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Rare Tautomers of 1-Methyluracil and 1-Methylthymine: Tuning Relative Stabilities through Coordination to Pt^{II} Complexes

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Abstract: We have computationally explored how the relative stabilities of 1-methyluracil (1-MeUH) tautomers can be tuned through coordination of these tautomers to Pt^{II} complexes with a particular set of ligands. This has been done using density functional theory at the BP86/TZ2P level. Thus, we have examined the water/1-MeUH exchange reactions of $[Pt^{II}(A)(B)(C)(OH_2)]^q$ + 1-MeUH to uncover: i) which tautomers are best stabilized by the Pt^{II} complex, and ii) how the net charge q in the complex affects the reaction energy. The net charge q depends on the ligands A, B, and C, which can be the neutral NH_3 or anionic Cl^-. To reveal the effect of solvation, all reaction systems are studied both in the gas phase and in water. Also the stabilization of tautomers of 1-methylthymine (1-MeTH) by cisplatin is investigated. The calculations reveal that relative energies of the metal (here: Pt^{II})-complexed forms of the various tautomers (here: of 1-MeUH and 1-MeTH) do not parallel those of the free tautomers. Rather, a rare nucleobase tautomer, despite its low natural abundance, may become favored over the predominant one when complexed to a metal ion.

Keywords: bioinorganic chemistry · coordination complexes · density functional calculations · nucleobase tautomers · platinum · thymine · uracil

Introduction

It is textbook knowledge by now that tautomer equilibria, including those of heterocycles, are subject to environmental influences such as temperature and bulk solvent (polarity, dielectric constant).[1] It is trivial to state that *any* chemical modification of a molecule capable of existing in different tautomers will affect its tautomeric equilibrium. Computational chemistry has made numerous efforts to better understand the influence of solvent[2a–g] and metal-binding[2h–n] on tautomer equilibria.

Such factors are of particular significance for the constituents of DNA, because even minor shifts in tautomeric equilibria of the nucleobases can give rise to DNA mismatches which, if not repaired, in turn can lead to mutations.[3] There are, of course, other pathways to mutagenesis resulting from more drastic alterations in DNA composition as a consequence of hydrolytic or oxidative damage of nucleobases, deletion of bases, or addition of new ones, for example. These will not be considered here, however.

Our interest is focused on the possible role of metal ions in mutagenic events and we have been interested for many years in modeling scenarios, which could rationalize metal-mediated processes of nucleobases.[4] These can feasibly include effects of metal coordination on DNA structure (e.g. DNA kinking), strand cross-linking by metal ions, or changes in electronic structure of nucleobases with effects on acid–base equilibria, base-pairing patterns, and base-pairing strength.[5] Among the more subtle changes that metal coordination can cause are alterations of keto–enol and amino–imino tautomeric equilibria of nucleobases.

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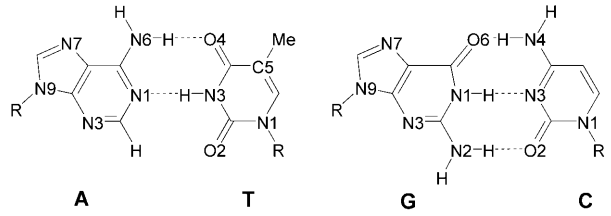
There are two principal possibilities of how metal binding to a nucleobase might achieve this. The first one involves binding of the metal to a site at the heterocycle that is remote from the Watson–Crick face of the nucleobase and hence is not involved in base pairing. Such a situation is realized if the metal is at the N7 site of a purine nucleobase, for example (Scheme 1). Thus, quantum-chemical ab initio



Scheme 1. Watson–Crick AT and GC base pairs with atom numbering.

calculations suggest that a dipositive $[Pt^{II}(NH_3)_3]^{2+}$ species bonded to N7 of an adenine base (A) can, unlike a neutral Pt species, lead to a stabilization of the rare imino tautomer form (A*).[6] Hydrogen bond formation between an ammine ligand at the Pt and the imino group of A* contributes to the existence of the rare tautomer. No such effect was detected in calculations involving an N7-platinated guanine (G) base, however.[7] It should be pointed out that attempts to determine such a shift in tautomeric equilibrium experimentally in water for adenine had been inconclusive.[8]

Abstract in Dutch: *Wij hebben langs computationele weg onderzocht, hoe de relatieve stabiliteit van 1-methyluracil- (1-MeUH) tautomeren veranderd kan worden door coördinatie van deze tautomeren aan Pt^{II}-complexen met een bepaalde set van liganden. Onze berekeningen zijn gebaseerd op dichtheidsfunctionaaltheorie op het BP86/TZ2P-niveau. We hebben de water/1-MeUH-uitwisselingsreacties van $[Pt^{II}(A)(B)(C)(OH_2)]^q$ + 1-MeUH bestudeerd om op te helderen: i) welke tautomeren het beste gestabiliseerd worden door een bepaald Pt^{II}-complex, en ii) hoe de nettolading q in het complex de reactie-energie beïnvloedt. De nettolading q hangt af van de liganden A, B en C, die in onze studie gegeven worden door het neutrale NH_3 of het anionische Cl^-. Om het effect van solvatatie op te helderen, worden alle reactiesystemen zowel in de gasfase als in water bestudeerd. We hebben eveneens de stabilisatie van tautomeren van 1-methylthymine (1-MeTH) door cisplatina in dit onderzoek mee genomen. De berekeningen laten zien, dat de relatieve energieën van de metaal- (hier: Pt^{II}-) gecomplexeerde vormen van de verschillende tautomeren (hier: van 1-MeUH en 1-MeTH) afwijken van die van de vrije, d.w.z. ongecomplexeerde tautomeren. Aldus kan een zeldzaam tautomeer van een kernbase, dat normaal gesproken slechts in geringe concentratie voorkomt, d.m.v. complexatie aan een metaalion toch de dominant voorkomende vorm worden.*

The second possibility involves metal binding to a nucleobase site that normally carries a proton when present in the predominant canonical tautomer form, for example, N1 or N2 of G, N6 of A, N4 of cytosine (C), and N3 of thymine (T). Metal binding to such sites thus "forces" the proton to bind to another nucleobase site and leads to the generation of a species which we have termed "metal-stabilized rare tautomer" (Scheme 2). Representations of this second type have been synthesized for the common model nucleobases 9-methyladenine,[9] 9-alkylguanine,[10] 1-methylcytosine,[11] 1-methyluracil,[12] and 1-methylthymine.[13] With unsubstituted parent nucleobases such as cytosine,[14] or thymine/uracil,[15] or related isocytosine,[16] metal complexes of individual tautomers have likewise been reported.

