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Synthesis and Characterization of Gold(I) N-Heterocyclic Carbene Complexes Bearing Biologically Compatible Moieties

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Summary: Two new gold(I) complexes bearing the bulky N-heterocyclic carbene IPr (IPr = bis(2,6-diisopropylphenyl)-imidazol-2-ylidene) and respectively 2,3,4,6-tetra-O-acetyl-1-thio-β-d-pyranosatothiolato [[IPr]AuTgt (1)] and a saccharin ligand [[IPr]AuSac (2)] have been synthesized in good yield and are fully characterized by NMR spectroscopy and by in situ MALDI-TOF. These complexes are well-behaved compounds analogous to gold drugs such as Auranofin and Solganol.

Introduction

The use of gold salts in medicinal chemistry was first described in 2500 B.C.1 In modern chemistry, the interest in these salts as potential pharmacophores emerged in 1890 with the discovery of Au(CN)2− and its bacteriostatic properties.2 Almost 40 years later, Forestier reported the first gold-based treatment against tuberculosis.3 Today in vivo biochemistry of gold remains enigmatic, mainly due to a paucity of adequate models and an inadequate understanding of the reactivity of gold.4 Moreover, as gold is not a metal naturally used in metabolism, it is believed that its chemistry in vivo differs from other transition metals such as iron and copper, which are carefully transported and stored by enzymatic processes.5 The biochemistry of gold with D-penicillamine,6 glutathione,7 thiomalic acid,8 2,3-dimercaptopropanol,9 and albumin10 has been studied. The reactivity of gold occurs though the thiolate function of these biological molecules and leads to the formation of gold(I) thiolates, also called chrysotherapy agents. These complexes are efficient against rheumatoid arthritis and even HIV11 and are commercialized under different trade names such as Myochrysine, Solganol, Krysolgan, and Allochrysine.12 Other types of gold complexes used in medicinal chemistry are gold(I) mono- or bis-phosphines. They can bind to DNA via the guanine and cytosine bases13 and act as antitumor agents against L1210 leukemia and M5076 reticulum cell sarcoma.14 In 1972, Sutton synthesized a gold complex with a thiolate and a phosphine ligand: the 2,3,4,6-tetra-O-acetyl-1-thio-β-d-pyranosato-s-(triethylphosphine)gold(I) compound also known by the trade name Auranofin. It became one of the most promising gold complexes in medicinal chemistry,15 with a great potency against rheumatoid arthritis and cancer cells such as P388 leukemia and B16.16

In 1991, Arduengo showed that free N-heterocyclic carbenes (NHCs) are stable enough species to be isolated,17 sparking an ever-growing interest in their chemistry. Since then, these ligands have been used extensively to stabilize transition metal complexes.18 Their unusual and tunable electronic and steric

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(1) Dyson, G. M. Pharm. J. 1929, 123, 249−250.
Properties have allowed for enhanced catalytic systems performance in palladium-catalyzed cross-coupling reactions, olefin metathesis, and copper-catalyzed hydrosilylation, as the most prominent examples. Gold(I) NHCs have been known since 1989, and they can be neutral or cationic, with the respective formulas (NHC)AuX and (NHC)2AuX. They are now widely used as catalysts for organic transformations such as nucleophile additions on alkynes. Nevertheless, their potential applications in pharmacology have only recently started to be examined, thanks to the work of Baker et al., who have reported the antitumor activity of a cationic gold(I) bis-carbene by a mitocondrial membrane permeabilization (MMP) mechanism and even synthesized the first carbene Auranofin mimics by substituting the phosphine ligand by different NHCs.

In this Note, we report the synthesis of a new NHC Auranofin mimic using an alternative approach than that recently employed by Baker. We also report the synthesis of a cationic gold(I) saccharin complex by using for the first time a cationic monoligated NHC gold(I) as reagent. This unstable complex has usually been proposed as an intermediate in gold-catalyzed transformations.

**Results and Discussion**

We first attempted to synthesize (IPr)AuTgt (I) (Tgt = 1-thio-β-glucose tetraacetate) by reacting directly the thiosugar with (IPr)AuCl in refluxing dichloromethane (DCM). While the formation of HCl was expected to act as a driving force, no reaction was observed and the two starting materials were recovered. To enhance the nucleophilic behavior of the thio-carbohydrate, we generated the stable cationic [(IPr)AuCl]+ (MeCN)[PF6−] complex, by adding AgPF6 in the presence of (IPr)AuCl. The addition of the saccharin salt allowed the slow formation of the desired complex with appearance of NaPF6 as a white precipitate (Scheme 2). To increase the kinetics of the reaction, an excess of saccharin salt (2:1) was used. After filtration over a plug of silica gel and evaporation of the DCM, the desired complex was obtained in good yield and analytically pure form as an off-white, air-stable powder. It is interesting to note that reaction of the cationic [(IPr)AuCl]+ (MeCN)[PF6−] generated in situ from IPrAuCl and AgPF6, with either the thiol or the thiolate failed, the NMR spectra indicating a decomposition pathway.

