FAB mass spectrometry of Au(I) complexes with 1,4-benzodiazepin-2-ones

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Abstract

FAB mass spectrometric measurements on several Au(I) derivatives of 1,4-benzodiazepin-2-ones provided information about the stability of these compounds. For all the complexes containing the moiety $Au(PPh_3)$, the base peak is the ionic species $[Au(PPh_3)]^+$. Otherwise, the positive charge is localized in the benzodiazepinic ligand.

Introduction

The synthesis and spectroscopic characterization of several derivatives of 1,4-benzodiazepin-2-ones (L) with d^8 metal ions have been described previously by some of us [1]. Among these, the gold(III) and the palladium(II) adducts, $(L)AuCl_3$ and *trans*-$(L)_2PdCl_2$ (L = Prazepam), have been shown, by X-ray structure determination, to contain the ligand bonded to the metal through the 4-nitrogen atom. Other palladium(II) species were found to be metallated derivatives having the ligand coordinated through the 4-nitrogen and the *ortho* carbon atom of the 5-phenyl substituent. Both dimers $[(L\text{-}H)PdCl]_2$ and monomers such as (L-H)(L′)PdCl (L′ = neutral ligand) or (L-H)Pd(acac) (acacH = acetylacetone) were described. The existence of the five-membered cyclometallated system was ascertained through the X-ray crystal structure of $(L\text{-}H)(Ph_3P)PdCl$ (L = Prazepam) [1c]. Quite recently [2], gold(I) derivatives were also described by us: they include neutral, (L)AuCl, and ionic $[(L)Au(PPh_3)]^+$, species (L = Diazepam, Prazepam, Nitrazepam and Nimetazepam). In addition, with Nitrazepam and Lorazepam, i.e. with benzodiazepines unsubstituted at the 1-nitrogen atom, neutral $(L\text{-}H)Au(PPh_3)$ complexes were obtained, where the deprotonated ligand is bonded to gold through the N(1) atom. From one of these, taking advantage of the 4-nitrogen atom, not involved in coordination, a dinuclear system $[(Ph_3P)Au\{\mu\text{-}(L\text{-}H)\}Au(PPh_3)]^+$ (LH = Nitrazepam) was built up.

Here, following our previous work on the behaviour in vapour phase of the palladium(II) derivatives [3], we report a mass spectrometric investigation of some of the gold(I) species, carried out under FAB conditions with metanitrobenzylalcohol (MNBA) as matrix. The complexes which were investigated are collected in Fig. 1.

Experimental

Mass spectrometric measurements were carried out by a VG ZAB2F instrument operating in FAB conditions [4]. Samples were dissolved in metanitrobenzylalcohol and bombarded by 8 keV Xe atoms. Metastable transitions were detected by either B/E linked scans [5a] or mass analysed ion kinetic energy spectrometry [5b].

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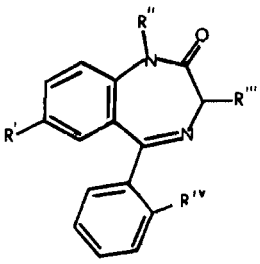
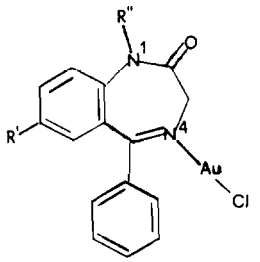


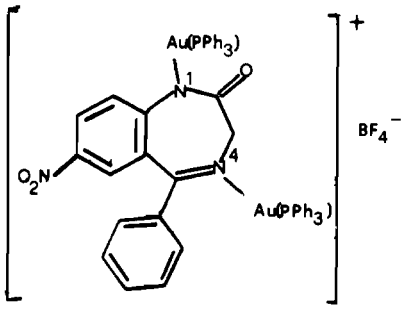
LIGANDS (L)

	R^I	R^{II}	R^{III}	R^{IV}
Diazepam	Cl	CH_3	H	H
Prazepam	Cl	CH_2—◁	H	H
Nitrazepam	NO_2	H	H	H
Lorazepam	Cl	H	OH	Cl
Nimetazepam	NO_2	CH_3	H	H

