

Macrocyclic-selective extractant for Pt (II) from aqueous metal solutions

Randhir Singh*, Amarendra Bhattacharya &
Mamta Sharma

Department of Chemistry, Gurukul Kangri University,
Hardwar 249 404, India

Received 25 January 2000; revised 7 August 2000

Dioxodimethyl macrocyclic ligand (A) has been used for selective extraction of platinum (II) from aqueous metal ion mixture. This is achieved by utilizing unique complexation properties of macrocyclic ligand (A) in the presence of sodium thiosulphate and showed very good results for the extraction of Pt (II).

Coordination complexes containing macrocyclic ligands play significant role in biological systems, yet chemical behaviour and sequestering properties are still poorly explored¹⁻⁷. Recently world-wide clinical use of antitumour Pt^{II} complexes {like cisplatin, cis-[Pt^{II}(NH₃)₂Cl₂]}⁸ calls for the development of selective and efficient sequestering agents of Pt, since the Pt drugs tend to adhere to biomolecules (e.g. nucleic acids, proteins), which may raise a serious problem of accumulation and may disturb excretory system^{9,10}.

Here, we report selective removal of cisplatin from aqueous metal ion mixtures by a lipophilic dioxodimethylmacrocyclic derivative (A_b) dissolved in organic solvents. The underlying principle is the unique chelating behaviour of the dioxomacrocyclic that possess the dual ligand functions of macrocyclic polyamine containing amide ligands¹¹. The dioxodimethylmacrocyclic ligand (A) encloses metal ions (like cyclam) with simultaneous deprotonation of two amides (like tripeptides) to yield square planar 1:1 complexes [M^{II}L]⁰ with Cu^{II}, Ni^{II}, Co^{II}, or Pd^{II} (ref. 12), in neutral to alkaline pH. It has been discovered¹⁶ that tripeptides bind with Pt^{II} whereby the deprotonation of peptide nitrogens occurs more favourably below pH 2.5 than with other metal peptides, e.g. Pd^{II}, pH 2.-3.5; Cu^{II}, pH 5-6.5; or 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. Keeping these points in view, it was considered that a similar dioxodimethylmacrocyclic ligand should form complex with Pt^{II}.

Experimental

During these studies, we isolated a diamagnetic 1:1 Pt^{II}-dioxodimethylmacrocyclic complex as whitish needles. The isolation of a Pt^{II} macrocyclic complex having doubly deprotonated amide coordination was carried out. The synthetic procedure of macrocyclic complex (B) is as follows: To a red brown solution of K₂Pt^{II}Cl₄ (419 mg, 1 mmol) and dioxodimethylmacrocyclic (A) (228 mg, 1 mmol) in water (10 ml) was added Na₂S₂O₃.5H₂O (496 mg, 2 mmol) and the mixture (pH ~ 9.0) was allowed to stand at ~ 40°C for overnight. The resulting yellow solution (pH ~ 7) was subjected to anion exchange Amberlite IRA-400 chromatography with water. The eluant was concentrated to about 5 ml and kept in refrigerator for overnight to obtain white needles of macrocyclic complex (B) in more than 70% yield. Satisfactory elemental analysis results were obtained. The compound is diamagnetic¹⁷. The IR spectra in (KBr pellet), 1595 cm⁻¹ for C=O, indicate the presence of deprotonated amides. The C=O for the free ligand (A) occurs at 1675 cm⁻¹ and for the deprotonated nickel complex¹⁵[Ni^{II}L]⁰ at 1586 cm⁻¹. UV (in H₂O); λ_{max}. 244 nm (9384). The Ni^{II} complex [Ni^{II}L]⁰ has λ_{max}. 246 nm (sh.~7028), while the free ligand has no such absorption. The slow complexation was accelerated by the addition of reducing agents such as Na₂S₂O₃, without which complexation did not occur. The Pt^{II} complex (B) was obtained in a similar manner starting from cisplatin, which can be monitored easily by the appearance of the characteristic UV absorption peak at 244 nm. The complex (B) can be rapidly dissociated into the free ligand (A) and Pt^{II} in 1molar HCl aqueous solution.

