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FAB Mass Spectrometry of Palladium(II) Derivatives with 1,4-Benzodiazepin-2-ones: Evidence of the Stability of Cyclometallated Species

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Abstract

The FAB spectra of the adducts *trans*-Pd(L)$_2$Cl$_2$ (**1**: L = DIAZEPAM, D = 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one; **2**: L = PRAZEPAM, P = 7-chloro-1-(cyclopropylmethyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one) and of the cyclometallated derivatives [Pd(L-H)Cl]$_2$ (L = D, **3**; L = P, **4**), Pd(Ph$_3$P)(L-H)X (L = P, X = Cl, **5**; L = D, X = Br, **6**), Pd(D)(D-H)Cl (**7**) have been studied in detail.

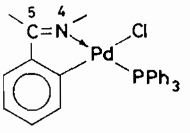
The main gas-phase fragmentation pathways of **1** and **2** consist in sequential HCl losses, while for compounds **3** and **4** only primary Cl• loss is observed. A peculiar behaviour is observed for **5** and **6**, i.e. the lack of protonated molecular ions.

Introduction

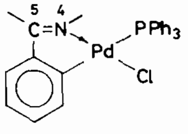
The coordination behaviour of 1,4-benzodiazepines, in spite of their wide use as drugs, is still largely to be explored [1]. In the last years, we have investigated the interaction of some 1,4-benzodiazepin-2-ones having a 5-phenyl-substituent, with ions such as gold(III) [2], gold(I) [3] and palladium(II) [4], and shown unambiguously, through X-ray structure determinations, that several coordination modes are possible. With palladium(II), adducts, Pd(L)$_2$Cl$_2$, as well as metallated species such as [Pd(L-H)Cl]$_2$ and Pd(L′)(L-H)Cl (L′ = neutral ligand), have been synthesized and characterized [4].

The X-ray analysis of the complex Pd(L)$_2$Cl$_2$ (L = PRAZEPAM, 7-chloro-1-(cyclopropylmethyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one) shows a *trans*-arrangement of the ligands around the palladium atom, the benzodiazepine being coordinated through the 4-nitrogen atom. The metal-coordinated PRAZEPAM is in the usual boat conformation and displays bond lengths and angles very close to those found in the free molecule, as observed previously in copper(II) [5] and gold(III) [2] derivatives having the ligand coordinated in the same fashion.

The cyclometallated derivatives [Pd(L-H)Cl]$_2$, Pd(Ph$_3$P)(L-H)Cl, Pd(L)(L-H)Cl and Pd(L-H)(acac) involve both C– and N– intramolecular coordination of the deprotonated ligand. The X-ray structure of the complex Pd(Ph$_3$P)(L-H)Cl (L = PRAZEPAM) has confirmed that the ligand is coordinated through the 4-nitrogen atom and the *ortho*-carbon of the 5-phenyl substituent: of the two possible isomers, **A** and **B**, only **A** was observed in the solid state [6].



A



B

The complexes belong to the series of the five-membered cyclopalladated systems with N-donor ligands which are known to be quite stable [7]. The achievement of these species is noteworthy as they are potential intermediates for the synthesis of 1,4-benzodiazepines functionalized on the *ortho*-carbon atom of the 5-phenyl substituent.

Following our recent interest in the behaviour of organometallic derivatives and coordination compounds in the vapour phase [8], here we report a mass spectrometric investigation, carried out under FAB conditions, of some adducts and cyclometallated species of palladium with PRAZEPAM (P) and DIAZEPAM (D), D = (7-chloro-1-methyl-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one).

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Experimental

The ligands DIAZEPAM and PRAZEPAM were provided by Roche and Parke-Davis, respectively.

The compounds **1**–**7**, *trans*-Pd(D)$_2$Cl$_2$ (**1**), *trans*-Pd(P)$_2$Cl$_2$ (**2**), [Pd(D-H)Cl]$_2$ (**3**), [Pd(P-H)Cl]$_2$ (**4**), Pd(Ph$_3$P)(P-H)Cl (**5**), Pd(Ph$_3$P)(D-H)Br (**6**) and Pd(D)(D-H)Cl (**7**), were synthesized and purified as previously described [4].

All mass spectrometric measurements were performed on a VG ZAB-2F instrument operating in FAB conditions (8 KeV Xe atoms bombarding 3-nitrobenzylalcohol sample solutions).