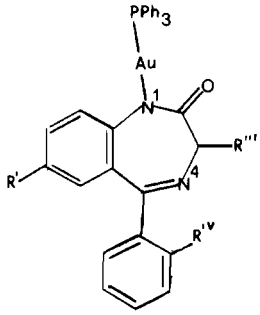


	R^I	R^{II}	Ligands
3	Cl	CH_3	Diazepam
4	Cl	CH_2—◁	Prazepam
5	NO_2	H	Nitrazepam

(L)AuCl

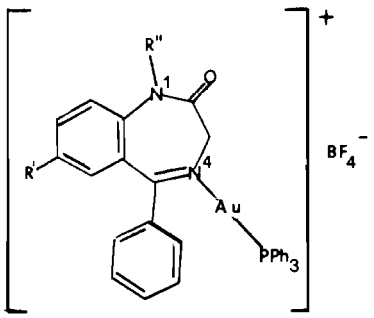


Compound **10**
L = Nitrazepam
$[(Ph_3P)Au\{\mu-(L-H)\}Au(PPh_3)]^+BF_4^-$



	R^I	R^{III}	R^{IV}	Ligands
1	NO_2	H	H	Nitrazepam
2	Cl	OH	Cl	Lorazepam

$(L-H)Au(PPh_3)$



	R^I	R^{II}	Ligands
6	Cl	CH_3	Diazepam
7	Cl	CH_2—◁	Prazepam
8	NO_2	H	Nitrazepam
9	NO_2	CH_3	Nimetazepam

$[(L)Au(PPh_3)]^+BF_4^-$

Fig. 1. Structures of compounds **1**–**10** and related ligands (L).

Compounds 1–10 were analytically pure samples synthesized and purified according to the literature [2].

Results and Discussion

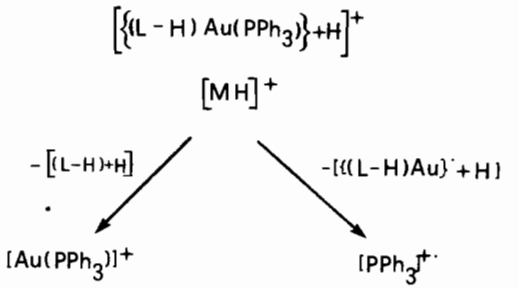
Due to the specific mass spectrometric behaviour of the compounds under investigation, which do not display a common fragmentation pattern, we will discuss separately the different classes of compounds.

*(L-H)Au(PPh$_3$) (**1**, L = Nitrazepam; **2**, L = Lorazepam)*

Compounds **1** and **2** give rise to similar FAB mass spectra (see Table 1 and Scheme 1). Both of them show protonated molecular species $[MH]^+$; the only fragment ions present are due to losses of [(L-H) + H] and [{(L-H)Au} + H] moieties. The

TABLE 1. Relative abundances of the most abundant ionic species in the FAB mass spectra of compounds (L-H)Au(PPh_3) (**1**: L = Nitrazepam, **2**: L = Lorazepam)

Ionic species	Compound	
	1	**2**
$[MH]^+$	740 (16%)	779 (10%)
$[M]^{\cdot+}$	739 (–)	778 (–)
$[Au(PPh_3)_2]^+$	721 (6%)	721 (24%)
$[Au(PPh_3)]^+$	459 (100%)	459 (100%)
$[PPh_3]^{\cdot+}$	262 (10%)	262 (7%)
$[(L\text{-}H)(AuPPh_3)_2]^+$	1198 (8%)	1237 (7%)



Scheme 1.

first process is a primary, gas-phase unimolecular decomposition as proved by metastable ion data, and leads to the formation of $[Au(PPh_3)]^+$ ions (m/z 459), base peak for both **1** and **2**. On the contrary no peaks related to $PPh_3^{\cdot+}$ ions were found in the B/E linked scan performed on $[MH]^+$ ions, proving that the $PPh_3^{\cdot+}$ ions are not primary fragments but they must be generated by other precursors or in condensed phase by FAB ionization. Remarkable is the complete absence of the benzodiazepine species, $[L]^+$ or $[LH]^+$ and fragment ions related to them. This behaviour indicates that no neutral benzodiazepines are formed in solution. If this was the case, abundant protonated molecular species $[LH]^+$ would be expected, as shown previously in a FAB mass spectrometric investigation on the free benzodiazepines [6]. The charge localization on the $[Au(PPh_3)]^+$ and $[PPh_3]^{\cdot+}$ ions can be explained in terms of the Stevenson–Audier rule [7], i.e. by the lower ionization potential of PPh_3-containing moieties with respect to the benzodiazepinic systems.