The complexation of Pt^{II} with the macrocyclic ligand (A) led us to perform Pt^{II} extraction experiments using a lipophilic ligand (A_b)^{19,20}. In a typical extraction experiment, aqueous solution of (A) (10 ml, pH 7.5) containing 2 mmoles of Pt^{II} (either as K₂PtCl₄ or cisplatin) and 20 mmoles of a reductant was shaken for 3 h by an automatic shaker (330 strokes/min) three times each with 10 ml of a CH₂Cl₂ solution containing 2 mmoles of (A_b). The aqueous solution and CH₂Cl₂ solution were analysed for Pt^{II} by atomic absorption spectrophotometry. The results obtained are given in Table 1.

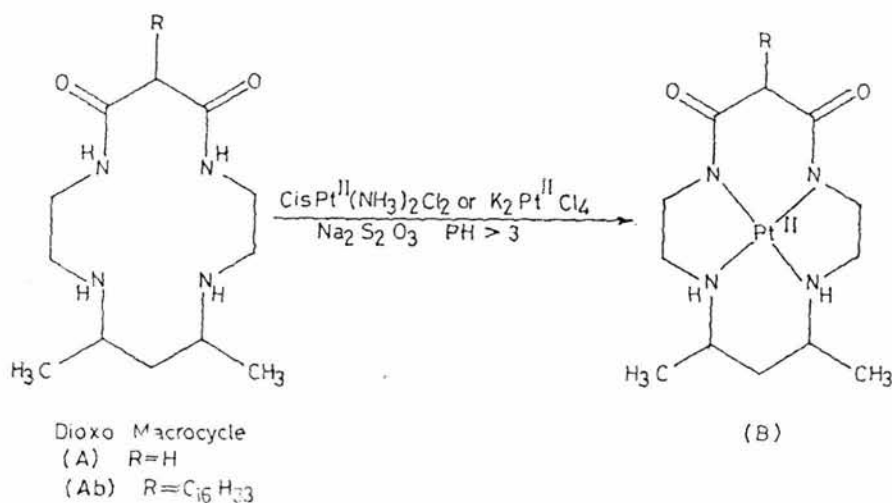


Table I—Dioxodimethylmacrocyclic-mediated extraction of Pt^{II} in shakeout tests with CH_2Cl_2 for a 1 h period in an automatic shaker (330 strokes/min), three times at 35°C

Run	Aqueous layer (I)			Conc. of (A _b) in CH_2Cl_2 (mM)	% Metal ^a remaining in aqueous layer (I)	% Metal ^a extracted into CH_2Cl_2 layer
	Metal ion (1.5 mM)	pH (15 mM)	Additive			
1	$\text{Pt}(\text{NH}_3)_2\text{Cl}_2$	7.2	None	0	95	1
2	$\text{Pt}(\text{NH}_3)_2\text{Cl}_2$	7.3	$\text{Na}_2\text{S}_2\text{O}_3$	0	100	0
3	$\text{Pt}(\text{NH}_3)_2\text{Cl}_2$	7.2	$\text{Na}_2\text{S}_2\text{O}_3$	3	0	95
4	$\text{Pt}(\text{NH}_3)_2\text{Cl}_2$	3.2	$\text{Na}_2\text{S}_2\text{O}_3$	3	25	75
5	$\text{Pt}(\text{NH}_3)_2\text{Cl}_2$	5.3	$\text{Na}_2\text{S}_2\text{O}_3$	3	25	70
6	$\text{Pt}(\text{NH}_3)_2\text{Cl}_2$	7.1	$\text{Na}_2\text{S}_2\text{O}_3$	0.75	5	105
7	$\text{Pt}(\text{NH}_3)_2\text{Cl}_2$	7.1	Ascorbic acid	3	50	45
8	$\text{Pt}(\text{NH}_3)_2\text{Cl}_2$	7	NaBH_4	3	65	35
9	$\text{Pt}(\text{NH}_3)_2\text{Cl}_2$	7	Glutathione	3	35	70
10	$\text{Pt}(\text{NH}_3)_2\text{Cl}_2$	7	$\text{Na}_2\text{S}_2\text{O}_3$	3	65	52
11	K_2PtCl_4	7	$\text{Na}_2\text{S}_2\text{O}_3$	3	34 (Pt)	63 (Pt)
	CuCl_2				89 (Cu)	9 (Cu)
	NiSO_4				57 (Ni)	42 (Ni)
	K_2PtCl_4				19 (Pt)	84 (Pt)
12	CuCl_2	3.2	$\text{Na}_2\text{S}_2\text{O}_3$	3	89 (Cu)	8 (Cu)
	NiSO_4				93 (Ni)	12 (Ni)
13	$\text{Pt}^{\text{II}}(\text{TriGly}^{2+})$	7.1	$\text{Na}_2\text{S}_2\text{O}_3$	3	12	85

