Metallation of Ligands with Biological Activity: Synthesis and X-Ray Characterization of $[(SDAZ)_2Au_2(dppe)]$ (SDAZ = Sulphadiazinide Anion; dppe = 1,2-Bis(diphenylphosphanyl)ethane)

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Z. Naturforsch. **60b,** 318 – 321 (2005); received August 2, 2004

Sulphadiazine, [4-amino-*N*-(2-pyrimidinyl)-benzenesulfonamide], reacts with $(dppe)Au_2Cl_2$ and triethylamine in methanol to produce $[(SDAZ)_2Au_2(dppe)]$. The structure of this novel complex was analyzed by single crystal X-ray diffraction. In $[(SDAZ)_2Au_2(dppe)]$ the ligands $SDAZ^-$ and dppe have approximately the same bond distances and angles as found for the protonated and free ligand, respectively. The compound is assembled essentially of two gold atoms bonded to the phosphorus centers of one 1,2-bis(diphenylphosphanyl)ethane molecule (in an *anti* conformation). The coordination sphere is completed with a *trans* sulphadiazine ligand on each gold atom. Because of their fairly high reactivity, the two aromatic amine groups in the SDAZ ligands represent important sites for the chemical modification of the complex with biological purposes.

Key words: Sulphadiazine Complexes, Bioinorganic Chemistry of Gold, Metallation of Biological Ligands

Introduction

It is well known that the sulfanilamide derivative 4-amino-*N*-(2-pyrimidinyl)-benzenesulfonamide (sulphadiazine) is an efficient antibacterial drug with the typical sulfonamide structure [1 – 3]. Through exchanges of different functional groups, but with the conservation of the structural features, sulfonamide derivatives can display a wide variety of pharmacological activities, such as antidiabetic, antibacterial and also antitumor [4 – 7]. In addition, some metal complexes of these ligands have been found to promote rapid healing of burns: the Ag(I)-sulphadiazine complex is used for human burn treatment [8, 9], and the Zn(II) complex for the prevention of bacterial infection in burned animals [10, 11]. The effectiveness of these compounds in the treatment of skin disorders does not depend solely on the slow release of Ag(I) or Zn(II), but depends strongly on the nature of the material to which the metal ion is bound [10].

Gold(I) complexes containing sulphur ligands have been extensively used in the medical treatment of rheumatoid arthritis [12, 13]. The explosive growth of gold chemistry in the last decade, besides to consolidate the antiarthritic activity of its compounds, has shown that some gold drugs seem to be also effective in the treatment of diseases such as tumors, psoriasis and AIDS [14, 15]. Of particularly great chemotherapeutical potential in cancer treatment are gold(I) complexes with bidentate phosphanes [16, 17], such as $[Au(dppe)_2]Cl$ (dppe = $Ph_2PC_2H_4PPh_2$), which, according to *Berners-Price* and co-workers [18], represent one class of lipophilic cationic antitumor agents. Among other biological important properties, $[Au(dppe)_2]Cl$ was shown to exhibit a spectrum of antitumor activity in mouse tumor models [19] in an antimitochondrial mode of action [20, 21]. The activity of the complex was retained when Au(I) was substituted by Ag(I) or Cu(I) [22, 23]. However, the replacement of the phenyl substituents on the phosphane by other substituents leads to a decrease or loss of antitumor activity [24]. This is probably related to the higher reactivity of alkyl- compared to aryl-phosphane towards disulphide bonds, and consequent oxidation, *i.e.* detoxification, *in vivo* [24, 25].

The noteworthy chemical ability of sulphadiazine (1), to act as a ligand, therefore allowing the synthesis of a variety of transition metal complexes,

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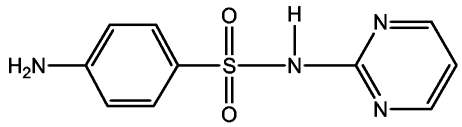

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is based upon the acidity of the $S(O)_2N$-H function, allied with the presence of two vicinal pyrimidine-N atoms as potential coordination sites.

