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COMMUNICATION

$[(C_3H_4N_2)_2Au]Cl$—a bis protic gold(I)-NHC†

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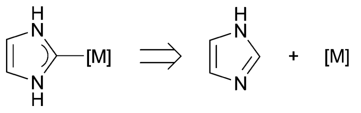
The gold(I) bis-NHC (NHC = imidazol-2-ylidene) parent compound was synthesised in high yield by a three step reaction starting from imidazole. The compound is highly water soluble and stable in concentrated hydrochloric acid.

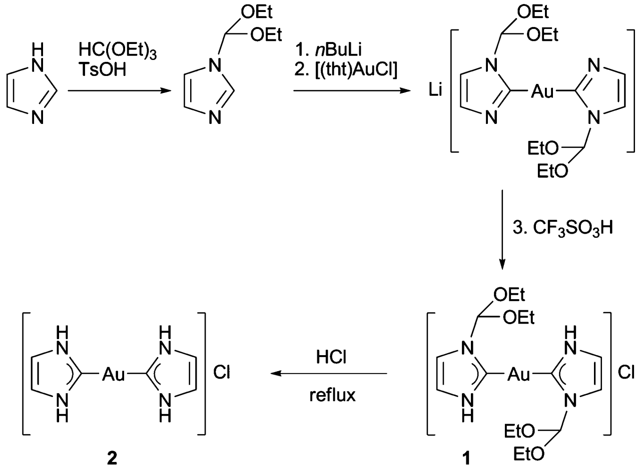
Since the first synthesis of stable *N*-heterocyclic carbenes (NHCs) as a "chemical curiosity" their application as versatile catalysts has stimulated the field and numerous stable carbenes and metal complexes have been prepared. The imidazol-2-ylidenes are the most commonly used NHC, although other NHCs are known.[1,2] The stability of the metal–carbon bond under physiological conditions has recently allowed therapeutic investigations. Most of them are related to their use as antimicrobials and anti-cancer agents.[3–10]

Usually, both *N*-atoms of the imidazol-2-ylidene NHCs are alkylated. A few examples exist where only one *N*-atom is alkylated and one is protonated.[11–13] Bis protic NHNH carbenes have been reported in complexes of imidazolidin-2-ylidenes and benzimidazol-2-ylidines.[14–16] The parental NHC, imidazol-2-ylidene, which is a tautomer of imidazole, and its metal complexes have been explored theoretically to calculate structural and electronic parameters of NHC complexes.[11,17–24] These "NHNH" NHCs can not be obtained using Arduengos route *via* deprotonation of the imidazolium ion.

We have developed a simple route towards a bis protic gold(I)-NHC starting from imidazole (Scheme 1). Imidazole was first *N*-protected with triethyl orthoformate, subsequently lithiated in 2-position and reacted with [(tht)AuCl] (tht = tetrahydrothiophene). The resulting anionic gold(I) bis(imidazolid) was protonated by CF_3SO_3H to give the *N*-protected bis-NHC (**1**, Fig. 1), which was then deprotected in concentrated hydrochloric acid under reflux for 6 h to give the parent bis-NHC gold(I) compound (**2**) in nearly quantitative yield (Scheme 2) as a white microcrystalline solid.‡



Scheme 1



Scheme 2

The bis protic gold(I)-NHC complex **2** is with 185 g L^{-1} very soluble in water. The distribution coefficient at pH 7.4 ($\log P_{7.4}$) in a *n*-octanol/water has been determined to be –0.87 and therefore **2** is more hydrophilic than analogues gold(I) bis(NHC) chlorides.[25] It is thermally stable and decomposes at temperatures above 190 °C.

Table 1 Selected experimentally determined structure parameters of **2** compared to calculated ones (HF/DFT (B3LPP/LANL2DZ and BHANH/LANL2DZ) and DFT (BP86))[11,17]

Distance/Å	Exp.[a]	HF/DFT[11,a]	DFT[19]
$Au–C_{carbene}$	2.015	2.027	2.030
$C_{carbene}–N$	1.344	1.360	1.357
N–C	1.375	1.393	1.385
C–C	1.360	1.364	1.361
Angle/°			
N–C–N	104.1	106.2	103.3

[a] Averaged.

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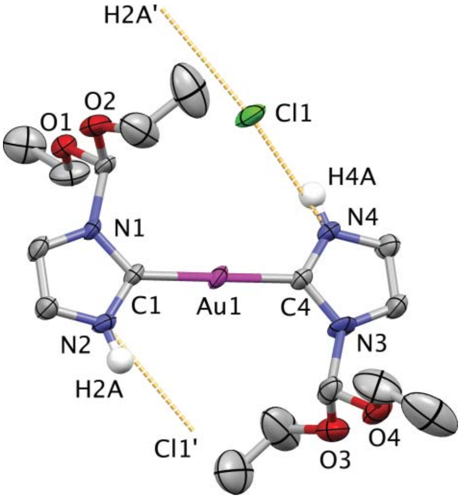

Fig. 1 Molecular structure of **1** with partial labelling. Displacement ellipsoids are drawn at 50%. Hydrogen bonds are indicated by dashed lines. Selected bond lengths (Å) and angles (°): Au(1)–C(1) 1.999(10), Au(1)–C(4) 2.007(9), C(1)–N(1) 1.359(10), C(1)–N(2) 1.361(12), C(4)–N(3) 1.384(11), C(4)–N(4) 1.323(12); C(1)–Au(1)–C(4) 179.1(4), Au(1)–C(1)–N(1) 130.8(7), Au(1)–C(1)–N(2) 126.0(6), Au(1)–C(4)–N(3) 129.5(7), Au(1)–C(4)–N(4) 125.5(7), N(1)–C(1)–N(2) 103.1(7), N(3)–C(4)–N(4) 105.0(8).

