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Hydrophobicity Parameters for Platinum Complexes

Since the discovery of the antitumor activity of *cis*-$[Pt(NH_3)_2Cl_2]$, many analogues of the type *cis*-$[PtA_2X_2]$ have been synthesized. In vivo the labile ligands, X, are replaced during substitution reactions with nucleophiles such as DNA while the nonleaving groups, A, remain attached to the metal.[1] Structure–activity studies have concluded that charged complexes are inactive because they are not sufficiently hydrophobic.[2] However, hydrophobicities of charged platinum complexes have not been measured.

The partition coefficient (log *P*) is a useful parameter for finding the optimal hydrophobicity of a series of molecules. It is usually calculated from the sum of partition coefficients of the chemical fragments composing the molecule and values permitting such calculations have been tabulated.[3-5] Since partition coefficients for Pt fragments were not available, we wished to determine hydrophobicity parameters for $[>PtCl_2]$ and $[>Pt(H_2O_2)]^{2+}$.

In order to measure hydrophobicity of these groups, we synthesized the molecules in Table I[6] and measured their partition coefficients in an octanol/water emulsion. The nitrato derivatives may undergo hydrolysis in aqueous solution to form aqua complexes such as $\{cis\text{-}[PtA_2(OH)(H_2O)]^{1+}; NO_3^-\}$, $\{cis\text{-}[PtA_2(H_2O)_2]^{2+}; 2NO_3^-\}$, and various dimers and trimers.[7,8] Several pieces of evidence indicate that the nitrato complexes used in our experiments formed uniquely diaqua complexes of the type $\{cis\text{-}[PtA_2(H_2O)_2]^{2+}; 2NO_3^-\}$. Molar conductivities of 10^{-3} to 10^{-4} M aqueous solutions of these compounds were between 230 and 280 (ohm cm^2 mol)$^{-1}$. Onsager plots of the conductivity had identical slopes for these molecules and for the doubly ionized model compounds $\{[Pt(ethylenediamine)(NH_3)_2]^{2+}; 2Cl^-\}$ and $\{[Pt(1,2\text{-diaminocyclohexane})(NH_3)_2]^{2+}; 2Cl^-\}$. After dissolving 3×10^{-2} M compound in water for 2 h at 37 °C, ^{195}Pt NMR spectra[6] contained a single peak corresponding to the monomer diaqua complex.[8]

Table I. Partition Coefficients of the Complexes *cis*-$[PtA_2X_2]$[a]

A	X	log P[b]	optimal dose, μmol/kg	T/C,[c] %
NH_3	Cl	−2.19 ± 0.06	27	200
CH_3NH_2	Cl	−1.68 ± 0.04	76	175
$(CH_3)_2CHNH_2$	Cl	−0.32 ± 0.02	ND	ND
Bu^cNH_2	Cl	0.36 ± 0.04	147	199
Pe^cNH_2	Cl	0.81 ± 0.04	572	172
NH_3	NO_3	−3.36 ± 0.11	3.5	123
CH_3NH_2	NO_3	−3.28 ± 0.08	26	161
Bu^cNH_2	NO_3	−1.71 ± 0.12	43	177
Pe^cNH_2	NO_3	−1.14 ± 0.06	51	193
Hx^cNH_2	NO_3	−0.91 ± 0.14	97	173
Hp^cNH_2	NO_3	−0.35 ± 0.05	92	133
4-$HOCH_2$Py	NO_3	−2.13 ± 0.06	ND	ND
4-CH_3COOPy	NO_3	−1.41 ± 0.13	ND	ND
Py	NO_3	−1.59 ± 0.12	105	125
4-$(CH_3)_2N$Py	NO_3	−0.83 ± 0.08	495	110
4-ClPy	NO_3	−1.06 ± 0.24	183	130

[a] Abbreviations are as follows: Bu^c, cyclobutylamine; Pe^c, cyclopentylamine; Hx^c, cyclohexylamine; Hp^c, cycloheptylamine; and Py, pyridine. [b] Mean ± range of 6–10 independent experiments. [c] Antitumor activity was measured against P388 murine leukemia.[13] Female DBA/2 mice were injected with 10^6 cells on day 0 and treated on day 1 with platinum compounds freshly dissolved in 0.4% Klucel. T/C is the median survival time of treated mice with respect to untreated controls.

