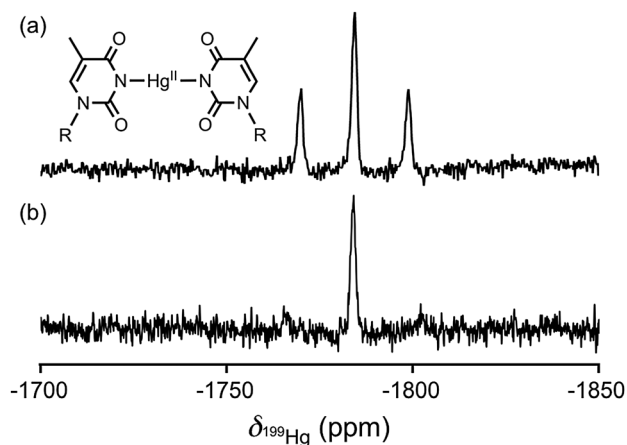


Fig. 1 One-dimensional ^{199}Hg NMR spectrum (71.667 MHz for ^{199}Hg frequency) of the thymidine- Hg^{II} -thymidine complex (25 mM) in $\text{DMSO}-d_6$ under natural abundance ^{199}Hg (16.84%). (a) The 1D ^{199}Hg NMR spectrum without ^{15}N -decoupling. (b) The 1D ^{199}Hg NMR spectrum with ^{15}N -decoupling. The ^{199}Hg NMR chemical shifts are displayed with respect to dimethylmercury (0 ppm) using 1 M HgCl_2 in $\text{DMSO}-d_6$ as a secondary reference (−1501 ppm).⁵⁵ The chemical structure of the T- Hg^{II} -T is depicted above the spectrum, with “R” denoting ribose.

To confirm if the splitting of the ^{199}Hg resonance is $^1J(^{199}\text{Hg}, ^{15}\text{N})$, we monitored the disappearance of the splitting upon ^{15}N -decoupling using a special NMR probe for detecting ^{15}N -heteronucleus correlations. Lastly, the derived $^1J(^{199}\text{Hg}, ^{15}\text{N})$ value was also investigated theoretically with relativistic density functional theory (DFT) including spin-orbit coupling effects.

In this study, we used ^{15}N -labeled thymidine to produce ^{15}N -labeled T- Hg^{II} -T. To suppress the exchange of Hg^{II} ligands, we prepared a sample that contained T- Hg^{II} -T exclusively, without any anion (competitive Hg^{II} -ligands against thymine). Such sample was prepared by the reaction $[\text{thymidine} + \text{HgO} \rightarrow \text{T-}\text{Hg}^{\text{II}}\text{-T} + \text{H}_2\text{O}]$ followed by H_2O evaporation.²⁴ The resulting pure ^{15}N -labeled T- Hg^{II} -T was subjected to ^{199}Hg NMR measurements in dimethyl sulfoxide- d_6 ($\text{DMSO}-d_6$) (Fig. 1). The ^{199}Hg NMR signal was successfully observed as a triplet resonance at $\delta(^{199}\text{Hg}) = -1784$ ppm, with the absolute 1J -value $|^1J(^{199}\text{Hg}, ^{15}\text{N})| = 1050$ Hz (Fig. 1 and Table 1). The observed $\delta(^{199}\text{Hg})$ value was the same as that observed previously in T- Hg^{II} -T,²³ which ensured successful sampling.

The ^{199}Hg NMR spectrum under ^{15}N -decoupling and ^{15}N NMR spectrum were recorded to exclude the possibility that the observed splitting of the ^{199}Hg signal might arise from a structural polymorphism. Notably, the splitting disappeared upon the ^{15}N -decoupling (Fig. 1b). It should be further noted that this ^{15}N -decoupled ^{199}Hg NMR spectrum can't be recorded with conventionally available probes. This measurement became possible only by using the special probe, which can perform a ^{15}N - ^{199}Hg double resonance spectroscopy. In addition, the splitting of the ^{15}N resonance (1050 Hz) was observed as satellite peaks at $\delta(^{15}\text{N}) = 184$ ppm in the 1-dimensional ^{15}N NMR spectrum (Fig. S1 in ESI†). Thus, the splitting of the ^{199}Hg resonance shown in Fig. 1a should be interpreted as $^1J(^{199}\text{Hg}, ^{15}\text{N})$.

