



Complexes of Rh(III)(η^5 -Cp*) with N/O-donor bidentate ligands: solution equilibrium and interaction with human serum albumin

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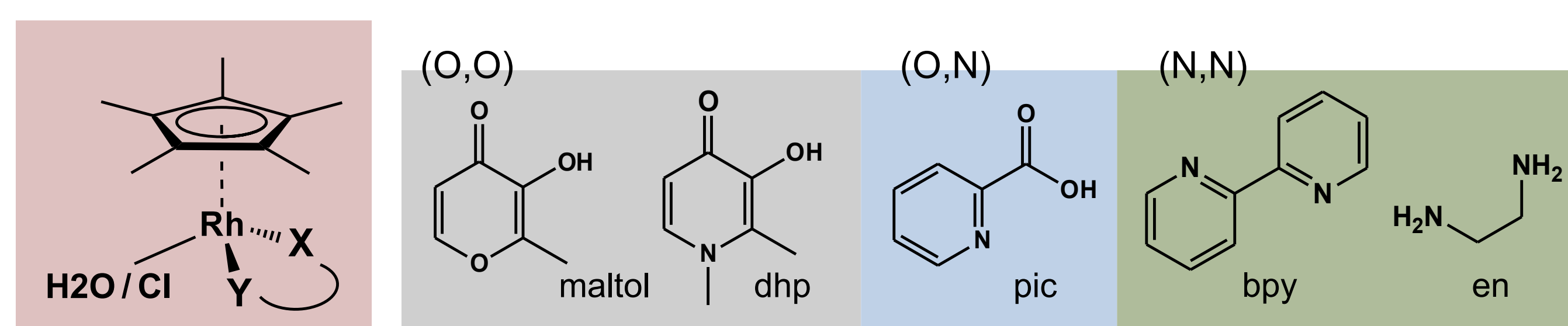
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Introduction

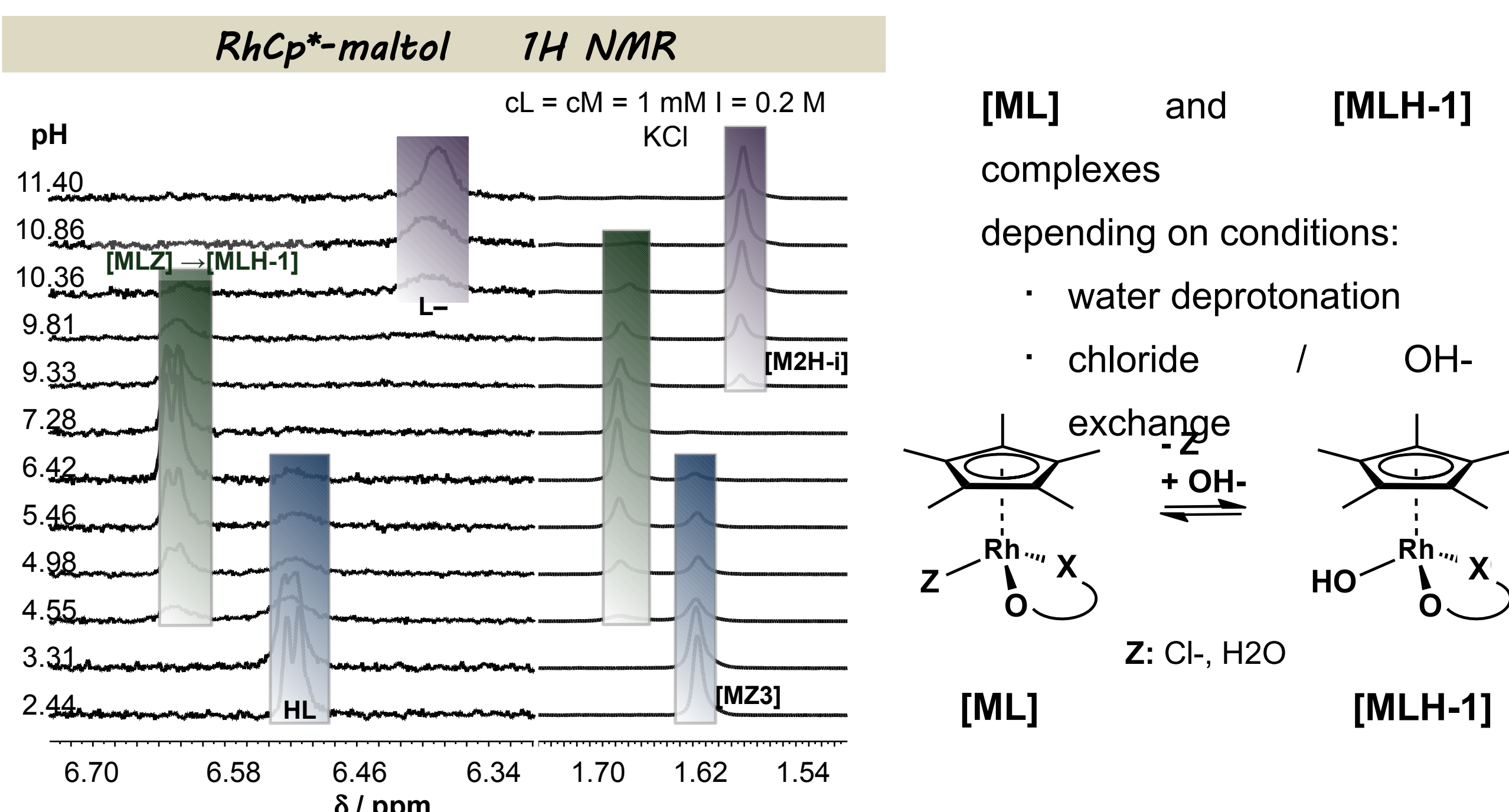
Recently, the interest in metal based anticancer research shows a pronounced shift towards compounds possessing cytotoxic effect different from platinum based compounds. The most promising candidates in this field are Ru(III)-based complexes KP1019 and NAMI-A, which have been investigated in clinical trials with promising results. At the same time there are clear evidences that the active forms contain the reduced metal ion, hence half sandwich Ru(II)-arene complexes are extensively investigated as well. Os(II), Rh(III), Ir(III) complexes are isoelectronic with Ru(II); and introducing of η^6 -arene or η^5 -arenyl ligands in the coordination sphere can increase the ligand exchange rate by several orders of magnitude, which is a prerequisite of efficacy for this type of complexes [1].

