Calculation of the Hydrophobicity of Platinum Drugs

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Models of the hydrophobicity of platinum drugs based on exposed surface areas of polar and nonpolar atoms are presented. For a total of 24 log P_{oct} data, the best model resulted in a standard deviation of 0.35 over a range of more than 4 log units, with regression coefficients in broad agreement with previous models of log P_{oct} for organic molecules. This model is used to compare log P_{oct} to cell uptake for five platinum drugs and hence to establish an exponential relation between these parameters.

Introduction

Platinum drugs are now established as effective antitumor agents,[1] the archetypal example of these being cisplatin, *cis*-[$PtCl_2(NH_3)_2$]. Many such platinum(II) complexes have been synthesized and tested as potential drugs, including many direct analogues of the general form *cis*-[PtX_2A_2][2] and more recently platinum(IV) compounds.[3,4] A major motivation behind such syntheses has been the desire to overcome inherent and acquired resistance to cisplatin.[5,6] A major component of resistance to cisplatin is reduced cellular uptake, and it has been shown that increasing lipophilicity, and hence passive diffusion, can overcome the reduced uptake.[5] It has also been shown that increasing lipophilicity can correlate with increased activity.[5]

Hydrophobicity, as measured by relative solubilities in water and chloroform[7−9] or partition between these solvents,[7] has been investigated as a factor relevant to anticancer activity for many years. A systematic study of the hydrophobicity, taken as the octanol−water partition coefficient (log P_{oct}), of such compounds was carried out by Souchard et al.,[10] who reported values for 16 *cis*-[PtX_2A_2] compounds, where A is an ammine, amine, or pyridine group, and X is either Cl^- or NO_3^-. The authors demonstrated that when X is unchanged, the hydrophobicity of a platinum complex is linearly related to that of the amine but also that this relation does not hold for complexes with different X groups and cannot therefore be used as a generally predictive method. More recently, the hydrophobicity of platinum(IV) complexes has also been measured using octanol−water partition.[11,12] Screnci et al.[12] reported partition coefficients of 8 platinum-containing drugs, including 4 platinum(IV) complexes, including a duplicate measurement of cisplatin itself. They went on to show that log P_{oct} has a close inverse correlation with the accumulation of platinum in peripheral nerve tissue of rats. Both studies used the standard 'shake-flask' method of measuring log P_{oct}, determining the platinum concentrations in the organic and aqueous phases.

Clearly, the hydrophobicity of platinum drugs is of substantial current interest, and a general method for its prediction would be a highly useful tool in the rational design of new drugs. We have therefore attempted to correlate the 24 log P_{oct} values from refs 10 and 12 (Table S1) with measures of the surface area of the drugs. Polar surface area (PSA) is an increasingly popular tool in the prediction of biological transport of organic molecules[13] − we now attempt to extend this methodology to the sphere of platinum-containing drugs. The main requirement for this is an accurate molecular geometry. X-ray crystallography and molecular mechanics could be used, but for generality and accuracy we chose to use ab initio molecular orbital methods, since these are applicable to any system and have been shown to reproduce important features of cisplatin.[14]

Methods

The geometries of the 23 platinum drugs (see Supporting Information) with log P_{oct} values (refs 6 and 7 both report values for cisplatin) were fully optimized without symmetry constraints at the HF/LANL1MB level[15] using Gaussian98.[16] For several of the smaller molecules (**1**, **2**, **6**, **7**, and **14**) these structures were confirmed as minima via harmonic frequency calculations. Using these ab initio optimized geometries, the surface area of each atom was calculated using the MOLVOL program of Dodd and Theodorou.[17] This treats the molecule as a set of overlapping spheres of van der Waals radii and evaluates the fraction of each sphere exposed and therefore able to interact with its environment. The PSA is defined[13] as the exposed surface area of O, N, OH, and NH atoms: the total surface area (TSA) and exposed surface areas of Pt and Cl (zero for non-chloro species) atoms were also used in regression against log P_{oct}.

