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Solvation of platinum anti-cancer drugs in methanol–water mixtures

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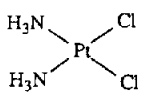
Solubilities and transfer chemical potentials of carboplatin, cisplatin, iproplatin, and several related platinum complexes have been determined in methanol-water mixtures. The range of solvation behaviour is discussed in relation to possible oral administration of complexes of this type.

Keywords: anticancer drugs, platinum complexes, solvation

Introduction

Cisplatin (**1**), carboplatin (**2**) and iproplatin (**3**) are the most successful of the first and second generation platinum anti-cancer drugs (Barnard *et al.* 1986, Reedijk *et al.* 1987, Kelland 1993). They are, however, not ideal, and considerable efforts are currently being expended to improve the properties, and extend the field of use, of platinum anti-cancer drugs, with a number of new compounds being recently and currently tested (Burgess 1993). One property which is of great importance is solvation, in that a drug, particularly if administered orally, has to cross a number of barriers before it reaches its site of action. An appropriate resultant of, and balance between, hydrophilic and lipophilic character is thus required. This may be assessed through solubility measurements in water–organic solvent mixtures (Burgess *et al.* 1987, Blandamer & Burgess 1988). A species which is soluble in both water and the organic co-solvent, and which is slightly more soluble in mixtures of the two, is likely to have solvation characteristics which will stabilize it at a membrane–aqueous medium interface. This will encourage it to be at the required interface and thus positioned ready for transmission through the membrane (Stein 1986). We have therefore assessed the solvation characteristics of the three platinum compounds named above and of several similar complexes. In particular we have included the compound bisacetatoamminedichlorocyclohexylamineplatinum (IV) (JM216), **4**, in view of its promise as a drug for oral administration (McKeage *et al.* 1994). We compare the solvation patterns for these platinum complexes with those for a number of organic and inorganic compounds of pharmacological relevance.



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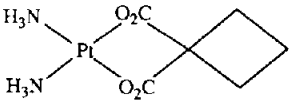

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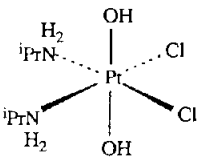

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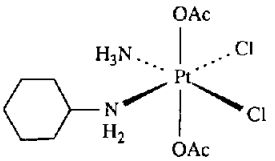

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Materials and methods

Solubilities were determined by equilibrating an excess of the respective solid (all the platinum compounds were provided by Johnson Matthey) with the various solvent media. Sealed tubes were agitated for several hours [about 30 min for carboplatin, whose decomposition might well be significant after several hours under these conditions (Canovese *et al.* 1988, Pujol *et al.* 1993)] in a thermostatted water bath. Water, dried methanol, and 20, 40, 60 and 80 volume % methanol–water mixtures were used. For the experiments involving cisplatin, all solvent media were 0.10 mol dm $^{-3}$ in sodium chloride, to suppress aquation. Aliquots of supernatant saturated solution were withdrawn and their platinum contents measured by atomic absorption (flame or graphite furnace; Perkin-Elmer 1100B). In all cases these determinations involved large dilutions, which were carried out with water. Calibration was carried out with standards consisting of aqueous solutions of K_2PtCl_4 in 1% $LaCl_3$/1% HCl.

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Results and discussion

Solubilities are reported in Tables 1 and 2, for aqueous solutions and solutions in methanol–water mixtures. Transfer chemical potentials (Blandamer & Burgess 1988) were calculated in the usual manner, from the relation

$$\delta_m\mu^\circ = -RT\ln\left\{\frac{\text{(solubility in medium 2)}}{\text{(solubility in medium 1)}}\right\}.$$

