Metal complexes of benzodiazepines. Kinetic properties of bromazepam toward square planar dimethyl sulfoxide complexes of platinum(II) and palladium(II)

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Abstract

The kinetics of substitution reactions of Me_2SO from the complexes $[MX_2(Me_2SO)_2]$ (M = Pt, X = Cl, CH_3, *cis*, M = Pd, X = Cl, *trans*) by the ligands bromazepam or bipy have been investigated in Me_2SO and/or CH_2Cl_2 at 25 °C. The results are interpreted in terms of an associative mechanism for *cis*-$[PtCl_2(Me_2SO)_2]$ and a dissociative mechanism for *cis*-$[PtMe_2(Me_2SO)_2]$. The substitution reaction for the complex *trans*-$[PdCl_2(Me_2SO)_2]$ proceeds without retention of stereochemistry, a consecutive displacement mechanism or a pseudo-rotation mechanism can be operative The kinetic behaviour of bromazepam and bipy is very similar

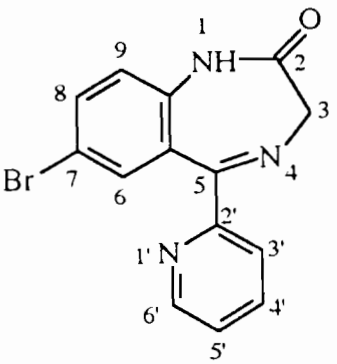
Key words Kinetics and mechanism, Platinum complexes, Dimethyl sulfoxide complexes; Bromazepam complexes

Introduction

The study of the coordination chemistry of 1,4-benzodiazepines, a class of compounds widely studied because of their interesting pharmacological properties [1], has mainly concerned synthetic aspects. So far numerous complexes of gold(I) and gold(III) [2], palladium(II) [3, 4], platinum(II) [5, 6], etc., in which the ligands display a variety of coordination, have been characterized unambiguously.

Very little has been done, however, as far as the kinetic studies of benzodiazepine reactions are concerned. In a recent paper some of us [7] have studied thermodynamically and kinetically the reactions between the bridged complex $[Pd_2I_4(PPr_3^n)_2]$ and five 1,4-benzodiazepines which are among the most commonly marketed drugs of this class. Although 7-bromo-1,3-dihydro-5-(2-pyridyl)-2*H*-1,4-benzodiazepin-2-one (bromazepam) bears two nitrogen donor atoms in suitable relative positions to chelate and only chelated complexes of this ligand have been reported, thermodynamic data in chloroform suggested mono-coordination to palladium(II).

In continuation of our studies of the kinetic behaviour of complexes of d^8 metal centres containing Me_2SO as ligand [8] and in order to assess the nucleophilicity of bromazepam, we have investigated the reactions between this ligand and the complexes *cis*-$[PtCl_2(Me_2SO)_2]$, *cis*-$[Pt(Me)_2(Me_2SO)_2]$ and *trans*-$[PdCl_2(Me_2SO)_2]$ in dimethyl sulfoxide at 25 °C. In addition, the above mentioned complexes have been reacted, under the same experimental conditions, with 2,2′-bipyridine (bipy), the reactivity of which is well established. The kinetic values of some of these reactions in methylene chloride are also reported.



Bromazepan

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Experimental

Materials and instrumentation

The ligands bromazepam and bipy, commercially available, were used without further purification. Solvents, of spectroscopic grade, were dried with use of standard procedures. Conductivity experiments were performed with a Radiometer CDM3 conductivity bridge IR spectra were recorded as Nujol mulls between CsI plates on a Perkin-Elmer FT-IR 1720 X instrument, ^{1}H NMR spectra on a Bruker AMX R300 instrument and the chemical shifts are in ppm downfield from internal tetramethylsilane.

Preparation of the complexes

The synthesis of the complexes *cis*-$[PtCl_2(Me_2SO)_2]$ [9], *cis*-$[Pt(Me)_2(Me_2SO)_2]$ [10], *trans*-$[PdCl_2(Me_2SO)_2]$ [11], $[PtCl_2(bipy)]$ [12], $[PtCl_2(bromazepam)]$ [5, 6], $[Pt(Me)_2(bromazepam)]$ [5], $[PdCl_2(bromazepam)]$ [4] and $[PdCl_2(bipy)]$ [12] have already been described in the literature.

