Unprecedented carbon–carbon bond formation induced by photoactivation of a platinum(IV)-diazido complex†

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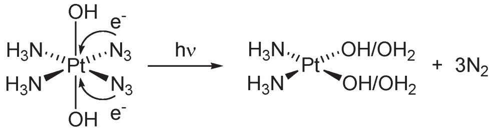
UVA-induced photodecomposition of a Pt^{IV}-diazido complex involves not only reduction to Pt^{II} and N_2 release, but also O_2 evolution and formation of nitrene intermediates, whose trapping with $(CH_3)_2S$ gives rise to an unusual *N*,*N*′-bis(ethyl)-sulfurousdiamide ligand in an apparently unprecedented process involving C–C bond formation.

Pt^{IV}-diazidodiam(m)ino complexes such as *cis*,*trans*,*cis*-$[Pt(N_3)_2(OH)_2(NH_3)_2]$ (**1**) are inert in the dark, but bind to DNA on photoactivation.[1] The site selectivity of plasmid DNA platination resembles that from reaction with the anticancer drug cisplatin (in the dark).[2] However, such Pt^{IV}-diazido complexes appear to kill cancer cells by a different mechanism from cisplatin; photoactivation can result in destruction of cancer cell nuclei.[3] We are therefore investigating the photodecomposition pathways of these complexes in order to elucidate novel chemical reactions which might be responsible for their biological mechanism of action. We report here discovery of photoinduced formation of carbon–carbon bonds during an attempt to trap nitrene intermediates. Such reactions appear to be unprecedented.

Pt^{IV}-azido complexes are well-known to be photoactive. On irradiation, they may undergo photoinduced reductive elimination in aqueous solution and liberate gaseous dinitrogen, leading to corresponding highly reactive Pt^{II} species (Scheme 1).[4]

We have investigated photodecomposition pathways using multinuclear NMR methods; in particular, ^{14}N NMR spectroscopy has allowed us to track photoreactions involving the azido ligands.

In the 1D $^{14}N\{^1H\}$ NMR spectrum of *cis*,*trans*,*cis*-$[Pt(N_3)_2(OH)_2(^{15}NH_3)_2]$ ($\mathbf{^{15}N_2}$**-1**, initial pH adjusted to 5.1, Ar-saturated) obtained after 2 h of irradiation with UVA light at 310 K (see ESI, Fig. S1†), a peak for N_2 was detected at 287.3 ppm.[5] Moreover a peak at −20.9 ppm was assigned to unlabelled free NH_3, leading to the conclusion that this NH_3 can be a side-product in the photodecomposition of the azido ligands.[6] Interestingly, the pH increased from 5.1 to 10.7 and, at the end of the irradiation, O_2 was detected in the sealed NMR tube (P_{O_2} 37 mmHg), suggesting that alternative photodecomposition pathways to that in Scheme 1 can operate.



(1)

Scheme 1 Expected mechanism for photoreduction of complex **1**.

After the ^{14}N NMR experiments, the pH of the solution was adjusted to 3.1 with dilute $HClO_4$ (to ensure slow exchange of NH protons), and 1D ^1H and 2D $[^1H,^{15}N]$ HSQC NMR spectra were recorded (see ESI, Fig. S2; NMR parameters summarized in Table S1†). Based on chemical shifts,[7] four of the peaks from products formed upon irradiation are assignable to Pt^{II} species, three of which are consistent with coordinated NH_3 groups *trans* to N-donor ligands. The detection of Pt^{II} species, together with the presence of a sharp peak in the 1D $^{14}N\{^1H\}$ NMR spectrum at 287.3 ppm assigned to evolved gaseous N_2, provide evidence for photoreduction processes, and are consistent with the expected photoactivation pathway (Scheme 1). The major Pt^{II} species detected (peak 3 at $\delta_{H/N}$ 4.04/−69.0), accounting for *ca.* 56% of the total amount of Pt-ammino species formed in solution, can be tentatively assigned to *trans*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$,[7] suggesting that photoisomerization can accompany photoreduction. Photoisomerization of both Pt^{II}- and Pt^{IV}-am(m)ino complexes has been reported previously,[8] occurring in the excited state by a twisting mechanism, *i.e.* without bond-breakage and bond-formation.

