Metal complexes of aminophosphonates in solution - stability constants and speciation

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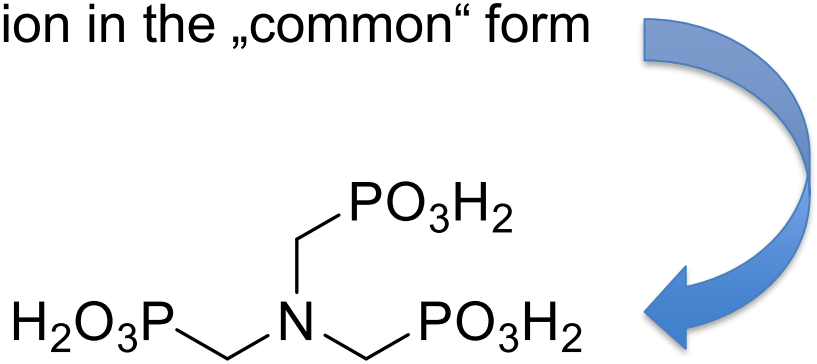
Aminophosphonates

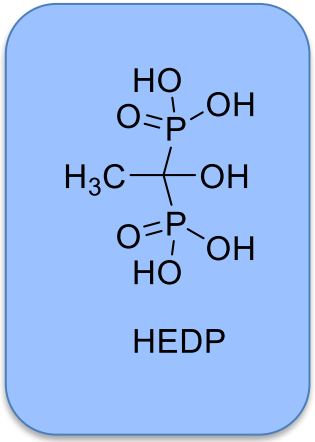
- Never present in solution in the „common“ form

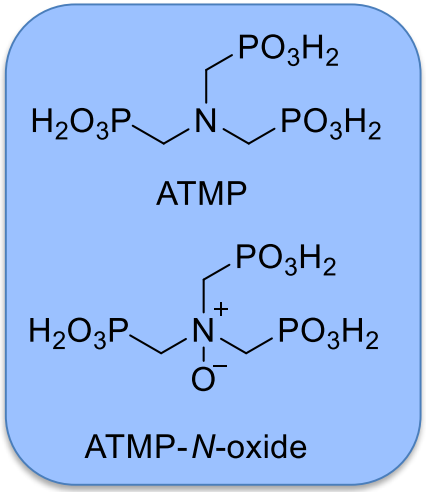


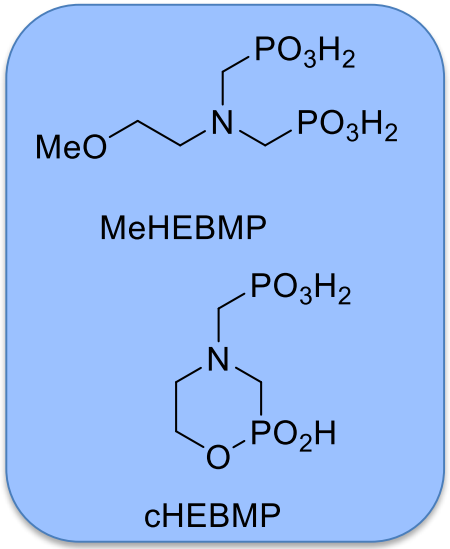
ATMP

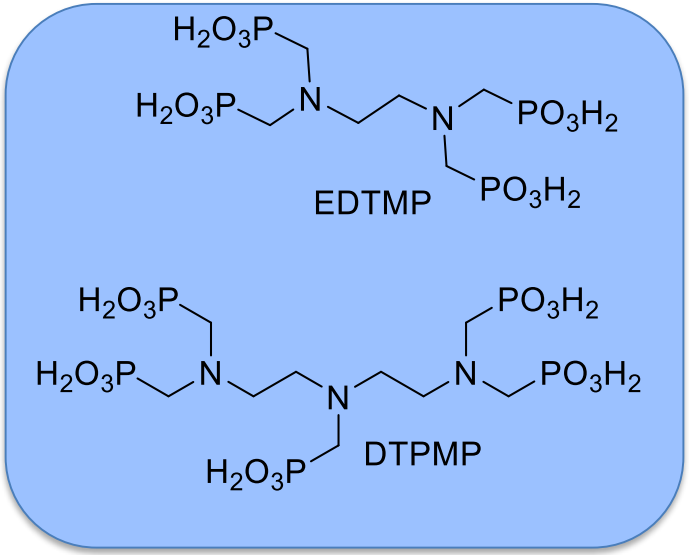
- Amine protonation, phosphonate dissociation
- Binding to metal ions
- Different charge, hydrophilicity, solubility, biodistribution etc.