Here we report **solution equilibrium studies** on four **[Rh(III)(η^5 -Cp*)] $^{2+}$ complexes** formed with **(O,O)** and **(N,N)** ligands performed using pH-potentiometry, UV-Vis spectrophotometry and ^1H NMR spectroscopy.



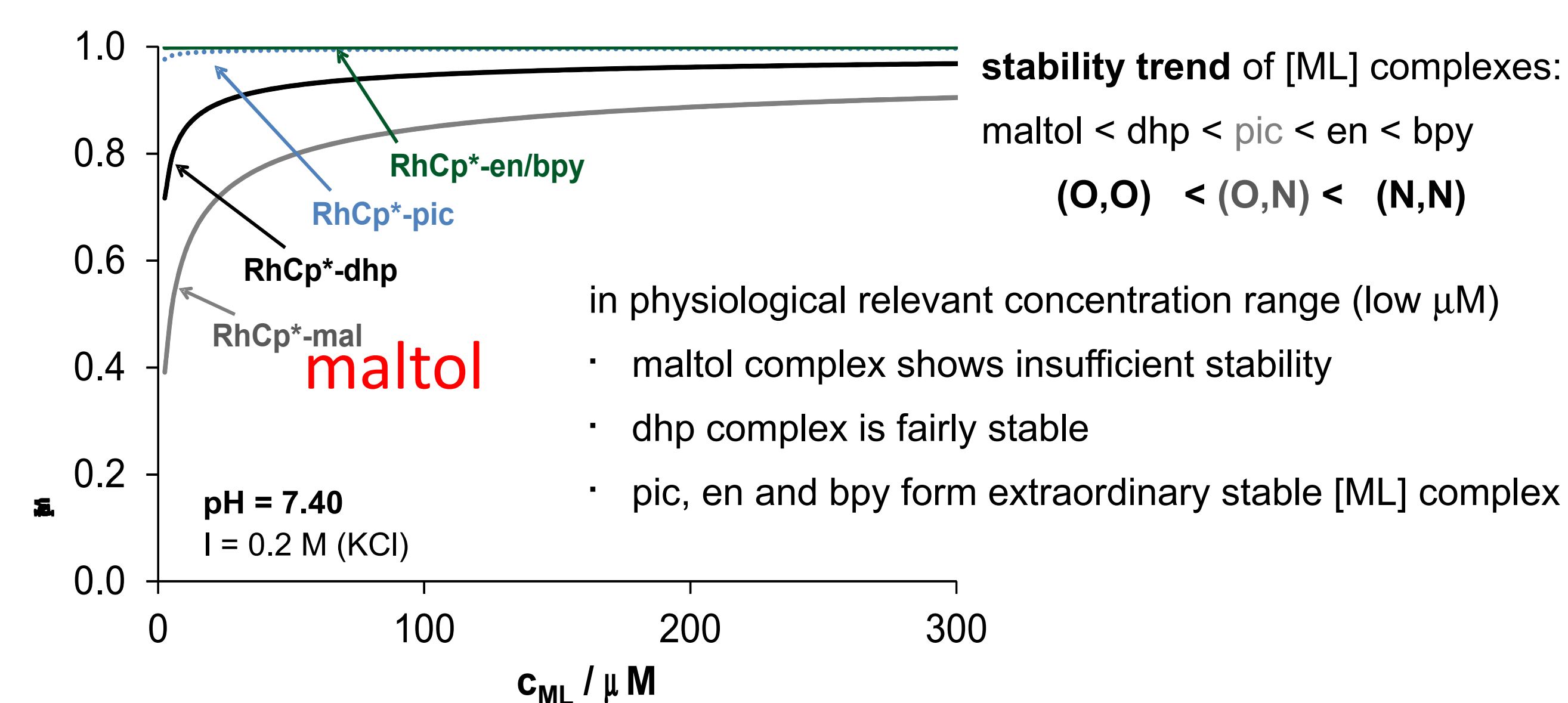
Further interesting question is the **exploration of possible transport mechanisms** in blood serum. The most abundant transporter in blood serum is **albumin** that has an extraordinary capacity to transport a wide variety of compounds. Therefore fluorometry, capillary electrophoresis (CZE), ^1H NMR and ultrafiltration-UV-Vis techniques were used to get a deeper insight into the nature and strength of the interaction of **complexes formed with (O,O) and (N,O) donor ligands** towards human serum albumin (HSA).

Complexes with (O,O) and (N,N) ligands



- reversible complex formation, fast equilibrium with (O,O) donors
- slower complexation with (N,N) donors (depending on pH and Cl- content of the medium)
- Cl- is a competitor ligand and shifts complex formation and hydrolysis to higher pH values

	maltol		dhp		en		bpy	
	KNO ₃	KCl	KNO ₃	KCl	KNO ₃	KCl	KNO ₃	KCl
pK1 (ligand)	8.45(1)	8.45[2]	3.67(1)	3.67[3]	7.20(1)	7.19(1)	4.51(1)	4.52(1)
pK2 (ligand)	-	-	9.66(1)	9.77[3]	10.00(1)	9.98(1)	-	-
log β [ML]	8.45(1)	6.73(1)	10.90(1)	8.93(1)	14.99(5)	14.48(1)	≥ 10.5	≥ 10.5
log β [MLH-1]	-1.06(4)	-3.87(9)	0.23(3)	-2.97(7)	-6.1	3.43(1)	≥ 2.07	≥ 0.46
pK [ML]	9.51	10.6	10.67	11.90	-8.9	11.05	8.43(3)	10.04(3)

