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Regioselectivity of the C-Metalation of 6-Furylpurine: Importance of Directing Effects

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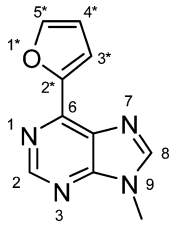
Supporting Information

ABSTRACT: We report the C-metalation of 6-furylpurine with Pt^{2+}, Pd^{2+}, and Hg^{2+}. The ligand binds the metal ions in a bidentate fashion, involving the N7 purine atom and one of the furyl carbon atoms. The regioselectivity is determined by the metal ion. Pt^{2+} and Pd^{2+} coordinate the furyl moiety in its β position and Hg^{2+} in its electronically preferred α position.

Purine-derived compounds are attractive ligands because they contain several nitrogen donor sites.[1] Their metalation properties have been extensively studied in the context of the mode of action of platinum-based drugs.[2] More recently, aryl-substituted purine derivatives have been devised for biomedical applications, owing to their cytostatic, antiviral, and antibacterial activity.[3] Because metal complexes comprising ligands with nitrogen donor sites often prove to be more bioactive than the respective free ligands,[4] studies have been initiated toward the metalation of such aryl-substituted purine derivatives.[5] The resulting compounds are also attractive building blocks for supramolecular metal complexes, which are well-known for the natural purine nucleobases adenine and guanine.[6] Depending on the identity of the aryl substituent, different coordination patterns are feasible. Provided that nitrogen, oxygen, or sulfur atoms are available as donor sites, Werner-type complexes may be formed.[7] In addition, various examples exist for C-metalated purine derivatives. Most of these involve N9-methylated caffeine,[8] with only the C8 position remaining available for metalation. C-metalated purine derivatives with vacant metal-binding sites are rare. Their regioselective C-metalation can be achieved, e.g., by oxidative addition[9] or via N-directed and/or hydrogen-bond-assisted C−H activation.[10] In the case of purine derivatives with an aryl moiety appended to the C6 position, only one metal complex with a C−metal bond involving the aryl substituent has been structurally characterized.[5]

We recently introduced 6-furylpurine as a nucleobase surrogate for artificial metal-mediated base pairing.[7a,b] Its N9-methylated derivative, 9-methyl-6-furylpurine (H6FP; Chart 1), can be applied as a model nucleobase for studying the metal-binding behavior of the nucleoside.[7b] A study on the reaction of H6FP with $CuCl_2$ indicated that N7 and O1* are preferred binding sites, with the Cu−O bond being rather long [2.5955(2) Å].[7b] We report here a study of the metal-binding behavior of H6FP toward metal ions or precursor complexes with d^8 or d^{10} electronic configuration, namely, $[PtCl_2(cod)]$ (cod = 1,5-cyclooctadiene), $PdCl_2$, and $Hg(ClO_4)_2$. In all three cases, the metal ions bind to the N7 position of $6FP^-$ [9-methyl-6-furylpurin anion (deprotonated at one of the furyl carbon atoms)] and, in addition, to one of the carbon atoms of the furyl substituent. So far, very few structurally characterized metal complexes of C-metalated furyl moieties with Pt^{2+},[11] Pd^{2+},[12] or Hg^{2+} exist.[13]

Chart 1. Chemical Structure of H6FP (including the Atom Numbering Scheme)



The ligand H6FP was synthesized by Stille coupling followed by methylation, according to the previously reported procedure.[7b] The reaction of H6FP with $[Pt(cod)(OH_2)_2]^{2+}$, generated in situ from $[PtCl_2(cod)]$ and $AgNO_3$, led to formation of the C3*-metalated product, which was obtained as a yellow powder (**1**) after the addition of aqueous $NaClO_4$. Vapor diffusion crystallization in acetonitrile with chloroform as the antisolvent gave single crystals of $[Pt(6FP)(cod)](ClO_4)\cdot CHCl_3$ suitable for X-ray diffraction analysis. The molecular structure of the cation of **1** is depicted in Figure 1. Bond lengths and angles are in the expected ranges [Pt1−N7 2.053(3) Å and Pt1−C3* 2.029(3) Å] and are summarized in Table S1 in the Supporting Information (SI). $6FP^-$ coordinates the Pt^{2+} ion in a bidentate manner, with N7 and C3* acting as donor sites, giving rise to the formation of a six-membered metallacycle. The square-planar coordination environment of Pt^{2+} is completed by the cod ligand. The formation of **1** was confirmed by ^1H, $^{13}C\{^1H\}$, and 2D correlation NMR spectroscopy and mass spectrometry. In the ^1H and ^{13}C NMR spectra, characteristic ^{195}Pt satellites were