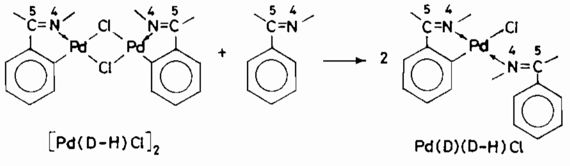
Metastable transitions were detected by B/E = const. and B^2/E = const. linked scans [9] and mass analyzed ion kinetic energy (MIKE) spectra [10].

Results and Discussion

In the vapour phase, under FAB conditions, the two series of palladium derivatives, i.e. the adducts and the cyclometallated species, behave quite differently.

The adducts *trans*-Pd(L)$_2$Cl$_2$ (**1**, L = D; **2**, L = P) show identical fragmentation patterns, mainly consisting of sequential losses of hydrogen chloride from the [MH]$^+$ ions (see Table 1 and Scheme 1). In the FAB spectra of both compounds, the base peak is due to the [LH]$^+$ ions; other abundant peaks are due to [LPd]$^+$ ionic species. The most interesting fragmentation pathway is the loss of two HCl molecules. It is reasonable to assume that such processes give rise to orthometallated species. Such decomposition reactions might occur, in principle, either directly in solution by a FAB-induced condensed phase reaction or as a unimolecular fragmentation process. B/E linked scans of the [MH]$^+$ and [MH – HCl]$^+$ species prove that the sequential HCl losses represent the only unimolecular fragmentation routes, though an analogous process in the matrix cannot be excluded.

The loss of the first HCl molecule should give [Pd(L)(L-H)Cl + H]$^+$ ions, i.e. the protonated molecular ion of the complex having both a deprotonated and a neutral benzodiazepine coordinated to the metal. Actually the complex Pd(D)(D-H)Cl (**7**) was isolated as a by-product in the synthesis of the dimeric [Pd(D-H)Cl]$_2$ [4], probably through a classical bridge splitting reaction.



3 **D** **7**

The loss of the second HCl molecule should give ions corresponding to the bis-orthometallated complexes Pd(L-H)$_2$, which have not been isolated in the condensed phase. However, species of this type have been obtained in the chemistry of other nitrogen ligands [7].

For both the mono- and dimetallated derivatives, more isomers are possible, e.g.:

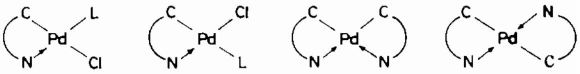
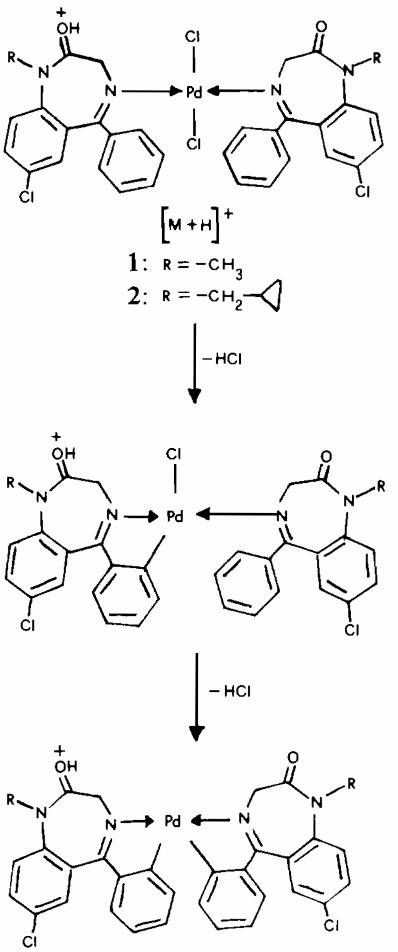


TABLE 1. The most abundant ionic species arising from unimolecular decomposition[a]

Ionic species	Compounds						
	1	2	3	4	5	6	7
[MH]$^+$	744 (4)	824 (2)	847 (22)	927 (5)			708 (6)
[M]$^{+\bullet}$	743 (2.5)	823 (0.5)	846 (6)	926 (2)	725 (7)		707 (4)
[MH – Cl]$^+$			812 (100)	892 (15)			
[MH – HCl]$^+$	708 (16)	788 (6)					672 (6)
[M – HCl]$^+$					689 (100)		
[MH – 2HCl]$^+$	672 (27)	752 (13)					
[M – HBr]$^+$						649 (100)	
[MH – PdCl]$^+$			707 (14)	787 (17)			
[M – PdCl]$^+$					585 (12)		
[MH – PdCl – Cl]$^+$			672 (22)	752 (45)			
[Pd$_2$Cl(D-H)]$^+$			528 (15)	568 (8)			
[Pd(L-H)]$^+$			388 (54)	428 (100)			388 (9)
[PdL]$^+$	389 (31)	429 (16)					
[LH]$^+$	285 (100)	325 (100)					285 (100)
[Pd$_2$(P-H)$_2$PPh$_3$Cl]$^+$					1153 (1)		
[Pd$_2$(D-H)$_2$PPh$_3$Br]$^+$						1117 (2)	

[a] All the reported m/z values and relative abundances are related to ^{105}Pd, ^{35}Cl and ^{79}Br isotopes.