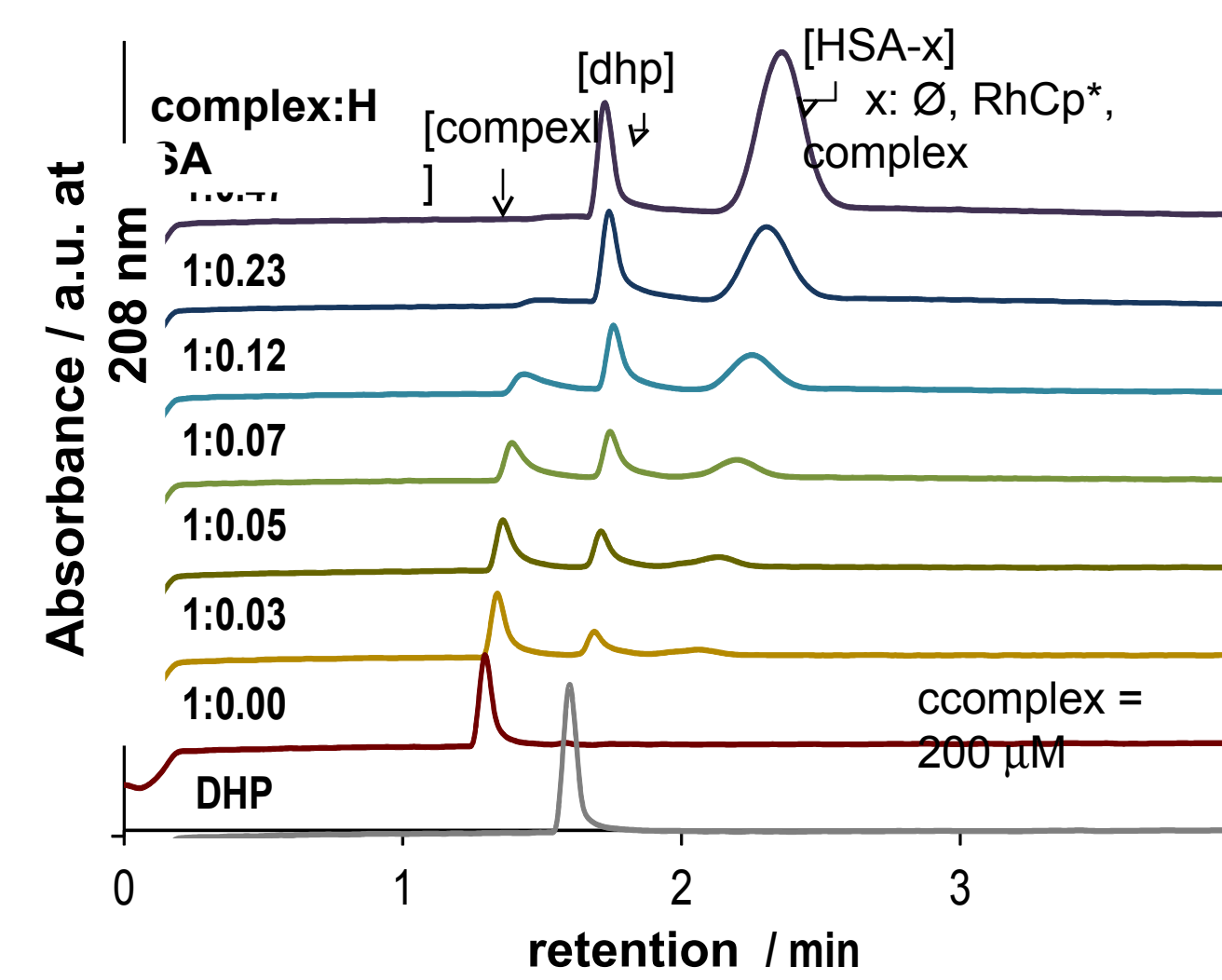


References

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- [2] Enyedy, É.A.; Dömötör, O.; Varga, E.; Kiss, T.; Trondl, R.; Hartinger, C.G.; Keppler B.K., J. Inorg. Biochem. 2012, 117 189–197.
- [3] Enyedy, É.A.; Lakatos, A.; Horváth, L.; Kiss, T., J. Inorg. Biochem. 2008, 102 1473–1485.