$[PdCl_2(bromazepam)]$ was obtained in a different way from the reported procedure by reacting *trans*-$[PdCl_2(Me_2SO)_2]$ with an equimolar amount of bromazepam in Me_2SO. Yellow–orange crystals of the product were separated from the reaction mixture in good yield.

All the complexes were characterized through elemental analysis and IR, ^{1}H NMR and electronic spectra

Kinetics

The kinetics were performed under pseudo-first-order conditions with respect to the complexes at 25 °C in Me_2SO or CH_2Cl_2. The rates of the reactions of platinum(II) complexes were followed spectrophotometrically in the visible and near-UV regions using a Perkin-Elmer Lambda 5 spectrophotometer in the repetitive scanning mode, or by following the absorbance at a selected wavelength as a function of time. The reactions of the palladium(II) complex required the use of a HI-TECH SF3 stopped-flow spectrophotometer. Pseudo-first-order constants k_{obs} were obtained either from the gradients of the plots $\log(A_t - A_\infty)$ versus time or from non-linear least-squares fits of the experimental data by $A_t = A_\infty + (A_0 - A_\infty)\exp(-k_{obs})$, where A_0, A_∞ and k_{obs} were the parameters optimized (A_0 = absorbance after the mixing of the reagents, A_∞ = that upon completion of reaction). The k_{obs} values were reproducible to better than $\pm 5\%$.

Results and discussion

Conductivity measurements of a solution of *cis*-$[PtCl_2(Me_2SO)_2]$ and *trans*-$[PdCl_2(Me_2SO)_2]$ in Me_2SO show that the complexes are non-electrolytes Furthermore, the molar conductance does not change with time and solvolytic equilibria involving the starting substrates can be ruled out. Reactions of L-L (L-L = bromazepam or bipy) with the above mentioned complexes and with *cis*-$[Pt(Me)_2(Me_2SO)_2]$ in Me_2SO and/or CH_2Cl_2 yield the complexes $[MX_2(bromazepam)]$ (M = Pt, X = Cl, CH_3; M = Pd, X = Cl) or $[MCl_2(bipy)]$ (M = Pt or Pd) according to eqn. (1)

$$[MX_2(Me_2SO)_2] + \text{L-L} \longrightarrow [MX_2(\text{L-L})] + 2Me_2SO \quad (1)$$

X-ray [6] and NMR [5] data of the complexes $[PtX_2(bromazepam)]$ have shown that bromazepam chelates to platinum through the imino N^4 atom and the pyridyl nitrogen $N^{1'}$. The same mode of coordination was also inferred from single X-ray data of $[PdCl_2(bromazepam)]$ [4]. The proton NMR spectrum of the palladium(II) complex has been recorded in $(CD_3)_2SO$ and the resonances are assigned as follows 3.97 and 5.33 (2H, two d, J_{gem} 12.2, $2H^3$), 7.25 [1H, d, J (H^8H^9) 8.8, H^9], 7.75 [1H, dd, J ($H^{3'}H^{4'}$) 7.7, J ($H^{3'}H^{5'}$) 0.8, $H^{3'}$], 7.90 (1H, m, $H^{5'}$), 7.93 [1H, dd, J (H^6H^8) 2.2, H^8], 8.03 (1H, d, H^6), 8 30 [1H, td, J ($H^{4'}H^{5'}$) 7 7, J ($H^{4'}H^{6'}$) 1 2, $H^{4'}$], 9.15 [1H, dd, J ($H^{5'}H^{6'}$) 4.9 Hz, H^6], 11.08 (1H, s, H^1). Protons H^3, resonating as only one signal for the free ligand [5], appear as a typical AB quartet for the complex, showing that the coordinated ligand is frozen in one limiting conformation Non-equivalence of the two H^3 protons was also observed for the analogous complex $[PtCl_2(bromazepam)]$ [5] Downfield shifts of proton resonances of bromazepam are generally observed upon coordination, roughly related to the distances from palladium, apart from the $H^{3'}$ signal, which shifts to high field. Actually, all pyridine resonances are distinctively affected by coordination and a significant shift to a much lower field of the $H^{6'}$ signal is observed. These data strongly indicate that coordination of bromazepam to palladium(II) through its N^4 atom and the pyridinic $N^{1'}$ is retained in dimethyl sulfoxide solution

