

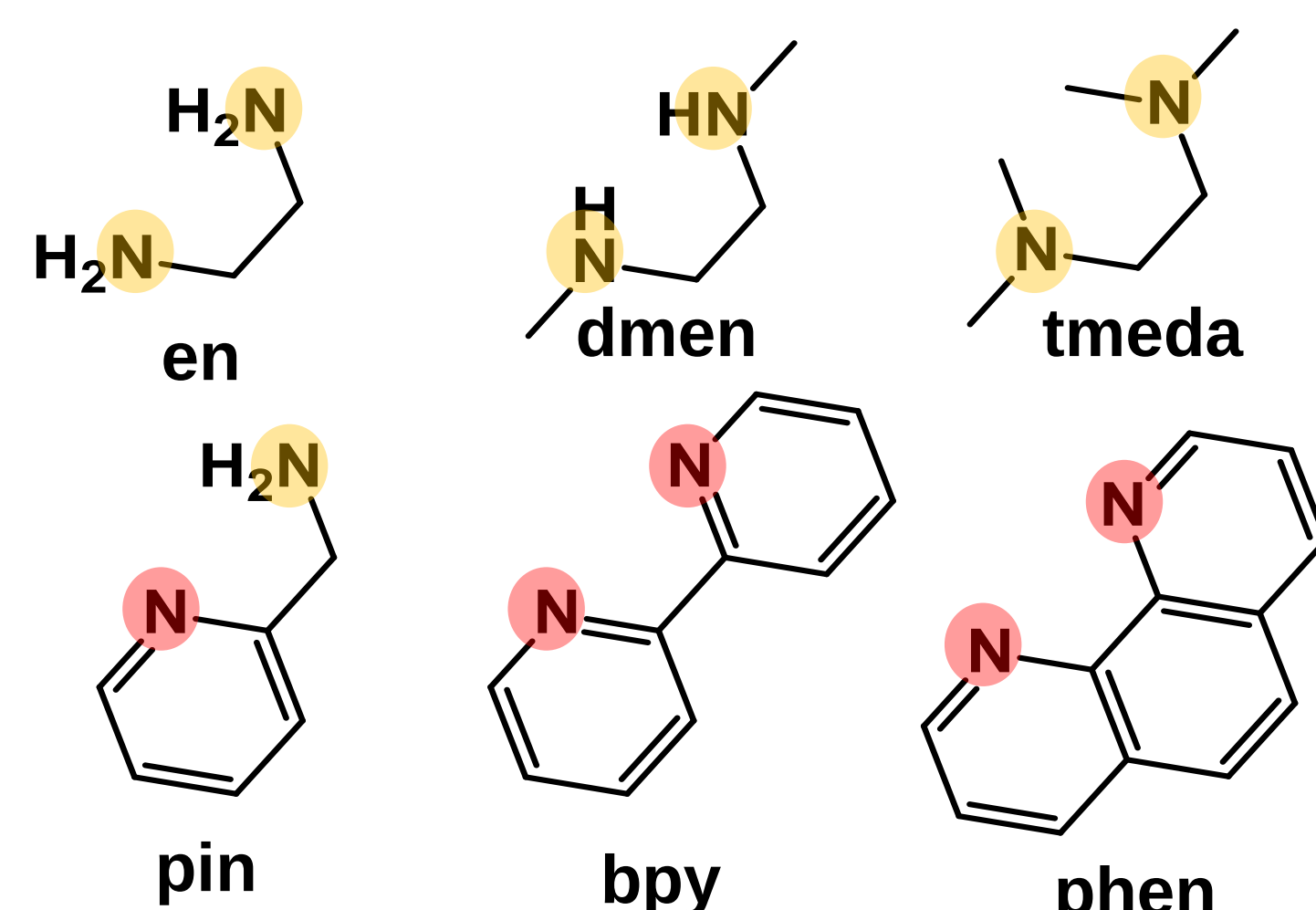
# Solution equilibria and structural characterizations of half-sandwich $\text{Rh}(\eta^5\text{-C}_5\text{Me}_5)$ complexes of (N,N) donor bidentate ligands