We first attempted to synthesize (IPr)AuSac (2) (Sac = saccharin) by directly reacting the sodium saccharin salt with (IPr)AuCl in DCM. While the formation of a gold–oxygen bond and the precipitation of NaCl were expected, no reaction was observed and the two starting materials were recovered. We attributed this lack of reactivity to the very poor affinity of gold for oxygen. To enhance the acidic character of the gold center, we generated the stable cationic [(IPr)Au+*(MeCN)][PF6−] complex, by adding AgPF6 in the presence of (IPr)AuCl. The adduction of the saccharin salt allowed the slow formation of the desired complex with appearance of NaPF6 as a white precipitate (Scheme 2). To increase the kinetics of the reaction, an excess of saccharin salt (2:1) was used. After filtration over a plug of silica gel and the evaporation of the volatiles, the desired complex was obtained in good yield and analytically pure form as an off-white air-stable powder.

In order to unambiguously characterize both complexes, NMR and X-ray diffraction studies were performed. A mass spectroscopy IA-MALDI-TOF study of both complexes was performed in order to study their stability in the gas phase. The 1H NMR resonances for the imidazole ring of both complexes appear as a singlet at 7.15 and 7.25 ppm, respectively.

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and appear between 3.37 and 4.93 ppm. For (IPr)AuSac (25) we can confirm that nitrogen adds a small amount of electronic density on the gold(I) center and is probably weakly bound, as expected from its hard base character.

Suitable crystals for X-ray diffraction were grown by slow diffusion of a mixture of DCM/heptane for (IPr)AuTgt (1) and (IPr)AuSac (2). In the solid state, both complexes (Figure 1) exhibit a two-coordinate gold(I) atom in a nearly linear environment with a C–Au–S bond angle of 173.49° and a C–Au–N bond angle of 177.09°. The respective Au–C(1) distances of 1.986(6) and 1.973(4) Å are in good agreement with previously reported structures of neutral and cationic gold(I) complexes, 30 and the Au–N distance of 2.031(3) Å for (IPr)AuSac (2) is similar to that found in complexes with nitrogen donor ligands. 31

It is noteworthy that the gold(I) center binds the saccharin ligand by the nitrogen due to the very poor affinity of gold for binding oxygen and triggers a rearrangement between both possible resonance forms of the saccharin salt, enabling the moiety oxygen and triggers a rearrangement between both possible resonance forms of the saccharin salt, enabling the moiety

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We investigated the stability of both complexes in the gas phase by using the mass spectroscopy technique. Inert-atmosphere MALDI-TOF mass spectrometric analysis 33 of 1 and 2 was carried out using pyrene as a charge-transfer matrix (Table 1).

Table 1. Summary of MALDI Mass Spectrometric Data Obtained from Analysis of (IPr)AuTgt (1) and (IPr)AuSac (2) in Positive Ion Mode (the asterisk indicates the base peak in each spectrum)

<table>
<thead>
<tr>
<th>m/z</th>
<th>assignment</th>
<th>m/z</th>
<th>assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>948.3</td>
<td>not detected</td>
<td>767.3</td>
<td>not detected</td>
</tr>
<tr>
<td>1819.1</td>
<td>[(IPr)AuS2]⁺</td>
<td>1532.5</td>
<td>[(IPr)Au(Sac)]⁺</td>
</tr>
<tr>
<td>1787.2*</td>
<td>[(IPr)AuS]⁺</td>
<td>1352.1</td>
<td>[(IPr)Au(Sac)]⁺</td>
</tr>
<tr>
<td>1564.4</td>
<td>[(IPr)Au(Sac)[Tgt]⁻-H]⁺</td>
<td>1266.3</td>
<td>[(IPr)AuS]⁺</td>
</tr>
<tr>
<td>1532.5</td>
<td>[(IPr)Au(Sac)[Tgt]⁻-H]⁺</td>
<td>1202.8</td>
<td>[(IPr)AuS]⁺</td>
</tr>
<tr>
<td>847.1*</td>
<td>[H(IPr)Cl]⁺</td>
<td>787.1*</td>
<td>[H(IPr)Au(pyrene)]⁺</td>
</tr>
<tr>
<td>787.1*</td>
<td>[(IPr)Au(pyrene)]⁺</td>
<td>787.1</td>
<td>[(IPr)Au(pyrene)]⁺</td>
</tr>
</tbody>
</table>

Notes

the thiolate ligand, Tgt), as well as signals for the [Sac]⁻ ligand for 2. In neither case could the intact molecular cations be observed in positive ion mode. Instead, prominent signals were present in each spectrum due to dinuclear Au complexes, resulting from agglomeration products in the gas phase. Ample precedents exist for aggregation of coordinatively unsaturated ions via ion—molecule interactions in the gas phase. Of particular interest are peaks assigned to [(IPr)₂Au₂(Tgt)-H]⁺ (1a) and [(IPr)₂Au₂-(Sac)]⁺ (2b), respectively, on the basis of the match between their simulated and observed isotope patterns (Figure 2). The complexity of the patterns is due to the isotopic composition of the ligands, as gold is monoisotopic.

