Dimethylsulfoxide–Ruthenium Complexes of Adenine

N. FARRELL and N. G DE OLIVEIRA

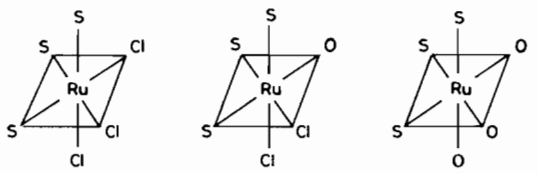
Universidade Federal de Minas Gerais Departamento de Quimica, ICEx Cidade Universitária, Pampulha 30000, Belo Horizonto, MG Brazil

Received January 8, 1982

Introduction

The discovery of the anti-tumour activity of *cis*-$[PtCl_2(NH_3)_2]$ has excited much interest in the search for other drugs based on transition-metal complexes [1]. The fact that the complex acts by inhibition of DNA synthesis has stimulated research into the interactions of metal complexes with nucleic acids and their component bases and the factors affecting these interactions [2, 3]. Because *cis*-$[RuCl_2(DMSO)_4]$, an octahedral complex of Ru(II), interacts with DNA and has been shown to have biological activity comparable to that of the platinum species [4], we have investigated the reactions of this and similar complexes with nucleic acid components. In this communication we present our results from studies on purines and pyrimidines [5].

Ruthenium forms a series of dimethylsulfoxide complexes, *mer*-$[RuCl_3(DMSO)_3]^-$, I, *cis*-$[RuCl_2(DMSO)_4]$, II and *mer*-$[Ru(DMSO)_6]^{2+}$, III, whose structures have all been determined [6–8] (Fig. 1):



$[RuCl_3(DMSO)_3]^-$ $[RuCl_2(DMSO)_4]$ $[Ru(DMSO)_6]^{2+}$

Fig. 1 Structure of dimethylsulfoxide–ruthenium complexes. (S and O stand for sulfur and oxygen-bound sulfoxide respectively).

The dimethylsulfoxide ligand can bind to a metal through either the oxygen or sulfur atom [9], and as oxygen-bound DMSO is known to be labile. The series represents an interesting opportunity to study the effect of charge and leaving group on reactions with nucleic acid bases.

Experimental

All ruthenium starting complexes were prepared by literature methods [6–8]. Purines and pyrimidines were purchased from Aldrich Chem. Co. and used without further purification. Infrared spectra were recorded as KBr disks on a PE 467 spectrometer. ^1H N.M.R. spectra were recorded on a Varian XL-100 machine. Conductivity data were obtained on a Metrohm E-527 meter. Microanalyses were performed by the Instituto de Pesquisas Tecnológicas (IPT) in São Paulo, Brasil and at the University of British Columbia.

Synthesis

In general, one equivalent of adenine for IV (see text) and two equivalents for V and VI, dissolved in DMSO, is added to a solution of the appropriate ruthenium complex 2×10^{-4} mol in 3 mls. DMSO. After heating to 100° the solution rapidly turns red-brown and after 45 min is cooled and evaporated to half-volume. Addition of acetone precipitates the complexes as red-brown solids. Analysis for $RuCl_2(Ade)(DMSO)_3$, Calcd: C, 24.4; H, 4.3; N, 13.0. Found: C, 23.9; H, 4.3; N, 13.0%. For $Ru(Ade)_2(DMSO)_4Cl_2$: Calcd: C, 28.6; H, 4.5; N, 18.6. Found: C, 28.5; H, 4.3; N, 18.9%. For $Ru(Ade)_2(DMSO)_4(BF_4)_2$: Calcd: C, 25.2; H, 4.0; N, 16.3. Found: C, 25.3; H, 3.4; N, 16.5%.

A $10^{-3}M$ solution of $[Ru(DMSO)_6(BF_4)_2]$ in DMSO gave Λ_M = 65 ohm^{-1} cm^2 mol^{-1}. $[RuCl_2(Ade)(DMSO)_3]$ was non-conducting in DMSO while $[Ru(Ade)_2(DMSO)_4]X_2$ gave values of Λ_M = 73 ohm^{-1} cm^2 mol^{-1} (X = Cl) and 58 ohm^{-1} cm^2 mol^{-1} ($X = BF_4$).