The relevance of "metal-stabilized rare tautomers" with regard to possible mutagenic events stems either from mispairing events of metalated rare tautomers (e.g. *anti* rotamers M–A* or M–C* via Watson–Crick face) or from a mispairing process of a rare tautomer generated by a metal species. For example, M–T* can dissociate into M and T*, thereby producing a (short-lived) rare tautomer with the potential of hydrogen bonding to a non-complementary nucleobase.[12a]

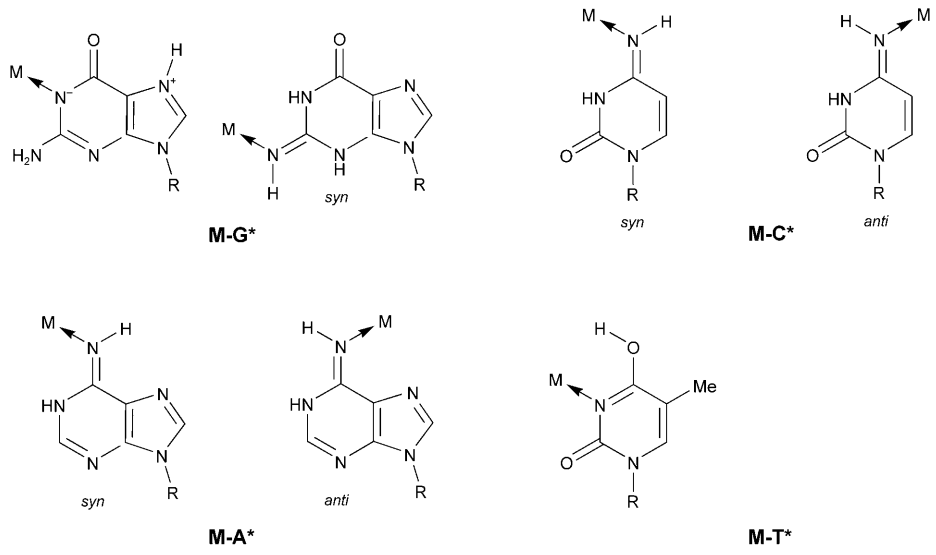
In the present study, we wish to computationally obtain insight into how one can tune the relative stabilities of 1-methyluracil (1-MeUH) tautomers through coordination to Pt^{II} complexes with a particular set of ligands, using relativistic density functional theory (DFT) at the ZORA-BP86/TZ2P level of theory. In previous work, we have shown that such a DFT approach is an excellent computational tool for the study of hydrogen bonds in DNA base pairs and mismatches thereof,[17] for the study of mimics[18] and tautomers[19] of the DNA bases, and for transition-metal complexes in which relativistic effects are important.[20] Thus, we have examined the water/1-MeUH exchange reactions of $[Pt^{II}(A)(B)(C)(OH_2)]^q$ + 1-MeUH, shown in Scheme 3, to investigate which tautomer is best stabilized by which $[Pt^{II}(A)(B)(C)]$ complex fragment.

Furthermore, we will try to clarify how the net charge q in the complex affects the reaction energy. The net charge q can be varied by choosing for the ligands A, B, and C different proportions of the neutral NH_3 and anionic Cl^-. To reveal the effect of solvation, all reaction systems are studied both in the gas phase and in aqueous solution using the COSMO approach for treating solvent effects.

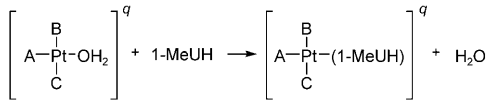
We also address the effect on thymine tautomerization by the anti-cancer drug cisplatin *cis*-$[Pt^{II}(NH_3)_2Cl_2]$, which is known to convert into *cis*-$[Pt^{II}(NH_3)_2Cl(OH_2)]$ (A, B = NH_3, and C = Cl^-, see Scheme 3) after the first hydrolysis and into *cis*-$[Pt^{II}(NH_3)_2(OH_2)_2]^+$ after the second hydrolysis.[21]

Computational Methods

All calculations were performed by using the Amsterdam Density Functional (ADF) program developed by Baerends and others,[22,23] and the QUantum-regions Interconnected



Scheme 2. Metal-stabilized rare tautomers (*) of G, C, A, and T bases.



Scheme 3. Water-(1-MeUH) exchange reaction at platinum complex.

by Local Descriptions (QUILD) program by Swart and Bickelhaupt.[24] The QUILD program is a wrapper around ADF (and other programs) and is used for its superior geometry optimizer which is based on adapted delocalized coordinates.[24a] The numerical integration was performed by using the procedure developed by te Velde et al.[23g,h]

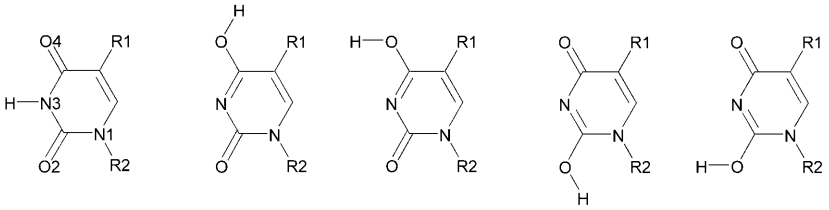
The MOs were expanded in a large uncontracted set of Slater type orbitals (STOs) containing diffuse functions: TZ2P (no Gaussian functions are involved).[23i] The basis set is of triple-ζ quality for all atoms and has been augmented with two sets of polarization functions, that is, 3d and 4f on C, N, O and 2p and 3d on H, and 5f and 6p on the Pt atom. The 1s core shells of carbon, nitrogen, and oxygen and up to the 4d core shell of the Pt atom were treated by the frozen-core approximation.[23c] An auxiliary set of s, p, d, f, and g STOs was used to fit the molecular density and to represent the Coulomb and exchange potentials accurately in each self-consistent field cycle.[23j]