Scheme 1.

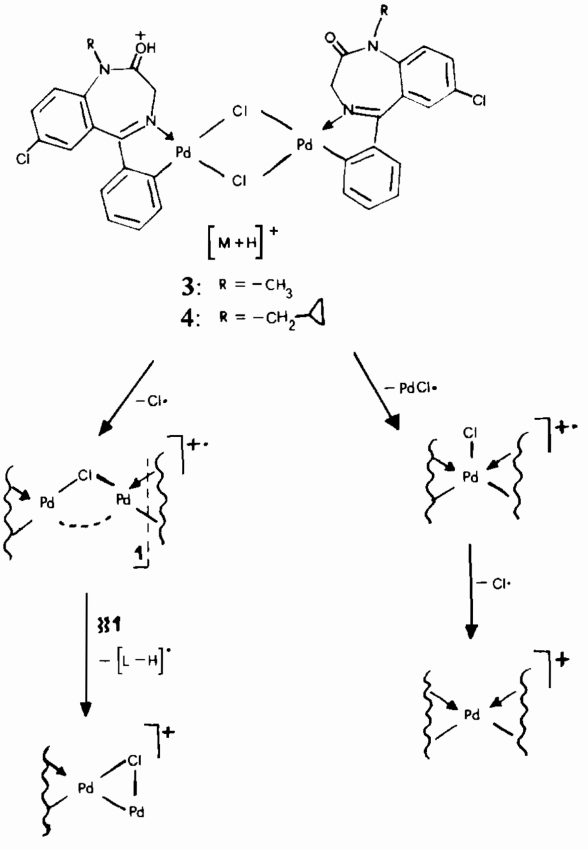
Unfortunately, the lack of further fragmentation processes prevented other investigations on their structures.

The absence of further decomposition routes also in B/E linked scans is evidence of the high stability of such metallated systems, even in the vapour phase, in agreement with the reported high stability of palladium(II) five-membered cyclometallated systems having nitrogen ligands [7].

Furthermore the lack of decomposition pathways related to cleavage of the benzodiazepine ring, does not allow us to get information on the protonation site, even though the high stability displayed by the metallated species suggests that protonation occurs quite far from the nitrogen(4) atom involved in the coordination.

The B^2/E linked scans of the ionic species $[LPd]^+$ and $[LH]^+$ do not show any precursor for these ions, proving that they originate through a condensed phase reaction.

Compounds **3** and **4**, in which cyclometallated species are already present, behave quite differently (see Table 1 and Scheme 2). In this case only primary losses of Cl$^\bullet$ and PdCl$^\bullet$ from $[MH]^+$ ions are shown from B/E linked scans. The loss of Cl$^\bullet$ leads to odd ions, at m/z 812 and m/z 892 respectively, which correspond to dinuclear monobridged species. In this respect it is noteworthy that monohalide-bridged binuclear platinum and palladium complexes have actually been isolated and characterized [11]. The further loss of [L-H], from the $[MH - Cl]^+$ species, suggests that in this case the dinuclear species are likely to be stabilized by a metal–metal interaction. In contrast with what was observed for the adducts **1** and **2**, sequential losses of PdCl$^\bullet$ and Cl$^\bullet$ from $[M + H]^+$ are observed in this case, leading eventually to the ionic species at m/z 672 and 752 identical to those already described for **1** and **2** respectively. Again, organic fragments are practically undetectable, proving once more the high stability of the orthometallated moieties.



Scheme 2.

The monomeric cyclometallated compound **5**, Pd(Ph$_3$P)(P-H)Cl, i.e. the species arising from a bridge splitting reaction of **3**, does not show any protonated molecular species $[MH]^+$ but only $[M]^{+\bullet}$ odd electron ions at *m/z* 725. The analogous complex **6**, $Pd(Ph_3P)(D\text{-}H)Br$, shows no molecular species at all (neither $[MH]^+$ nor $[M]^{+\bullet}$).

For both **5** and **6** primary HX loss (X = Cl and Br respectively) leads to the most abundant ionic species (*m/z* 689 and 649 respectively, base peaks of the FAB spectra) which are likely to involve C— and P— intramolecular coordination.