Statistical analysis consisted of single and multiple linear regression of the calculated surface area parameters against literature log P_{oct} values. Student's *t*-test of significance was employed throughout − a probability $p < 0.05$ being taken as significant. Overall measures of the fit are R^2, the square of the correlation coefficient; SD, the standard deviation of fit; and R^2_{CV}, the cross-validated or leave-one-out R^2 value. All statistical analysis employed the JMP package.[18]

Results and Discussion

Initially regressions of log P_{oct} against the TSA and PSA, as well as the exposed areas of platinum and chlorine atoms, indicated that no one parameter results in acceptable accuracy ($R^2 < 0.3$), the best being either volume or TSA. It is no surprise that these single-

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Table 1. Statistics of Multiple Linear Regressions Against log P_{oct}

model[a]	R^2	R^2_{CV}	SD
TSA + PSA	0.839	0.784	0.426
volume + PSA	0.826	0.770	0.442
TSA + PSA + ClSA	0.898	0.840	0.346
TSA + PSA + PtSA	0.894	0.834	0.354

[a] TSA denotes total surface area; PSA is polar surface area as defined in ref 9; PtSA is exposed surface area of platinum; ClSA is exposed surface area of chlorine atom(s).

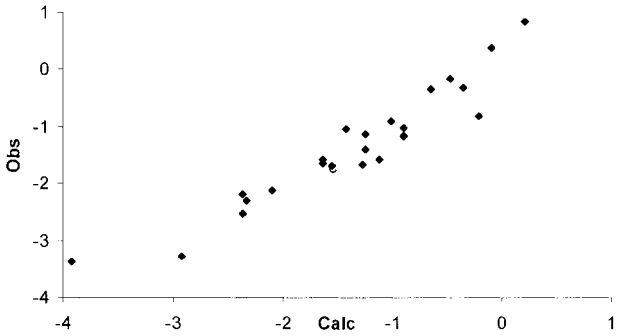


Figure 1. Observed vs calculated log P_{oct} from eq 1.

parameter models are poor, since partition processes are known to depend on size, polarity, and hydrogen-bonding capacity.[19] We therefore carried out multiple linear regression of the 24 log P_{oct} values against combinations of surface area measures, the best of which are reported in Table 1. Combining the TSA and PSA yields encouraging statistics, with $R^2 = 0.84$ and SD = 0.43 (the largest experimental error reported was 0.24 log unit). Replacing TSA with volume in this two-parameter regression yields similar statistics: we use the marginally more accurate TSA in all that follows.

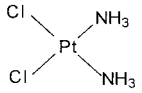
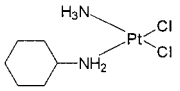
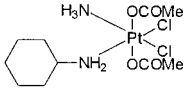
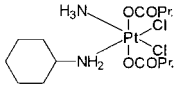
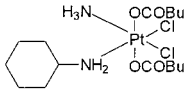
Including a term accounting for the exposed surface area of chlorine atoms further improves the fit: this three-parameter model yields $R^2 = 0.90$ and SD = 0.35, with all three parameters >99% significant. Thus, the standard deviation of fit is only 50% greater than the largest experimental error, while the maximum residual is 0.62 (compound **15** in Supporting Information). A plot of observed vs calculated log P_{oct} using this model is presented in Figure 1. We note that a slightly less accurate fit is obtained when the platinum surface area replaces that of the chlorines. Further log P_{oct} values are required to distinguish these models; for now we concentrate on the former since it is slightly more accurate.

The best model of log P_{oct} is shown below as eq 1, with regression standard errors in parentheses:

$$\log P_{oct} = \underset{(0.395)}{-1.697} + \underset{(0.00081)}{0.00917}(\text{TSA}) - \underset{(0.00248)}{0.02181}(\text{PSA}) - \underset{(0.00259)}{0.00887}(\text{ClSA}) \quad (1)$$

The signs of the coefficients are in line with previous models of log P_{oct},[19] in that size increases and polarity and/or hydrogen bonding reduces log P_{oct}. This model of the hydrophobicity of platinum drugs is therefore physically realistic as well as being statistically valid. It is also encouraging to note the structural variety of compounds used to construct eq 1, including both

Table 2. Observed and Calculated Platinum Content

	log P_{oct} (eq 1)	Observed [Pt] (mmol/mg protein)	Calc [Pt] (eq 2)	Calc [Pt] (eq 3)
	-2.36	1.0	0.96	0.64
	-0.87	1.9	1.78	2.83
	-0.47	3.5	4.01	4.22
	0.47	13.5	12.60	10.81
	0.86	17.0	17.54	15.97

platinum(II) and platinum(IV) compounds, chloro, nitrate, and acetate leaving groups, and a variety of amine and pyridine ligands. This contrasts with the model of log *P* developed by Souchard et al.,[10] which was applicable only to a specific X group in compounds of the type *cis*-[PtX_2A_2].