Thus, the deprotonation of the NH group yields an anionic donor ligand, with two nitrogen atoms at the pyrimidine ring, which provide the stereochemical requisites for the achievement of complexes with a monodentate, chelate or bridge-forming ligand. Earlier workers have reported sulphadiazine complexes of Ag [26], Zn, Cd and Hg [27], and more recently a sulphadiazine complex of Cu has also been described [28]. In the past year we have reported the first sulphadiazine complexes of gold [29, 30], with triphenylphosphane and triphenylarsane as co-ligands. We now report the synthesis and the X-ray structural characterization of the first binuclear (SDAZ)-Au-dppe complex. In this novel compound, an open (centered) Au-PPh_2-C_2H_4-Ph_2P-Au chain is linked to the sulfonamide-N atoms of two deprotonated sulphadiazine molecules, both containing two aromatic amino groups as reactive sites for the chemical modification of the SDAZ ligands with biological aims [3, 31, 32].

Results and Discussion

$[(SDAZ)_2Au_2(dppe)]$ (**1**) crystallizes in the monoclinic, centrosymmetric space group $P2_1/n$. The crystal data and experimental conditions are given in Table 1. Fig. 1 shows the contents of the asymmetric unit. Selected bond distances and angles are listed in Table 2.

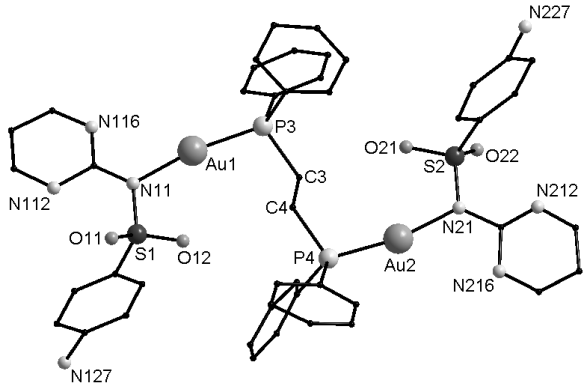

Fig. 1. Molecular structure (asymmetric unit) of $[(SDAZ)_2Au_2(dppe)]$.

Table 1. Crystal data and structure refinement for $[(SDAZ)_2Au_2(dppe)]$.

Empirical formula	$C_{46}H_{38}Au_2N_8O_4P_2S_2$
Formula weight	1286.84
Temperature [K]	298(2)
Radiation, λ [Å]	0.71073
Crystal system, space group	monoclinic, $P2_1/n$
Unit cell dimensions a,b,c [Å]	$a = 8.1606(19)$
	$b = 25.580(6)$
	$c = 23.536(6)$
α,β,γ [°]	$\alpha = 90$
	$\beta = 97.912(4)$
	$\gamma = 90$
Volume [Å^3]	4866(2)
Z, Calculated density [g·cm^{-3}]	4, 1.756
Absorption coefficient [mm^{-1}]	6.224
$F(000)$	2488
Crystal size [mm]	$0.57 \times 0.11 \times 0.05$
θ Range [°]	1.59 – 26.00
Limiting indices	$-10 \le h \le 9$, $-31 \le k \le 26$,
	$-29 \le l \le 27$
Reflections collected	22339
Reflections unique	9020 [$R_{int} = 0.1486$]
Completeness to theta max.	94.5%
Absorption correction	semi-empirical from equivalents
Max. and min. transmission	0.7460 and 0.1255
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9020 / 0 / 307
Goodness-of-fit on F^2	0.891
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0951$, $wR_2 = 0.2020$
R Indices (all data)	$R_1 = 0.2744$, $wR_2 = 0.2557$
Largest diff. peak and hole [e·A^{-3}]	3.848 and −3.466

Table 2. Selected bond lengths [Å] and angles [°] for $[(SDAZ)_2Au_2(dppe)]$.