Table 1. Solubilities of platinum complexes in water at 298.2 K

Complex[a]	Solubility	
	mol dm^{-3}	g dm^{-3}
[Pt(mal)(NH$_3$)$_2$]	6.9×10^{-4}	0.23
cis-, *trans*-, *cis*-[PtCl$_2$(OAc)$_2$(NH$_3$)(cxNH$_2$)]	8.3×10^{-4}	0.42
[Pt(cbdc)(iPrNH$_2$)$_2$]	2.0×10^{-3}	0.91
cis-[PtCl$_2$(NH$_3$)$_2$]{cisplatin}	6.5×10^{-3}	1.95
[Pt(mal)(en)]	2.4×10^{-2}	8.6
[Pt(cbcd)(NH$_3$)$_2$] {carboplatin}	4.8×10^{-2}	17.8
cis-, *trans*-, *cis*-[PtCl$_2$(OH)$_2$(iPrNH$_2$)$_2$] {iproplatin}	6.2×10^{-2}	25.9
[Pt(etmal)(NH$_3$)$_2$]	7.5×10^{-2}	26.9

[a]Abbreviations: mal, malonate; OAc, acetate; cx, cyclohexyl; cbdc, 1,1-cyclobutanedicarboxylate; en, 1,2-ethanediamine; etmal, ethylmalonate.

It is assumed that the ratio of the activity coefficients in the two media is unity in all cases, which seems a reasonable assumption for these uncharged and generally sparingly soluble compounds. Values for transfer from water are included in Table 2. The transfer chemical potential trends for cisplatin and carboplatin are shown in Figure 1, where they are compared with the few trends available for other platinum(II) and palladium(II) complexes (Blandamer *et al.* 1981, Burgess & Abu-Gharib 1984). Cisplatin and carboplatin occupy positions intermediate between the strongly hydrophilic $[PtCl_6]^{2-}$ and $[PtCl_4]^{2-}$ anions and the predominantly hydrophobic complexes *cis*-$[PtCl_2(4CNpy)_2]$ and $[Pd(Et_4dien)Cl]^+$.

The transfer chemical potential trends for all eight platinum complexes are shown in Figure 2. There is a range of solvation preference, from a marked preference for water for the upper complexes in Figure 2 to a significant preference for methanol for the bottom two complexes. Preferential hydration of the top six complexes and preferential solvation by methanol for JM 216 is reflected in the curvature of the plots. Addition of small amounts of water leads to a marked increase in overall solvation (decrease in chemical potential) for the former, very little change for the latter. The bis-isopropylamine-cyclobutanedicarboxylate complex shows synergic solvation, with a solubility maximum (Figure 2 inset) and transfer chemical potential minimum, corresponding to

Table 2. Solubilities (expressed as parts per million, p.p.m., of platinum in saturated solution) in methanol–water mixtures and derived transfer chemical potentials (from water) at 298.2 K

Vol % MeOH	0	20	40	60	80	100
Carboplatin						
p.p.m. Pt	9300	7900	6050	4550	2225	475
$\delta_m\mu^\circ$/kJ mol^{-1}		+0.4	+1.1	+1.8	+3.6	+7.4
Cisplatin[a]						
p.p.m. Pt	1263	782	568	417	173	69
$\delta_m\mu^\circ$/kJ mol^{-1}		+1.2	+2.0	+2.8	+4.9	+7.2
Iproplatin						
p.p.m. Pt	12060			8600	8200	6740
$\delta_m\mu^\circ$/kJ mol^{-1}				+0.8	+1.0	+1.5
JM216						
p.p.m. Pt	163	207	367	770	1360	1610
$\delta_m\mu^\circ$/kJ mol^{-1}		−0.6	−2.0	−3.9	−5.3	−5.7
[Pt(mal)(en)]						
p.p.m. Pt	4470	3260	2150	1080	340	57
$\delta_m\mu^\circ$/kJ mol^{-1}		+0.8	+1.8	+3.5	+6.4	+11.0
[Pt(mal)(NH$_3$)$_2$]						
p.p.m. Pt	133	92	57	31	10.2	1.6
$\delta_m\mu^\circ$/kJ mol^{-1}		+0.9	+2.1	+3.6	+6.4	+11.0
[Pt(etmal)(NH$_3$)$_2$]						
p.p.m. Pt	14880	12540	11500	9350	4810	1160
$\delta_m\mu^\circ$/kJ mol^{-1}		+0.4	+0.6	+1.2	+2.8	+6.3
[Pt(cbdc)(iPrNH$_2$)$_2$]						
p.p.m. Pt	390	590	990	1820	2570	1820
$\delta_m\mu^\circ$/kJ mol^{-1}		−1.0	−2.3	−3.8	−4.7	−3.8

[a]0.10 mol dm^{-3} sodium chloride present in all solvent media.