Equilibrium structures were optimized by using analytical gradient techniques.[23k] Geometries and energies were calculated at the BP86 level of the generalized gradient approximation (GGA): exchange is described by Slater's Xα potential[23l] with nonlocal corrections due to Becke[23m,n] added self-consistently and correlation is treated in the Vosko–Wilk–Nusair (VWN) parameterization[23o] with nonlocal corrections due to Perdew[23p] added, again, self-consistently (BP86).[23q] Energy minima in the gas phase have been verified to be equilibrium structures through vibrational analysis.[25] Almost all species were found to have zero imaginary frequencies. However, in a few cases, we found very small imaginary frequencies (in the order of i 20 cm^{-1}). Analyses of the corresponding normal modes revealed that they are spurious in the sense that they refer to essentially unhindered internal rotation of an ammine group or of the DNA base tautomer relative to the $[Pt^{II}(A)(B)(C)]^q$ fragment.

Scalar relativistic effects were accounted for using the zeroth-order regular approximation (ZORA).[26] Solvent effects in water have been estimated by using the conductor-like screening model (COSMO), as implemented in the ADF program.[27] For the approach and settings to obtain our solvation energies in water, see reference [28]. We have verified that our COSMO BP86/TZ2P solvation free energies (see ref. [28]) of methylated DNA bases 9-me-A, 9-me-G, 1-me-C, 1-me-T, and 1-me-U (i.e., −12.4, −22.2, −18.6, −11.7, −12.7 kcal mol^{-1}) agree within about one kcal mol^{-1} with the solvation free energies obtained with AMBER/TI by Miller and Kollman[29] (i.e., −12.0, −22.4, −18.4, −12.4, −14.0 kcal mol^{-1}). Basis set superposition errors (BSSEs) have not been calculated because we have shown in previous work[17a,c,30] that for the basis set used, which is of triple-ζ quality, this correction is small (less than a kcal mol^{-1}) and that it is normally of the same magnitude for similar systems.

Results and Discussion

Tautomer energies of uracil and thymine: Before starting with the stabilization of 1-MeUH by a platinum complex, we calculated in the gas phase and in water for the different tautomeric forms of 1-MeUH, the relative energies compared to the canonical form 1-MeUH (R1 = H, R2 = Me in Scheme 4 and Table 1). This was also done for unsubstituted uracil (R1 = H, R2 = H) and thymine (R1 = Me, R2 = H) as well as 1-MeTH (R1 = Me, R2 = Me). The relative order that comes out is for all four bases **1** < **3** < **2** < **5** < **4**. Therefore, we can conclude that methylation on N1 or C5 has little effect on the relative energy of the tautomers. This relative order is maintained in water. Furthermore, the magnitude of the computed relative energies indicates that under experimental conditions the likeliness of rare tautomers to occur is quite small. Thus, the tautomeric forms of all four bases are in the condensed phase at least 10 kcal mol^{-1} higher in energy than the canonical form. Our DFT results are consistent with gas-phase ab initio results of Rejnek et al.[2d] at the RI-MP2/TZVPP//RI-MP2/TZVPP



Scheme 4. Different tautomeric forms of uracil (R1, R2 = H), 1-methyluracil (R1 = H, R2 = Me), thymine (R1 = Me, R2 = H), and 1-methylthymine (R1, R2 = Me). Forms **2** and **4** are structures with the acidic proton *anti* with respect to N3, and **3** and **5** are structures with the acidic proton *syn* relative to N3.

Table 1. Relative energies (in kcal mol^{-1}) for the tautomers of uracil (R1, R2 = H), thymine (R1 = Me, R2 = H), 1-methyluracil (R1 = H, R2 = Me), and 1-methylthymine (R1 = Me, R2 = Me) in the gas phase and in water.

	R1 = H			R1 = Me		
	Gas phase		Water	Gas phase		Water
	BP86[a]	MP2[b]	BP86[a]	BP86[a]	MP2[b]	BP86[a]
R2 = H						
1	0.0	0.0	0.0	0.0	0.0	0.0
2	17.8	20.3	11.6	18.9	21.8	13.0
3	11.6	12.5	10.3	12.5	13.4	11.0
4	29.2	31.3	18.0	28.3	32.1	17.4
5	19.7	19.8	15.5	18.9	19.2	14.9
R2 = Me						
1	0.0		0.0	0.0		0.0
2	17.0		10.8	18.0		12.1
3	10.9		9.6	11.8		10.2
4	29.6		19.2	28.6		18.4
5	20.3		15.8	19.4		15.1

[a] Computed at the BP86/TZ2P level under C_S symmetry constraint; this work. [b] Computed at the RI-MP2/TZVPP level under C_S symmetry constraint; from reference [2d].