In addition, for **5** and **6**, dinuclear moieties become well detectable at *m/z* 1153 and 1117 respectively. Isotopic cluster analysis confirms the presence, in these ionic species, of two palladium atoms and only one halogen atom (see Table 1). These ions can originate mainly from two different mechanisms, both induced by FAB:

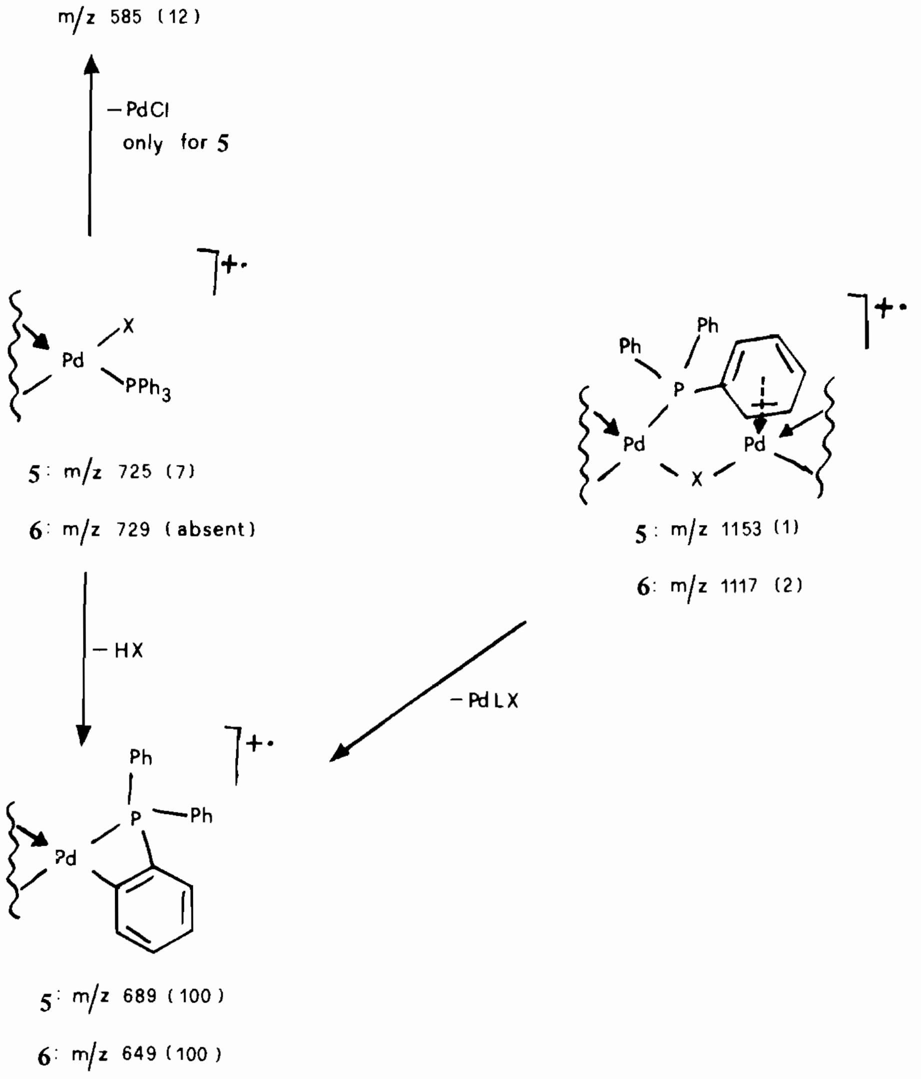
(i) $$[Pd(Ph_3P)(L\text{-}H)X] \xrightarrow{\text{FAB}} [Pd(Ph_3P)(L\text{-}H)X]^+ \longrightarrow [Pd(Ph_3P)(L\text{-}H)]^+ + X^\bullet$$

$$[Pd(Ph_3P)(L\text{-}H)]^+ + [Pd(Ph_3P)(L\text{-}H)X] \longrightarrow [Pd_2(PPh_3)(L\text{-}H)_2X]^+ + Ph_3P$$