Interaction with HSA: global binding

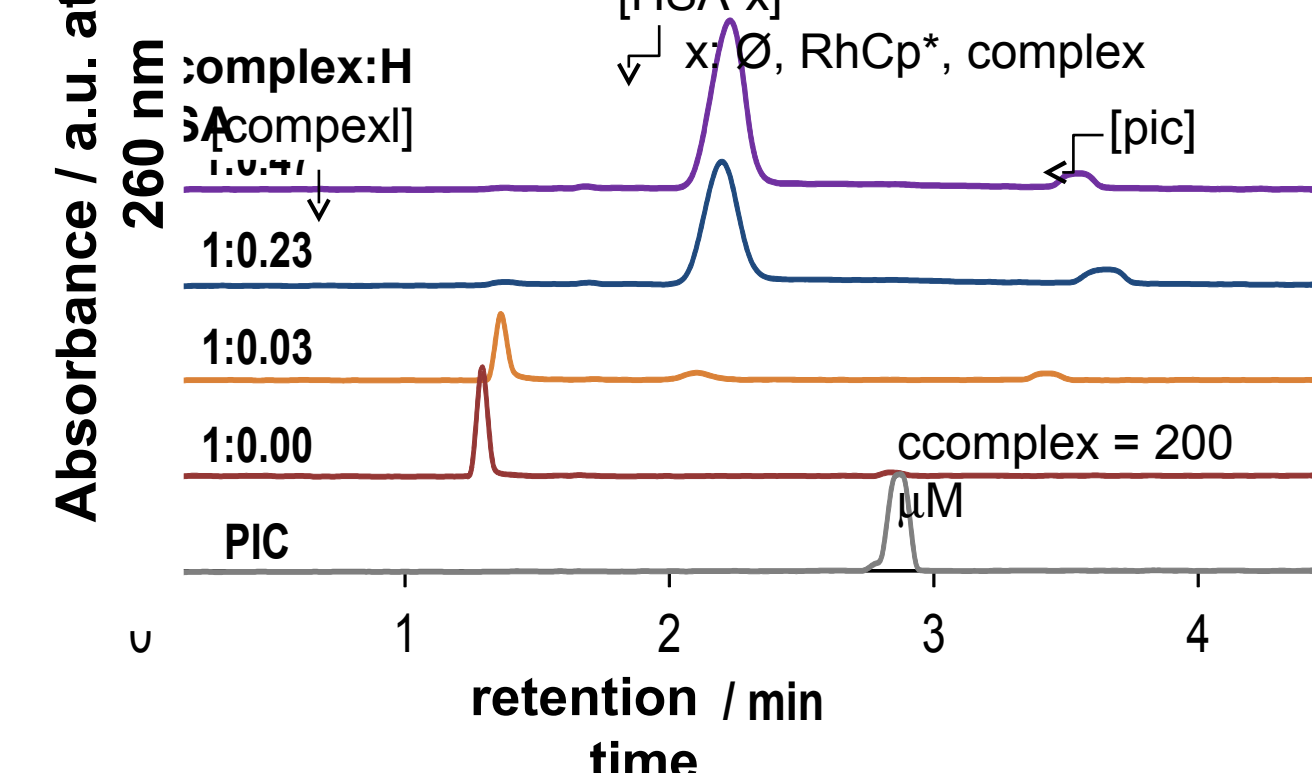
[RhCp**dhp*] electropherograms



capillary zone electrophoresis CZE

- addition of more HSA to the Rh complex causes decreasing free Rh complex concentration in samples and free dhp content increases in parallel
- explicit competition between HSA and dhp for RhCp*