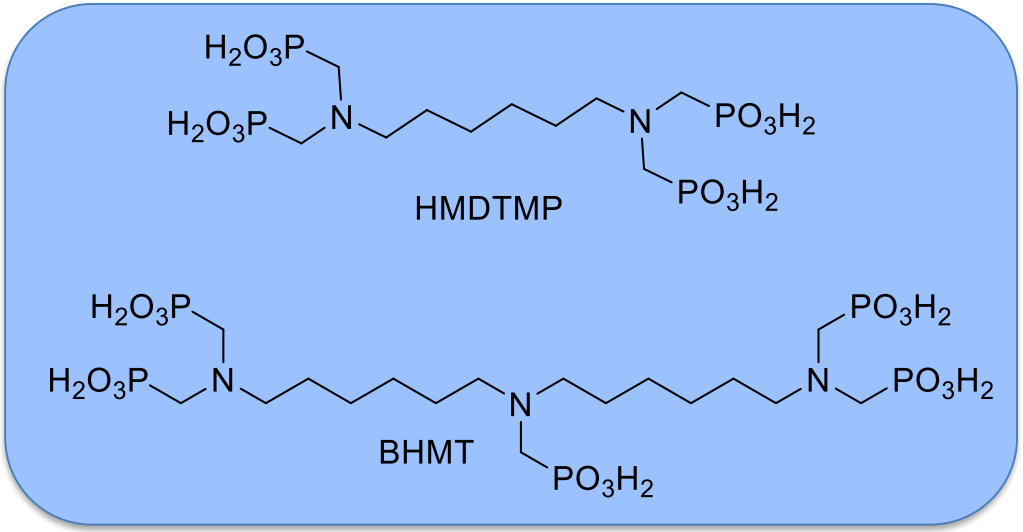
Aminophosphonates



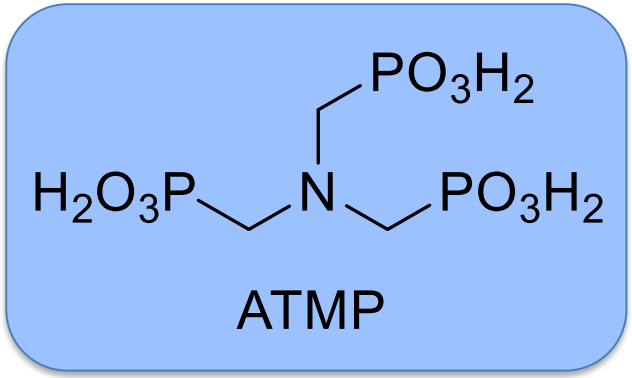




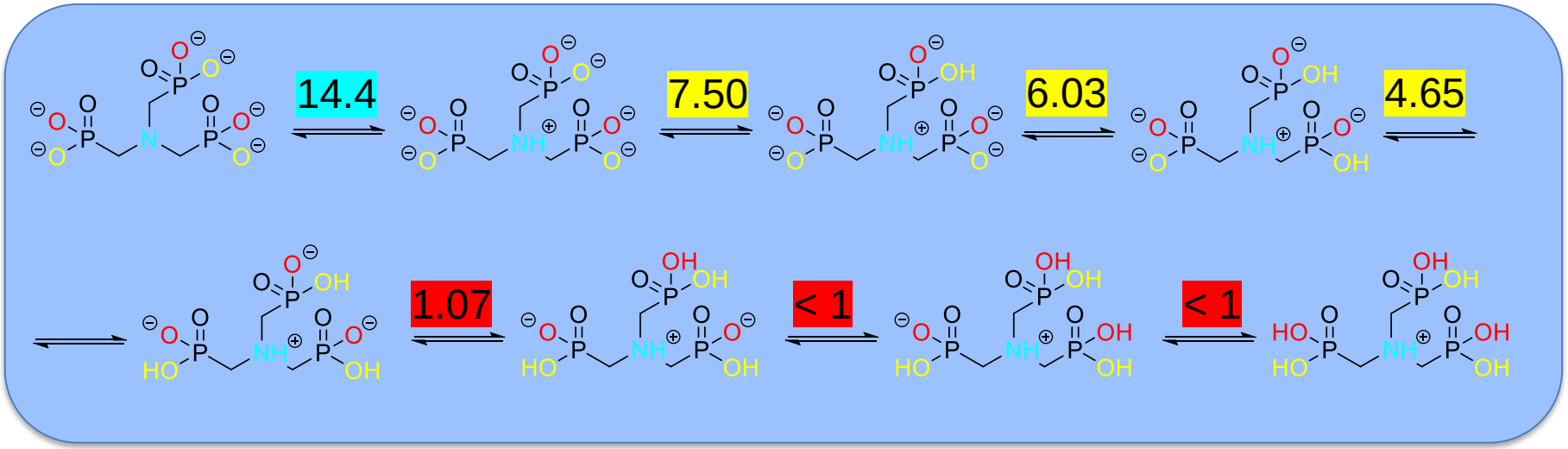




Ligand protonation

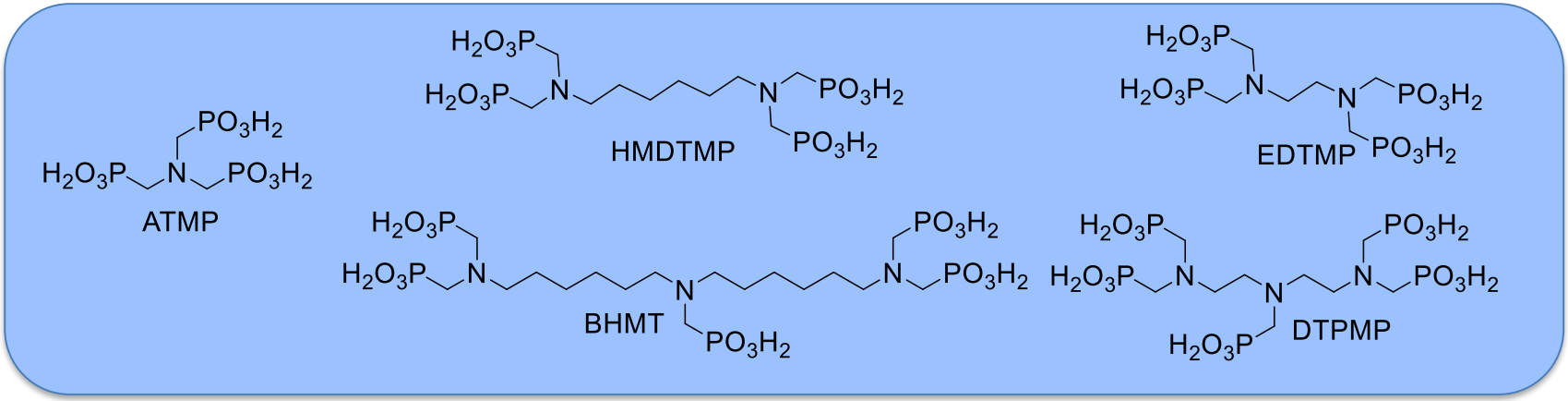


Species	pK_a	
HL	14.4	amine protonation
H_2L	7.50	phosphonate – first protonation
H_3L	6.03	
H_4L	4.65	
H_5L	1.07	phosphonate – second protonation



Ligand protonation

Species	ATMP	HMDTMP	BHMT	EDTMP	DTPMP
HL	14.4	13.8	14.1	14.34	14.2
H_2L	7.50	12.8	13.8	10.24	13.2
H_3L	6.03	7.11	12.16	7.93	9.70
H_4L	4.65	6.28	7.11	6.51	8.26