Upon irradiation, $\mathbf{^{15}N_2}$**-1** also gave rise to several new Pt^{IV} products, with no starting compound remaining. Most have chemical shifts which are consistent with NH_3–Pt^{IV} *trans* to O-donor ligands (*i.e.* replacement of azido ligands by H_2O/OH groups), thus confirming that photosubstitution takes place on Pt^{IV} rather than photoisomerization (which only seems to occur during photoreduction to Pt^{II}). Free $^{15}NH_4^+$ was also detected, and arises from the photolabilization of the coordinated ammine ligands, accounting for the large increase in pH during the irradiation. Some precipitate formed during the photoreaction (0.9 mg) and is likely to arise from polymeric hydroxo-/oxo-bridged Pt species, but this was not further characterized due to its insolubility. Nevertheless, the possible formation of insoluble hydroxo-bridged species is supported by the presence of a large amount of free ammonia in solution, which might have been released from Pt upon irradiation, substituted by H_2O molecules, and subsequently deprotonated as the pH increased while photoreactions occurred.[1]

We next investigated whether the photochemical decomposition pathways for **1** involve nitrene intermediates (Scheme 2). In other

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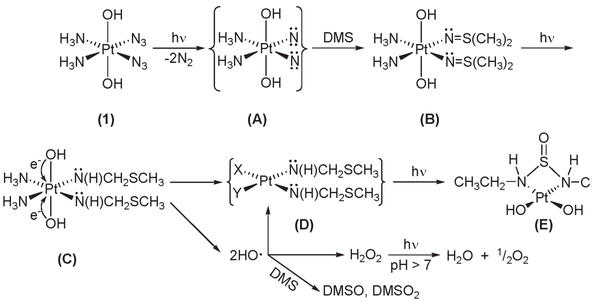

Scheme 2 Possible mechanisms for nitrene-trapping and photoreduction (X,Y = NH_3 and/or OH).

reported systems, the involvement of six-electron triplet and singlet nitrene intermediates has been claimed.[8c] Nitrenes can be efficiently trapped with dimethyl sulfide (DMS).[9]

We treated an Ar-saturated 10.9 mM acidic (pH 4.9) aqueous solution of **1** containing $^{15}NH_3$ and ^{15}NNN azides (**$^{15}N_4$-1**, see ESI†) with excess DMS (molar ratio 1 : 6), and irradiated with UVA light for 2 h at 310 K. The photoproducts were characterized by NMR spectroscopy and ESI-MS. Dioxygen was again evolved (P_{O_2} 39 mmHg) upon irradiation, and the pH increased to 10.4. Surprisingly, no precipitate formed on irradiation. Only one $^{14}N\{^1H\}$ NMR peak was observed at 284.4 ppm, assignable to evolved N_2. Other products were identified with the aid of 1D ^1H and 2D [^1H,^{13}C] HMBC NMR experiments (Fig. 1; see also ESI, Table S2 and Fig. S3†). Peaks **α** (3 H, t, CMe) and **β** (2 H, q, NCH_2) belong to an ethyl group. Peaks **γ**, **δ** and **ε** can be assigned to species derived from DMS: $DMSO_2$, DMSO, and unreacted DMS, respectively.[10]

2D [^1H,^{15}N] HSQC/HMBC NMR experiments (at pH 3.2) allowed identification of a major Pt^{II}-ammino species (accounting for *ca.* 63% of the total amount of Pt-ammino species detected in solution) at $\delta_{H/N}$ 3.65/−64.5 characterized by $^1J(^{15}N–H)$ of 91 Hz, together with a long-range correlation peak with the ethyl $–CH_2–$ (Fig. 2). These data are consistent with a $CH_3CH_2{}^{15}NH–$ group coordinated to a Pt^{II} metal center. This species was identified by ESI-MS as the Pt derivative $C_4H_{15}N_2O_3PtS$ (*m*/*z*: calcd 367.33; expt 367.29), consistent with the protonated species **E** shown in Scheme 2.

Other minor $Pt–NH_3$ species were detected, consistent with those previously observed upon irradiation in the absence of DMS (see ESI, Table S3†). In particular, the species at $\delta_{H/N}$ 4.02/−69.0, tentatively assignable to *trans*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ and previously detected as the major Pt^{II} photoproduct, now accounted for only 13% of the total amount of Pt-ammino species in solution, supporting the hypothesis that the entrapment of the nitrene intermediates by DMS hinders the normal progress of the photoreaction.

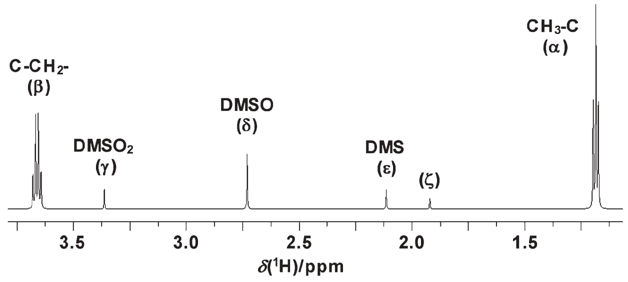

Fig. 1 1D ^1H NMR spectrum of **$^{15}N_4$-1** (10.9 mM) in the presence of DMS (molar ratio 1 : 6) in 90% H_2O–10% D_2O (Ar-saturated, initial pH 4.9) after 2 h of irradiation (λ_{max} 365 nm, *P* 6.4 mW cm^{-2}, dose 49.5 J cm^{-2}; 310 K; final pH 10.4) (see ESI, Table S2 and Fig. S3†).