[RhCp**pic*] electropherograms

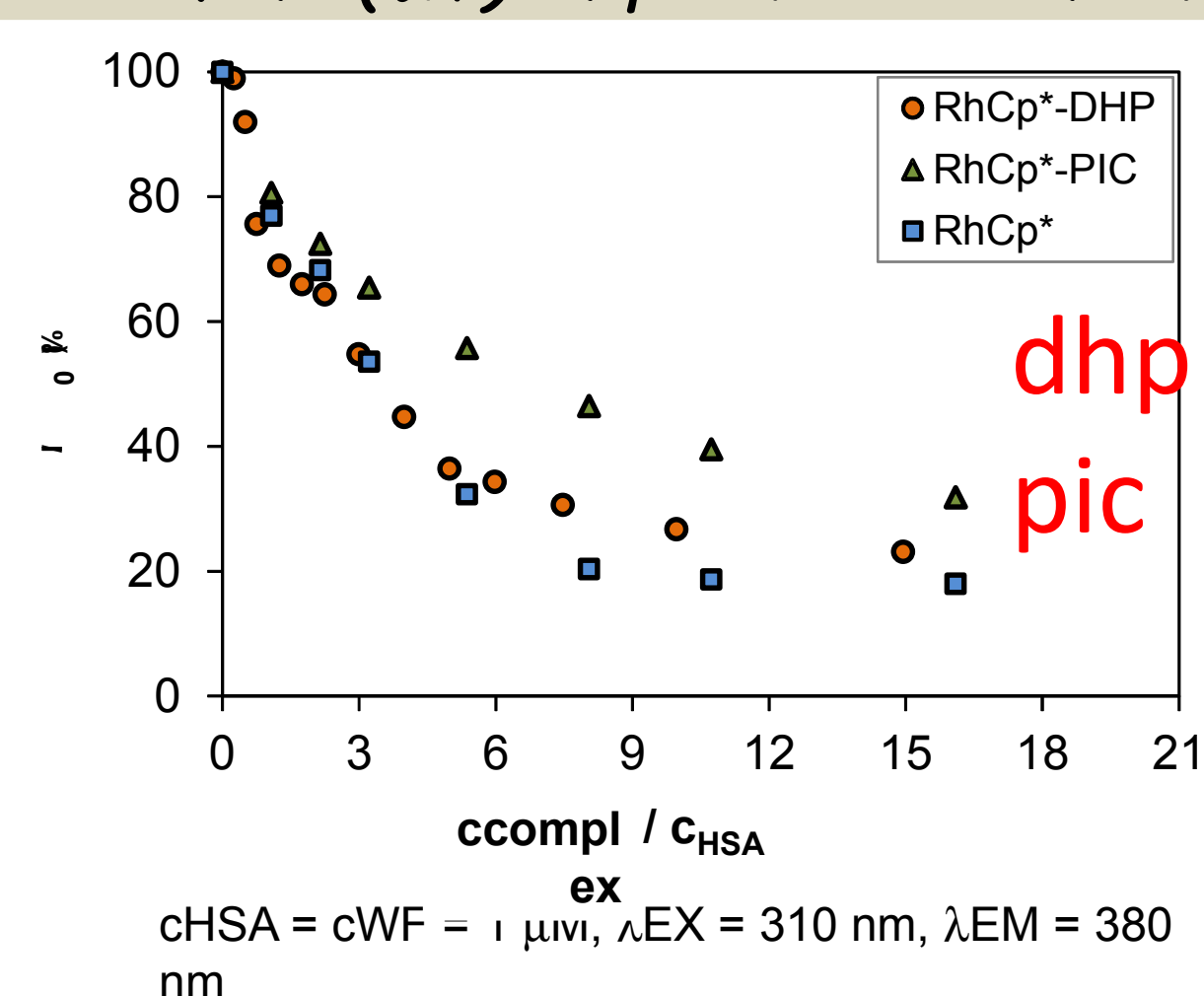


- experiments with pic complex show lesser extent of pic displacement from complex compared to dhp
- free Rh complex concentration decreases in a similar way