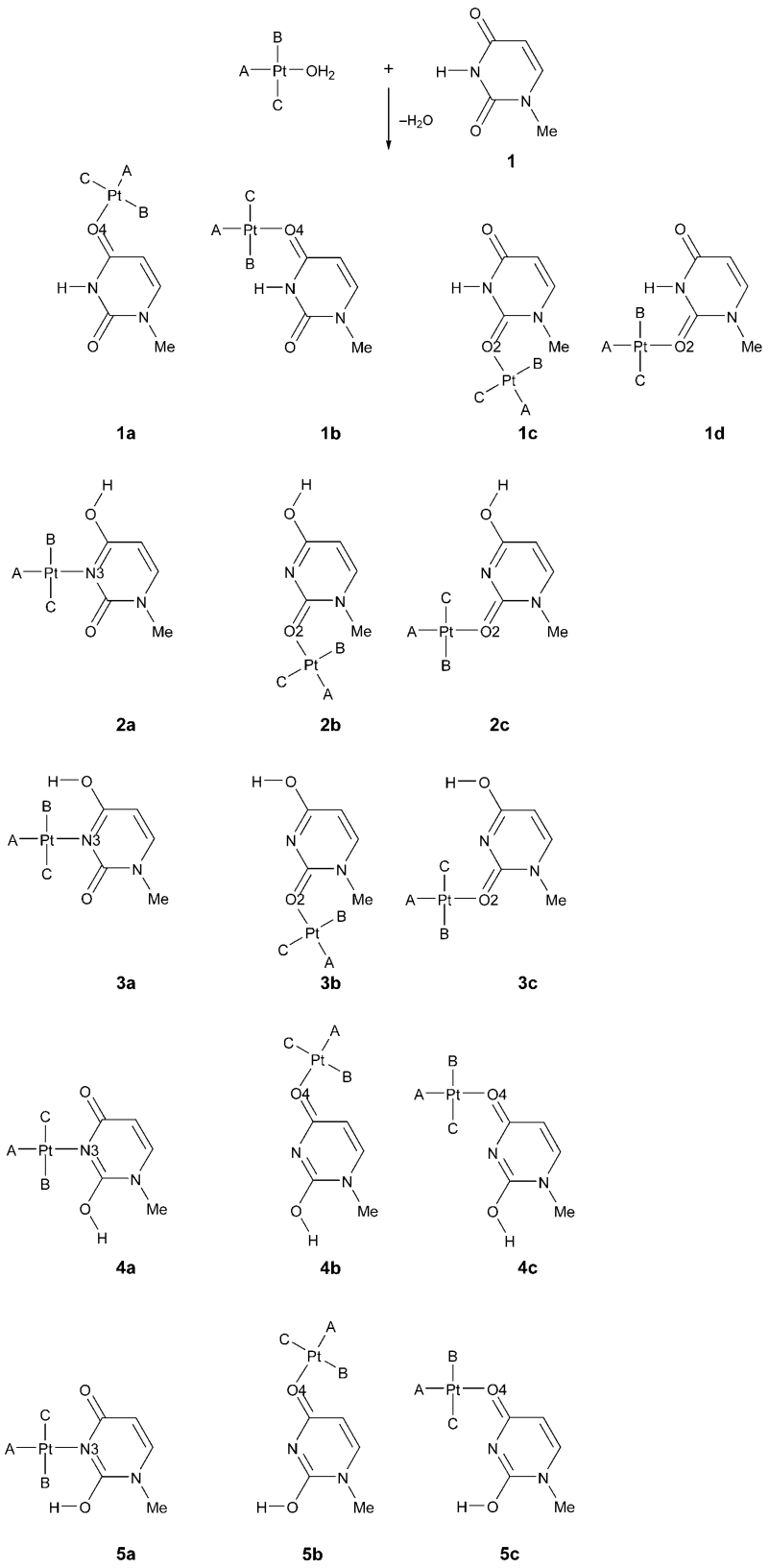
level of theory. The relative order of the MP2 results is very similar although not exactly the same: **1** < **3** < **5** < **2** < **4**. The reason for the seeming discrepancy in the relative order of tautomers **2** and **5** is that they are essentially at the same energy both, at the BP86/TZ2P level and at the RI-MP2/TZVPP level of theory. For the other tautomeric forms of uracil and thymine see Figure S1 and Table S1 in the Supporting Information.

Reaction energies for exchange of water by 1-MeUH at Pt^{II} complexes: *Gas phase*: The schematic representation of the exchange reaction of water by 1-MeUH plus tautomerization of the latter is given in Scheme 5. Note that we have taken into account in the calculation of the reaction energy that 1-MeUH (**1**) can transform into one of its tautomeric forms **2**, **3**, **4**, or **5** during this exchange reaction. Each of these tautomers can coordinate to the Pt^{II} complex in four different ways (in the case of the canonical form **1**) or in three different ways (in the case of tautomers **2**–**5**; see Scheme 5). The calculated energies of all these possible exchange reactions are given in Table 2 and the geometries of the reaction products can be found in the Supporting Information.

Analyzing the reaction energies, which in the case of the tautomers also include the tautomerization energies, shows that in the gas phase it is most favorable to bind to the highly positively charged Pt^{II} complex, forming $[Pt^{II}(NH_3)_3(1\text{-MeUH})]^{2+}$, where 1-MeUH can be any of the five tautomeric forms. The reaction energies range from −24.5 kcal mol^{-1} for **1d** to −39.0 kcal mol^{-1} for **2c**. Thus, tautomers **2** to **5** can be stabilized by Pt^{II} with three neutral NH_3 ligands.

The reaction energy becomes less favorable as the total charge of the reacting complex goes from +2 to −1. For most tautomers and even in some cases for the canonical form of 1-MeUH, the reaction energy becomes positive (i.e., destabilizing) for the uncharged and the negatively charged complex. The canonical form of 1-MeUH and tautomer **3** can bind to the Pt^{II} complex for all six variations of the ligands A, B, and C to form stable reaction products $[Pt^{II}(A)(B)(C)(1\text{-MeUH})]^q$. The canonical form of 1-MeUH (**1**) can coordinate through O4 to the Pt^{II} complex in a *syn* conformation leading in all cases to the stable reaction product **1b**. Interestingly, it is viable in terms of having an exothermic reaction that 1-MeUH can also tautomerize into tautomer **3** and form the stable reaction product **3a**.

Briefly, we will also discuss some interesting geometrical features (Cartesian coordinates of all the structures can be found in the Supporting Information). Structures **1b** and **1d**, with ligand B being Cl^-, are approximately flat, when a Cl^- ligand can form a favorable interaction with the hydrogen on the N3 atom of 1-MeUH. However, when both ligands B and C are NH_3, the plane formed by the three ligands A, B, and C has a dihedral angle of almost 90° with the plane of the base 1-MeUH. Furthermore, in the systems **2c**, **3c**, **4c**, and **5c**, when both B and C ligands are Cl^-, the plane formed by the ligands A, B, and C is almost perpendicular to the plane of 1-MeUH* due to the repulsive interaction between Cl^- and the lone pair on N3 of 1-MeUH*. From Table 2, one can see that some *anti* structures **1c**, **2b**, and **3b** turn spontaneously (i.e., without a barrier) into *syn* structures **1d**, **2c**, and **3c**, respectively, when two or all three ligands are NH_3. This occurs only when the Pt^{II} complex is coordinated to the O2 atom (for 1-MeUH and 1-MeTH, the O4-coordinated *anti* structures do exist). The double-well potential energy surface (PES) with a global minimum for the *syn* structure and a higher-lying local minimum for the *anti* structure changes in these cases into a single-well PES. The minimum of the *anti* structure can rise in energy due to repulsive interactions and/or the barrier between the minima can drop due to attractive interaction leading to the *anti* structure becoming a shoulder (but no longer a stationary point) on the PES.