Interestingly, product ions corresponding to the addition of an $[Au(PPh_3)]^+$ moiety to the molecular species **1** and **2** are detected. The resulting species correspond to the dinuclear complexes $[(L\text{-}H)\{Au(PPh_3)\}_2]^+$: one of them (L = Nitrazepam) has been isolated even in the solid state as the tetrafluoroborate salt, **10**. Different mechanisms of their formation, i.e. ion–molecule, radical–molecule and molecule–molecule reactions, can be considered in principle; however taking account of the high concentration of $[Au(PPh_3)]^+$ ions (100% for both **1** and **2**) and of the behaviour in the condensed phase, it is reasonable to assume that they arise from the reaction

$$[Au(PPh_3)]^+ + M \longrightarrow [M\text{-}Au(PPh_3)]^+$$

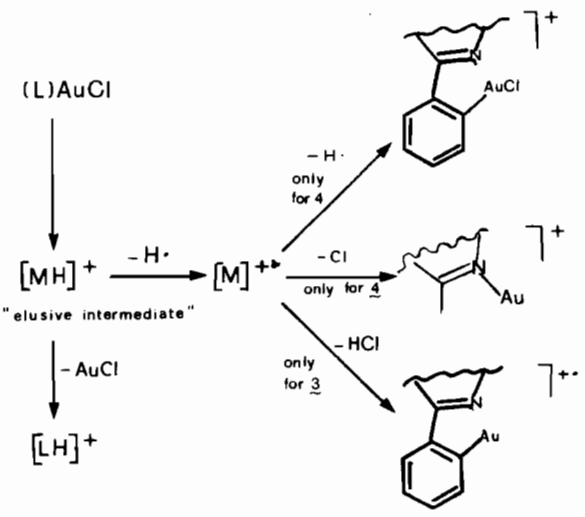
The reaction implies a competition between two strong electrophiles, H^+ and $[Au(PPh_3)]^+$, toward the molecular species M.

*(L)AuCl (**3**, L = Diazepam; **4**, L = Prazepam; **5**, L = Nitrazepam)*

The FAB mass spectra of compounds **3**–**5** are reported in Table 2. The fragmentation patterns, as obtained by B/E linked scan data, are shown in Scheme 2. None of the examined compounds exhibits the protonated molecular species $[MH]^+$, usually observed in FAB conditions, e.g. in the

TABLE 2. Relative abundances of the most abundant ionic species in the FAB mass spectra of compounds (L)AuCl (**3**: L = Diazepam, **4**: L = Prazepam and **5**: L = Nitrazepam)

Ionic species	Compound		
	3	**4**	**5**
$[MH]^+$			
$[MH]^{\cdot+}$	516 (0.1%)	556 (2%)	513 (–)
$[M-H]^+$	515 (–)	555 (1%)	512 (–)
$[M-Cl]^+$	481 (–)	521 (2%)	478 (–)
$[M-HCl]^{\cdot+}$	480 (1%)	520 (–)	477 (–)
$[M-(HCl+H_2O)]^{\cdot+}$	462 (–)	502 (–)	459 (12%)
$[LH]^+$	285 (100%)	325 (100%)	282 (100%)
$[L]^{\cdot+}$	284 (5%)	324 (5%)	281 (5%)
$[LH+H_2O]^+$	303 (7%)	343 (10%)	300 (1%)



Scheme 2.

palladium adducts $(L)_2PdCl_2$ [3]. Molecular odd electron ions are present for **3** and **4** only, at m/z 516 (0.1%) and 556 (2%), respectively. Hence it seems that in this case the reductive processes which are usually observed in positive ion FAB conditions, are unfavoured, allowing oxidative processes to take place alternatively. The very low abundance of $M^{\cdot+}$ can be related to an intrinsic instability of N–AuCl systems: gold(I) complexes with nitrogen donors are known to be stabilized by strong π-acceptor ligands [8]. The unimolecular fragmentation patterns, as obtained by B/E linked scans, are however different: in fact, while for **4** the primary $Cl^{\cdot}$ and $H^{\cdot}$ losses are observed, for **3** an alternative HCl loss is present. The losses of $H^{\cdot}$ or HCl are likely to originate the formation of carbon–gold bonds.

Compound **5** behaves quite differently: in fact no molecular and/or fragment ions related to the original structure are present. Only a peak at m/z 459 (12%) was detected, corresponding to losses of both HCl and H_2O. Most of the total ion current is due to $[LH]^+$ ions and related fragments. This behaviour indicates that compound **5** is more unstable than **3** and **4** which can be ascribed to the electron withdrawing power of the nitro group.

The abundant $[LH]^+$ ions, present in all the spectra, are not unimolecular fragments arising from gas-phase processes, as proved by B^2/E linked scan experiments.

