EMMI Intensive Programme "Design, Synthesis and Validation of Imaging Probes„ - 2011

2011 September 26, Monday

Gd(III) complexes: the importance of kinetic and thermodynamic stability

Imre Tóth, University of Debrecen, Hungary

Content

Introduction

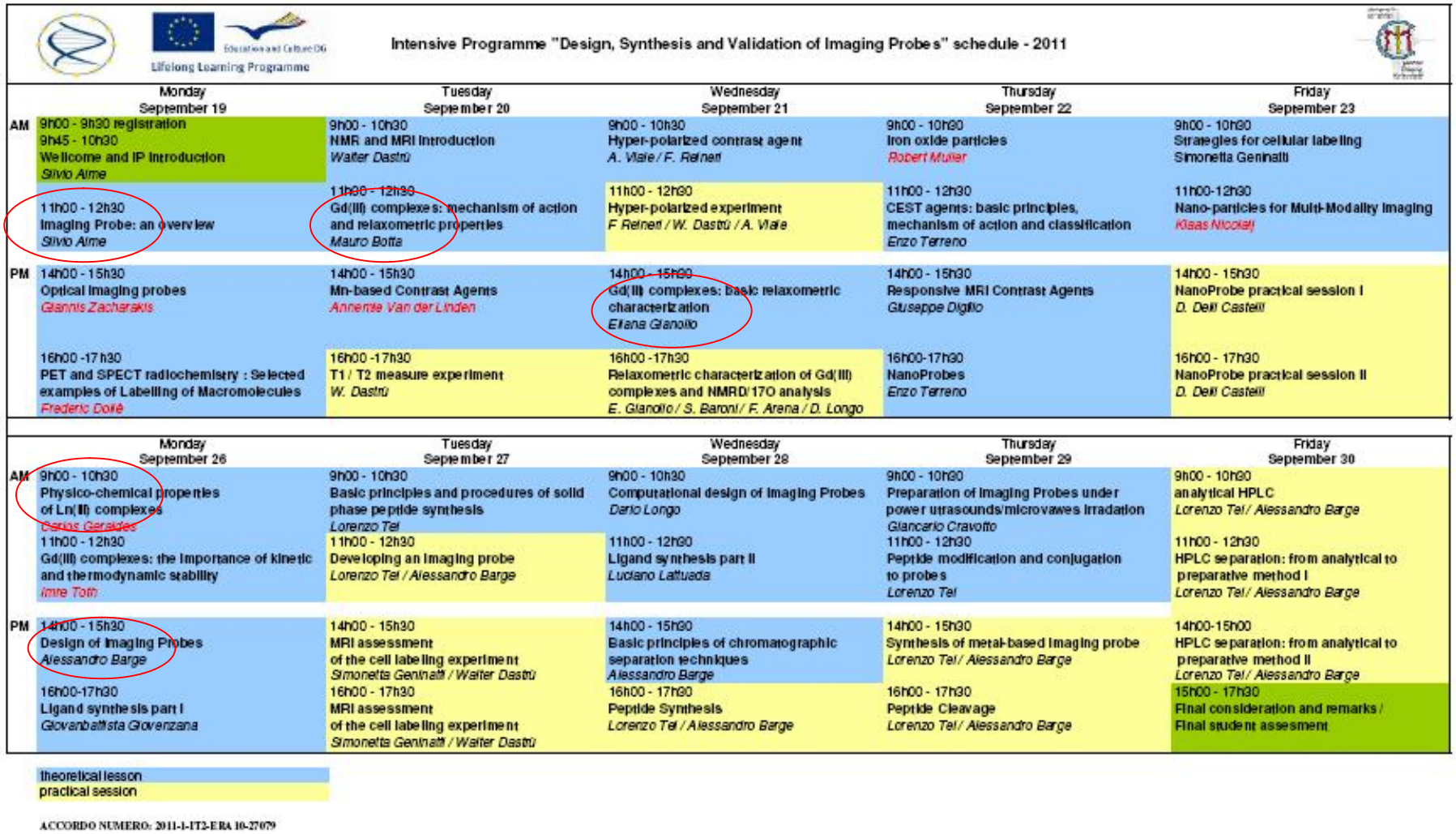
Equilibrium

- Stability constants
- Conditional stability constants
- Simultaneous/competitive equilibria
- Data bases, modelling
- Measuring of stability constants of LnMC
- Case studies

Kinetics

- Rate of chemical reactions
- Formation of metal complexes
- Formation of Ln-complexes
- Dissociation of Ln-complexes
- Case studies

Introduction



Intensive Programme "Design, Synthesis and Validation of Imaging Probes" schedule - 2011