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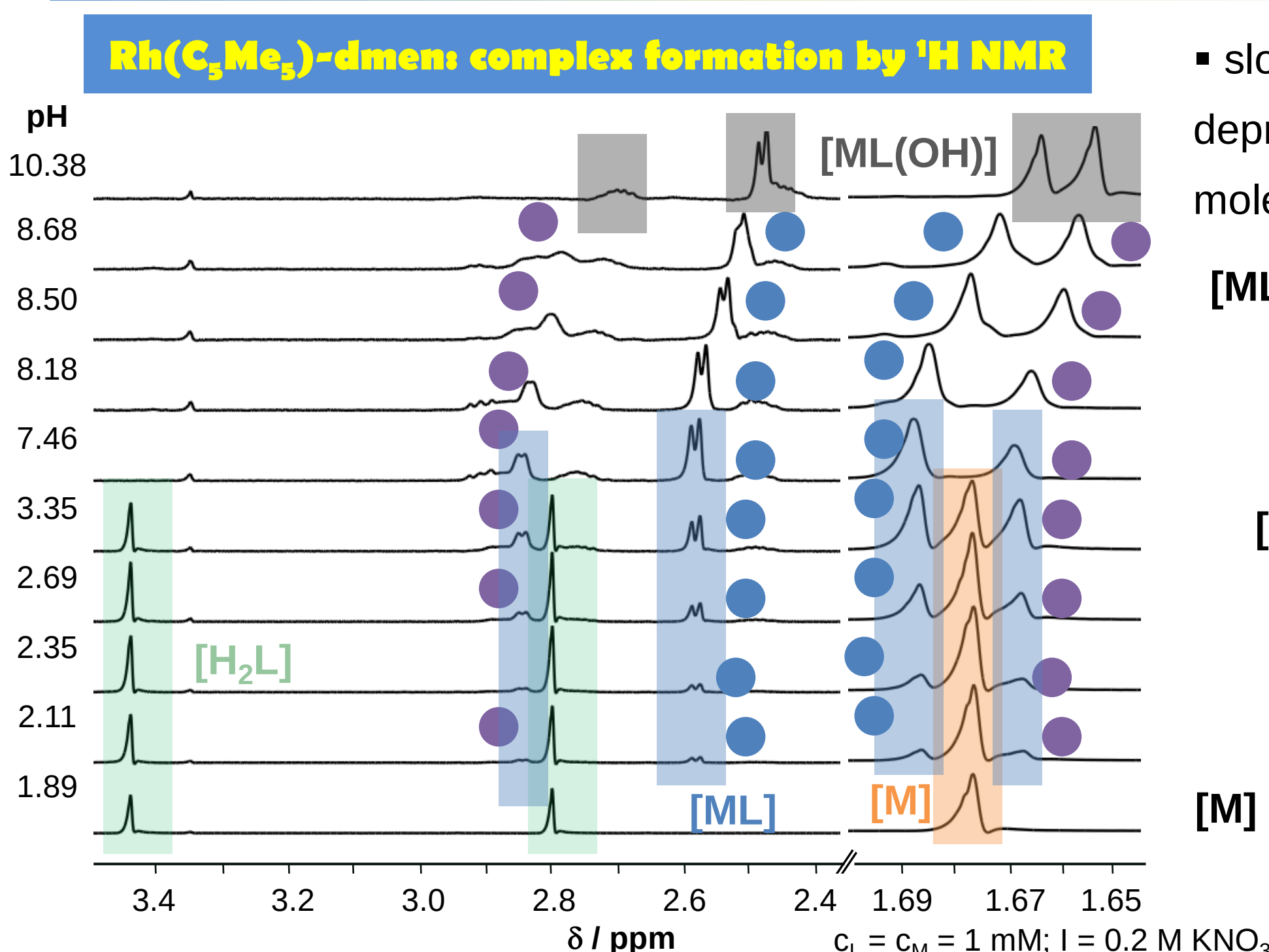
## Introduction