At first sight, such $[LH]^+$ ions could be thought as being generated in the MNBA solution by the cleavage of the N(4)–Au bond to give the free benzodiazepines (L). The formation of $[LH]^+$ would therefore be due to the FAB ionization of L. Surprisingly, these $[LH]^+$ ions show an unimolecular fragmentation pattern strongly different from that observed by FAB analysis of genuine benzodiazepine samples [6]. In fact while MIKE of $[LH]^+$ shows in the latter case a quite complex fragmentation pattern, well related to the benzodiazepinic structure, in the present case only H loss is detected. Thus it seems that the energy content of the $[LH]^+$ species is, in the present case, lower. Such consideration, together with the observation of $M^{\cdot+}$ species, leads us to conclude that acutally a reductive process, not an oxidative one, is operative for compounds **3–5**. The protonated molecular ions, $[MH]^+$, should be so unstable that they decompose immediately through two different pathways, i.e. competitive $H^{\cdot}$ and AuCl losses, leading to the above described $[M]^{\cdot+}$ and $[LH]^+$ ionic species. What was considered as the product of an oxidative process consequently results from a $H^{\cdot}$ loss originating from the 'elusive' $[MH]^+$ moiety.

*$[(L)Au(PPh_3)]^+BF_4^-$ (**6**, L = Diazepam; **7**, L = Prazepam; **8**, L = Nitrazepam; **9**, L = Nimetazepam)*

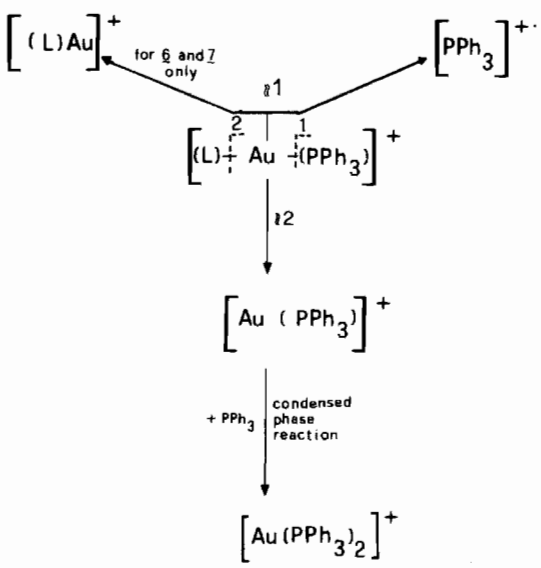
The mass spectrometric behaviour of compounds **6–9** is quite homogeneous. All the compounds show abundant ions corresponding to the cations $[(L)Au(PPh_3)]^+$ (see Table 3 and Scheme 3), at variance with the neutral compounds **1** and **2**, $(L\text{-}H)Au(PPh_3)$; in this case the stability of the $[M]^+$ ions is due to their pre-existence, in non-protonated form, in the solution.

The related fragmentation processes consist in the cleavage of both N(4)–Au and P–Au bonds. These processes seem at first sight to be analogous to those observed for **1** and **2**, also if in the present case a different N atom is involved in coordination. For **6** and **7** both ionic species $[PPh_3]^{\cdot+}$ and $[M-PPh_3]^+$, i.e. $[(L)Au]^+$, are present, whereas for **8** and **9**, the positive charge is retained by the phosphine moiety. Again this behaviour can be explained in terms of the Stevenson–Audier rule: the presence of the nitro group on the ligand clearly increases its ionization energy, which becomes higher than that of PPh_3.

Finally, as observed for **1** and **2**, the $[Au(PPh_3)]^+$ ions are found to react with neutral PPh_3, to $[Au(PPh_3)_2]^+$ (see further comments).

*$[(Ph_3P)Au\{\mu\text{-}(L\text{-}H)\}Au(PPh_3)]^+BF_4^-$ (**10**, L = Nitrazepam)*

In order to get a better insight on the stability of the two different types of Au–N bonds, a FAB-MS investigation was carried out on compound **10**, where a $AuPPh_3$ unit substitutes the isolobal H atom in position 1, and another $AuPPh_3$ is coordinated to the 4-N atom. The



Scheme 3.