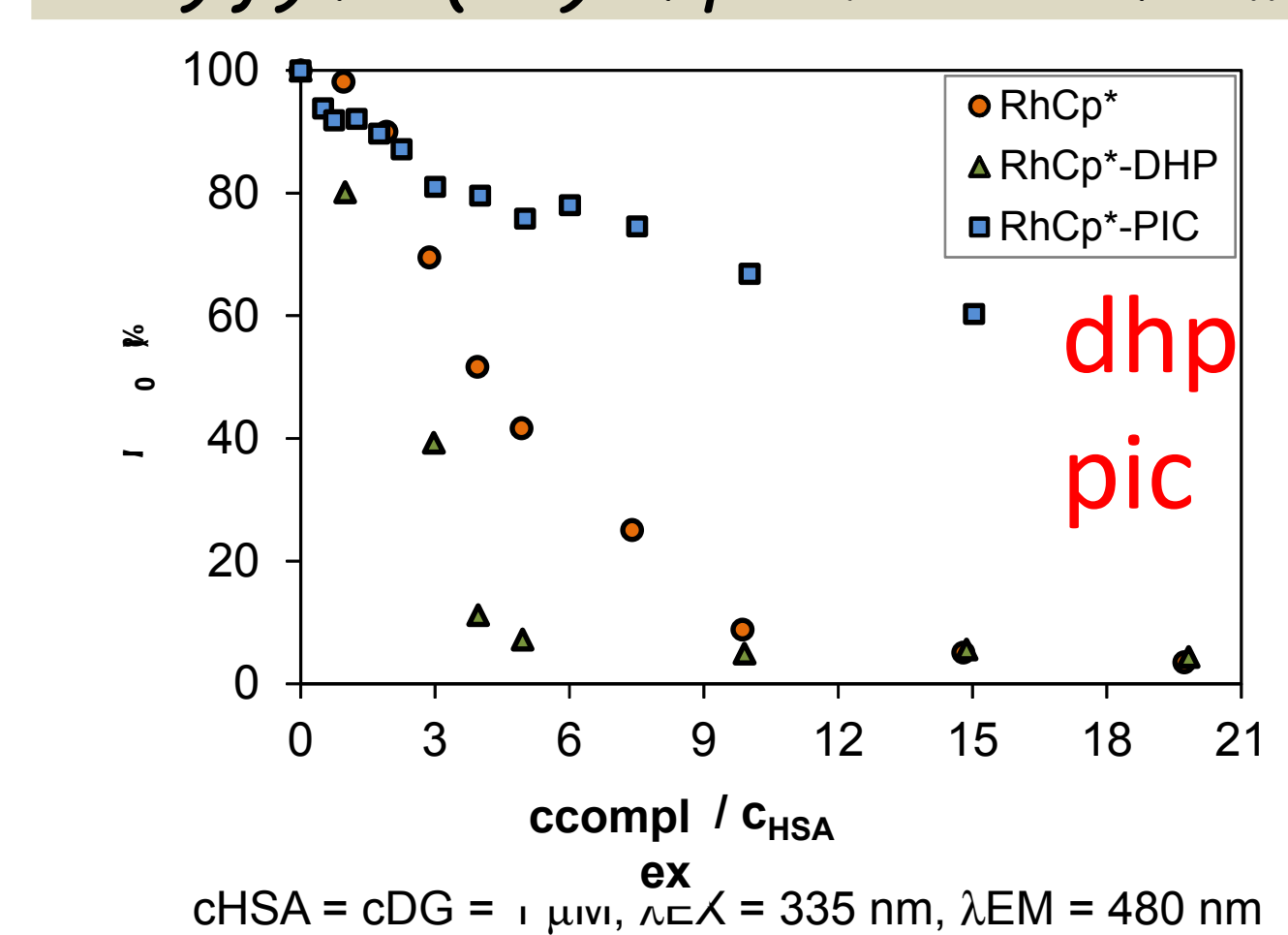
ultrafiltration-UV-Vis and ^1H NMR measurements confirm these tendencies

Interaction on single binding sites

warfarin (WF) displacement: site I



dansylglycine (DG) displacement: site II



site I: Trp emission is quenched practically in the same degree by RhCp* and its dhp complex

pic complex quenches Trp emission in lesser extent

$\log K'_{\text{quenching}}$ = 5.9(1) RhCp* 5.9(1) RhCp*-dhp 5.1(1) RhCp*-pic

WF displacement study confirms this behavior

site II: pic complex can displace DG from its side hardly
RhCp* and dhp complex show similar high affinity here

model compounds: RhCp* and its complexes show no remarkable interaction with the protected **Cys** analog measurements with 1-Me-Im reveal the role of **His** imidazoles on protein surface as possible coordinative monodentate binding sites

Conclusions

- chloride as a non innocent ligand shifts complexation and hydrolysis to higher pH values
- complexes with [ML] and [MLH-1] stoichiometries are formed
- general stability trend for the complexes: (O,O) < (O,N) < (N,N)
- existence of more than one binding sites on HSA
- explicit competition between dhp and HSA for RhCp*; dhp complex shows very similar binding affinity on hydrophobic binding pockets (site I and II)
- dissociation of pic complex is not significant during binding on HSA and has moderate affinity to sites I and II
- His imidazole nitrogens provide possible monodentate binding places on protein surface for RhCp*-complexes

Acknowledgement

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