The complexes $[MCl_2(bromazepam)]$ are sparingly soluble in chlorinated solvents, but dissolve to a fair extent in Me_2SO As previously discussed [4, 5], we have no evidence of solvolytic equilibria or of M–N bond dissociation in dimethyl sulfoxide involving the reactions products.

The kinetics of the reactions of eqn. (1) were followed spectrophotometrically under pseudo-first-order conditions The reactions go to completion; the final spectra are identical with those of independently prepared solution of $[MX_2(bromazepam)]$ or $[MCl_2(bipy)]$ at the same concentration.

Kinetics of the reactions of L-L with Pt(II) complexes

The reaction of *cis*-$[PtCl_2(Me_2SO)_2]$ with bromazepam and bipy in Me_2SO or CH_2Cl_2 causes a spectral

change without increasing the conductivity of the solution and so excluding the possible involvement of chlorides, which would yield ionic species. The kinetics follows a first-order course and the k_{obs} values (Table 1) are linearly correlated (eqn. (2)) to the nucleophile concentrations. The linear plots pass through the

$$k_{obs} = k_2[\text{L-L}] \quad (2)$$

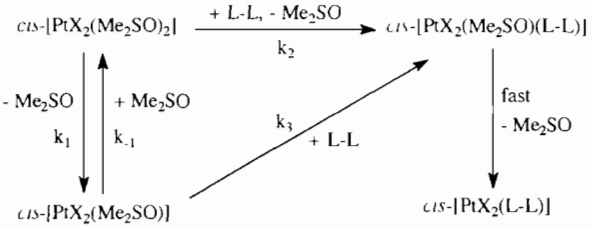
origin within the limits of experimental error.

Equation (2) can be reasonably interpreted by an associative mechanism in which the rate-determining step is the substitution of the first dimethyl sulfoxide to yield a mono-sulfoxide species (k_2 path of Scheme 1), followed by a fast ring closing to give the observed products (Me_2SO being again the leaving group).

TABLE 1. Pseudo-first-order rate constants for the reactions of eqn (1) at 25 °C

Complex	Solvent	10^3[L-L] (mol dm^{-3})		k_{obs} (s^{-1})
cis-$[PtCl_2(Me_2SO)_2]$	Me_2SO	brom[a]	1 0	0.0024
			2.0	0 0046
			3.0	0.0068
			5 0	0 0113
			7.5	0 0170
			10 0	0.0228
	CH_2Cl_2		1 0	0.0064
			2.0	0.0118
			3 0	0.0178
			5 0	0.0301
			7.5	0 0472
			10 0	0.0611
	Me_2SO	bipy	1 0	0.0011
			2 5	0.0027
			5 0	0 0051
			10 0	0.0104
			25 0	0.0251
			50.0	0.0510
cis-$[Pt(Me)_2(Me_2SO)_2]$	Me_2SO	brom		very slow
	CH_2Cl_2	brom[b]	1.0	0.0106
			2 0	0.0162
			3 0	0.0190
			5.0	0 0215
			10 0	0.0252
trans-$[PdCl_2(Me_2SO)_2]$	Me_2SO	brom	1 0	0.602
			2 0	1.02
			5.0	2.59
			7 5	4.02
			10.0	5.75
		bipy	1.0	0.343
			2.0	0.560
			3 0	0 807
			5.0	1 45
			10.0	2.85
			15.0	4.47
			20 0	6 14
			30.0	8.90
			50.0	14.4

[a]brom = bromazepam. [b][Me_2SO] = 0.0005 mol dm^{-3}.