Bond lengths		O(12)-S(1)-O(11)	116.1(12)
Au(1)-N(11)	2.05(2)	O(12)-S(1)-N(11)	103.9(11)
Au(1)-P(3)	2.228(8)	O(11)-S(1)-N(11)	111.7(13)
Au(2)-N(21)	2.08(2)	O(12)-S(1)-C(121)	108.3(12)
Au(2)-P(4)	2.211(7)	O(11)-S(1)-C(121)	107.4(12)
S(1)-O(12)	1.377(17)	N(11)-S(1)-C(121)	109.3(12)
S(1)-O(11)	1.42(2)	O(22)-S(2)-O(21)	115.5(11)
S(1)-N(11)	1.63(2)	O(22)-S(2)-N(21)	113.2(12)
S(2)-O(22)	1.430(18)	O(21)-S(2)-N(21)	104.4(11)
S(2)-O(21)	1.467(18)	O(22)-S(2)-C(221)	107.1(12)
S(2)-N(21)	1.63(2)	O(21)-S(2)-C(221)	107.2(11)
P(3)-C(3)	1.86(3)	N(21)-S(2)-C(221)	109.1(11)
P(4)-C(4)	1.85(2)	C(3)-P(3)-Au(1)	106.3(9)
C(3)-C(4)	1.55(3)	C(4)-P(4)-Au(2)	110.0(8)
		S(1)-N(11)-Au(1)	116.7(12)
Bond angles		S(2)-N(21)-Au(2)	115.6(12)
N(11)-Au(1)-P(3)	169.8(6)	C(4)-C(3)-P(3)	110.4(17)
N(21)-Au(2)-P(4)	169.2(6)	C(3)-C(4)-P(4)	109.0(17)

In $[(SDAZ)_2Au_2(dppe)]$, the ligands SDAZ and dppe have approximately the same bond distances and angles as found for the protonated and free ligand [33],

respectively. The compound is assembled essentially of two gold atoms bonded to the phosphorus centers of one 1,2-bis(diphenylphosphanyl)ethane molecule (in an *anti* conformation). The coordination sphere is completed with a *trans* sulphadiazine ligand on each gold atom. The pairs of P-Au and N-Au distances are identical considering the standard deviations, Au(1)-P(3) / Au(2)-P(4) at 2.228(8) / 2.211(7) Å, Au(1)-N(11) / Au(2)-N(21) at 2.05(2) / 2.08(2) Å respectively (see Table 2). The bond angles surrounding the gold atoms are also identical, 169.8(6)° [N(11)-Au(1)-P(3)] and 169.2(6)° [N(21)-Au(2)-P(4)].

The simple architecture of the molecule should be considered a major plus regarding its biological activity, since many biologically active metal complexes of sulphadiazine or dppe are also not highly structured. Finally, the two aromatic amino groups are suitably distant of the core of the molecule, so that chemical transformations of these sites for biological purposes should not be difficult.

Experimental Section

*Preparation of [(SDAZ)$_2$Au$_2$(dppe)] (**1**)*

After dissolving 0.05 g (0.2 mmol) of sulphadiazine in 5 ml of methanol a few drops of triethylamine were added. Under stirring the solution was slowly added to 0.063 g (0.1 mmol) of (dppe)Au_2Cl_2 previously dissolved in 5 ml of hot methanol. After 3 h a rose-colored precipitate was isolated by filtration. The product was dried under vacuum and recrystallized from a mixture (1:1) of dichloromethane and petroleum ether: 0.21 g (80% based on sulphadiazine) of air-stable gray crystals, m. p. 312 °C.

IR (KBr): ν = 3459 (m, $\nu_{as}(NH_2)$), 3364 (s, $\nu_s(NH_2)$), 3246 (m, $\delta(NH_2)$), 3056 (s, (C-H)$_{aryl}$), 2907 cm^{-1} (s, (C-H)$_{alkyl}$); the $\nu(SO_2)$ absorptions between 1300 – 1100 cm^{-1} could not be detached from the bands of the aromatic rings (1300 – 1000 cm^{-1}). Analysis for $C_{46}H_{38}Au_2N_8O_4P_2S_2$ (1286.84): calcd. C 39.13, H 3.14; found C 42.80, H 3.28. Highly divergent N values were not considered.

Structural determination

Data were collected on a Bruker SMART CCD diffractometer. The structure of [(SDAZ)$_2$Au$_2$(dppe)] was solved by direct methods (SHELXS-97 [34]). Refinements were carried out with the SHELXL-97 [35] package. All refinements were made by full-matrix least-squares on F^2 with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were included in the refinement in calculated positions. The carbon atoms were refined with isotropic parameters. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre, CCDC-246335 (**1**). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: int. code +(1223)336-033; e-mail for inquiry: fileserv@ccdc.cam.ac.uk).

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