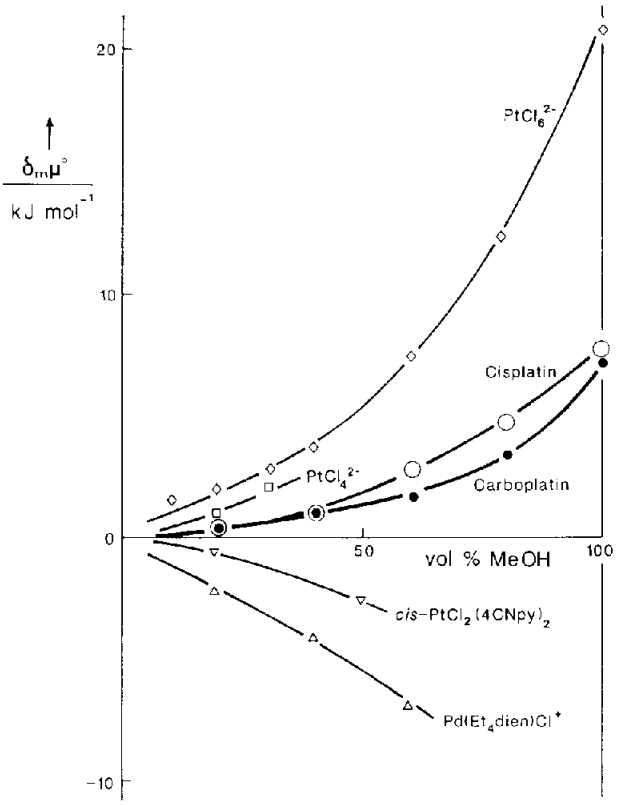
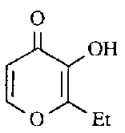


Figure 1. Transfer chemical potentials for selected platinum and palladium complexes to methanol–water mixtures (at 298.2 K).

better solvation in methanol-rich mixtures than in methanol or water separately. Presumably such synergic solvation arises from hydration at hydrophilic patches on the complex reinforced by solvation by methanol elsewhere on its periphery.



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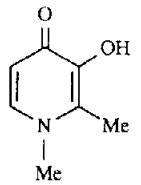

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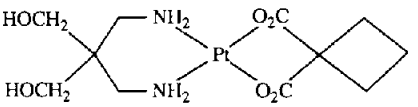
The transfer chemical potential trend for JM 216 is compared with those for a number of organic compounds and inorganic complexes of pharmacological relevance in Figure 3. These include the typical sulfa drug sulfathiazole (Shkadova 1969), the pyrone ethylmaltol (**5**) and its iron(III) complex (Alshehri *et al.* 1994), the pyridinone L1 (**6**) and its aluminum(III) complex (Burgess & Patel 1990), and the tris-8-hydroxyquinolinate complex of indium, [In(oxine)$_3$] (Burgess *et al.* 1994). This last complex provides a lipophilic reference—its hydrophobicity minimizes washout but precludes oral administration. On the other hand, pyrones and pyridinones can be administered orally; they are of considerable interest in that they may prove of value in reducing body levels of iron and of aluminum. Their complexes may, conversely, prove useful for the oral introduction of isotopes such as ^{90}Y or ^{67}Ga, or of gadolinium, for radiotherapeutic or diagnostic purposes. Most of the species included in Figure 3, and indeed a number of other organic and inorganic pharmaceuticals, show modest minima in transfer chemical potential plots such as those apparent in Figure 3, implying usefully balanced hydrophilic and lipophilic properties. It seems that cisplatin, carboplatin and iproplatin do not show such potentially advantageous solvation characteristics, but rather show solubility behavior approximating to the linear dependence of log(solubility) on volume % organic cosolvent often used as a rule-of-thumb guide for estimating solubilities of lipophilic organic drugs (Hardaway & Yalkowsky 1991). Interestingly, the CBDC (cyclobutane-1,1-dicarboxylate) ligand of carboplatin is markedly hydrophilic, with a transfer chemical potential curve (Burgess & Drasdo 1993) rather close to that shown in Figure 1 for $[PtCl_6]^{2-}$. It may be that third generation platinum anticancer drugs containing rather more lipophilic ligands may prove to have better membrane-crossing properties and thus prove more effective. The recently developed Zeniplatin (**7**) and Enloplatin (**8**), and the recently reported analog (**9**) (Morikawa *et al.* 1991), all contain the hydrophilic CBDC ligand, but in each case the second bidentate ligand is predominantly lipophilic. These compounds probably have solvation characteristics similar to JM216, with hydrophilic/lipophilic balances (HLB) (Griffin 1954, Hansch and Leo 1979, Rekker and Mannhold 1992) similar to the pyrone and pyridinone ligands and complexes shown in Figure 3.