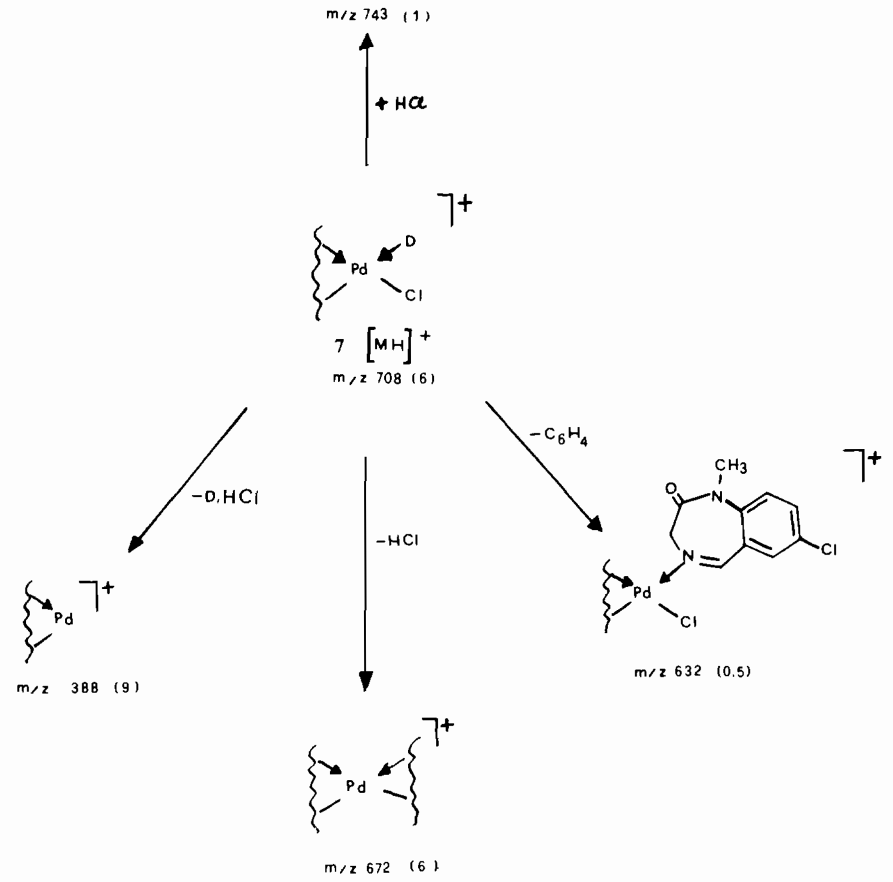
(ii) $$[Pd(Ph_3P)(L\text{-}H)X] \longrightarrow [Pd(Ph_3P)(L\text{-}H)]^\bullet + X^\bullet$$

$$[Pd(Ph_3P)(L\text{-}H)]^\bullet + [Pd(Ph_3P)(L\text{-}H)X] \longrightarrow [Pd_2(PPh_3)(L\text{-}H)_2X]^\bullet + Ph_3P$$

$$[Pd_2(PPh_3)(L\text{-}H)_2X]^\bullet \xrightarrow{\text{FAB}} [Pd_2(PPh_3)(L\text{-}H)_2X]^+$$



Scheme 3.



Scheme 4.

The absence of the possible charged reacting species $[M - Cl]^+$ can be due to its high reactivity which immediately leads to dinuclear products. The only fragmentation pathway of the dinuclear species, observed by B/E linked scans, is a retrosynthetic one with hydrogen rearrangement (see Scheme 3).

As for **5** and **6**, it is remarkable that, contrary to what was observed for the mononuclear adducts **1** and **2** and for the binuclear metallated compounds **3** and **4**, no protonated molecular species are detectable. This can be related to a lower proton affinity of **5** and **6** or to a particular unstability of the $[MH]^+$ ions.

Finally, compound **7**, where both neutral and deprotonated DIAZEPAM ligand are present, shows together $[MH]^+$ and $[M]^{+\bullet}$ ions, primary losses of HCl, C_6H_4 and contemporary losses of DIAZEPAM and HCl (see Scheme 4). The base peak is due to the $[LH]^+$ moiety as observed in **1** and **4**. The loss of HCl reminds us of that already described for **1**, **2**, **5** and **6**. On the contrary, the C_6H_4 loss is peculiar to **7**. The complete lack of this fragmentation pathway in the mass spectrometric behaviour of the DIAZEPAM ligand [12], indicates that the hydrogen rearrangement involved in the C_6H_4 loss must be necessarily induced by the metal center. Hence, the fragmentation pattern of **7** is very different from that of the isobaric ions originating from **1** through HCl loss. This can be reasonably ascribed to the different energy content of these ionic species. While for **7** the ion at m/z 708 represents the molecular species, for **1** the analogous ions are fragments: consequently their energy content is surely lower.

An HCl addition product is detected at m/z 743. This could be, in principle, due to an oxidative addition reaction or, more likely, to the formation of adduct **1**.

Acknowledgements

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