While numerous peaks for aggregated Au complexes are evident in the spectrum of 1, including the peak for 1a, 2b is the sole agglomeration product observed in the spectrum for 2 (see Table 1 for a summary of mass spectrometric data). Additional signals at high m/z in the mass spectrum of 1 are due to aggregation products resulting from the cleavage of the sugar moiety from the thiolate ligand, rather than loss of the entire (Tgt) ligand. Prominent among these signals is [(IPr)₂Au₂S]⁺ (which is observed as the base peak) and [IPr]Au(Sac)]⁺. Retention of the sulfur donor, whether by rearrangement or by recapture following fragmentation, reflects the thiolphile nature of gold. It is worthy to note that for 2 there is no retention of nitrogen, emphasizing the low affinity of gold to bind nitrogen. The gold(I) cation, present in the ion fragments, remains bound to the IPr ligand, highlighting the very strong bond between gold and NHC ligands, responsible for the exceptional stability of the complex type. Present in the MALDI spectra for both 1 and 2 are peaks corresponding to [HI(Pr)][Cl]⁺ (indeed, this signal is the base peak in the spectrum of 2). Presumably results from dimerization of the N-heterocyclic carbene, IPr, and the capture of chloride ions from residual AuCl and/or starting material. It should be noted that the relative intensity of ion peaks in the mass spectra does not necessarily correlate with abundance; the kinetic stability of the ion also plays a key role. The proportion of AuCl in the analyte itself is negligible, as judged from microanalysis. Also evident in the positive ion spectra are peaks due to [(IPr)Au(pyrene)]⁺, which we attribute to scavenging of the coordinatively unsaturated [(IPr)Au]⁺ by pyrene in the gas phase.

Figure 2. Inert-atmosphere MALDI-MS spectra (pyrene matrix) showing simulated (top) and observed (bottom) isotope patterns for (a) [(IPr)₂Au₂(Tgt)-H]⁺ (1a) (observed m/z 1532.5, calculated m/z 1532.3) and (b) [(IPr)₂Au₂-(Sac)]⁺ (2b) (observed m/z 1352.1, calculated m/z 1352.3).
added, and the solution was stirred for 30 s, with the rapid appearance of a precipitate (AgCl). Then the saccharin sodium salt (54 mg, 0.24 mmol, 2 equiv) was added, and the solution was stirred overnight at rt. Acetonitrile was removed under reduced pressure and replaced by cold DCM. The excess saccharin sodium and AgCl salts are not soluble in cold DCM; the solution was filtered over Celite, and the solids were discarded. Evaporation of the DCM gave a white powder (60 mg, 65%). 1H NMR (400 MHz, CDCl3): δ 7.71 (d, J = 6.4 Hz, 1H, CH-aromatic), 7.62 (d, J = 6.8 Hz, 1H, CH-aromatic), 7.52 (m, 4H, CH-aromatic), 7.32 (d, J = 7.2 Hz, 4H, CH-aromatic), 7.25 (s, 2H, CH-imidazole), 2.59 (sept, J = 6.8 Hz, 4H, CH(CH3)2), 1.42 (m, J = 6.8 Hz, 12H, CH(CH3)2), 1.25 (m, J = 6.8 Hz, 12H, CH(CH3)2). 13C NMR (100 MHz, CDCl3): δ 175.2 (s, NCO), 165.6 (s, C-carbene), 145.9 (s, CH-aromatic), 142.0 (s, CH-aromatic), 133.9 (s, CH-aromatic), 132.8 (s, CH-aromatic), 132.7 (s, CH-aromatic), 132.1 (s, CH-aromatic), 131.1 (s, CH-aromatic), 124.5 (s, CH-imidazole), 124.1 (s, CH-aromatic), 123.5 (s, CH-aromatic), 120.2 (s, CH-aromatic), 29.2 (s, CH(CH3)2), 24.7 (s, CH(CH3)2), 24.3 (s, CH(CH3)2). Anal. Calcd for C41H55N2O9-SAu (948.44): 53.14 C, 5.21 H, 5.47 N. Found: 52.97 C, 5.30 H, 5.37 N.

Crystallographic information files (CIF) of complexes (IPr)AuTgt (1) and (IPr)AuSac (2) have been deposited with the CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K., and can be obtained on request free of charge, by quoting the publication citation and deposit numbers 615644 and 615645.

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Supporting Information Available: Crystallographic information files (CIF) of complexes (IPr)AuTgt (1) and (IPr)AuSac (2) and the IA-MALDI TOF spectra of the complexes are available free of charge via the Internet at http://pubs.acs.org.