Solutions of nitrato complexes were freshly prepared in triply distilled water and chloro compounds in 0.15 M NaCl. In some experiments complexes were dissolved in octanol. Equal volumes of the two phases were shaken at 300 agitations/min at 37 °C. At various times the two phases were separated, aliquots removed, and platinum concentrations determined in the octanol and the water phase with use of a Perkin-Elmer atomic absorption spectrometer Model 603 equipped with a graphite furnace.[9] Results are reported as log *P* where *P* is the concentration of platinum compound in the octanol phase divided by the aqueous phase.

After 3 min the chloro compounds reached an equilibrium between octanol and water. log *P* was independent of concentration and of the phase in which the compound was initially dissolved.

For the nitrato complexes, Pt passed from the aqueous to the organic phase during the first hour of agitation. In the extreme case, $\{cis\text{-}[Pt(Hp^c)_2(H_2O)_2]^{2+}; 2NO_3^-\}$, log *P* varied from −0.38 ± 0.05 to −0.008 ± 0.006. The kinetics were identical whether the emulsion was continuously agitated or not. Hence this phenomena appears to be independent of the partition between the two phases which occurs rapidly. log *P* did not change if complexes were kept in aqueous solution for 2 h at 37 °C prior to mea-

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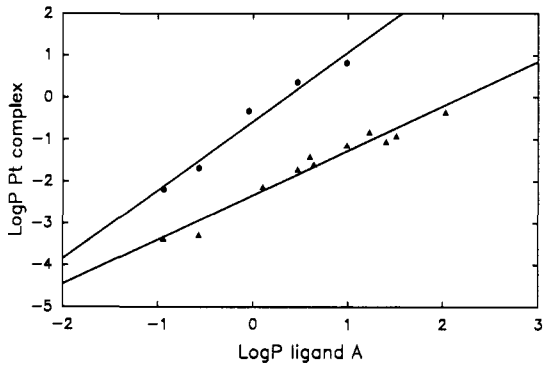

Figure 1. Experimental partition coefficients of *cis*-$[PtA_2X_2]$, X = Cl (●) and X = NO_3 (▲), as a function of the partition coefficient of the nonleaving group A. Partition coefficients of isopropylamine and the cyclic amines were calculated according to Rekker,[10] and the values for methylamine and the pyridine derivatives were observed experimentally.[11]

surement of partition. Therefore these time-dependent changes may involve a chemical reaction such as solvolysis in octanol which would raise the total platinum concentration in the organic solvent. In order to eliminate this effect, we extrapolated the initial concentration in each phase and used these values to calculate partition coefficients.

The values for the nitrato compounds in Table I are the initial partition coefficients which were extrapolated from the linear part of the curves for log P vs time. Results did not vary with concentration from 2×10^{-5} to 5×10^{-4} M.

log P of *cis*-$[PtA_2X_2]$ was plotted as a function of the partition coefficient of a single uncomplexed ligand, A, (Figure 1). The equations for X = Cl, $\log P_{\text{Pt complex}} = 1.64$ (±0.14) $\log P_{\text{ligand A}} - 0.60$ (±0.10) $n = 5$, $r = 0.989$, $s = 0.191$, and for X = H_2O, $\log P_{\text{Pt complex}} = 1.06$ (±0.07) $\log P_{\text{ligand A}} - 2.34$ (±0.08) $n = 11$, $r = 0.979$, $s = 0.197$, permit the calculation of log P for new Pt complexes *cis*-$[PtA_2X_2]$ from the partition coefficients of the ligand A. The intercepts theoretically represent the log P values for the $[>PtCl_2]$ and $[>Pt(H_2O)_2]^{2+}$ moieties.