Scheme 5. The reaction of exchanging water by 1-MeUH in the $[Pt^{II}(A)(B)(C)(OH_2)]^q$ complex. The methyl group at C5 in 1-MeTH (see Scheme 1) is not shown here.

The reaction energies for 1-MeTH are very similar to the ones for 1-MeUH, although the methyl substituent at C5 in the former does cause a few minor differences (see Table 3). Thus, the reactions with the positively charged complex are all exothermic and thus feasible in the gas phase, whereas most of the reactions with the negatively charged complex are again endothermic and thus not accessible.

Situation in water: The reaction energies for the exchange of the H_2O ligand by 1-MeUH in $[Pt^{II}(A)(B)(C)(OH_2)]^q$ have also been determined in aqueous solution using the COSMO approach. In water, contrary to the situation in the gas phase, the net charge of the Pt^{II} complex becomes almost irrelevant for the exchange reaction energy (see Table 4). For each reaction product (**1a** to **5c**), we see that the reaction energy varies by only a few $kcal\,mol^{-1}$ as the set of ligands A, B, and C and, thus, the charge of the Pt^{II} complex changes. Roughly, we see that only tautomers **2** and **3** can be stabilized by the Pt^{II} complex to form reaction products **2a** and **3a**. Reaction product **5a** is, depending on the set of ligands, slightly stabilized or destabilized by about 1 kcal mol^{-1}. Complexation with the canonical form of 1-MeUH **1** is also still feasible, resulting in the formation of the reaction products **1a** and **1b**. Reaction product **1d** is associated with only a very small reaction energy: -0.8 to $-1.8\,kcal\,mol^{-1}$ for all sets of ligands. We see that under experimental conditions it is possible that the coordination of the Pt^{II} complex occurs to the O4 (**1a** and **1b**) as well as to the N3 atom (**2a** and **3a**) of 1-MeUH. The difference in the reaction energy between the reaction products with Pt^{II}

Table 2. Reaction energy (in kcal mol^{-1}) in the gas phase for the exchange of H_2O by 1-MeUH in $[Pt^{II}(A)(B)(C)(OH_2)]^q$ forming $[Pt^{II}(A)(B)(C)(1\text{-MeUH})]^q$.[a]

Ligands A		NH_3	NH_3	Cl	Cl	NH_3	Cl
B		NH_3	Cl	NH_3	Cl	Cl	Cl
C		NH_3	NH_3	NH_3	NH_3	Cl	Cl
Charge q		2	1	1	0	0	−1
normal tautomer							
1a	O4	−35.7	−15.9	−17.5	−2.1	−2.3	3.8
1b	O4	−34.8	−19.1	−18.3	−7.2	−5.4	−1.0
1c	O2	**1d**[b]	**1d**[b]	−4.8	3.2	3.7	5.3
1d	O2	−24.5	−10.5	−11.7	−1.4	−2.4	0.3
rare tautomer							
2a	N3	−38.9	−14.7	−17.0	4.8	5.2	18.3
2b	O2	**2c**[b]	**2c**[b]	**2c**[b]	16.4	18.1	24.9
2c	O2	−39.0	−7.9	12.3	14.3	15.4	29.9
3a	N3	−35.1	−21.6	−20.6	−10.8	−7.6	−3.3
3b	O2	**3c**[b]	**3c**[b]	**3c**[b]	10.8	12.0	18.4
3c	O2	−36.4	−8.9	−13.0	10.0	8.9	22.0
4a	N3	−27.4	−4.8	−5.0	**5a**[b]	17.7	31.8
4b	O4	−24.6	0.9	0.8	21.5	22.9	34.3
4c	O4	−37.0	0.4	−6.8	24.7	24.7	41.5
5a	N3	−27.6	−16.6	−12.9	−6.1	0.4	4.1
5b	O4	−32.1	−6.9	−7.6	13.0	13.7	24.9
5c	O4	−38.3	−6.9	−10.9	15.4	14.8	29.3

[a] Computed at the ZORA-BP86/TZ2P level without any symmetry constraint, that is, full optimization in C_1 symmetry. [b] Expected species spontaneously transforms into indicated species.

Table 3. Reaction energy (in kcal mol^{-1}) in the gas phase for the exchange of H_2O by 1-MeTH in $[Pt^{II}(A)(B)(C)(OH_2)]^q$ forming $[Pt^{II}(A)(B)(C)(1\text{-MeTH})]^q$.[a]

Ligands A		NH_3	NH_3	Cl	Cl	NH_3	Cl
B		NH_3	Cl	NH_3	Cl	Cl	Cl
C		NH_3	NH_3	NH_3	NH_3	Cl	Cl
Charge q		2	1	1	0	0	−1
normal tautomer							
1a	O4	−32.9	−13.0	−14.0	1.2	0.4	6.5
1b	O4	−35.9	−18.9	−18.8	−6.7	−5.6	−1.2
1c	O2	**1d**[b]	**1d**[b]	−8.0	2.5	3.1	5.7
1d	O2	−28.5	−12.6	−13.8	−2.1	−3.0	0.7
rare tautomer							
2a	N3	−41.4	−15.6	−17.8	5.1	5.9	19.7
2b	O2	**2c**[b]	**2c**[b]	**2c**[b]	16.7	18.4	26.3
2c	O2	−42.2	−9.0	−13.5	14.7	15.9	31.3
3a	N3	−37.5	−22.5	−21.4	−10.6	−7.2	−2.4
3b	O2	**3c**[b]	**3c**[b]	**3c**[b]	10.9	12.2	19.7
3c	O2	−39.8	−10.2	−14.3	10.2	9.1	23.2
4a	N3	−31.5	−7.0	−7.3	**5a**[b]	16.5	31.3
4b	O4	−22.7	4.4	3.7	25.4	25.7	37.6
4c	O4	−39.4	−2.1	−8.4	22.8	23.2	40.5
5a	N3	−31.5	−18.5	−15.1	−6.7	−0.7	3.8
5b	O4	−29.9	−3.6	−4.4	16.8	16.5	28.0
5c	O4	−40.5	−8.2	−12.3	14.6	13.5	28.4

