A New Platinum(II)–Dioxocyclam Complex and Its Application to Selective Extraction of Pt^{II} from Aqueous Metal Ion Mixtures

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Selective extraction of platinum(II) is achieved by utilizing unique complexation properties of macrocyclic dioxotetra-amine (**1**) specific for Pt^{II} at low pH in the presence of $Na_2S_2O_3$.

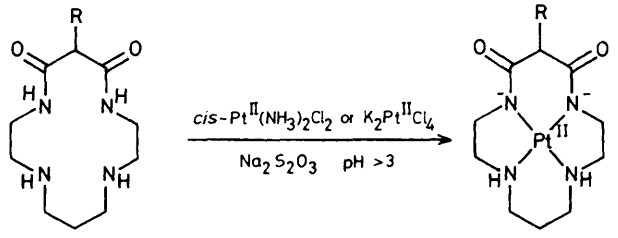
Selective chelating agents for platinum(II) are scarce. The recent world-wide, clinical use of antitumour Pt^{II} complexes {*e.g.* cisplatin, *cis*-$[Pt^{II}(NH_3)_2Cl_2]$}[1a] calls for development of selective and efficient sesquestering agents of Pt, since the Pt drugs tend to adhere to biomolecules (*e.g.* nucleic acids, proteins), posing serious problems of accumulation and slow excretion from the body.[1b,c]

In the present communication, we report selective removal of cisplatin from aqueous metal ion mixtures by a lipophilic dioxocyclam derivative (**1b**) dissolved in organic solvents

Table 1. Dioxocyclam-mediated extraction of Pt^{II} in shakeout tests with CH_2Cl_2 for a 1 h period in an automatic shaker (325 strokes/min), three times at 37 °C.

Run	Aqueous layer (I): Metal ion (1.5 mM)	pH	Additive (15 mM)	Conc. of (**1b**) in CH_2Cl_2 (mM)	% Metal[a] remaining in aqueous layer (I)	% Metal[a] extracted into CH_2Cl_2 layer
1	$Pt(NH_3)_2Cl_2$	7	None	0	98	1
2	$Pt(NH_3)_2Cl_2$	7	$Na_2S_2O_3$	0	100	0
3	$Pt(NH_3)_2Cl_2$	7	$Na_2S_2O_3$	3	0	94
4	$Pt(NH_3)_2Cl_2$	3	$Na_2S_2O_3$	3	20	72
5	$Pt(NH_3)_2Cl_2$	5	$Na_2S_2O_3$	3	28	69
6	$Pt(NH_3)_2Cl_2$	7	$Na_2S_2O_3$	0.75	5	104
7	$Pt(NH_3)_2Cl_2$	7	Ascorbic acid	3	50	42
8	$Pt(NH_3)_2Cl_2$	7	$NaBH_4$	3	65	31
9	$Pt(NH_3)_2Cl_2$	7	Glutathione	3	35	69
10	$Pt(NH_3)_2Cl_2$	7	Na_2SeO_3	3	61	52
11	K_2PtCl_4, $CuCl_2$, $NiSO_4$	7	$Na_2S_2O_3$	3	34 (Pt) 89 (Cu) 57 (Ni)	63 (Pt) 9 (Cu) 43 (Ni)
12	K_2PtCl_4, $CuCl_2$, $NiSO_4$	3	$Na_2S_2O_3$	3	19 (Pt) 89 (Cu) 93 (Ni)	84 (Pt) 8 (Cu) 12 (Ni)
13	$Pt^{II}(TriGly^{2+})$	7	$Na_2S_2O_3$	3	12	87

[a] All the values have ±5% errors.



Dioxocyclam (**1a**), R = H
(**1b**), R = $C_{16}H_{33}$

(**2**)

(such as CH_2Cl_2). The underlying principle is the unique chelating behaviour of the dioxocyclams (**1**) that possess the dual ligand functions of a macrocyclic polyamine containing amide ligands.[2] The dioxocyclam (**1a**) encloses metal ions (like cyclam) with simultaneous deprotonation of the two amides (like tripeptides) to yield square planar 1 : 1 complexes $[M^{II}L]^0$ with Cu^{II},[3a,b] Ni^{II},[3c] Co^{II},[4] or Pd^{II},[5] in neutral to alkaline pH. Recently,[6] it was discovered that tripeptides bind with Pt^{II} whereby the deprotonation of the peptide nitrogens occurs more favourably below pH 2.5 than with other metal peptides, *e.g.* Pd^{II}, pH 2.5—3.5; Cu^{II}, pH 5—6; Ni^{II}, pH 8—9. From the fact that Pt^{II}, like Pd^{II}, Cu^{II}, or Ni^{II}, forms square planar complexes with tripeptides and furthermore its ionic radius is similar,[6] we felt that a similar dioxocyclam complex should form with Pt^{II}.