Cisplatin and its derivatives are successful therapeutics in cancer chemotherapy. Due to their severe side effects Ru(III)-based complexes NAMI-A and NKP-1339 were developed and investigated in clinical trials. Other promising candidates in the development of anticancer metallodrugs are organometallic Ru complexes and prominent representatives are RAED and RAPTA complexes. These drug candidates contain Ru(II) metal centres bonded to an arene ring [1]. Their isoelectronic Os, Rh and Ir congeners are also synthesized and characterized. Herein we report the comparative X-ray structural and solution equilibrium study of six organometallic  $\text{Rh(III)}(\eta^5\text{-C}_5\text{Me}_5)$  (M) complexes formed with various (N,N) donor bidentate ligands, namely: ethylenediamine [2], N,N'-dimethylethylenediamine, N,N,N',N'-tetramethylethylenediamine, 2-picolyamine, 2,2'-bipyridine [2] and 1,10-phenanthroline.

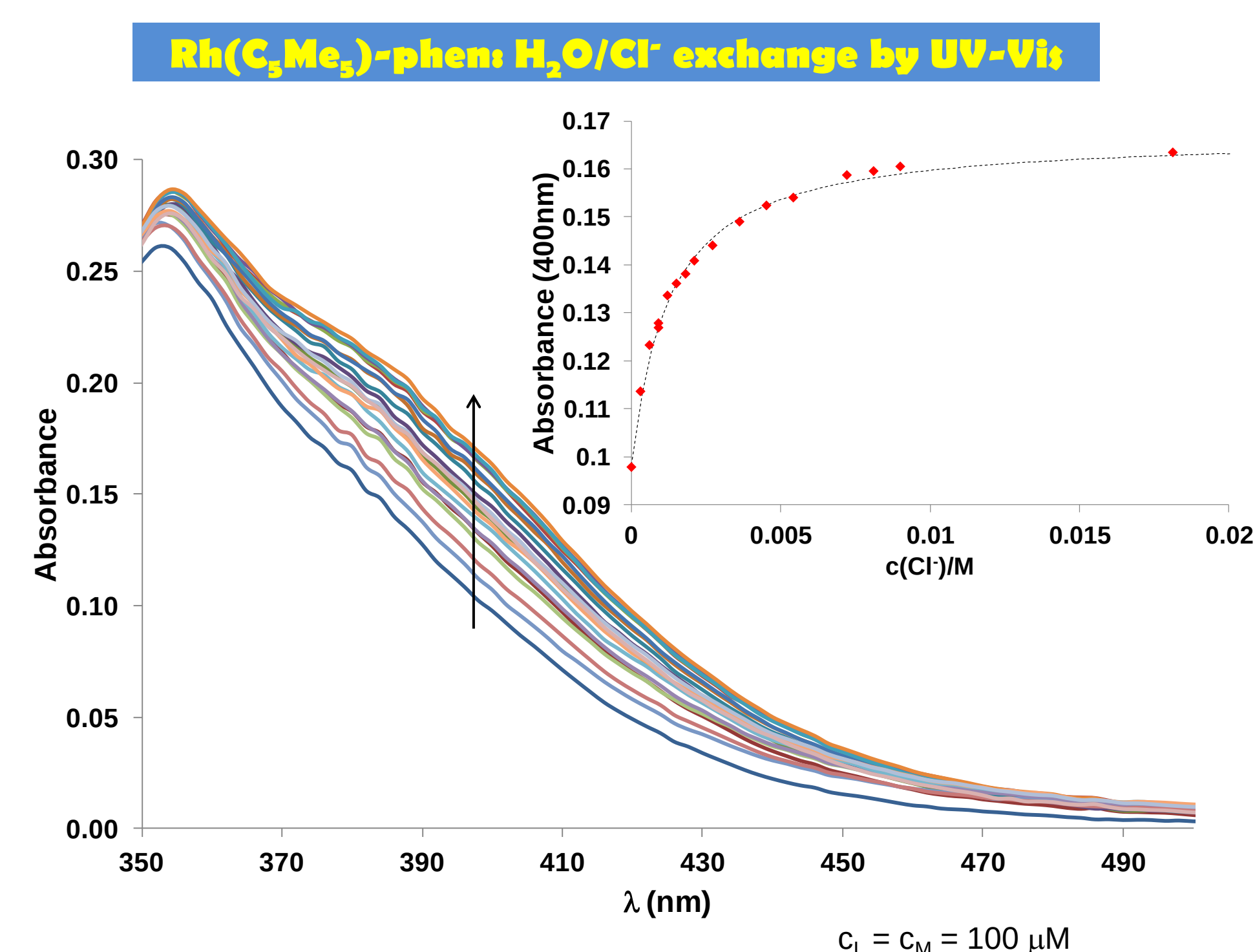
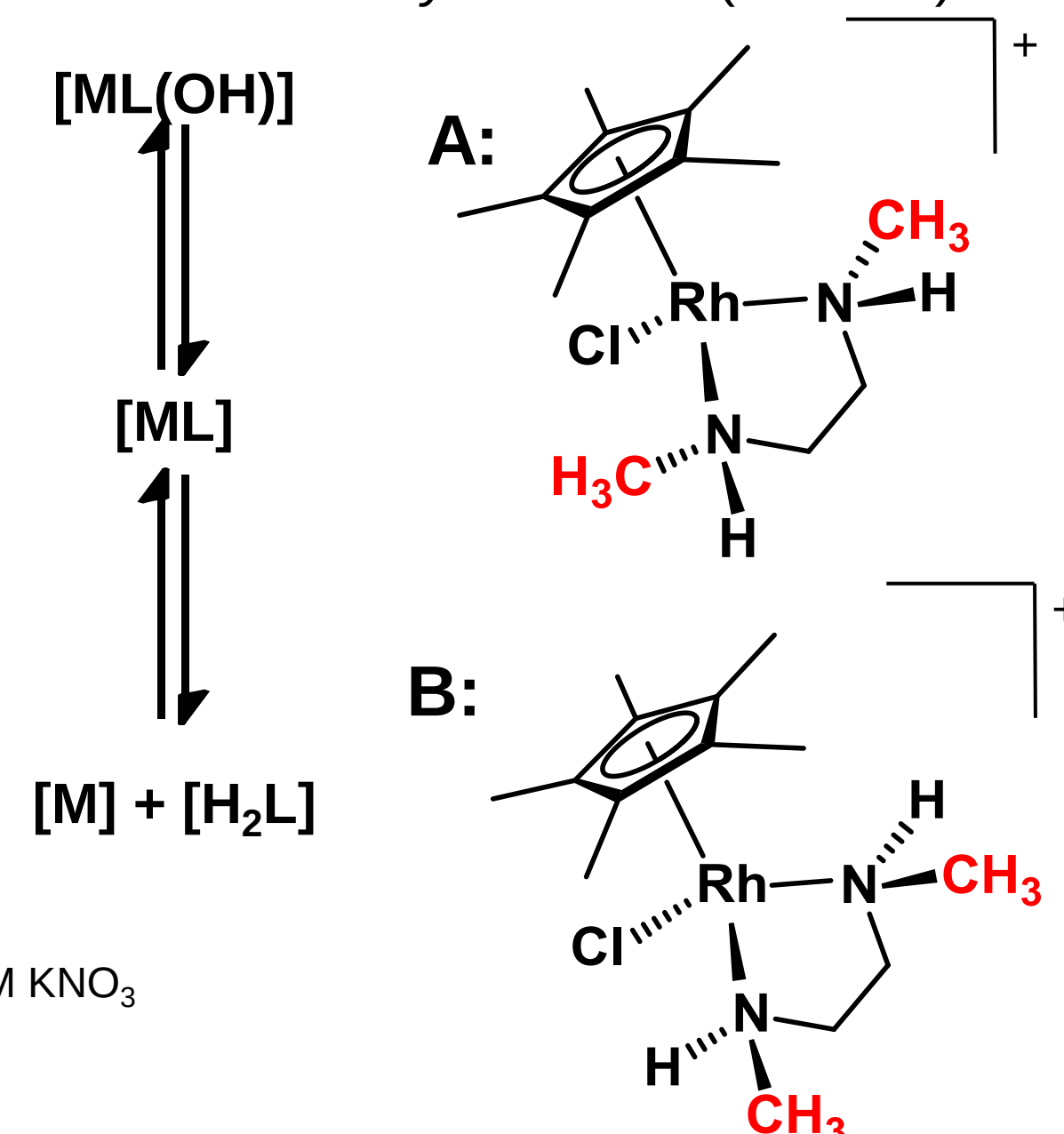