The partition coefficients of the dichloro compounds were 1 or 2 orders of magnitude greater than the corresponding charged diaqua complexes. For a given leaving group, X, the partition coefficient of the complex increased with the hydophobicity of the nonleaving group, A. Many charged compounds (*cis*-$[PtA_2(H_2O)_2]^{2+}$; $2NO_3^-$, A = Bu^cNH_2, Pe^cNH_2, Hx^cNH_2, Hp^cNH_2, and the pyridine derivatives) were more lipophilic than the neutral parent compound *cis*-$[Pt(NH_3)_2Cl_2]$.

Surprisingly, the slopes of the curves in Figure 1 are less than 2 which is predicted from the additivity of log P[3-5,9] for the two A ligands. These results indicate that the log P values of the free ligand do not equal their contribution to the hydrophobicity of the platinum complex; the electron-withdrawing properties of transition metals might be expected to modify the lipophilicity of the nonleaving group, A. In addition the slope for the dichloro and diaqua compounds are significantly different which demonstrates a potential influence of the labile ligand, X, on the fragment hydrophobicity of the nonleaving group.

We propose that log P values for dichloro and diaqua platinum complexes of the type *cis*-$[PtA_2X_2]$ and *cis*-$[PtA_2(H_2O)_2]^{2+}$ may be estimated from the partition coefficient of the free nonleaving group, A, by using Figure 1. Accurate determination of the hydrophobic fragment constants of organic compounds complexed to platinum will require further work.

It is worth noting that several charged compounds which were more lipophilic than uncharged *cis*-$[Pt(NH_3)_2Cl_2]$, for example *cis*-$[PtA_2(H_2O)_2]^{2+}$ (A = Bu^cNH_2, Pe^cNH_2, Hx^cNH_2, Hp^cNH_2) showed antitumor activity against P388 leukemia (Table I). The increased lipophilicity due to the presence of the cyclic amine ligand may facilitate transport across the cellular membrane. On the other hand, pyridine derivatives with comparable hydrophobicity were not antitumoral (Table I), indicating that reactivity or steric parameters also play a role in the antitumor activity of these compounds.

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Book Reviews

Heterocyclic Compounds. Volume 48. Pyrroles. Part 1. The Synthesis and the Physical Chemical Aspects of the Pyrrole Ring. By D. J. Chadwick, G. P. Bean, A. H. Jackson, M. Artico, H. J. Anderson, C. E. Loader, A. Gossauer, P. Nesvadba, N. Dennis, and M. P. Sammes. R. A. Jones, Editor. Wiley, New York. 1990. xvii + 742 pp. 16 × 24 cm. ISBN 0-471-62753-4. $295.00.

The crucial importance of the pyrrole ring in biological systems has been responsible for its extensive study since the discovery of pyrrole by Runge in 1834. In this the first volume of the series dealing with pyrroles the authors carry on the excellent tradition set by previous volumes. The format, being easily recognized from earlier works, lends itself to the rapid location of information and makes it an essential addition to chemical reference libraries both in industry and academia.

One of the advantages of a modern day treatise of a class of compounds is that it may include information made available relatively recently through the advent of sophisticated techniques of computation and spectroscopy. Thus chapter 1 deals with the physical and theoretical aspects of 1*H*-pyrroles, laying an excellent foundation for the rest of the book.

Much of the early synthetic work in the pyrrole area was directed toward porphyrins and polypyrroles. The scope of these investigations broadened with the discovery of the antibiotic pyrrolonitrin and the search for other pyrroles of therapeutic interest. Chapter 2 systematically examines available routes to 1*H*-pyrroles, classifying them according to the carbon–carbon bonds formed during ring construction.

Chapter 3 is concerned with the reactivity of the 1*H*-pyrrole ring system and after a brief introduction is subdivided according to the transformation involved. Finally in chapter 4 the chemistry of 2*H*- and 3*H*-pyrroles is reviewed according to the same framework as their 1*H*-counterparts but in a single chapter. Liberal use of tables throughout the text helps one to locate data and references for specific compounds. The text is well supported by nearly 3000 references to the original literature through 1988,