H_5L	1.07	5.40	6.35	5.02	7.15
H_6L	-	4.64	5.80	2.71	6.34
H_7L	-	1.12	5.13	-	5.46
H_8L	-	-	4.58	-	4.24
H_9L	-	-	1.19	-	2.00



Complexes

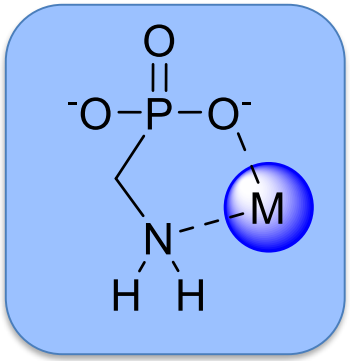
- Divalent metal ions – Cu^{II}, Zn^{II}, Ni^{II}, Co^{II}, Ca^{II}, Mg^{II}
- Monovalent metal ions – Na^{I}, K^{I}
- Trivalent metal ion – Fe^{III}

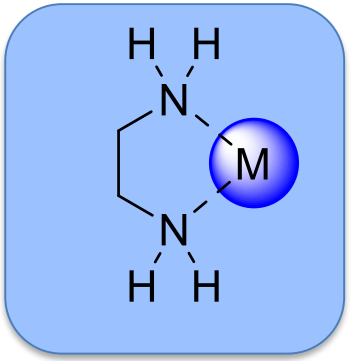
- Challenging systems
- Various ligand to metal ratios
- Many protonation states
- Formation of mixed hydroxidocomplexes
- Solubility changing with pH