These studies were performed using pH-potentiometry,  $^1\text{H}$  NMR spectroscopy and UV-Vis spectrophotometry. The experiments revealed high complex stability and chloride ion affinity. Probably these properties have influence on the mode of action in cells. We have also investigated the possible binding modes to human serum albumin via spectrofluorometry and  $^1\text{H}$  NMR spectroscopy.

## Solution equilibria



slow complex formation and fast deprotonation of coordinated water molecule: two syn-isomers (A and B)



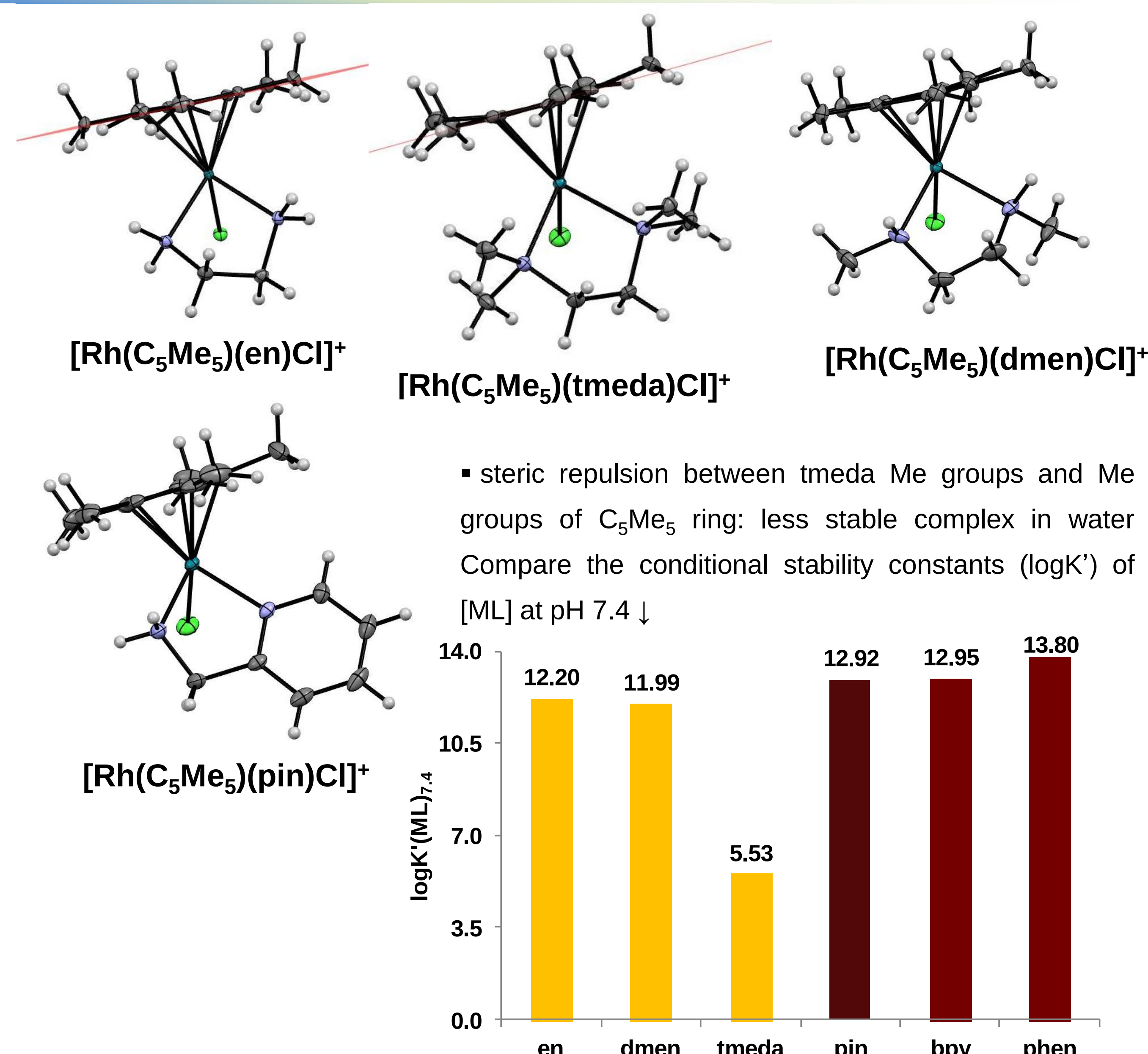
high chloride ion affinity  
the predominant form (77%) is the biologically less active chlorido complex  
at  $c(\text{ML}) = 1 \mu\text{M}$ ,  $c(\text{KCl}) = 4 \text{ mM}$  (equal to the  $\text{Cl}^-$  concentration in the nucleus)

