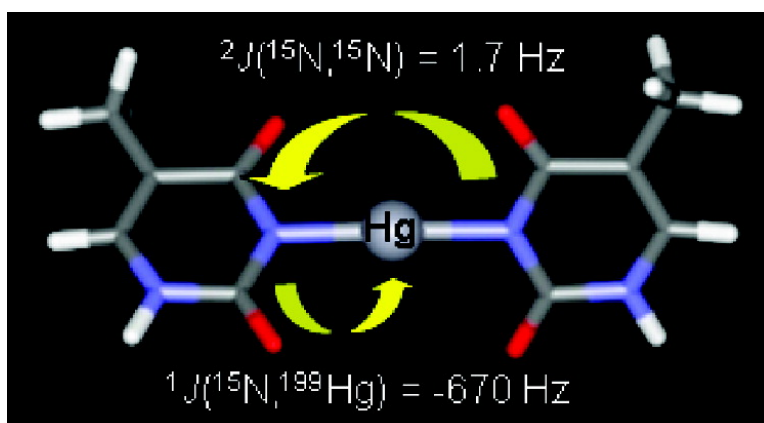Communication

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Metal-Mediated *J* Coupling in DNA Base Pairs: Relativistic DFT Predictions

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Despite the obvious importance and occurrence of interactions between metals and nucleobases, their investigation is comparatively less developed than with proteins.[1] NMR techniques play an outstanding role in these studies; in this Communication, we show that relativistic DFT methods lead to a correct prediction of NMR parameters implicated in the addition of Hg(II) to thymine according to a suggested motif[2] and indicate trends in other properties, also with other d^{10} metal ions.

Several metals are known to form diamagnetic complexes with nucleotides, notably, Mg, Ca, Ru, Cd, Zn, Hg, and Pt. In favorable cases (isotopes having $I = 1/2$ and good sensitivity, such as ^{113}Cd and ^{195}Pt), it is possible to detect NMR signals from the metal itself.

Titration experiments involving ^{15}N chemical shifts (nitrogen is almost always involved in the coordination) can probe the onset and extent of metalation even under fast exchange; however, changes in $\delta(^{15}$N) are difficult to interpret by themselves.[1] More direct information can be provided by the detection of spin−spin coupling between a well-defined pair of nuclei since its existence can be ascribed with high confidence to the existence of bonding between the two, provided that exchange is slow. Again, however, the magnitude of such couplings is very difficult to predict on an empirical basis.

A cogent example of these difficulties is borne out by ^{15}N NMR measurements of a DNA duplex bound to Hg(II) through a thymine−thymine (T−T) mismatch.[2] The observation of J_{NN} coupling (ca. 2 Hz) was taken as direct evidence of the formation of a T−Hg−T adduct (Scheme 1), the observed coupling being classified as a Hg-mediated $^2J_{NN}$.

While this observation supports the proposed motif, it leaves several issues open. There is hardly any reference value for this coupling constant; a fair approximation was suggested to be [Ru^{II}-Cl(PPh$_3$)(BPM)$_2$]$^+$ (BPM = bis(1-pyrazolyl)methane, **1**), with a Ru-mediated $^2J_{NN}$ of ca. 4 Hz.[3] However, the latter complex bears only a formal resemblance to those of interest. Given the propensity of third-row elements (notably ^{199}Hg) to give rise to strong couplings,[4] one can legitimately argue whether (a) **1** is a significant reference and (b) the observed coupling is a reliable indicator of the proposed structure. By the same token, the observation[2] that changes in δ-(^{15}N) upon addition of Hg(II) are the opposite of those found for inner-sphere coordination of d^{10} ions to guanine[1] leaves much room for guesswork. Last but not least, failure to detect a $^1J(^{15}$N,^{199}Hg) deserves special attention since analogous couplings to amines are 200−400 Hz.[4] Given the importance attached to Hg (and other metal) adducts to DNA bases,[1,2] it is apparent that a method that allows one to make reliable predictions of NMR properties as a function of metal, structure, solvent, etc. is highly desirable.

Modern quantum chemistry methods are an established methodology to predict molecular structures and NMR properties.[5] Sychrovsky et al. have reported on the spin−spin couplings relevant

