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Impact of structural aspects of ruthenium acetates in their interactions with human serum albumin: a comparative analysis

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The trinuclear ruthenium acetates of general formula $[Ru_3O(CH_3COO)_6(L)_3]^{n+}$ had their *in vitro* activity against murine melanoma (B16F10 strain), lung cancer (A549 strain) and the Chagas disease parasite (*T. cruzi*) in its acute and chronic forms described in [1]. In this scenario, address their interaction with biotargets is necessary, being Human Serum Albumin (HSA) one of the most useful and accessible model. Table 1 depicts the results of interaction with HSA, obtained from spectroscopic measurements. In most cases, interaction with HSA is spontaneous and the mechanism is static (probed by the invariance of the $\tau_{1/2}$ excited state lifetime of HSA, where available). For the group of the more hydrophobic complexes (**1-5**), the values of K_b with HSA are higher (10^9) than the values observed for the others (10^3-10^4). ΔG increases with hydrophobicity, being approximately double those observed for the more hydrophilic complexes (**6-10**). Positive values of ΔH and ΔS characterize the compounds containing phenazine ligands, suggesting that the nature of the complex-protein interaction is hydrophobic indeed. The ΔH and ΔS are negative for **9** and **10**, revealing the main contribution of hydrogen bonding [2]. These compounds interacts with HSA in a non-specific way, shown by the unmodified CD spectrum profiles. The exceptions are compounds **1-5**, bearing the intercalator phenazines in their structures. Compounds containing NO constituted an intermediate group, with low binding constants, unaltered CD spectral profile, but with the other properties aligned with those of the hydrophobic derivatives. Preliminary results on clusters containing solvent in their composition point to the only group interacting through the dynamic quenching mechanism. The results obtained so far suggest that more hydrophobic compounds interact more with HSA, indicating that this is a desirable property for increasing the degree of protein-complex interaction.

Table 1. Data obtained for the interaction between HSA and a variety of trinuclear ruthenium acetates

Compound	Binding Constant at 310 K (M^{-1})	Half-life time measurements	Thermodynamic parameters (van't Hoff plots) ΔH (kJ mol^{-1})	ΔS (J mol^{-1} K^{-1})	ΔG at 310 K(kJ mol^{-1})	α-helix (%)
Orthometallated phenazine derivatives $[Ru_3O(CH_3COO)_6(py)_2(L)]PF_6$ (py = pyridine)						
enzo[i]dipyrido[3,2-a:2',3'-c]phenazine **1**	$78.2\ 10^9$	Invariable (static mechanism)	+ 174.6	+ 750.7	- 58.71	3.35[a]
L = dipyrido[3,2-a:2',3'-c]phenazine **2**	$3.80\ 10^9$		+ 132.1	+ 612.2	- 56.85	2.30[a]
-methyldipyrido[3,2-a:2',3'-c]phenazine **3**	$2.96\ 10^9$		+ 75.1	+ 426.5	- 56.21	50.3[a]
chlorodipyrido[3,2-a:2',3'-c]phenazine **4**	$14.5\ 10^9$		+ 116.9	+ 574.4	- 60.30	4.47[a]
L = 1,10-phenanthroline **5**	$9.80\ 10^9$		+ 604.5	+ 2162.2	- 59.29	76.6[a]
Nitrosyl complexes $[Ru_3O(CH_3COO)_6(NO)(L)_2]PF_6$						
L = 3-picoline **6**	$178.4\ 10^3$	Not measured	+ 215	+ 796	- 30.96	-
L = 4-acetylpyridine **7**	$3.20\ 10^3$	Invariable (static mechanism)	+48.10	+238.02	- 27.02	little changes
L = 4-terbutylpyridine **8**	$7.02\ 10^3$		+ 80.81	+ 334.71	-23.95	
Water-soluble complexes $[Ru_3O(CH_3COO)_6(L)_3]Cl$ (L = imidazol derivatives) - *more data in development*						
L = 4-aminopyridine **9**	$2.40\ 10^4$	Invariable (static mechanism)	- 35.7	- 29.8	- 26.4	little changes
Solvato complexes $[Ru_3O(CH_3COO)_6(S)(L)_2]PF_6$ (S = solvent molecule as a ligand) - *more data in development*						
L = 3-picoline **10**	$4.78\ 10^3$	Not measured	- 75.5	- 231	- 3.99	-
L = quinazoline **11**	$1.64\ 10^4$			-		
Binuclear hydrophilic complexes $[Ru_2O(CH_3COO)_2(L)_2(py)_2](PF_6)_2$ (py = pyridine)						
L = 5-methyl-1,10-phenantroline **12**	$11.63\ 10^4$	Invariable (static mechanism)	+ 50.24	+ 278.83	- 32.94	78.11[b]
L = 1,10-phenanthroline **13**	$9.49\ 10^4$		+ 141.95	+ 554.03	- 37.58	78.76[c]

[a] data for [complex] = 2.8 x 10^{-6} M departing from 86.2% of a-helix of pure HSA (1 x 10^{-6} M); [b] data for complex] = 5.72 x 10^{-6} M departing from 80.2% of a-helix of pure HSA (1 x 10^{-6} M); [c] data for [complex] = 6.88 x 10^{-6} M departing from 78.06% of a-helix of pure HSA (1 x 10^{-6} M)

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