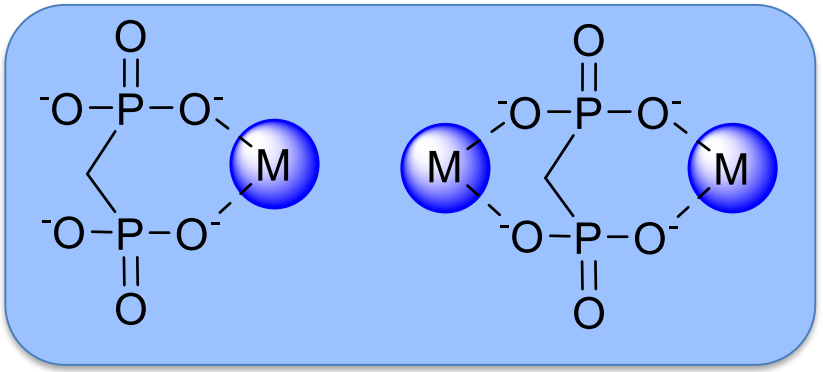
Coordination modes

Acidic region

- Only phosphonates coordinated
- Highly protonated complexes
- Low stability
- Often polymeric and insoluble

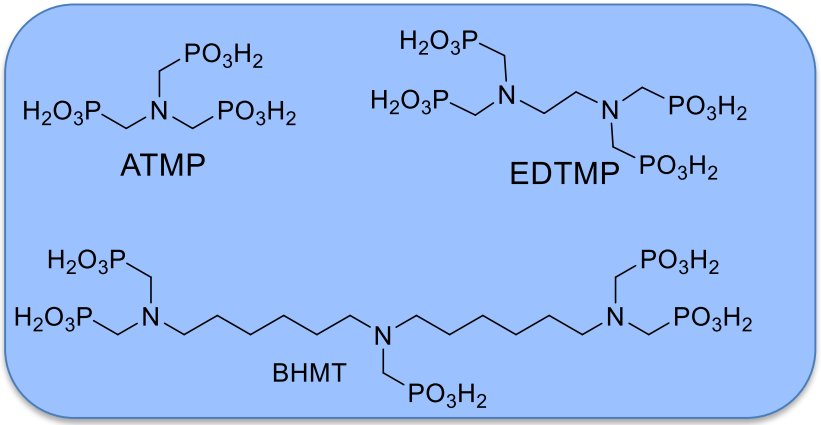






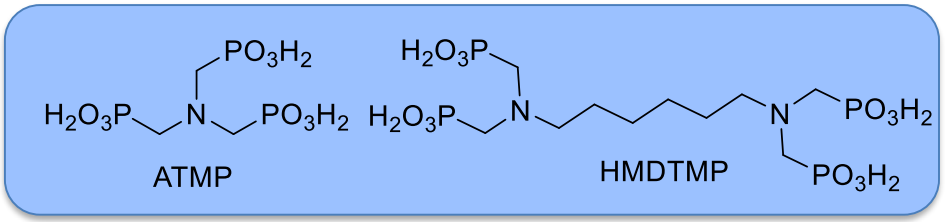
Neutral and alkaline region

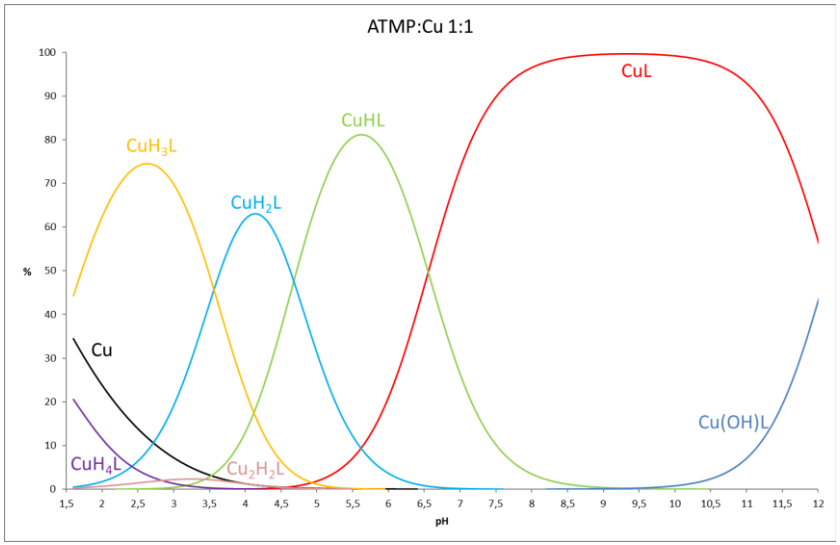
- Amines and phosphonates coordinated
- High stability
- Formation of chelates