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Scheme 1. Top: Proposed Adduct Formation between Thymine and Hg^{2+}. Bottom: Structure and Numbering of [RuCl(PPh$_3$)(BPM)$_2$]$^+$, **1**
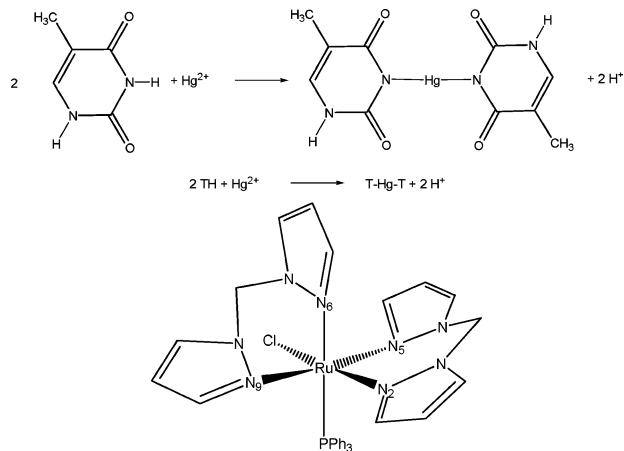
for nucleobase interactions with Mg^{2+} or Zn^{2+}.[6] On the other hand, quantum chemical calculations involving heavy atoms such as Hg are hampered by difficulties related to relativistic effects, joined with the need for an accurate modeling of core orbitals. Methodological and validation contributions[7] have pointed out the need to include spin−orbit coupling (SO) effects on nuclear shieldings, whereas such effects only have a marginal influence on coupling constants. Indeed, modern relativistic DFT methods based on the ZORA formalism and Slater basis sets are capable of yielding accurate values of chemical shifts and coupling constants which can be employed to make structural predictions or assignments.

Several recent works have concerned the computational prediction of NMR properties of heavy-atom nuclei,[8−15] including Hg.[15,16] Based on these notions, we have evaluated the possibility of modeling through-Hg coupling between base pairs. To this effect, we have investigated the proposed adduct in a model T−M−T system, with M = Zn, Cd, Hg, and thymine. We have also included the readily available Hg$_2^{2+}$ (T−Hg−Hg−T) since $^1J(^{199}$Hg,^{199}Hg) values are of the order of 10^5 Hz.[15,16] We have therefore calculated the values of ^{15}N and metal shifts, $^2J(^{15}$N,^{15}N) and $^1J(^{15}$N,M).[17]

As a validation step, we have computed the couplings in **1** (Table S1). All ^2J(N,N) values agree with experimental values to within ca. 1 Hz.[3] In particular, the coupling in **1** deemed to be most similar to the one in the T−Hg−T motif (^2J(N5,N9), 4.3 Hz) is predicted to be 5.7 Hz. We conclude that the computational level adopted here is adequate for modeling through-metal couplings and proceed with the examination of TMT complexes. Results are reported in Table 1; details are in Tables S2 and S3.

We first note that only Hg derivatives feature a linear coordination of thymine ligands; those with Zn and Cd are bent as a result of the increased stabilization due to donation by carbonyl groups to the less polarizable Zn and Cd (Figure 1). This arrangement is reminiscent of that suggested for other metal−nucleotide interac-

Table 1. Calculated NMR Parameters for Thymine Adducts with Zn^{2+}, Cd^{2+}, Hg^{2+}, and Hg_2^{2+} [a]

parameter	TZnT	TCdT	THgT	THg(1)Hg(2)T
N–M–N angle (deg)	146	156	178	178[b]
N···N distance (Å)	3.781	4.246	4.153	6.938
$\sigma(N)$[c]	33.3	24.1	19.6	−5.2
$\Delta\delta(N)$[d]	33.6	42.8	47.3	72.1
$\sigma(M)$[c]	1732	4059	10041	9505
$\Delta\sigma(M)$[e]	530	942	3406	4716
$\delta(M)$[f]		−648	−1727	−1189
$^nK(N,M)$[g]	369[h]	835[h]	3037[h]	723[h]; 1879[i]
$^nJ(^{15}N,M)$[j]	−28.2[k]	227[k]	−670[k]	−159[k]; −415[l]
$^nJ(^{15}N,^{15}N)$[j]	0.8[m]	0.4[m]	1.7[m,n]	2.4[o]

[a] TH (thymine); T (deprotonated thymine), see Scheme 1. M = ^{67}Zn, ^{113}Cd, ^{199}Hg. All results at the BLYP/TZ2P level. [b] N–Hg–Hg angle. [c] Shielding in ppm at the ZORA SO level. [d] $\sigma(TH) − \sigma(TMT)$, with $\sigma(TH)$ = 66.9 ppm. [e] Shielding anisotropy $\Delta\sigma = \sigma_{33} − (\sigma_{22} + \sigma_{11})/2$. [f] $\delta = \sigma_{ref} − \sigma$, relative to the respective standards Me_2Cd and Me_2Hg. A corresponding calculation for Zn would be questionable since the reference is $Zn^{2+}_{(aq)}$. [g] Reduced coupling constant in 10^{19} kg m^{-2} s^{-2} A^{-2}. [h] $^1K(N,M)$. [i] $^2K(N,M)$. [j] In hertz at the ZORA scalar level. [k] $^1J(^{15}N,M)$. [l] $^2J(^{15}N,M)$. [m] $^2J(^{15}N,^{15}N)$. [n] Experimental value 2.4 Hz. [o] $^3J(^{15}N,^{15}N)$.
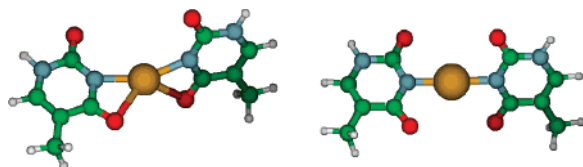
Figure 1. Structure of thymine adducts with Cd(II) (left) and Hg(II) (right).

tions,[1] where a phosphate group also acts as ligand, or where Ag is the binding metal.