Indeed, we have isolated a diagmagnetic 1:1 Pt^{II}-dioxocyclam complex $[Pt^{II}L]^0$ (**2a**) as white needles. This is the first isolation of a Pt^{II} macrocyclic complex having doubly deprotonated amide co-ordination. The procedure for the synthesis of (**2a**) is as follows: to a red-brown solution of $K_2Pt^{II}Cl_4$ (419 mg, 1 mmol) and dioxocyclam (**1a**) (228 mg, 1 mmol) in water (10 ml) was added $Na_2S_2O_3 \cdot 5H_2O$ (496 mg, 2 mmol) and the mixture (pH ~9.5) was allowed to stand at 35—40 °C for 6 h. The resulting yellow solution (pH ~7) was subjected to anion exchange Amberlite IRA-400 chromatography with water. The eluant was concentrated to *ca.* 5 ml and kept under 4 °C for 3 h to obtain white needles of $[Pt^{II}L]^0$ (**2a**) in more than 80% yield. Satisfactory elemental analyses were found. The compound is diamagnetic.[7] I.r. spectra (KBr pellet), 1590 cm^{-1} for $\nu_{C=O}$, indicate the presence of deprotonated amides. The $\nu_{C=O}$ for the free (LH_2) ligand (**1a**) occurs at 1670 cm^{-1} and for the deprotonated nickel complex[3c] $[Ni^{II}L]^0$ at 1585 cm^{-1}. U.v. (in H_2O); $\lambda_{max.}$ 243 nm (ε 9130). The Ni^{II} complex $[Ni^{II}L]^0$ has $\lambda_{max.}$ 245 nm (*sh.* ε ~7000), while the free ligand has no such absorption. The sluggish metal complexation (Pt^{II} is well known to be kinetically inert)[8] was accelerated by addition of reducing agents such as $Na_2S_2O_3$ or ascorbic acid. Without the reductants, practically no complexation occurred.† The same Pt^{II} complex (**2a**) was obtained in the same manner starting from cisplatin, which can be monitored easily by the appearance of the characteristic u.v. absorption peak at 243 nm. The complex (**2a**) can be rapidly and quantitatively dissociated into the free ligand (**1a**) and Pt^{II} in 1 M HCl aqueous solution.

The successful enclosure of Pt^{II} by the macrocycle (**1a**) led us to perform Pt^{II} extraction experiments using a lipophilic ligand (**1b**).[9,10] In a typical extraction experiment, aqueous solution (I) (10 ml, pH 7.4 nonbuffered) containing 1.5 mM of Pt^{II} (either as K_2PtCl_4 or cisplatin) and 15 mM of a reductant was shaken for 1 h by an automatic shaker (325 strokes/min) three times each with 10 ml of a CH_2Cl_2 solution containing 3 mM (**1b**). The aqueous solution and CH_2Cl_2 solution were analysed for Pt^{II} by atomic absorption spectroscopic measurements. The results are summarised in Table 1.

It is evident from Table 1 that the platinum(II) ion in cisplatin can be *effectively* transferred into the organic layer by our lipophilic carrier (**1b**) only in the presence of reducing agents. Evidently, the Pt^{II} transfer occurs by the formation of the CH_2Cl_2-soluble Pt^{II}–dioxocyclam (**1b**) complex, which can

† An exact mechanism is uncertain. However, the reductive Pt^{II}–X bond weakening may be responsible for the ligand exchange reactions.

be confirmed by emergence of the u.v. absorption peak at 243 nm in the CH_2Cl_2 layer. Moreover, Pt^{II} can be *selectively* extracted at pH 3 from a mixture of Pt^{II}, Cu^{II}, and Ni^{II} using our system (see Run 12 in Table 1). This is due to the more favourable deprotonation of amide nitrogens in forming $[Pt^{II}L]^0$ than in forming other metal–dioxocyclam complexes where the deprotonation pH's are observed to be higher: Cu^{II}, pH 5—6; Ni^{II}, pH 8—9. It is shown in Run 13, Table 1, that the Pt^{II} ion is transferred from the aqueous solution of Pt^{II}–glycylglycylglycine (prepared by the method of Margerum[6]) to the CH_2Cl_2 solution containing dioxocyclam (**1b**). The Pt^{II}–macrocyclic complex (**2**) should be thermodynamically more stable than the Pt^{II}–linear-glycylglycylglycine complex. This may suggest that the macrocyclic ligands (**1**) are potentially useful as a drug for excretion of Pt^{II} which is accumulated in the body as Pt^{II}–peptide complexes. Platinum(II) complexed with a ten fold excess of adenine, guanine, thymine, or cytosine can also be extracted (more than 50%) with (**1b**) at pH 7, indicating that nucleic acid-bound Pt^{II} can be removed by our method. Finally, it is to be noted that the lipophilic cyclam [(**1b**)-analogue with reduced amides] is ineffective for selective extraction of Pt^{II}.

The efficiency and selectivity of (**1**) for Pt^{II} also demonstrate the potential usefulness of macrocyclic oxopolyamines in analytical and mineralogical applications.

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