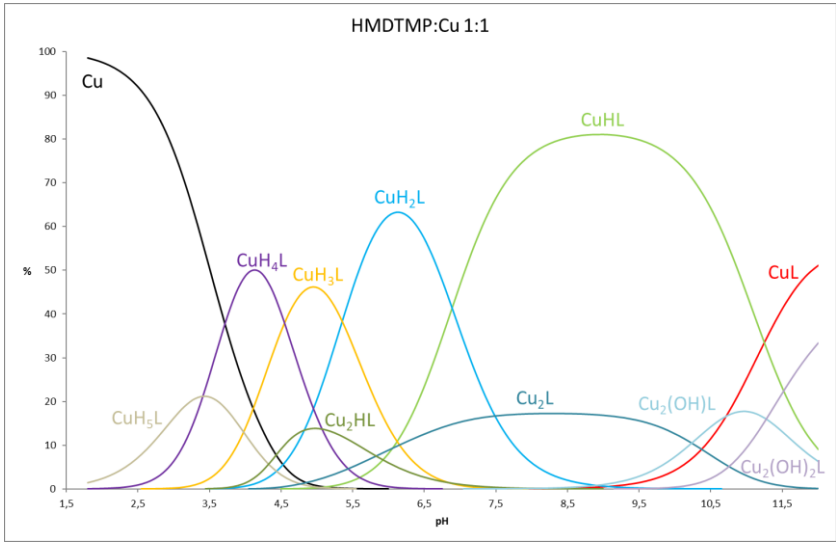


Stability and speciation of complexes

Cu^{II}	ATMP		HMDTMP	
	logβ	pK_a	logβ	pK_a
[M(L)]	19.26		18.23	
[M(HL)]	25.82	6.56	29.09	10.86
[M(H_2L)]	30.50	4.68	35.75	6.66
[M(H_3L)]	34.06	3.56	41.06	5.31
[M(H_4L)]	35.33	1.27	45.53	4.47
[M(H_5L)]	-		49.03	3.50
[M(L)(OH)]	7.14	12.12	-	
[M_2(L)]	-		29.17	
[M_2(HL)]	-		34.83	
[M_2(H_2L)]	32.79		-	
[M_2(L)(OH)]	-		19.06	
[M_2(L)(OH)$_2$]	-		7.95	





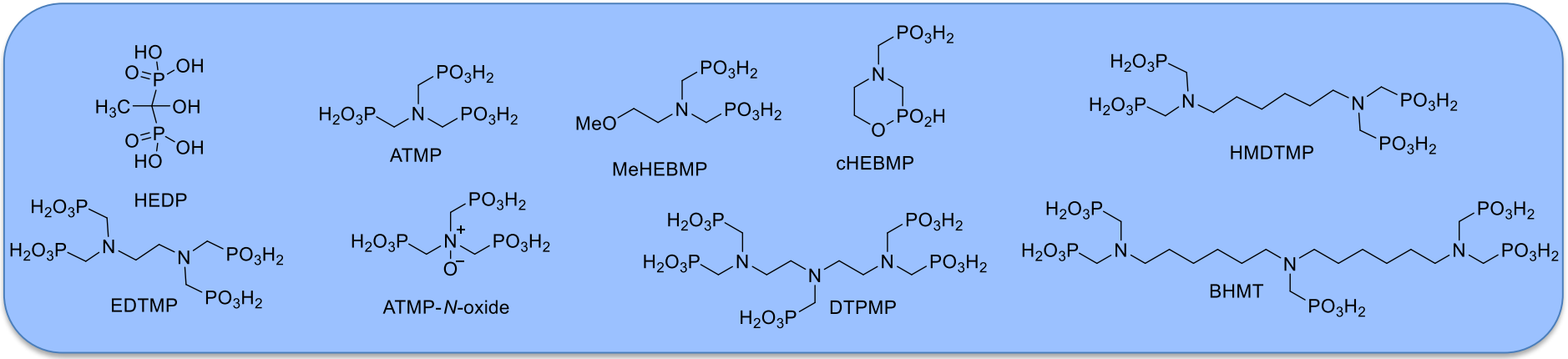


Stability and speciation of complexes

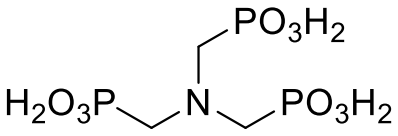
ATMP

log*K*	Cu^{II}	Zn^{II}	Ni^{II}	Co^{II}	Ca^{II}	Mg^{II}	Fe^{III}	Na^{I}	K^{I}
[M(L)]	19.26	17.19	13.34	16.25	10.20	9.66	22.4	4.74	< 2

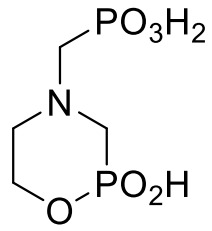
	ATMP	HMDTMP	BHMT	DTPMP	HEBP	EDTMP	ATMPO	MeHEBMP	cHEBMP
Cu^{II}	19.26	18.23	19.30	26.76	12.49	23.96	14.24	15.38	7.69
Zn^{II}	17.19	-	16.19	20.68	11.56	20.83	16.35	10.99	5.13