Results and discussion

Reaction of one equivalent of adenine with 1 and two equivalents with either II or III and work-up as described in the Experimental section gives red-brown solids as products. Analytical and conductometric data support the formulation of monomeric products containing neutral adenine, the reactions being:

$$[RuCl_3(DMSO)_3]^- + Ade \rightarrow [RuCl_2(Ade)(DMSO)_3] \quad \text{IV}$$

$$[RuCl_2(DMSO)_4] + 2Ade \rightarrow [Ru(Ade)_2(DMSO)_4]Cl_2 \quad \text{V}$$

$$[Ru(DMSO)_6]^{2+} + 2Ade \rightarrow [Ru(Ade)_2(DMSO)_4](BF_4)_2, \quad \text{VI}$$

The compounds are all air stable solids, soluble in DMSO, very sparingly soluble in H_2O and CH_3OH and insoluble in acetone and non-polar solvents. Similar crude products are obtained upon reaction of I, II or III with guanine, but upon recrystallisation

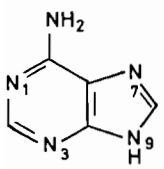
0020-1693/82/0000-0000/$02.75

guanine is displayed by DMSO and no isolatable products can be obtained. Thymine does not react under these conditions, while the products of the reaction with cytosine appear to be a mixture and no single species has been isolated.

The infrared spectra of products IV, V and VI show a typical lowering [10] of ν(C=N) from 1620 to 1590 cm^{-1}. A weak band at approx. 500 cm^{-1} in all three complexes may be attributed to ν(M–N). The disappearance of ν(Ru–Cl) at 345 cm^{-1} [11] in V further confirms the displacement of chloride in this complex. The appearance of three bands in the ν(SO) region at 1100(s), 1030(s) and 920 cm^{-1} (m) for V and VI respectively suggests the presence of three sulfur-bound and one oxygen-bound DMSO as in the parent complexes, while the absence of the band at 920 cm^{-1} attributable to ν(S–O), oxygen-bound, indicates three sulfur-bound DMSO ligands in IV.

A number of ruthenium complexes with purines and pyrimidines have been reported. Khan *et al.* [13] reported adducts of adenine and cytosine with both $RuCl_3$ and $RuCl_2(DMSO)_4$. For the latter, complex species of formula $[Ru_2(Ade)_3(DMSO)_4Cl_4]$ and $[Ru_2(Cyt)_4(DMSO)_2Cl_4(CH_3OH)_4]$ were isolated. The discrepancy between these and the adenine complexes reported here may be explained by the fact that the solvent used by Khan was CH_3OH. Hydrolysis of both O- and S-bonded sulfoxides has been observed for these ruthenium complexes [14] and a similar process in methanol, especially under the reaction conditions employed, [10–12 hr, reflux temp.) will result in loss of ligated DMSO as observed. Use of solvent DMSO avoids this problem and results in well-defined products. In an extensive survey of the reactions of the $[Ru(NH_3)_5(H_2O)]^{2+}$ ion with purines and pyrimidines, Clarke [15] has isolated the adenosine and adenine adducts $[Ru(NH_3)_5Ad]^{2+}$.

An important aspect of the study of metal–purine complexes is the determination of the binding site in the complex. When diamagnetic metal–purine complexes are formed, ^{1}H N.M.R. is often a useful tool in that the proton closest to the metal will be most affected by metal-binding and will be shifted downfield with respect to the other protons present [2]. However, this is by no means definitive, especially for adenine where a total of five possible nitrogen-binding sites are available:



It is difficult in our case to assign exact binding sites as the signals due to the H_2 and H_8 protons in d_6-DMSO are not clearly resolved, occurring at 8.18 δ for the free base and shifting to 8.25 δ and 8.3 δ for IV and V respectively. The analogous adenosine complexes show well-defined resonances indicative of N_7 binding, but the prolonged purification necessary (Soxhlet extraction in CH_3OH) results in loss of DMSO and the exact stoichiometry is uncertain. However, the rhodium complex *mer*-$[RhCl_3(DMSO)_3]$, containing 2S and 10 bound sulfoxide [16], readily gives a 1:1 adduct with adenosine $[RhCl_3(Ado)(DMSO)_2]$ where the ^{1}H N.M.R. data (8.60 δ (H_8), 8.44 δ (H_2)) strongly implies N_7 binding [17, 18]. The lack of spectral features indicative of N_1, N_7 bridging as observed for the square-planar platinum complexes $[PtCl_2(DMSO)_2]$ and $[PtCl_3(DMSO)]^-$ [17, 19], eliminates this possible mode of binding in the ruthenium complexes.