[a] Computed at the ZORA-BP86/TZ2P level of theory without any symmetry constraint, that is, full optimization in C_1 symmetry. [b] Expected species spontaneously transforms into indicated species.

coordinated to O4 (**1a** and **1b**) and the products with Pt^{II} coordinated to N3 (**2a** and **3a**) is small. In the case of all three ligands being neutral (NH_3) and thus the total charge of the complex +2, coordination to O4 is favored by only 0.5 kcal mol^{-1} over coordination to N3. However, for all other net charges ($q=+1$, 0, −1), 1-MeUH **1** tautomerizes to **2** or **3** and coordinates preferentially via N3 to yield **2a** and **3a**. For $q=+1$, complex **3a** is 0.6 kcal mol^{-1} more stable than **1b** (see Table 4). For $q=-1$, complex **3a** is 3.6 kcal mol^{-1} more stable than **1b**.

Table 4. Reaction energy (in kcal mol^{-1}) in water for the exchange of H_2O by 1-MeUH in $[Pt^{II}(A)(B)(C)(OH_2)]^q$ forming $[Pt^{II}(A)(B)(C)(1\text{-MeUH})]^q$.[a]

Ligands A		NH_3	NH_3	Cl	Cl	NH_3	Cl
B		NH_3	Cl	NH_3	Cl	Cl	Cl
C		NH_3	NH_3	NH_3	NH_3	Cl	Cl
Charge q		2	1	1	0	0	−1
normal tautomer							
1a	O4	−5.8	−5.2	−5.2	−3.4	−3.8	−2.3
1b	O4	−5.1	−5.6	−5.3	−4.6	−4.9	−4.2
1c	O2	4.4	2.3	3.9	3.2	3.5	4.3
1d	O2	−0.8	−1.8	−1.0	−0.9	−1.6	−1.2
rare tautomer							
2a	N3	−3.8	−3.9	−4.8	−3.1	−3.6	−3.3
2b	O2	10.7	12.3	11.5	10.6	10.9	12.0
2c	O2	2.3	4.8	3.7	6.4	6.2	7.2
3a	N3	−4.6	−6.4	−5.9	−6.4	−7.4	−7.8
3b	O2	10.3	8.1	10.4	9.7	10.0	10.9
3c	O2	3.1	4.6	3.7	6.0	5.6	6.5
4a	N3	4.8	4.4	4.2	5.5	5.7	6.0
4b	O4	8.7	10.0	10.0	12.0	11.5	13.3
4c	O4	7.1	9.5	8.3	11.4	11.3	12.3
5a	N3	1.8	−0.7	0.2	−0.2	−1.3	−1.7
5b	O4	5.5	6.7	6.7	8.9	8.3	10.1
5c	O4	4.8	7.1	5.7	8.6	8.3	9.5

[a] Computed at the ZORA-BP86/TZ2P level of theory without any symmetry constraint, that is, full optimization in C_1 symmetry.

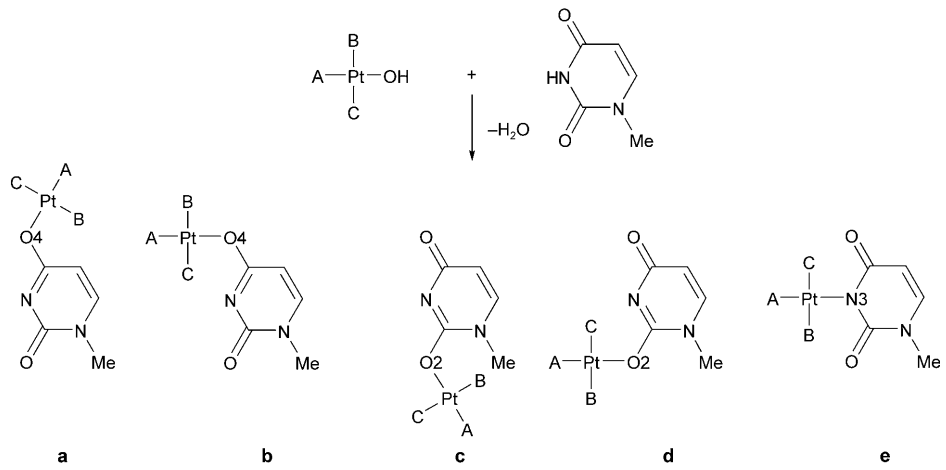
The results for 1-MeTH are again very similar to the results of 1-MeUH (see Table 5). The charge of the Pt^{II} complex becomes almost irrelevant in water and the most feasi-

Table 5. Reaction energy (in kcal mol^{-1}) in water for the exchange of H_2O by 1-MeTH in $[Pt^{II}(A)(B)(C)(OH_2)]^q$ forming $[Pt^{II}(A)(B)(C)(1\text{-MeTH})]^q$.[a]

Ligands A		NH_3	NH_3	Cl	Cl	NH_3	Cl
B		NH_3	Cl	NH_3	Cl	Cl	Cl
C		NH_3	NH_3	NH_3	NH_3	Cl	Cl
Charge q		2	1	1	0	0	−1
normal tautomer							
1a	O4	−1.3	−1.7	−0.8	0.5	−0.5	0.9
1b	O4	−4.2	−5.1	−4.5	−4.3	−5.0	−4.6
1c	O2	3.3	2.7	3.6	2.5	2.8	3.7
1d	O2	−1.0	−2.2	−1.6	−1.4	−2.0	−1.6
rare tautomer							
2a	N3	−2.3	−2.3	−2.9	−1.7	−2.1	−2.0
2b	O2	11.7	9.8	12.3	11.2	11.8	12.9
2c	O2	3.6	6.1	5.0	7.8	7.4	8.4
3a	N3	−3.7	−5.8	−5.4	−6.1	−7.2	−7.9
3b	O2	10.5	7.9	10.4	9.3	10.1	11.0
3c	O2	3.2	4.7	3.8	6.3	5.8	6.8
4a	N3	4.2	3.8	3.4	5.1	4.6	4.9
4b	O4	13.0	13.4	14.1	16.1	14.8	16.6
4c	O4	6.5	9.3	8.0	11.0	10.6	11.6
5a	N3	0.9	−1.3	−0.4	−0.3	−2.0	−2.6
5b	O4	9.7	10.6	10.9	12.9	11.7	13.4
5c	O4	4.2	7.4	5.6	8.1	7.8	8.8