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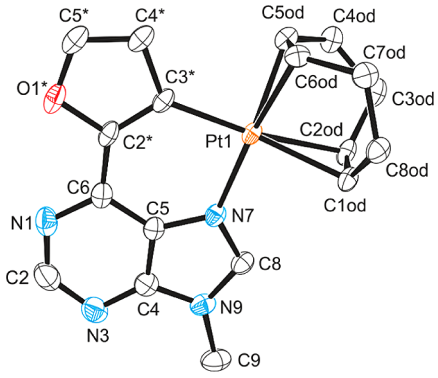

Figure 1. Molecular structure of the cation of **1**. Hydrogen atoms have been removed for clarity.

observed ($^3J_{H4*,Pt}$ = 20.5 Hz, $^2J_{C4*,Pt}$ = 30.6 Hz, $^3J_{H8,Pt}$ = 16.6 Hz, and $^2J_{C8,Pt}$ = 40.1 Hz).

Similarly, the reaction of H6FP with an in situ generated solvate of Pd^{2+} and acetonitrile led to the formation of a C3*-metalated product, $[Pd_2(6FP)(CH_3CN)_4Cl](BF_4)_2{\cdot}2CH_3CN$ (**2**). The molecular structure of the cation of **2** is given in Figure 2. Again, bond lengths and angles are in the expected ranges [Pd1−N7 2.005(4) Å and Pd1−C3* 1.982(5) Å]. They are listed in Table S2 in the SI.

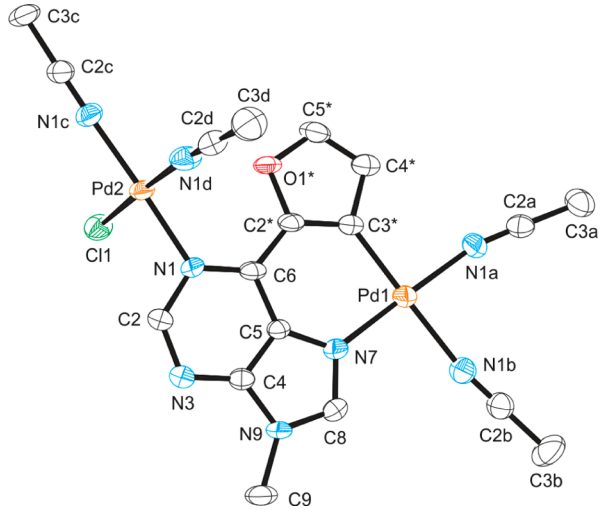

Figure 2. Molecular structure of the cation of **2**. Hydrogen atoms have been removed for clarity.

In contrast to complex **1**, compound **2** is dinuclear. Pd1 is part of the metallacycle and is coordinated to N7 and C3*. Its square-planar coordination environment is completed by two acetonitrile ligands. The C-metalation was again confirmed by ^{1}H, ^{13}C{^{1}H}, and 2D correlation NMR spectroscopy as well as mass spectrometry. Pd2 binds in a monodentate fashion to N1. Its remaining coordination sites are occupied by two acetonitrile ligands and one chlorido ligand, indicating that the initial chloride abstraction from $PdCl_2$ by means of $AgBF_4$ was incomplete. It is interesting to note that the Pt1−N7 and Pt1−C3* bonds in complex **1** are longer by about 2.4% than the corresponding Pd1−N7 and Pd1−C3* bonds in compound **2**, despite almost identical radii of Pd^{2+} and Pt^{2+}. Possible explanations are the steric bulk of the cod ligand in **1** and the large trans influence of the ene moieties. Formation of the dinuclear complex is likely to proceed via intermediate formation of the C-metalated mononuclear complex $[Pd(6FP)(CH_3CN)_2](BF_4)$, which was also observed as a side product in the NMR spectra. Generally, the possibility of the stepwise formation of a dinuclear complex may open a route to heterodinuclear complexes with catalytically active metal ions for dual or cooperative catalysis.