The assignment of N_7 binding is consistent with the observation that this binding mode occurs when there is favourable H-bonding interaction between the oxygen of a metal-bound ligand (H-bond acceptor) and the exocyclic amino group, as in *trans*-$[Co(acac)_2(NO_2)(Ado)]$ [20] and $[Rh_2(acetate)_4(Ado)H_2O]$ [21]. The observed binding and the enhanced stability of the adenine derivatives over those of guanine is in contrast to the $[Ru(NH_3)_5H_2O]^{2+}$ system where the most probable site of adenine binding is the exocyclic amine, although the guanine complexes are bound in a normal manner through N_7. The results demonstrate again how different ligands (*e.g.* NH_3, hydrogen-bond donor and DMSO, hydrogen-bond acceptor) can affect the site and specificity of purine binding to metal complexes.

Acknowledgements

We wish to thank Prof. B. R. James for his interest and encouragement. Johnson-Matthey is thanked for a loan of ruthenium trichloride and the financial support of CNP (Conselho Nacional de Desenvolvimento Cientifico e Tecnologico) is acknowledged.

References

1 For a recent review see J. J. Roberts and A. J. Thomson, 'Progress in Nucleic Acid Research and Molecular Biology', *22*, 71 (1979).
2 L. Marzilli, *Prog. Inorg. Chem.*, *23*, 255 (1977).
3 D. Hodgson, Prog. *Inorg. Chem.*, *23*, 211 (1977).
4 C. Monti-Bragadin, L. Ramani, L. Samer, G. Mestroni and G. Zasinovich, *Antimicrob. Agents and Chemotherapy*, *7*, 825 (1975).
5 Presented at the ACS meeting, Honolulu, April, 1979, Abstract No. INOR 476.
6 R. S. McMillan, A. Mercer, B. R. James and J. Trotter, *J. Chem. Soc. (Dalton)*, 1000 (1975).
7 A. Mercer and J. Trotter, *J. Chem. Soc. (Dalton)*, 2480 (1975).
8 A. R. Davies, F. W. B. Einstein, N. P. Farrell, B. R. James and R. S. McMillan, *Inorg. Chem.*, *17*, 1965 (1978).
9 W. L. Reynolds, *Prog. Inorg. Chem.*, *12*, 1 (1970).

10 J. Dehand and J. Jordanov, *J. Chem. Soc. (Chem. Comm.)*, 598 (1976).
11 I. P. Evans, A. Spencer and G. Wilkinson, *J. Chem. Soc. (Dalton)*, 204 (1973).
12 N. Farrell and N. G. de Oliveira, to be submitted.
13 B. T. Khan and A. Mehmood, *J. Inc. Nuc. Chem., 60,* 1938 (1978), B. T. Khan, M. R. Somayagulu and M. M. Tsgin Khan, *J. In. Nuc. Chem., 40,* 1251 (1978).
14 N. Farrell and N. G. de Oliveira, *Inorg. Chim. Acta, L255* (1980).
15 M. J. Clarke, *J. Amer. Chem. Soc., 100,* 5068 (1978).
16 V. I. Sokol and M. A. Porai-Koshits, *Koord. Khim., 1,* 577 (1975).
17 N. Farrell, *J. Chem. Soc., Chem. Comm.*, 1014 (1980).
18 N. Farrell, unpublished results.
19 C. J. Lock, R. A. Speranzini, G. Turner and J. Powell, *J. Amer. Chem. Soc., 98,* 7865 (1976).
20 T. Sorrell, L. A. Epps, T. J. Kirstenmacher and L. G. Marzilli, *J. Amer. Chem. Soc., 99,* 2173 (1977).
21 N. Farrell, *J. Inorg. Biochem., 14,* (3) (1981).