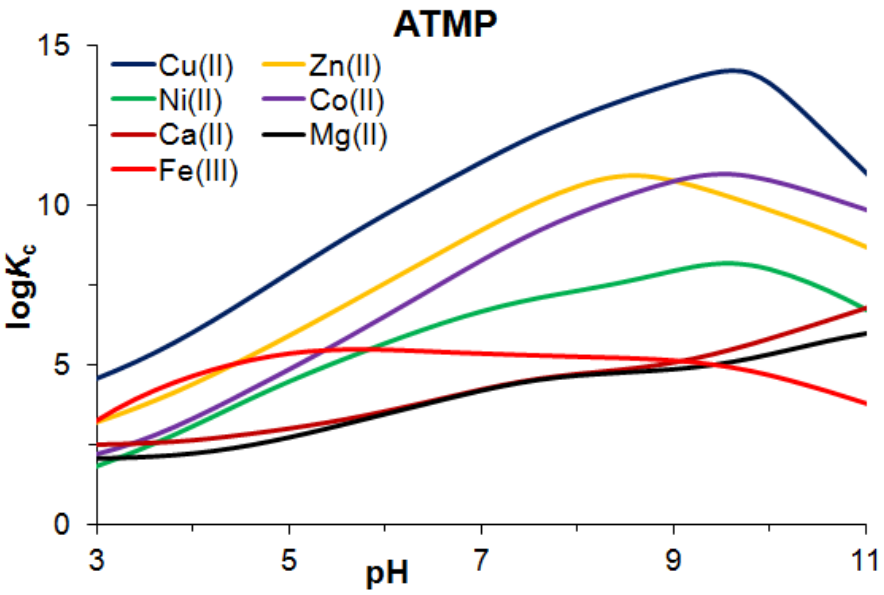
Conditional stability

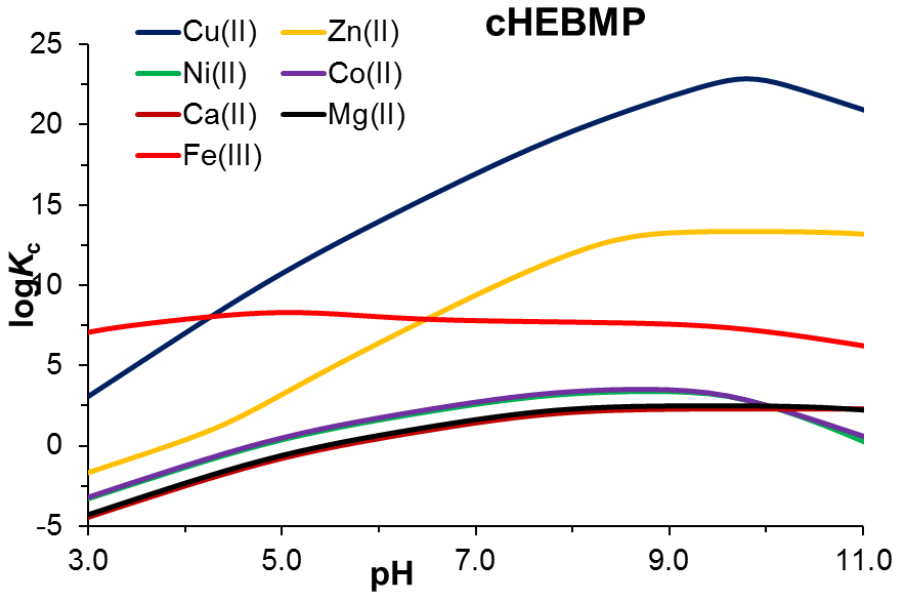


ATMP



cHEBMP

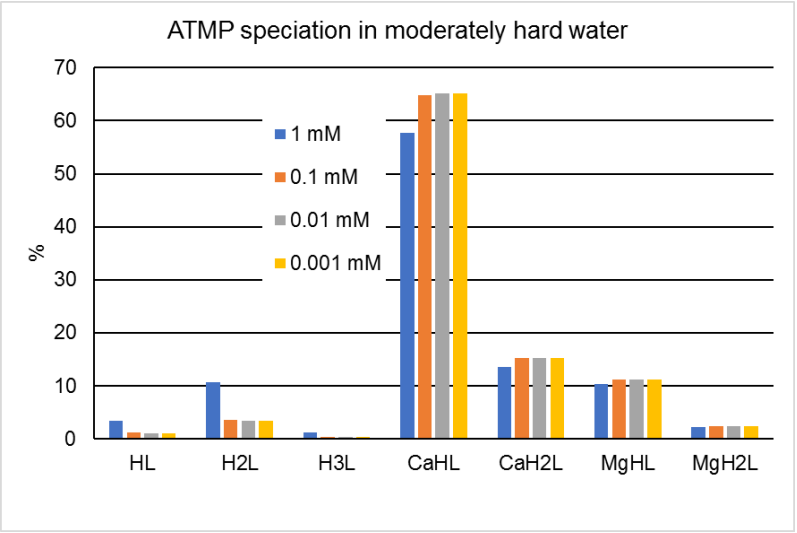


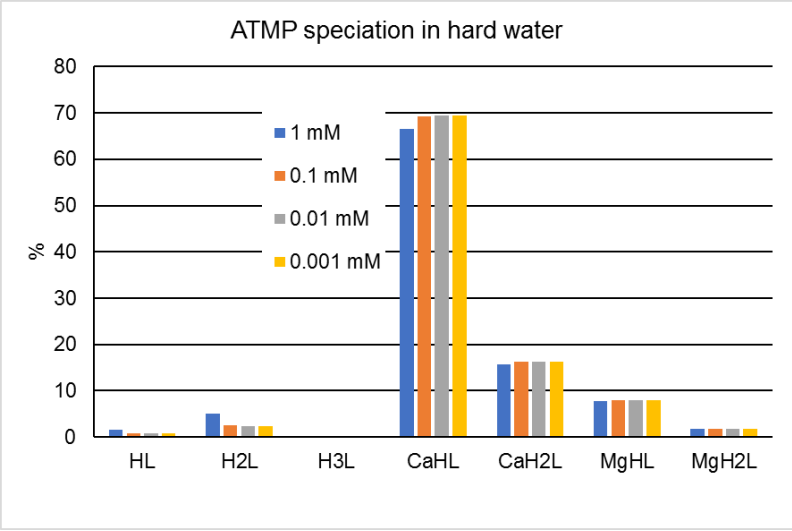


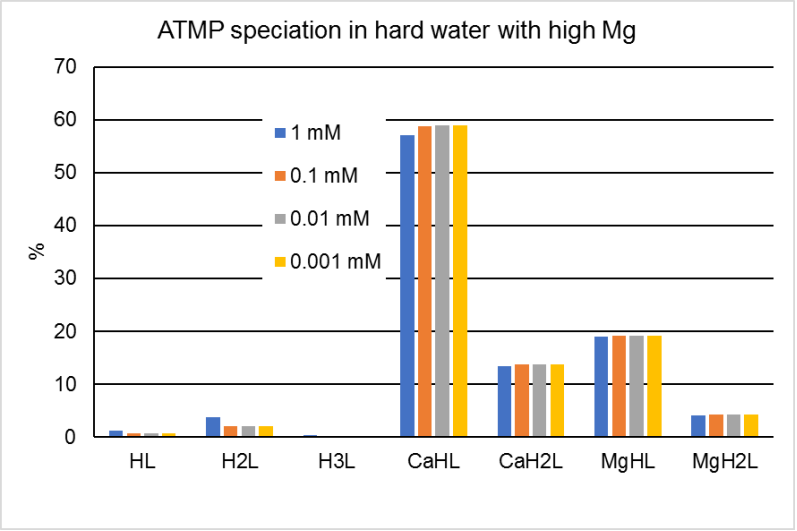
Speciation in model systems – river water

ATMP

Concentration [M]	Moderately hard water	Hard water	Hard water with high Mg
Ca^{II}	1.0×10^{-3}	1.5×10^{-3}	1.5×10^{-3}
Mg^{II}	1.8×10^{-4}	1.8×10^{-4}	5.0×10^{-4}
Na^{I}	2.6×10^{-4}	2.6×10^{-4}	2.6×10^{-4}
K^{I}	7.0×10^{-5}	7.0×10^{-5}	7.0×10^{-5}
pH	7	7	7