The $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ value of 1050 Hz for T- Hg^{II} -T was strikingly larger than the 1J -coupling of $(\text{Me}_3\text{Si})_2\text{N-}\text{Hg}^{\text{II}}\text{-N}(\text{SiMe}_3)_2$ (316.2 Hz),¹⁹

Table 1 Experimental and theoretical ^{199}Hg NMR parameters

Ligand	Method	N-hybrid ^a	$ ^1J_{\text{HgN}} ^b$	$\delta(^{199}\text{Hg})^c$
Thymine ^d	Experiment	sp^2	1050	−1784
	Theory ^e	sp^2	931 ^f	−1848
$\text{N}(\text{SiMe}_3)_2$ ^g	Experiment	$\text{sp}^2\text{-like}^h$	316.2 ⁱ	−992 ^j
	Theory ^e	$\text{sp}^2\text{-like}^h$	278.4 ^f	−827

^a Hybridization state of nitrogen atoms. ^b The “absolute” 1-bond ^{199}Hg - ^{15}N -coupling, $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$, in Hz. ^c ^{199}Hg NMR chemical shift in ppm with respect to dimethylmercury (0 ppm). ^d The T- Hg^{II} -T complex. ^e The theoretical calculation (ZORA-SO-B3LYP/TZ2P) in this work. The average values of $^1J(^{199}\text{Hg}, ^{15}\text{N})$ and $\delta(^{199}\text{Hg})$ were calculated for rotational conformers of thymidine- Hg^{II} -thymidine, because the energy barrier for rotation around the N- Hg^{II} -N axis was smaller than 1.1 kcal mol^{−1}. The calculated $\delta(^{199}\text{Hg})$ and $^1J_{\text{HgN}}$ values were therefore averaged over respective rotamers (Table S5 in ESI†). ^f The “−” sign was calculated for J -coupling (Table S4 in ESI†). ^g The $(\text{Me}_3\text{Si})_2\text{N-}\text{Hg}^{\text{II}}\text{-N}(\text{SiMe}_3)_2$ complex. ^h See Supporting discussion (ESI†) for details. ⁱ Ref. 19. ^j Ref. 53. For chemical shift referencing see the footnote to Table S1 in ESI†. It should be noted that $^{15}\text{N}^6$ and $^1\text{H}^{54}$ chemical shift perturbations for the thymidine- Hg^{II} -thymidine complexation were coherent with those observed for the formation of the T- Hg^{II} -T base-pairs in a DNA duplex (Table S1 in ESI†).

Hg^{II} -CyDTA complexes (365.7–395.5 Hz),²⁰ and $\text{Hg}^{\text{II}}\text{-(NHMe}_2)_2\text{Cl}_2$ (14.7 Hz)²¹ (Table 1 and Tables S1 and S2 in ESI†). Thus, the observed $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ value for T- Hg^{II} -T is the largest of all 1J -values reported to date.

Here we investigate the correlation between $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ value and N-hybridization state. Within the compounds whose $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ were reported, T- Hg^{II} -T and $(\text{Me}_3\text{Si})_2\text{N-}\text{Hg}^{\text{II}}\text{-N}(\text{SiMe}_3)_2$ possess the linear two-coordinate structure, and their $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ values can be compared. Regarding the N-hybridization state of $(\text{Me}_3\text{Si})_2\text{N-}\text{Hg}^{\text{II}}\text{-N}(\text{SiMe}_3)_2$, an sp^2 -like planar structure of the nitrogen atoms was suggested from the electron diffraction study,¹⁹ which is further supported by Bent's rule⁴⁵ (see Supporting discussion in ESI† for Bent's rule). Therefore, the Hg^{II} -bound nitrogen atoms in both samples belong to the sp^2 category basically, and the current data of $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ are insufficient for us to correlate between $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ and N-hybridization, due to the lack of the 1J -values for $\text{N}(\text{sp})\text{-}\text{Hg}^{\text{II}}$ and $\text{N}(\text{sp}^3)\text{-}\text{Hg}^{\text{II}}$ bonds.

As a further investigation, $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ values for the “ sp^2 nitrogen” in T- Hg^{II} -T and “ sp^2 -like nitrogen” in $(\text{Me}_3\text{Si})_2\text{N-}\text{Hg}^{\text{II}}\text{-N}(\text{SiMe}_3)_2$ were strikingly different (Table 1). However, this may be because the sp^2 -like N-hybridization in $(\text{Me}_3\text{Si})_2\text{N-}\text{Hg}^{\text{II}}\text{-N}(\text{SiMe}_3)_2$ might be different from the “canonical sp^2 nitrogen” in T- Hg^{II} -T. This possibility was also inferred from $^{14}/^{15}\text{N}$ NMR spectroscopic data,⁴⁶ where the ^{14}N NMR chemical shift for the $\text{Si}_2\text{N-}\text{Hg}^{\text{II}}\text{-NSi}_2$ linkage showed a rather sp^3 -like value ($\delta(^{14}\text{N}) = 66.2$ ppm,⁴⁶ Table S1 in ESI†). By contrast, $\delta(^{15}\text{N})$ for Hg^{II} -linked N3 in T- Hg^{II} -T is 184 ppm, and the value is located within the empirical range for an sp^2 -hybridized nitrogen (Fig. S1 and Table S1 in ESI†). From these facts, the N-hybridization state of $(\text{Me}_3\text{Si})_2\text{N-}\text{Hg}^{\text{II}}\text{-N}(\text{SiMe}_3)_2$ can't be unambiguously assigned (see also Supporting discussion in ESI† for details). However, on the basis of the investigations mentioned above, the $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ value might be a sensitive NMR parameter for detecting differences in the fine electronic structures of T- Hg^{II} -T and $(\text{Me}_3\text{Si})_2\text{N-}\text{Hg}^{\text{II}}\text{-N}(\text{SiMe}_3)_2$.