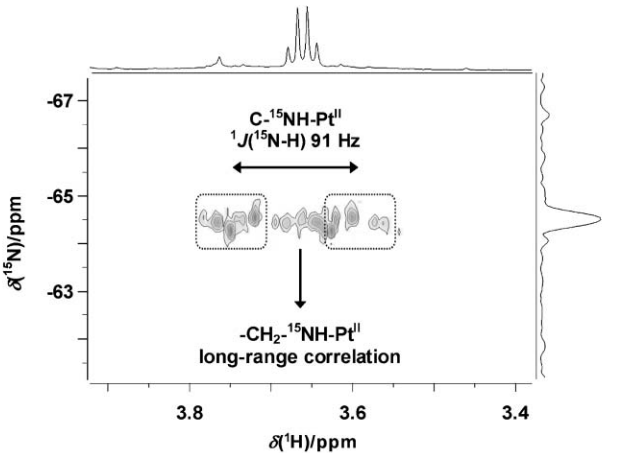

Fig. 2 Part of the 2D [^1H,^{15}N] HMBC NMR spectrum of **$^{15}N_4$-1** (10.9 mM) in the presence of DMS (molar ratio 1 : 6) in 90% H_2O–10% D_2O (Ar-saturated, initial pH 4.9) after 2 h of irradiation (λ_{max} 365 nm, *P* 6.4 mW cm^{-2}, dose 49.5 J cm^{-2}; 310 K; final pH 10.4), and pH adjustment to 3.2.

We can speculate on the mechanism for nitrene trapping and on the photoreduction pathways (Scheme 2). Based on literature reports,[9] it seems likely that in the primary photochemical step the azido ligands are converted to nitrene intermediates (**A**) which react with DMS to form dimethylsulfilimine adducts (**B**), and can subsequently undergo a Stevens-like rearrangement[11] to give the corresponding *N*-(methylthiomethyl)amido derivative (**C**). Upon irradiation, species **C** may undergo photoreduction involving a one-electron transfer from each of the two hydroxo ligands, leading to the corresponding Pt^{II} species **D** together with the formation of hydroxyl radicals. At this stage, photosubstitution of ammino ligands with H_2O/OH groups may also occur. No NMR peaks assignable to any of **B**, **C** or **D** were observable (Fig. 1), whereas our results are consistent with the proposed Pt^{II}-(*N*,*N′*-bis(ethyl)sulfurous)diamido species (**E**). This derivative may be produced by direct reaction of species **D** with hydroxyl radicals, giving rise to the subsequent rearrangement to (*N*,*N′*-bis(ethyl)sulfurous)diamide followed by the release of an inorganic oxidized sulfur species (SO_4^{2-}, see ESI†). The oxidation of the sulfur atoms, together with the observed evolution of O_2, is consistent with the possible formation of reactive oxygen species, since hydroxyl radicals, when generated at high local concentrations, may readily dimerize to H_2O_2 which, upon irradiation with UV light at basic pH, is known to decompose by dismutation to H_2O and O_2. With this in mind, we can also speculate on pathways which lead to oxidation of free DMS. Both H_2O_2 and hydroxyl radicals are known to oxidize DMS in aqueous solution to DMSO and, subsequently, to $DMSO_2$.[12] Thus, the detection of both these species by NMR spectroscopy (Fig. 1) provides indirect evidence for the formation upon irradiation of reactive oxygen species which can play roles in such photoreactions.

The identification of species **E** is based also on ESI-MS experiments (see ESI, Fig. S4†). Given that the final pH after irradiation is highly basic, we cannot rule out the possibility that such a photoproduct might be a dinuclear hydroxo-bridged Pt^{II} derivative, whereas the identified monomer may be a consequence of the adjustment to acidic pH and/or the ESI-MS experimental conditions. The formation of a carbon–carbon bond under such experimental conditions appears to be unprecedented, although complexes containing related (*N*,*N*′-dialkylsulfurous)diamides are known for other metals, prepared by different synthetic routes.[13]

These results suggest that, under some conditions, both highly reactive oxygen species and nitrene intermediates can arise from the photoreduction of Pt^{IV}-diazido complexes, even though the major photoproducts (Pt^{II} species and N_2) are consistent with the proposed photoreduction mechanisms (Scheme 1).

Use of DMS as a trap has led to the formation of an unusual (*N*,*N*′-bis(ethyl)sulfurous)diamide ligand in a process that appears to involve unprecedented C–C bond formation. This photoactivation strategy could open up new synthetic routes. Moreover, although these experiments were not carried out under physiological conditions, we note that dialkylsulfides are readily available in biological components, *e.g.* as methionine side-chains. Hence the capability of these photoactivated complexes to interact in such an unusual way with DMS, may provide insight into their potential as photochemotherapeutic agents.‡

Notes and references

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