Souchard et al.[10] considered *cis*-[$Pt(NO_3)_2A_2$] complexes to exist as *cis*-[$Pt(OH_2)_2A_2]^{2+}$ $2(NO_3^-)$ in aqueous solution, although it is unclear whether this is still the case in the (wet) octanol layer. To avoid complications, we have simply used the discrete nitrate complexes. Superficially, it seems unlikely that surface areas calculated for these should correlate so well with partition data for species that may exist as water complexes. However, it may be that the ion pair *cis*-[$Pt(OH_2)_2A_2]^{2+}$ $2(NO_3^-)$ has essentially the same surface characteristics as the solvated nitrate complex *cis*-[$Pt(NO_3)_2A_2]\cdot 2H_2O$, such that it matters little which we use. Further work is required to test this hypothesis, but there is no doubt that eq 1 models the log P_{oct} values of the 11 nitrate complexes at least as accurately as the remaining 13.

Loh et al.[5] demonstrated that resistance to cisplatin may be circumvented by the use of more hydrophobic molecules. Analogues of JM216 (compound **23** in Supporting Information) with axial propanoate or pentanoate ligands are preferentially taken up by cancerous ovarian cell lines, although decanoate ligands gave anomalous behavior compared to these. Table 2 reports platinum content in cells for five platinum drugs (taken from Figure 6a in ref 5) and calculated log P_{oct} values from eq 1, and Figure 2 shows a plot of these. Their relationship is clearly nonlinear: both parabolic and exponential relations are statistically valid and are summarized below:

$$\text{Pt content} = 2.66(\log P^2) + 9.14(\log P) + 7.72 \quad (2)$$

$$R^2 = 0.994$$

$$\text{Pt content} = 6.76(e^{0.94 \log P}) \quad (3)$$

$$R^2 = 0.930$$

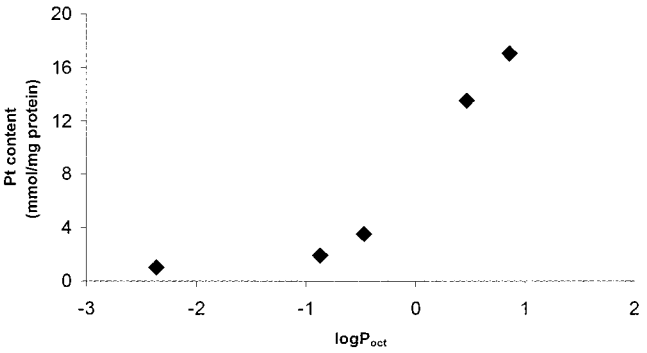


Figure 2. Platinum content of cells vs log P_{oct} for five drugs.

Although eq 2 is statistically better, it is unrealistic as it predicts the platinum content to be a minimum at log $P = -1.72$ and to rise for log P values below this. The exponential fit (eq 3) correctly predicts the platinum content to tail off to zero as log P falls below the value of cisplatin. We believe the very high R^2 for eq 2 is fortuitous in any case and may be a product of 'overfitting', since there are considerable errors associated with both the calculation of log P and the measurement of platinum content. Equation 3 employs one less parameter, is more physically realistic, and is therefore preferred.

Our method for prediction of log P_{oct} is a two-step process, involving initial geometry optimization (we used HF/LANL1MB here, other methods will be explored in future studies) followed by surface area calculations[13] and application of eq 1. For the molecules considered here this is a straightforward process, taking between 0.5 and 10 h per molecule on the hardware used (Compaq ES40 cluster). We believe our method is complementary to experimental determinations of hydrophobicity and related properties, since each has its own advantages. Experimental determination of log P_{oct} is likely to be more accurate than calculation, but synthesis and measurement may be costly and time-consuming. Perhaps most importantly, our method allows predictions for unknown or unavailable compounds, e.g. new lead compounds or metabolites, opening up the possibility of virtual screening of platinum drugs for favorable physicochemical properties or pharmacokinetic profiles.

Conclusions

In summary, we have demonstrated that surface areas of polar and nonpolar atoms, taken from ab initio calculations, accurately model the hydrophobicity of 23 structurally diverse platinum drugs, yielding a physically realistic and statistically valid model. We believe this to be the first general predictive model of log P_{oct} for such compounds. We also show that calculated hydrophobicity is exponentially correlated with the cell uptake of five diverse drugs.

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Supporting Information Available: Table containing data for compounds **1**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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