### $\text{pK}_a$ of the ligands and stability constants of the complexes

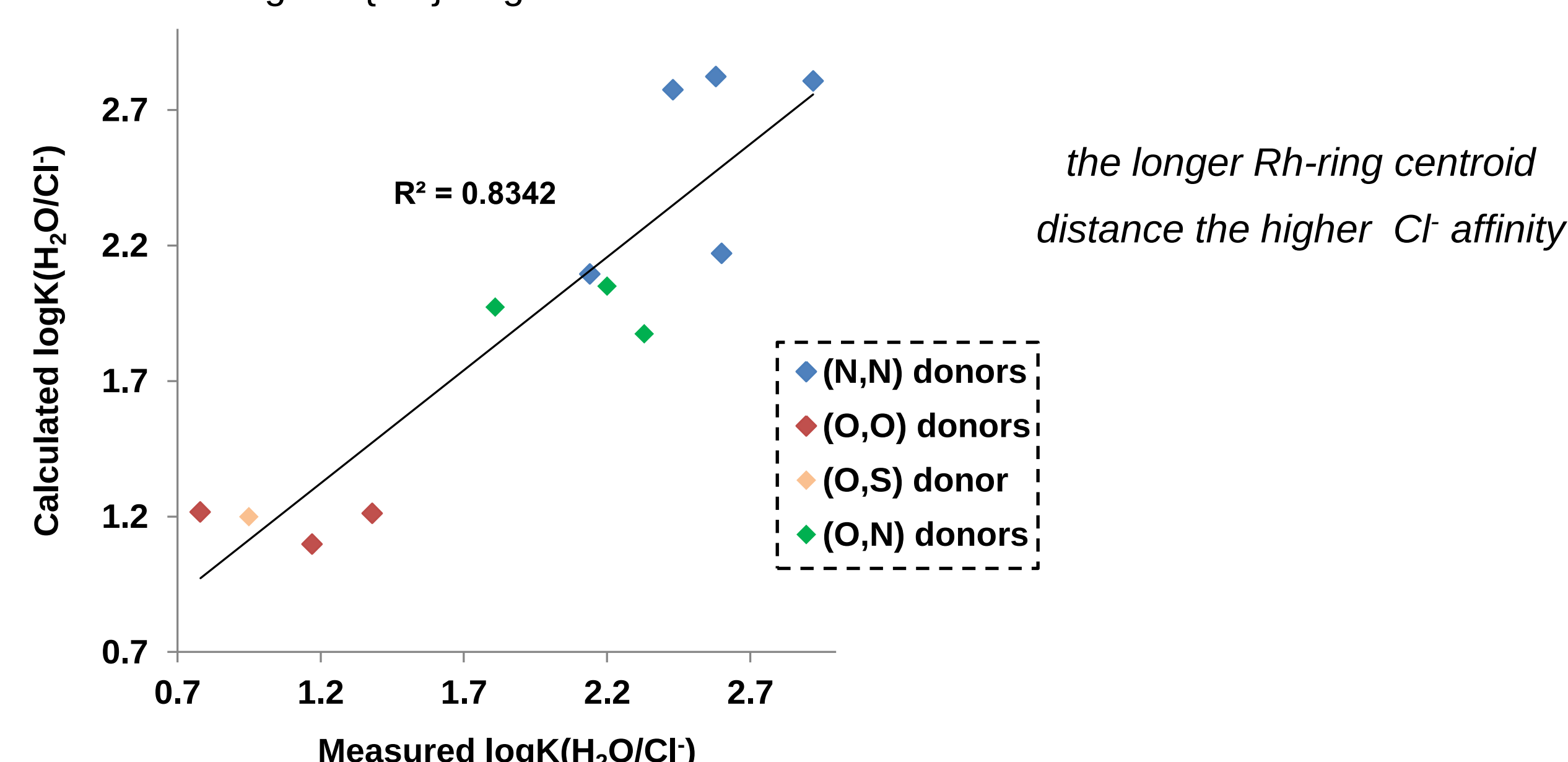
| I = 0.2 M KNO <sub>3</sub>               | en [2]             | dmen                     | tmeda                 | pin                    | bpy [2]             | phen               |
|------------------------------------------|--------------------|--------------------------|-----------------------|------------------------|---------------------|--------------------|
| $\text{pK}_1$ (ligand)*                  | 7.25               | 7.16(1)                  | 5.95(2)               | 2.29(2)                | 4.41                | 4.92(1)            |
| $\text{pK}_2$ (ligand)*                  | 10.01              | 10.04(1)                 | 9.25(1)               | 8.69(1)                | -                   | -                  |
| $\log \beta$ [ML]                        | 15.04 <sup>a</sup> | 14.80(2) <sup>b</sup>    | 7.40(10) <sup>c</sup> | 14.23(17) <sup>d</sup> | >12.95 <sup>d</sup> | >13.8 <sup>d</sup> |
| $\text{pK}$ [ML] <sup>c</sup>            | 9.58               | A: 8.61(9)<br>B: 8.40(6) | 8.42(3)               | 8.48(3)                | 8.61                | 8.68(2)            |
| $\log K(\text{H}_2\text{O}/\text{Cl})^e$ | 2.14               | 2.60(1)                  | -                     | 2.43(1)                | 2.58                | 2.92(1)            |