Adduct formation with all metals causes a marked deshielding (30−50 ppm) at the ^{15}N donor site, qualitatively similar to that induced by deprotonation (71 ppm); the value for Hg (47 ppm) compares favorably with experiment (30−35 ppm).[2,20] This result indicates a different electronic origin of the upfield shift ($\Delta\delta$ < 0) observed for guanosine coordination (a pyridine-type rather than an imidate nitrogen).

Metal chemical shifts are important only for ^{113}Cd and ^{199}Hg (signals from ^{67}Zn are probably undetectable). It is of particular interest to estimate their chemical shift anisotropy (CSA) $\Delta\sigma$, which is implicated in the relaxation of these nuclei.[21] At B_0 = 18.8 T, we estimate line widths $W_{1/2}$ of 240 and 28 Hz for ^{199}Hg and ^{113}Cd, respectively. Even at 7 T, $W_{1/2}(^{199}Hg)$ will be 20−30 Hz. These findings have an obvious bearing on the detection of such signals and on the observability of splittings in the spectra.

Direct couplings $^1J(^{15}N,M)$ are quite sizable and steadily increase upon going from Zn to Hg, as expected.[22] $^1J(^{15}N,^{199}Hg)$ is especially significant since at low B_0 it should be much larger than the line width, thus giving rise to observable splittings in the ^{199}Hg spectrum. The prospect is even better for ^{113}Cd, for which $\Delta\sigma$ is smaller.[23]

Finally, we discuss metal-mediated $^2J(^{15}N,^{15}N)$ couplings. In the case of THgT, we estimate a coupling of 1.7 Hz, to be compared with the experimental value of 2.4 Hz.[2] Thus, our calculation provides strong support for the binding of Hg(II) to DNA with the proposed motif. Couplings across Cd and Zn are weaker but might be measurable. Except for Zn, all couplings depend critically on the metal electrons; replacement of M with the corresponding ghost atom leads to negligible (<0.05 Hz) couplings. When M = Zn, the N···N distance is shortest and $^2J(^{15}N,^{15}N)$ retains a sizable value of 0.2 Hz.[24]

Coordination with Hg_2^{2+} exhibits several peculiarities: (a) $\Delta\delta$-(N) is negative; (b) $^2J(^{15}N,^{199}Hg)$ is larger than $^1J(^{15}N,^{199}Hg)$;[15,16] (c) the metal-mediated coupling $^3J(^{15}N,^{15}N)$ is largest.[15,16] Furthermore, the huge $^1J(^{199}Hg,^{199}Hg)$ of 60 kHz may give rise to a corresponding splitting if complexation removes magnetic equivalence.

Supporting Information Available: Cartesian coordinates and energies of all species, individual contributions to shieldings and couplings, results from other functionals. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Calculations have been carried out with ADF[18] with the BLYP[19] functional and relativistic corrections with the ZORA method at the scalar or spin−orbit levels. Results from other functionals are reported in Tables S2 and S3. TMT systems were first optimized at the BLYP/TZ2P level. **1** was optimized using the TZP basis set with frozen cores up to 3d for Ru, 2p for Cl and P, and 1s for C and N at the nonrelativistic level. The "ghost" of a given atom has the same basis functions but no nuclear charge nor electrons. All structures were checked to be minima on the potential energy surface. NMR properties were calculated with the *nmr* and *cpl* modules; σ values were computed at the scalar and SO levels, J-couplings only at the scalar level, including the Fermi contact, diamagnetic, and paramagnetic spin−orbit and spin−dipole contributions.
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(20) The larger computed $\Delta\delta$ probably stems from the neglect of solvent and the surrounding nucleotide chain; a spread of 5 ppm was found according to the actual thymine N considered.[2]
(21) $1/T_1^{CSA} = (2/15)\gamma^2 B_0^2 \Delta\sigma^2 \tau_c$ and $T_2^{CSA} = (6/7)T_1^{CSA}$.[4] τ_c is the correlation time.[3] Assuming τ_c = 300−500 ps (Noggle, J. H.; Schirmer, R. E. *The Nuclear Overhauser Effect*, Academic: New York, 1971), one estimates T_2^{CSA} = 1−2 and 11−20 ms for Hg and Cd, respectively. In actual DNA oligomers T_2 will be even shorter, owing to longer τ_c.
(22) This is best appreciated from the reduced couplings K. $J_{MN} = (\hbar/2\pi)\gamma_M\gamma_N K_{MN}$.
(23) Fast relaxation of ^{67}Zn will prevent the detection of any splitting.
(24) Further work is necessary to ascertain whether a genuine through-space interaction is implicated.

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