Scheme 1.

It is known that the *trans* effect of dimethyl sulfoxide is considerably greater than that of chloride [13]. However, displacement of dimethyl sulfoxide in preference to chloride, as proposed in Scheme 1, has been reported for the substitution reactions of *cis*-$[PtCl_2(Me_2SO)_2]$ with a variety of substituted pyridines in 1,2-dimethoxyethane and accounted for in terms of a mutual labilization effect between two *cis* sulfoxides [14].

The proposed mechanism for the reaction between *cis*-$[PtCl_2(Me_2SO)_2]$ and bromazepam is consistent with the observed solvent effect ($k_2 = 6.19 \pm 0.10$ mol^{-1} dm^3 s^{-1} in CH_2Cl_2 and $k_2 = 2.27 \pm 0.01$ mol^{-1} dm^3 s^{-1} in Me_2SO at $t = 25$ °C). In fact, if the rate-determining step were the displacement of the first chloride by bromazepam to yield a charged transient species, the substitution process should be favoured in the polar solvent Me_2SO.

The values of k_2 for the reaction of *cis*-$[PtCl_2(Me_2SO)_2]$ with bipy in Me_2SO at 25 °C was 1.01 ± 0.01 mol^{-1} dm^3 s^{-1}. Thus the dependence of the rate constant on the nature of L-L is rather small. In this respect one should not forget that the donor atom is the same and that the micropolarizability of the nucleophile, i.e. its polarizability in the anisotropic electric field encountered in the transition state [15], which is the most important factor in determining the reactivity, should be essentially the same.

The rate of reaction of the complex *cis*-$[Pt(Me)_2(Me_2SO)_2]$ with bromazepam in dimethyl sulfoxide was so slow that an appreciable amount of the product was formed only after several months. This reaction was much faster in methylene chloride. The dependence of k_{obs} on concentrations of the leaving group Me_2SO and bromazepam was analogous to that found for the reaction of this organometallic substrate with bipy and other bidentate ligands [16], the process being retarded by the free dimethyl sulfoxide and exhibiting saturation kinetics. Accordingly, the observed first-order rate constant is given by the relationship

$$k_{obs} = \{k_1[\text{L-L}]/((k_{-1}/k_3)[Me_2SO] + [\text{L-L}])\} + k_2[\text{L-L}] \quad (3)$$

This is consistent with a mechanism consisting of two or more reaction steps, one involving competition for an intermediate by Me_2SO and L-L (Scheme 1). Initial dissociation of one dimethyl sulfoxide in the k_1 path

gives a three-coordinate intermediate. The second step (k_3 path) leads to the formation of an open ring monosulfoxide species, also formed by a parallel associative attack of L-L on the starting complex (k_2 path). A fast ring closing gives the observed product. If the term k_2[L-L] of eqn. (3) is negligible, a plot of $1/k_{obs}$ against 1/[L-L] gives a straight line with a slope of (k_{-1}/k_1k_3) [Me_2SO] and an intercept of $1/k_1$. In the case of the reaction of the complex *cis*-[$Pt(Me)_2(Me_2SO)_2$] with bromazepam, at a constant value of [Me_2SO] = 0.0005 mol dm^{-3} (see Table 1), such a plot is indeed linear and yields a value of k_1 of 0.030 ± 0.001 s^{-1} at 25 °C. The ratio k_3/k_{-1}, which gives the competition ratio for the three-coordinate intermediate between bromazepam and Me_2SO, is 0.28, comparable with the value found when L-L is bipy [16]

A requirement of the dissociative mechanism as proposed for the system *cis*-[$Pt(Me)_2(Me_2SO)_2$]–bromazepam is that k_1 be independent of the nature of L-L. A value of $k_1 = 0.00626$ s^{-1} can be calculated at 25 °C in benzene from the rate data of ref 16 for the reaction of this organometallic substrate with bipy The increase in the value of k_1 on changing from bipy to bromazepam is likely to arise from the differing abilities of the two solvents, benzene and CH_2Cl_2, to interact with the released Me_2SO [17]. An analogous increase on the value of k_1 on changing from benzene to chloroform was also observed for the reaction between *cis*-[$Pt(C_6H_5)_2(Me_2SO)_2$] and bipy [18].