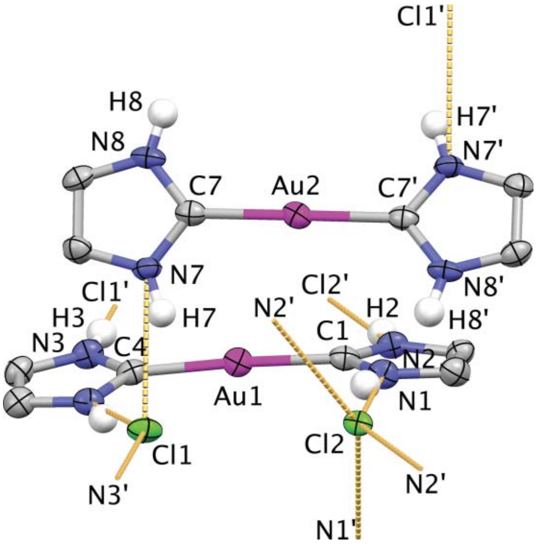

Fig. 2 Molecular structure of **2** with partial labelling. Displacement ellipsoids are drawn at 50%. Hydrogen bonds are indicated by dashed lines. Selected bond lengths (Å) and angles (°): Au(1)–C(1) 2.013(4), Au(1)–C(4) 2.018(4), Au(2)–C(7) 2.015(4), C(1)–N(1) 1.345(4), C(1)–N(2) 1.337(4), C(4)–N(3) 1.358(4), C(4)–N(4) 1.346(4), C(7)–N(7) 1.342(5), C(7)–N(8) 1.341(4); C(1)–Au(1)–C(4) 176.67(13), C(7)–Au(2)–C(7′) 178.31(18), N(1)–C(1)–N(2) 104.1(3), N(3)–C(4)–N(4) 103.7(3), N(7)–C(7)–N(8) 104.2(3).

The structural parameters of **2** are in good agreement with those calculated by Raubenheimer *et al.*[11] at HF/DFT (B3LPP/LANL2DZ and BHANH/LANL2DZ) and Frenking *et al.*[19] at the DFT (BP86) level of theory (Table 1), although calculated for the gas phase and in the solid state the structure of **2** is determined by hydrogen bonds towards the chloride counter ions (Fig. 2).

In the solid state of **2** isosceles Au_3-triangles are found ($d_{\text{Au–Au}}$ = 4.346 and 4.904 Å, $\angle(Au_3)$ = 55.62° and 68.75°, Fig. 3). The metric parameters found in **2** are within the range of previously described linear gold(I) bis(NHC) complexes.[25,26] The separation of the Au atoms are a result of the before mentioned formation of hydrogen bonding networks. Therefore no aurophilic contacts are observed.[27] The absence of aurophilic contacts is also reflected by the absorption spectrum of **2** in water which shows only three bands in the UV regime (223, 252, 276 nm) for to the imidazolydene ligands. Upon irradiation at 270–240 nm no emission was observed in methanolic solution or the solid state.

A preliminary cytotoxicity screening at K562 and A2780$_{\text{sens.}}$ cancer cell lines showed no cytotoxicity of compound **2** up to 10^{-5} M.† Interestingly, a significantly higher cytotoxicity of **2**

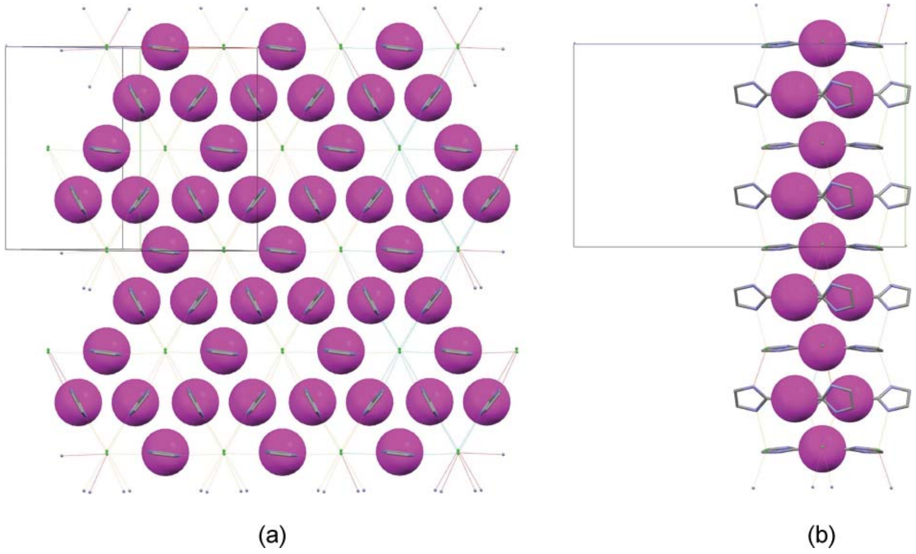

Fig. 3 Packing of **2** in the solid state, only one layer shown; left: view along C–Au–C axis, right: view along *a*-axis. Gold atoms are shown in space filling model, all others as capped sticks.