[a] Computed at the ZORA-BP86/TZ2P level of theory without any symmetry constraint, that is, full optimization in C_1 symmetry.

ble coordination modes are to O4 and N3 of 1-MeTH resulting in the complexes **1b**, **2a**, and **3a**. The addition of the methyl group has some influence on the reaction energies. Due to the steric repulsion by the methyl group at the C5 position, the reaction energies for product **1a** (and also for **4b** and **5b**) are less favorable for 1-MeTH than for 1-MeUH. The formation of complex **3a**, which is obtained from tautomer **3** and a coordination of Pt^{II} to N3 of 1-MeTH, is again most likely to occur. Reaction energies are up to 3.3 kcal mol^{-1} more favorable for **3a** than for **1b** where metal coordination is through O4.



Scheme 6. The reaction of exchanging OH^- by 1-MeU^- in the $[Pt^{II}(A)(B)(C)(OH)]^{q-1}$ complex.

The comparisons made here reveal another interesting feature of the exchange reaction (see Scheme 3). Deubel[31] has shown that the reaction energy for the exchange of water in $[Pt^{II}(NH_3)_3(OH_2)]^{2+}$ by a ligand become less exothermic (in one case they go from exo- to endothermic) as the dielectric constant goes from 1 (gas phase) to 78.4 (water). This behavior is confirmed by our results for $[Pt^{II}(NH_3)_3(OH_2)]^{2+}$ (compare Table 2 with Table 4, and Table 3 with Table 5). However, we find that this appears to hold only for the positively charged Pt^{II} complexes. Thus, in the gas phase, the exchange reactions of $[Pt^{II}(NH_3)_3(OH_2)]^{2+}$ with $q=+2$ are highly exothermic, whereas in water, they are much less exothermic (compare Table 2 with Table 4, and Table 3 with Table 5). At variance, the exchange reactions of $[Pt^{II}(Cl)_3(OH_2)]^-$ with $q=-1$ are in the gas phase slightly *endothermic* and in water they become somewhat slightly *exothermic*. In other words, solvation in water makes the reactions of the positively charged complexes less favorable, whereas it promotes those of the negatively charged complexes.

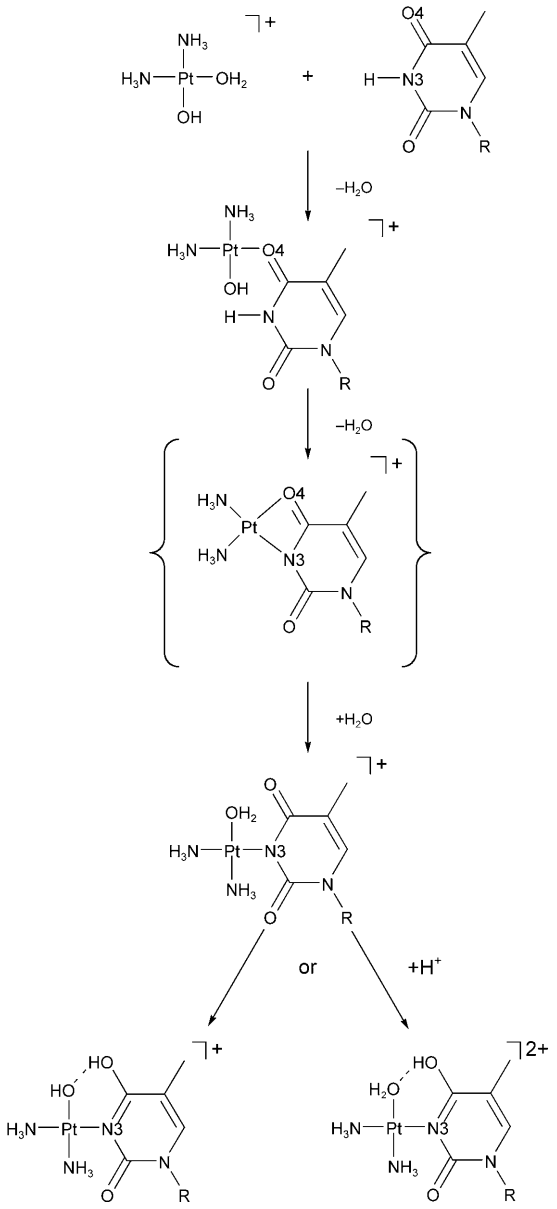
Complexes containing the 1-MeU$^-$ ion: In the large majority of X-ray structurally determined cases of Pt^{II} complexes of 1-methyluracil or 1-methylthymine, these nucleobases are present as anions, hence as 1-MeU^- and 1-MeT^-, respectively.[32] Formally, and considering the higher acidity of a Pt^{II}–OH_2 group relative to that of 1-MeUH or 1-MeTH (see below), reactions leading to complexes containing these nucleobases in their deprotonated forms can be viewed as shown in Scheme 6. Three different linkage isomers plus two additional rotamers are feasible as reaction products (**a**–**e**, Scheme 6). The calculations for these exchange reactions have been carried out for aqueous solution (COSMO) at the BP86/TZ2P level of theory (Table 6). Now, for all six combinations of co-ligands A, B, and C, the only feasible product is the one in which Pt^{II} is bonded to the N3 atom of 1-MeU (isomer **e** in Scheme 6).