<sup>a</sup> pH-potentiometry  
<sup>b</sup> UV-vis pH = 1.8-6; 2 kinds of isomers (A and B)  
<sup>c</sup>  $^1\text{H}$  NMR  
<sup>d</sup> displacement:  $\text{Rh}(\text{C}_5\text{Me}_5)(\text{en}) + \text{L}$   
<sup>e</sup> UV-vis, pH 7.4 phosphate buffer,  $c(\text{KCl}) = 0.0\text{-}0.2 \text{ M}$

## X-ray structures and structure-property relationships



Multilinear regression between steric factors and  $\log K(\text{H}_2\text{O}/\text{Cl})$   
used steric factors: Rh-ring centroid distance,  $\text{C}_5\text{Me}_5$  methyl group torsion angle, chelate bite and the charge of {ML} fragment:



## Binding of complexes to DNA and HSA

### DNA

DNA is a possible target molecule  
the bound amount is shown with the intercalator ethidium bromide (EB) as standard

ultrafiltration-UV-vis, 20 mM PBS\* buffer: pH = 7.4,  $c(\text{CT-DNA}) = c(\text{complex}) = 100 \mu\text{M}$

### HSA

in the blood, binding to transport proteins is a crucial step  
4-5 complexes/HSA (determined by ultrafiltration-UV-vis)  
coordination - as {ML} fragment - on His side chains ( $^1\text{H}$  NMR)

## Conclusions

high stability of these complexes, except tmeda because of steric hindrance of Me groups of the ligand and the  $\text{C}_5\text{Me}_5$  ring  
two syn-isomers formed in water in the case of dmen  
high chloride affinity, which possibly has effect on biological activity  
SPR: single-crystal XRD data are correlated well to equilibrium constants  
coordination to His side chains in HSA  
less amount binds to CT-DNA, than without the (N,N) ligands

### Acknowledgement

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### References

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