We then quantum chemically computed $|^1J(^{199}\text{Hg}, ^{15}\text{N})| = 931 \text{ Hz}$ and $\delta(^{199}\text{Hg}) = -1848 \text{ ppm}$ for T-Hg^{II}-T using DFT including relativistic corrections from the zeroth-order regular approximation (ZORA) with spin-orbit (SO) coupling, as implemented in the ADF program^{47–49} (see Table 1 and Tables S3–S5 in ESI†). The theoretical $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ and $\delta(^{199}\text{Hg})$ values agree well with the experimental data (Table 1). With reference to the theoretical values given by Bagno and Saielli ($|^1J(^{199}\text{Hg}, ^{15}\text{N})| = 670 \text{ Hz}$, $\delta(^{199}\text{Hg}) = -1727 \text{ ppm}$),⁵⁰ the theoretical $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ value was refined by using the complex where it was actually recorded (Table S3 in ESI†). The $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ value of 278.4 Hz calculated for (Me₃Si)₂N-Hg^{II}-N(SiMe₃)₂ also agreed satisfactorily with experiment (316.2 Hz).¹⁹ The signs of $^1J(^{199}\text{Hg}, ^{15}\text{N})$ for T-Hg^{II}-T and (Me₃Si)₂N-Hg^{II}-N(SiMe₃)₂ were both “–” theoretically (Table S4 in ESI†).

In order to investigate the correlation between $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ values and N-hybridization states theoretically, we further analyzed the theoretical $^1J(^{199}\text{Hg}, ^{15}\text{N})$. The calculated $^1J(^{199}\text{Hg}, ^{15}\text{N})$ values were dependent on the “Fermi Contact” + “Spin Dipole coupling” (FC + SD) term (Table S4 in ESI†). With the dominance of this FC term, one may find the correlation between the N-hybridization and $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ in the future, although it should be experimentally explored.

Empirically, the $\delta(^{199}\text{Hg})$ values are clustered in terms of linked elements, hybridization states, and other factors of Hg^{II}-linked atoms (Table S2 in ESI†). Such phenomena were explained on the basis of the empirical correlation of $\delta(^{199}\text{Hg})$ with the ionicity of the X-Hg^{II} bond (high ionicity → up-field shift of $\delta(^{199}\text{Hg})$),⁵¹ Unfortunately, owing to both a paucity of experimental $\delta(^{199}\text{Hg})$ values for a linear two-coordinate N-Hg^{II}-N linkage and the uncertain N-hybridization state in (Me₃Si)₂N-Hg^{II}-N(SiMe₃)₂, the correlation between $\delta(^{199}\text{Hg})$ and the N-hybridization state of Hg^{II}-linked nitrogen also remains obscure. Nevertheless, the highly up-field-shifted $\delta(^{199}\text{Hg})$ value for T-Hg^{II}-T among those of N-mercurated compounds suggests that N(sp²)-Hg^{II}-N(sp²) covalent linkages possess significant ionic character, which agrees with our previous studies (Table 1 and Tables S1 and S2 in ESI†).^{7,52} This observation suggests that $\delta(^{199}\text{Hg})$ values can be used as a sensitive indicator for probing the Hg^{II} coordination environment not only in C-mercurated complexes but also in N-mercurated complexes, including metalloproteins¹ and metallo-DNA/RNA.

Accordingly, ^{199}Hg NMR parameters, especially $^1J(^{199}\text{Hg}, ^{15}\text{N})$, are sensitive parameters for characterizing the electronic structures of N-mercurated complexes and their N-Hg^{II} bonds as well as their Hg atoms. Hence, the $^1J(^{199}\text{Hg}, ^{15}\text{N})$ value could be a key parameter for predicting the physicochemical properties of N-mercurated complexes and making them into molecular devices, based on a bottom-up approach.

The $|^1J(^{199}\text{Hg}, ^{15}\text{N})|$ value of 1050 Hz has been reported for canonical sp²-hybridized nitrogen for the first time. From this result, the T-Hg^{II}-T system provides a comprehensive and reliable $^{199}\text{Hg}/^{15}\text{N}$ NMR dataset for probing the Hg^{II} environment in N-mercurated compounds. This newly observed $^1J(^{199}\text{Hg}, ^{15}\text{N})$ coupling can be used for detecting N-Hg bond formations and precisely characterizing these bonds.

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