Table 6. Reaction energy (in kcal mol^{-1}) in water for the exchange of OH^- by 1-MeUH in $[Pt^{II}(A)(B)(C)(OH)]^{q-1}$ forming H_2O and $[Pt^{II}(A)(B)(C)(1\text{-MeU})]^{q-1}$.[a]

Ligands A			NH_3	NH_3	Cl	Cl	NH_3	Cl
B			NH_3	Cl	NH_3	Cl	Cl	Cl
C			NH_3	NH_3	NH_3	NH_3	Cl	Cl
Charge ($q-1$)			1	0	0	−1	−1	−2
a	O4	*anti*	3.3	2.7	2.6	3.4	1.2	2.2
b	O4	*syn*	−0.2	1.3	−0.1	1.9	1.1	1.4
c	O2	*anti*	**d**[b]	9.7	**d**[b]	9.5	8.9	9.1
d	O2	*syn*	4.5	5.5	4.1	5.8	4.9	5.1
e	N3		−7.5	−6.8	−9.2	−7.3	−8.5	−9.0

[a] Computed at the ZORA-BP86/TZ2P level of theory without any symmetry constraint, that is, full optimization in C_1 symmetry. [b] Expected species **c** spontaneously transforms into indicated species **d**.

N3 coordination and implications for biology: Compared to guanine, adenine, and cytosine, thymine is not a kinetically preferred target of cisplatin in DNA, and neither is it uracil in RNA. Nevertheless, there can be no doubt that cisplatin is capable of binding to N3 of T or U, both in the free state and when present in DNA (or RNA).[33] It does so in moderately alkaline medium at, neutral pH and, surprisingly, even at a pH as low as 3.5–4[33b,34] despite a relatively high pK_a of 9–10 for N(3)H![35] There are at least two factors facilitating Pt^{II} binding to N3 at pH values well below the pK_a of N(3)H (Scheme 7): First, initial Pt^{II} binding to O4 and/or O2 of the canonical tautomer will acidify the proton at N3.[36] Second, the aquated cisplatin carries its own base Pt−OH (pK_{a1} of *cis*-$[Pt(NH_3)_2(H_2O)]^{2+}$ is about 5.5[37]). A shift in tautomer structure of the nucleobase could thus be rationalized in terms of initial N3 deprotonation by Pt^{II}–OH, followed by metal migration from O4/O2 to N3,[38] and reprotonation of either O4 and O2. As discussed elsewhere,[5,12] substitution of the proton at N3 by a Pt^{II} entity increases the basicity of the exocyclic oxygens, thereby permitting their protonation to produce a neutral ligand in a rare tautomer structure. The pK_a values of these O-bonded protons are dependent on, for example, co-ligands, complex charge etc., but can easily approach (at least) 3–4 in model systems.[39] If



Scheme 7. Proposed tautomerization pathway of thymine accomplished by *cis*-$[Pt(NH_3)_2(H_2O)(OH)]^+$ in weakly acidic medium.

one allows "shifted pK_a values", a phenomenon which presently gets wide attention and implies that pK_a values of nucleobases (metalated or not) may be subject to considerable shifts in either direction depending on the microenvironment,[40] then the existence of a Pt complex of a rare thymine or uracil tautomer even at physiological pH is not fully unrealistic. In other words, species **2a** or **3a** may exist both in a pH range, where Pt–N3 binding takes place (weakly acidic pH), and at a pH approaching 7. At alkaline pH the pyrimidine base undoubtedly is deprotonated, with no ambiguity in tautomer structure possible.

Regarding possible mispairing scenarios of Pt-T*, it is unlikely that the metal complexes **2a** and **3a** could do so with either G, C, or T, simply because of steric hindrance caused by the metal as well as the co-ligands at N3 of the Watson-Crick edge of thymine. On the other hand, complex **3b** could mispair with G, but formation of the corresponding 1-MeTH complex **3b** is endothermic (7.9 kcal for formation of *cis*-$[Pt^{II}(NH_3)_2Cl(1\text{-MeTH})]^+$, 8.8 kcal mol^{-1} for formation of *cis*-$[Pt^{II}((NH_3)_2(H_2O)(1\text{-MeTH})]^+$) and consequently such processes are irrelevant. The only feasible way by which T* could become involved in mispair formation[12a,13a] would be after loss of the metal fragment from N3 and retention of the rare tautomer for the short time necessary for the base pairing step. While under strongly acidic conditions cleavage of the Pt–N3 bond indeed has been observed,[12a] it is unclear whether such a reaction can take place at a biologically relevant pH.

In summary, it is unlikely that a rare thymine tautomer in its platinated form is responsible for base mispairing and eventually for a mutagenic event. While we do not want to exclude the possibility that a rare tautomer in its free form, generated through the action of Pt^{II}, can mispair, there are numerous other mechanisms by which Pt^{II} complexes, and specifically cisplatin, could cause mutagenesis.[4,41]

Conclusion

We have computationally investigated how rare tautomers of, among others, 1-MeUH can be stabilized by coordination to Pt^{II} species through the exchange reaction of the water ligand in $[Pt^{II}(A)(B)(C)(OH_2)]^q$ by 1-MeUH (ligands A, B, C = NH_3, Cl^-). We find that in the gas phase, the net charge q of the Pt^{II} complex plays an important role for the magnitude of the tautomer stabilization. Thus, all tautomers are stabilized in the gas phase by reaction with the positively charged $[Pt^{II}(NH_3)_3(OH_2)]^{2+}$, whereas this stabilization diminishes along $q = 2, 1, 0, -1$. However, in water the picture changes completely. Now, only a few tautomers, particularly N3-coordinated systems, are stabilized, and variations in the net charge q have a relatively small influence of only a few kcal mol^{-1} on the 1-MeUH/H_2O exchange reaction energy.

Importantly, we have found that while solvation makes the 1-MeUH/H_2O exchange reactions of the positively charged complexes less favorable, it *promotes* those of the negatively charged complexes. This strongly suggests that studies on rare DNA tautomer stabilization must take solvent effects into account, as the latter may completely and qualitatively change trends in relative stabilities.

Finally, our computations indicate that N3 coordination of Pt^{II} to 1-MeUH and 1-MeTH is preferred over O2 and O4 coordination. While this preference is not unexpected for the respective deprotonated nucleobase, it is surprising to see that this binding pattern can be realized for these nucleobases in their neutral forms as well. The latter implies that the pyrimidine nucleobases adopt oxo, hydroxo tautomer forms, which in the absence of coordinated Pt^{II} are extremely rare in comparison to the favored dioxo tautomers (estimated $K \approx 10^{-5}$). The term "metal-stabilized rare nucleobase tautomer" thus is truly adequate.

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