In the displacement of L by nucleophiles for complexes of the type *cis*-[PtX_2L_2] (L = dimethyl sulfoxide or substituted thioethers), the change from an associative mode of activation for classical coordination compounds (X = halide) to a dissociative one for organometallic compounds (X = Me, Ph), is well established [14, 16, 18, 19]. Very recently, a comparative kinetic and theoretical study has evidenced the role of electron density at the metal centre in determining the reaction pathway [20]

Kinetics of the reactions of L-L with trans-[$PdCl_2(Me_2SO)_2$]

The reactions of the complex *trans*-[$PdCl_2(Me_2SO)_2$] with L-L have been studied in dimethyl sulfoxide Precipitation of the products prevented a kinetic study in CH_2Cl_2. The rate constants for the substitution reactions obey eqn. (2). The values of k_2 obtained from a linear least-squares analysis of the slope of the k_{obs} against [L-L] plots (Table 1) are 568 ± 23 and 291 ± 3 mol^{-1} dm^3 s^{-1} for bromazepam and bipy, respectively Again, the sensitivity of rate to the nature of L-L is rather small

As the overwhelming majority of substitution reactions of square planar complexes of platinum(II) and palladium(II) are stereospecific, a most important feature of these reactions is the change in stereochemistry on going from the reagents to the products A consecutive displacement mechanism, simply involving two stereospecific ligand substitutions (eqn (4)) or a pseudo-rotation of five-coordinate intermediates (eqn. (5)) can account for the observed rate law.

trans-[$PdCl_2(Me_2SO)_2$] + L-L ⟶

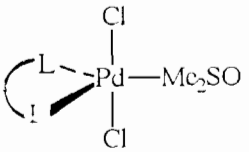
[$PdCl(Me_2SO)$(L-L)]Cl ⟶ [$PdCl_2$(L-L)] (4)

trans-[$PdCl_2(Me_2SO)_2$] + L-L ⟶

[$PdCl_2(Me_2SO)$(L-L)] ⟶ [$PdCl_2$(L-L)] (5)

The leaving group Me_2SO has been omitted for clarity.

In view of the fact that the *trans* effect of dimethyl sulfoxide is considerably greater than that of chloride, the rate-determining step is considered to be the displacement of the first Me_2SO. Fast ring closing yields a monocationic species, and finally, fast displacement of Me_2SO by Cl^- gives the products (eqn. (4)). However, if a pseudo-rotation mechanism is operative, the symmetric five-coordinate intermediate I with Me_2SO and both arms of L-L in the equatorial plane and the chlorides in axial position can be formed Dissociation of Me_2SO yields [$PdCl_2$(L-L)].



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This intermediate could be sufficiently stable to be a long-enough lived species. Several reports of the isolation and characterization of five-coordinate species of Pt(II) and Pd(II) with a diimine chelate ligand, an olefinic ligand and two chloride ligands have appeared [21]. X-ray, IR and NMR data of these species show that the two chlorides occupy equivalent axial positions and an alkene and a diimine are in the equatorial plane. Five-coordination for complexes [Pt(dmphen)(L)$(X)_2$] (dmphen = 2,9-dimethyl-1,10-phenanthroline; L = C_2H_4, CO, PH_3 or ONPh; X = Cl or I), where dmphen acts as bidentate or monodentate ligand, is dependent from the π-accepting ability of the L ligand and C_2H_4 is the most efficient in stabilizing five-coordination by reducing in this way the electron density on the metal centre [22]. Ethylene and dimethyl sulfoxide, as ligands of platinum(II) complexes, have comparable properties and the *trans* effect of sulfoxide springs much from its ability to act as π-acceptor transition-state stabilizer [23]. Therefore, in the intermediate I, the dimethyl sulfoxide in the equatorial position can well act as a π-acceptor ligand through S low lying empty 3d orbitals

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