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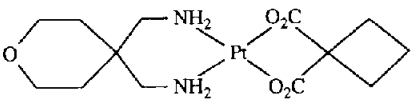

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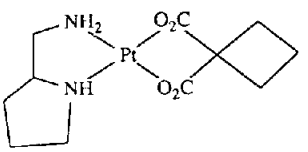

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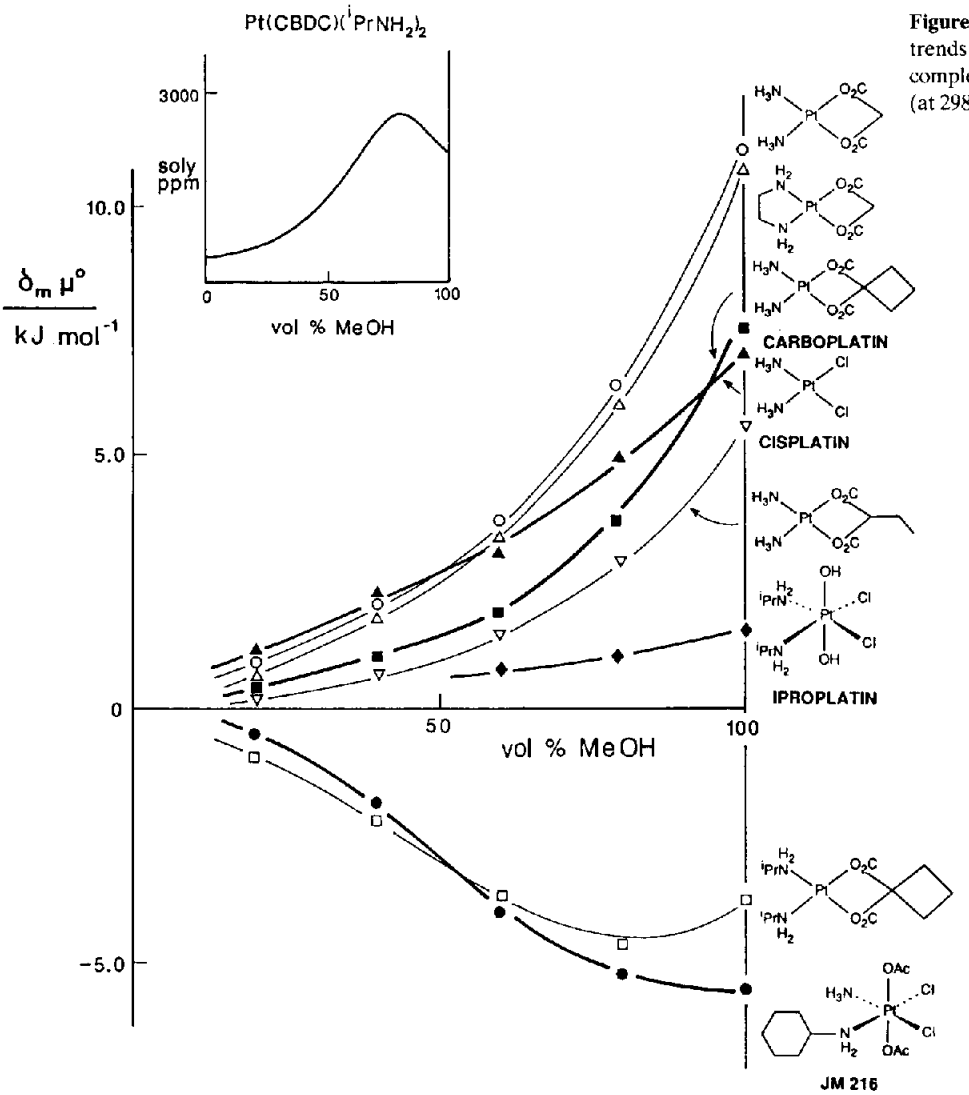