When reacting H6FP with $Hg(ClO_4)_2$, formation of the centrosymmetric dimer $[Hg_2(6FP)_2](ClO_4)_2{\cdot}4H_2O$ (**3**) was observed. The molecular structure of the cation of **3** is shown in Figure 3. The metal ion is coordinated by the C5* atom of the

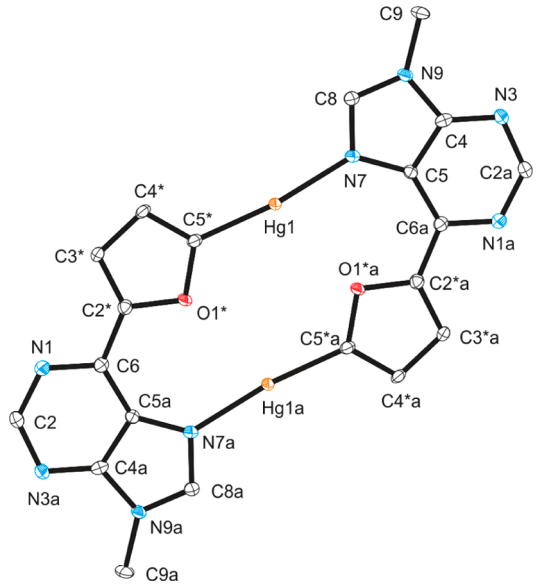

Figure 3. Molecular structure of the cation of **3**. Hydrogen atoms have been removed for clarity.

furyl moiety of one ligand [Hg1−C5* 2.028(4) Å] and the N7 atom of the purine ring of the second ligand [Hg1−N7 2.097(3) Å], resulting in an almost linear coordination environment [N7−Hg1−C5* 172.9(1)°]. Four additional ligands bind to each Hg^{2+} ion with significantly longer bond lengths but still below the sum of the van der Waals radii,[14] namely, a furyl oxygen atom [Hg1−O1*a 2.745(3) Å], two aqua ligands [Hg1−O1w 2.793(3) Å and Hg1−O1x 2.852(3) Å], and a perchlorate oxygen atom [Hg1−O3 2.821(3) Å]. Hence, including this second coordination sphere, the environment of Hg1 may also be described as distorted octahedral (Figure S1 in the SI). The separation between two Hg^{2+} ions within one dimer amounts to 4.1706(3) Å, suggesting the absence of any direct interaction. ^{1}H, ^{13}C{^{1}H}, and 2D correlation NMR spectra confirm the metalation sites, with characteristic ^{199}Hg satellites being observed ($^2J_{C4*,Hg}$ = 371 Hz and $^3J_{H4*,Hg}$ = 35 Hz).

It is interesting to note that Pt^{2+} and Pd^{2+}, both of which have a d^8 electronic configuration and therefore prefer a square-planar coordination geometry, form C-metalated complexes with $6FP^-$ with coordination via C3*, i.e., in the β position with respect to the furyl oxygen atom. In contrast, Hg^{2+} coordinates via C5*, i.e., in the energetically preferred α position.[15] The most likely mechanism for formation of the Pt^{2+} and Pd^{2+} complexes is an initial coordination via the purine N7 atom because this had previously been shown to be the preferred metal binding site of the ligand.[7b] This step brings the metal ions into close proximity of the C3* position of the furyl moiety. Hence, C−H activation

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followed by C-metalation takes place for Pt^{2+} and Pd^{2+} because the resulting M−C3* bond is formed at a perfect 90° angle with respect to the M−N7 bond [**1**, 90.0(1)°; **2**, 89.6(2)°], supporting the preferred coordination geometry. To investigate why an M−C5* bond is formed in the case of Hg^{2+}, additional density functional theory (DFT) calculations were performed. A complete discussion of the computations can be found in the SI. In short, attempts to optimize a hypothetical complex with a single N7-coordinated Hg^{2+} led to unreasonable structures. In contrast, all hypothetical mononuclear complexes with a C-mercurated furyl moiety are stable, supporting the notion that C-metalation takes place first. It can be assumed that such a metalation would follow the S_EAr mechanism, which is well-established for the mercuration of electron-rich aromatic substrates.[15] The calculations indicate that the C3*-metalated products represent the most stable mononuclear isomers, stabilized by an additional intramolecular Hg−N bond (to N1 or N7, depending on the orientation of the furyl ring). However, the computations also confirm that the dinuclear complex **3** with C5*-metalation is even more stable, probably because here Hg^{2+} with its d^{10} electronic configuration is able to adopt its preferred linear coordination environment and is additionally stabilized by a weak Hg−O1* interaction.

In conclusion, we have demonstrated the synthesis of three C-metalated complexes of H6FP. Such structurally characterized C-metalated furyl complexes are extremely rare. In each case, the metal selectively coordinates the N7 position of the purine residue. The position of the C-metalation varies depending on the preferred coordination environment of the transition metal. For Pd^{2+} and Pt^{2+}, the C-metalation regioselectively takes place in an N-directed process at the energetically less favored β position.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data, DFT calculations, figure representing the full coordination environment of Hg1 in compound **3**, and crystallographic data for compounds **1**−**3** in CIF format (CCDC 1050689−1050691). This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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