^a All the values have $\pm 5\%$ errors

Results and discussion

Table I data clearly show that platinum (II) ion in cisplatin can be effectively transferred into the organic layer by lipophilic carrier (A_b) only in the presence of reducing agents. It is clear that Pt^{II} transfer occurs by the formation of CH_2Cl_2 -soluble Pt^{II} -dioxodimethylmacrocyclic (A_b) complex, which can be confirmed by an absorption peak at 244 nm in CH_2Cl_2 layer. Moreover, Pt^{II} can be selectively extracted at pH 3.5 from a mixture of Pt^{II} , Cu^{II} , and Ni^{II}

using the reported system¹². This may be due to the favourable deprotonation of amide nitrogens in forming complex than in forming other metal-dioxodimethylmacrocyclic complexes where the deprotonation was observed to be at higher pH; Cu^{II} , pH 5-6; Ni^{II} , pH 8-9. It has been observed in Run 13, Table I, that Pt^{II} ion is transferred from the aqueous solution¹⁶ to the CH_2Cl_2 solution containing dioxodimethylmacrocyclic (A_b). It is assumed that Pt^{II} -macrocyclic complex (B) should be thermodynamically

cally stable. This may suggest that the macrocyclic ligands (A) are potentially useful as a drug for excretion of Pt^{II} which is accumulated 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 macrocycle (A_b) at pH 7, indicating that nucleic acid bound Pt^{II} can be removed by this method. Ultimately, it is to be noted that the lipophilic macrocyclic analogue (A_b) with reduced amides, is ineffective for selective extraction of Pt^{II} .

The selectivity of (A) for Pt^{II} also demonstrates the potential usefulness of such type of macrocycles in analytical applications.

Acknowledgement

The author is thankful to the UGC, New Delhi, India, for financial support for this work.

References

- 1 a) Ghosh P, Tyeklar Z, Karlin K D, Jacobson R R & Zubieta J, *J Am chem Soc*, 109 (1987) 6889; b) Casella L, Gulloti M, Pallanza G & Rigoni L, *J Am chem Soc*, 110 (1988) 4221.
- 2 Tyeklar Z & Karlin K D, *Acc chem Res*, 22 (1989) 241.
- 3 Acholla F V, Takusagawa F & Mertes K B, *J Am chem Soc*, 107 (1985) 6902.
- 4 Van Staveren G J, Van Eerden J, Van Veggel F C J M, Harkema S & Reinhoudt D N, *J Am chem Soc*, 110 (1988) 4994.
- 5 Singh A K, Chandra Sudeshna & Singh Randhir, *J Ind chem Soc*, 74(1) (1997) 5.
- 6 Hosseini M W & Lehn J M, *Helv chim acta*, 71 (1988) 749.
- 7 a) Jahansouz H, Jiang Z, Himes R H, Mertes M P & Mertes K B, *J Am chem Soc*, 3 (1989) 1409; b) Anderson C J, Connet J M, Guo L W, Schwarz S W, Zinn K R & Welch M J, *J nucl med*, 35 (1994) 161.
- 8 Rosenberg B, *Metal ions in biological systems*, Vol. 2, edited by H Sigel, (Marcel Dekker, New York) 1980, pp 127-196.
- 9 Cleare M J & Hydes P C, *Metal ions in biological systems*, Vol. 2, edited by H Sigel, (Marcel Dekker, New York) 1980, pp 1-62.
- 10 Hay R W & Hassan M M, *Trans met Chem*, 19 (1994) 129.
- 11 Kimura E, *J coord Chem*, 15 (1986) 1.
- 12 Singh Randhir & Chandra Sudeshna, *Indian J Chem*, 34A (1995) 1003.