TABLE 3 Relative abundances of the most abundant ionic species in the FAB mass spectra of compounds $[(L)Au(PPh_3)]BF_4 = (MBF_4)$ (**6** L = Diazepam, **7** L = Prazepam, **8** L = Nitrazepam and **9** L = Nimetazepam)

Ionic species	Compound			
	6	**7**	**8**	**9**
$[M]^+$	743 (45%)	783 (40%)	740 (25%)	745 (15%)
$[M - PPH_3]^+$	481 (0 5%)	521 (0 1%)	478 (–)	492 (–)
$[Au(PPh_3)_2]^+$	721 (15%)	721 (10%)	721 (18%)	721 (27%)
$[Au(PPh_3)]^+$	459 (100%)	459 (100%)	459 (100%)	459 (100%)
$[PPh_3]^+$	262 (8%)	262 (5%)	262 (6%)	262 (5%)
$[L]^+$	284 (–)	324 (–)	281 (–)	295 (–)
$[LH]^+$	285 (9%)	325 (10%)	282 (5%)	296 (2 5%)

more abundant ionic species are reported in Table 4 For this compound the molecular ion M^+ is well detectable as for compounds **6–9** The base peak is again the ionic species $[Au(PPh_3)]^+$, furthermore ions at m/z 918(1%), $[(AuPPh_3)]^+$, are detected In addition the presence of a peak at m/z 740, corresponding to the substitution of a $[Au(PPh_3)]^+$ group with a H^+, suggests the occurrence of a formal retrosynthetic reaction

$$[(L\text{-}H)\{Au(PPh_3)\}_2]^+ \longrightarrow (L\text{-}H)Au(PPh_3) + [Au(PPh_3)]^+$$

Finally, it is worth noting that ions related to the presence of the $[Au(PPh_3)]^+$ group are observed for all the complexes **1**, **2**, **6–10** In particular, besides the base peak $[Au(PPh_3)]^+$ (m/z 459), ions at m/z 721, attributable to $[Au(PPh_3)_2]^+$, are always present in significative abundance The reaction of the $[Au(PPh_3)]^+$ ions with the neutral ligand PPh_3, leading to $[Au(PPh_3)_2]^+$, can be considered typical of these ions In FAB conditions such behaviour has already been observed in a study [9] on a different series of heterometallic clusters, containing the triphenylphosphinegold group in strictly analogous experimental conditions, abundant $[Au(PPh_3)_2]^+$ ions were always observed The presence of this species was ascertained also in solution by $^{31}P\{^1H\}$ NMR for compounds **6–9** [2]

Also $[Au(PPh_3)]_2^+$ ions at m/z 918 could be present sometimes together with species of very low abundance at m/z 935 and/or m/z 953, $[\{Au(PPh_3)\}_2 \cdot nOH]^+$, $n = 1, 2$ Ions attributable to $[\{Au(PPh_3)\}_3O]^+$ species, a stable cation characterized in the solid state by X-ray crystal structure determination [10], were not observed

TABLE 4 Relative abundances of the most abundant ionic species of the FAB mass spectrum of compound $[(Ph_3P)Au\{\mu\text{-}(L\text{-}H)\}Au(PPh_3)]^+BF_4^-$, (**10** L = Nitrazepam)

Ionic species	
$[M]^+$	1198 (16%)
$[M - \{Au(PPH_3)\} + H]^+$	740 (6%)
$[Au(PPh_3)_2]^+$	721 (15%)
$[Au(PPh_3)]^+$	459 (100%)
$[PPh_3]^+$	262 (8%)
$[LH]^+$	282 (1%)
$[(AuPPh_3)_2]^+$	918 (1%)

Conclusions

As previously observed for the gold adducts **3–5**, fragment ions related to the benzodiazepinic ligands are also present in low abundance in the positive FAB mass spectra of the phosphine complexes **6–10** The difference between the $[LH]^+$ species generated by FAB of **3–10** and those obtained by FAB of pure benzodiazepines is remarkable In the latter case well detectable fragment ions related to fragmentation of diazepine rings and highly diagnostic from the structural point of view, were obtained either in the FAB mass spectra or in unimolecular decomposition of the $[MH]^+$ ions (MIKE spectra) In the gold complexes no fragmentations products of $[LH]^+$, formally corresponding to the $[MH]^+$ of benzodiazepines, were detected This result implies a lower internal energy of $[LH]^+$ fragments with respect to $[MH]^+$ arising from the uncoordinated benzodiazepine ligands, as a reasonable consequence of the distribution of the internal energy among the different fragments This behaviour necessarily implies the absence of free benzodiazepine in the solution of gold complexes

To further investigate $[LH]^+$ species, we studied the behaviour of $LH^+BF_4^-$, where L= Nitrazepam, i e a species in which the ligand is in the protonated form The FAB mass spectrum shows a very intense molecular ion $[MH]^+$, already pre-existent, which also in this case does not easily originate other fragment ions These results suggest that when a benzodiazepine L, is present in solution the molecular ions $[L + H]^+$ do not originate from a simple acid–base reaction in the matrix, but arise from the protonation reaction representing the reductive process which is the

base of FAB, with a gain of internal energy by $[LH]^+$.

Acknowledgements

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