is found in cells in which the copper transporter CTR1 is over expressed.

Therefore, such "NHNH" NHCs may find applications in biomedical applications as water soluble delocalised cations or in supramolecular assemblies as hydrogen bond directing units. Overall the work illustrates a simple and efficient route towards water soluble metal complexes of "NHNH" NHCs. Currently, we are exploring the scope of this reaction.

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Notes and references

‡ Syntheses: $[(C_8H_{14}N_2O_2)_2Au]Cl$ (**1**): a solution of *n*-butyl lithium in hexane (1.6 M, 1.25 mL, 2.0 mmol) was added to a solution of 1-diethoxymethylimidazole (0.34 g, 2.0 mmol) in THF (50 mL) at −78 °C. The solution was kept at −78 °C, after 45 min a solution of [(tht)AuCl] (0.32 g, 1.0 mmol) in THF (5 mL) and after further 30 min CF_3SO_3H (0.18 mL, 2.0 mmol) were added. The solution was slowly warmed to ambient temperature. A precipitate formed after a few minutes, which was collected by filtration, washed with diethyl ether, dried *in vacuo* and recrystallised from methanol–CH_2Cl_2. Yield 0.41 g (72%). Crystals suitable for single crystal structure analysis were grown by slow evaporation of a solution of **1** in methanol. ^1H NMR (methanol-d_4) δ/ppm: 1.25 (t, J = 7.1 Hz, 12 H, OCH_2CH_3), 3.57 (m, 8 H, OCH_2CH_3), 6.61 (s, 2 H, C*H*), 7.35 (d, J = 2 Hz, 2 H, H_{im}), 7.57 (d, J = 2 Hz, 2 H, H_{im}). MALDI-TOF (MeOH): m/z = 537 $[M - Cl]^+$, 435 $[M - Cl - CH(OEt)_2]^+$, 333 $[M - Cl - 2CH(OEt)_2]^+$. ESI^+ (MeOH): m/z = 333.5 $[M - Cl - 2CH(OEt)_2]^+$. $C_{16}H_{28}N_4AuClO_4{\cdot}CH_2Cl_2$ (656.77): calcd C 32.21, H 4.75, N 9.11; found C 32.49, H 4.82, N 9.20. Crystal data of **1**. $C_{16}H_{27}AuClN_4O_4$ M = 571.83 g/mol, monoclinic, a = 7.4555(3), b = 13.2831(8), c = 22.2966(7) Å, β = 96.996(3)°, V = 2191.64(18) $Å^3$, T = 183 K, space group $P2_1/n$, Z = 4, 12 129 reflections measured, 4842 unique (R_{int} = 0.0375). The final wR was 0.0657 ($I > 2\sigma(I)$) and wR_2 was 0.1290 (all data).

$[(C_3H_4N_2)_2Au]Cl$ (**2**): a suspension of **1** (0.35 g, 0.6 mmol) in 15 mL hydrochloric acid (3.5 M) was heated to reflux for 5 h. All volatiles were removed *in vacuo* to give **2** as a white micro-crystalline solid in quantitative yield. Crystals suitable for single crystal structure analysis were grown by slow diffusion of diethyl ether into a solution of **2** in methanol. Yield 0.21 g (93%). ^1H NMR (methanol-d_4): δ/ppm: 7.35 (pseudo t, 4 H, H_{im}), 12.58 (s, br, 4 H, N*H*). MALDI-TOF (MeOH): m/z = 332.86 $[(C_3N_2H_4)_2Au]^+$. ESI^+ (MeOH): m/z = 333.5 $[M - Cl]^+$, 283.1 $[(C_3H_4N_2)Au(H_2O)]^+$. $C_6H_8N_4AuCl{\cdot}H_2O$ (386.59): calcd C 18.64, H 2.61, N 14.49; found C 18.97, H 2.77, N 14.55. Crystal data of **2**. $C_6H_8AuClN_4$ M = 368.59 g/mol, monoclinic, a = 8.51512(18), b = 14.1757(2), c = 23.3727(5) Å, β = 97.774(2)°, V = 2795.35(9) $Å^3$, T = 183 K, space group $C2/c$, Z = 12, 24 088 reflections measured, 6769 unique (R_{int} = 0.0338). The final wR was 0.0279 ($I > 2\sigma(I)$) and wR_2 was 0.0642 (all data).

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