Figure 2. Transfer chemical potential trends for platinum drugs and related complexes to methanol–water mixtures (at 298.2 K).

Acknowledgments

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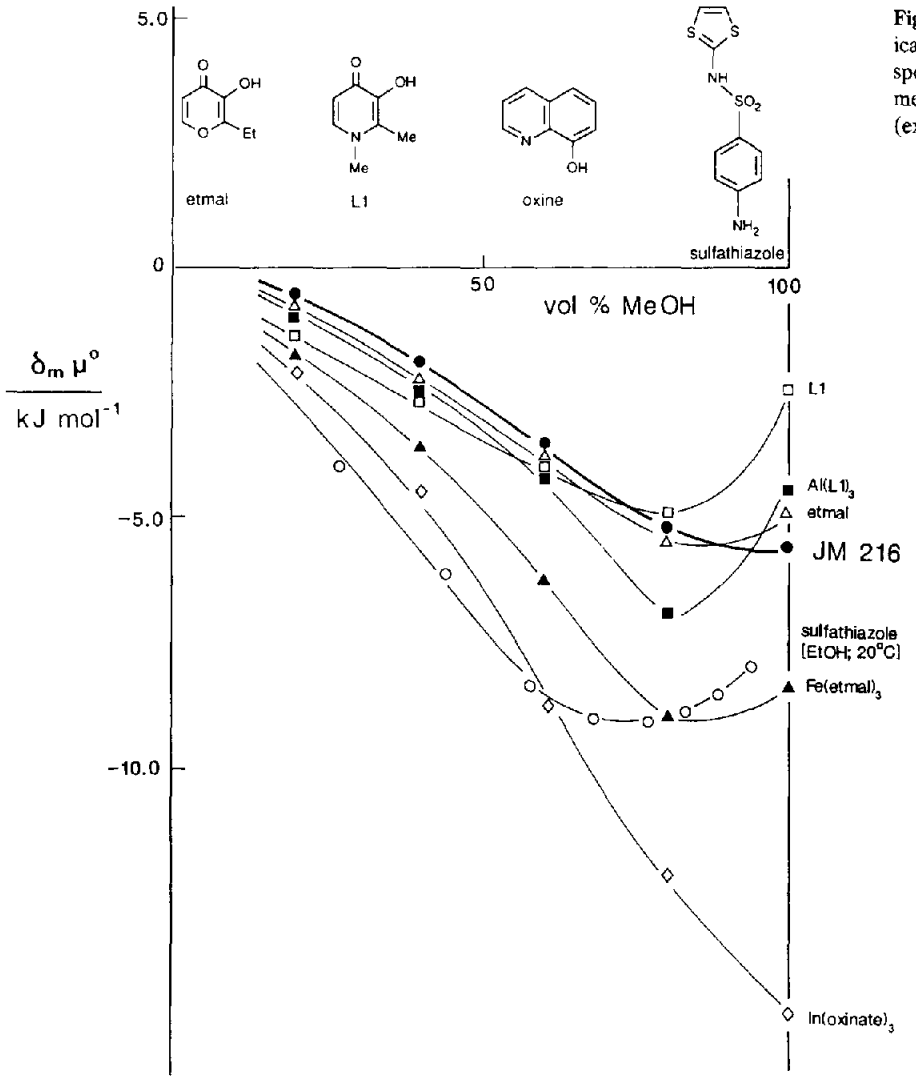

Figure 3. Comparison of transfer chemical potential trends for JM216 with other species of pharmaceutical interest; to methanol–water mixtures at 298.2 K (except sulfathiazole).

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