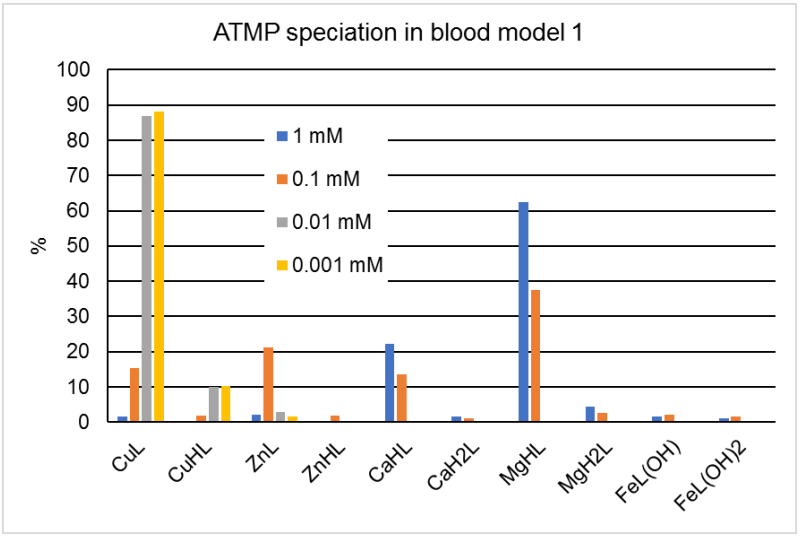


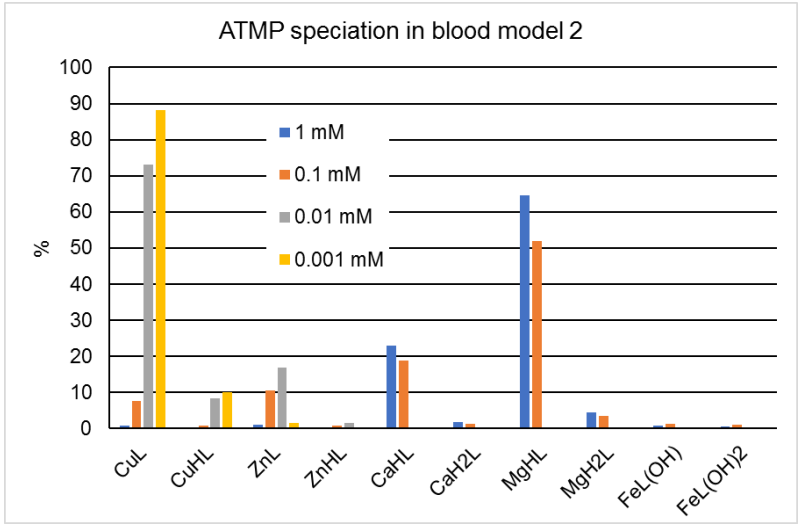


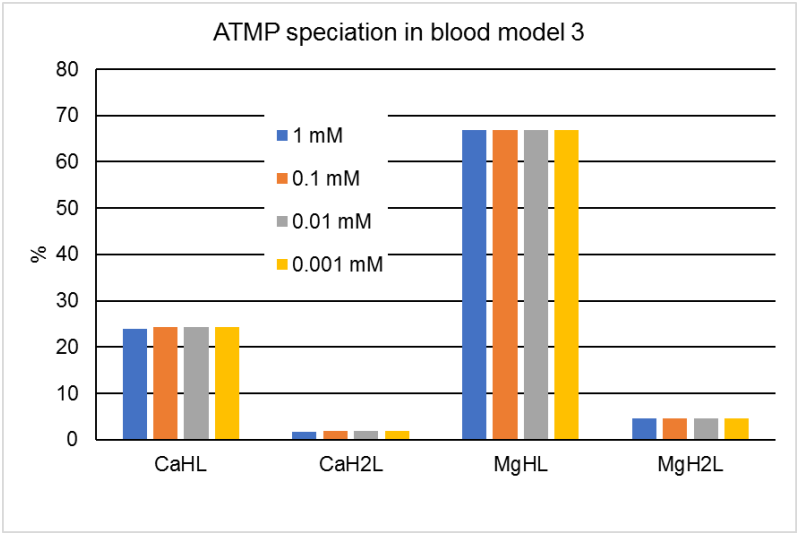
Speciation in model systems – blood

ATMP

Concentration [M]	Model 1	Model 2	Model 3
Cu^{II}	1.7×10^{-5}	8.5×10^{-6}	0
Zn^{II}	2.3×10^{-5}	1.2×10^{-5}	0
Ca^{II}	8.5×10^{-4}	8.5×10^{-4}	8.5×10^{-4}
Mg^{II}	2.4×10^{-3}	2.4×10^{-3}	2.4×10^{-3}
Fe^{III}	4.1×10^{-5}	2.1×10^{-5}	0
Na^{I}	1.4×10^{-1}	1.4×10^{-1}	1.4×10^{-1}
K^{I}	4.0×10^{-4}	4.0×10^{-4}	4.0×10^{-4}
pH	7.5	7.5	7.5







Conclusion

Aminophosphonates

- Strong complexing agents
- Zwitterions in the free form
- Quantitative binding of divalent and trivalent transition metal ions
- Complexes with alkaline earth metal ions dominant in natural water and body fluids
- Complexes with alkaline metal ions formed only in strongly alkaline solutions
- Precise speciation impossible due to limited solubility, sorption on solid materials, slow kinetics of natural processes and uncertain availability of metal ions in natural systems

Group of Coordination and Bioinorganic Chemistry
Faculty of Science, Charles University, Prague

- Determination of protonation and stability constants
- Formation and dissociation kinetics of complexes
- Synthesis of polydentate ligands

Applications of polydentate ligands (mainly macrocyclic)

- Radiodiagnosis
- Radiotherapy
- Magnetic resonance imaging

Acknowledgement

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Thank you for your attention!

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