Lifelong Learning Programme

	Monday September 19	Tuesday September 20	Wednesday September 21	Thursday September 22	Friday September 23
AM	9h00 - 9h30 registration 9h45 - 10h30 Wellcome and IP introduction *Silvio Aime*	9h00 - 10h30 NMR and MRI introduction *Walter Dastrù*	9h00 - 10h30 Hyper-polarized contrast agent *A. Viale / F. Reineri*	9h00 - 10h30 Iron oxide particles *Robert Muller*	9h00 - 10h30 Strategies for cellular labeling Simonetta Geninatti
	11h00 - 12h30 Imaging Probe: an overview *Silvio Aime*	11h00 - 12h30 Gd(III) complexes: mechanism of action and relaxometric properties *Mauro Botta*	11h00 - 12h30 Hyper-polarized experiment *F Reineri / W. Dastrù / A. Viale*	11h00 - 12h30 CEST agents: basic principles, mechanism of action and classification *Enzo Terreno*	11h00-12h30 Nano-particles for Multi-Modality Imaging *Klaas Nicolay*
PM	14h00 - 15h30 Optical Imaging probes *Giannis Zacharakis*	14h00 - 15h30 Mn-based Contrast Agents *Annemie Van der Linden*	14h00 - 15h30 Gd(III) complexes: basic relaxometric characterization *Eliana Gianolio*	14h00 - 15h30 Responsive MRI Contrast Agents *Giuseppe Digilio*	14h00 - 15h30 NanoProbe practical session I *D. Delli Castelli*
	16h00 -17h30 PET and SPECT radiochemistry : Selected examples of Labelling of Macromolecules *Frederic Dollé*	16h00 -17h30 T1 / T2 measure experiment *W. Dastrù*	16h00 -17h30 Relaxometric characterization of Gd(III) complexes and NMRD/17O analysis *E. Gianolio / S. Baroni / F. Arena / D. Longo*	16h00-17h30 NanoProbes *Enzo Terreno*	16h00 - 17h30 NanoProbe practical session II *D. Delli Castelli*

	Monday September 26	Tuesday September 27	Wednesday September 28	Thursday September 29	Friday September 30
AM	9h00 - 10h30 Physico-chemical properties of Ln(III) complexes *Carlos Geraldes*	9h00 - 10h30 Basic principles and procedures of solid phase peptide synthesis *Lorenzo Tei*	9h00 - 10h30 Compurational design of Imaging Probes *Dario Longo*	9h00 - 10h30 Preparation of Imaging Probes under power ultrasounds/microwaves irradation *Giancarlo Cravotto*	9h00 - 10h30 analytical HPLC *Lorenzo Tei / Alessandro Barge*
	11h00 - 12h30 Gd(III) complexes: the importance of kinetic and thermodynamic stability *Imre Toth*	11h00 - 12h30 Developing an Imaging probe *Lorenzo Tei / Alessandro Barge*	11h00 - 12h30 Ligand synthesis part II *Luciano Lattuada*	11h00 - 12h30 Peptide modification and conjugation to probes *Lorenzo Tei*	11h00 - 12h30 HPLC separation: from analytical to preparative method I *Lorenzo Tei / Alessandro Barge*
PM	14h00 - 15h30 Design of Imaging Probes *Alessandro Barge*	14h00 - 15h30 MRI assessment of the cell labeling experiment *Simonetta Geninatti / Walter Dastrù*	14h00 - 15h30 Basic principles of chromatographic separation techniques *Alessandro Barge*	14h00 - 15h30 Synthesis of metal-based Imaging probe *Lorenzo Tei / Alessandro Barge*	14h00-15h00 HPLC separation: from analytical to preparative method II *Lorenzo Tei / Alessandro Barge*
	16h00-17h30 Ligand synthesis part I *Giovanbattista Giovenzana*	16h00 - 17h30 MRI assessment of the cell labeling experiment *Simonetta Geninatti / Walter Dastrù*	16h00 - 17h30 Peptide Synthesis *Lorenzo Tei / Alessandro Barge*	16h00 - 17h30 Peptide Cleavage *Lorenzo Tei / Alessandro Barge*	15h00 - 17h30 Final consideration and remarks / Final student assesment

theoretical lesson
practical session

ACCORDO NUMERO: 2011-1-IT2-ERA 10-27079

Step-vice formation of complexes:

$M(H_2O)_n + L \rightleftharpoons ML(H_2O)_{n-1} + H_2O$ $\quad K_1 = \dfrac{[ML(H_2O)_{n-1}]}{[M(H_2O)_n][L]}$

$ML_{n-1}(H_2O) + L \rightleftharpoons ML_n + H_2O$ $\quad K_n = \dfrac{[ML_n]}{[ML_{n-1}(H_2O)][L]}$

Stepvice constants

Overall reaction

$M(H_2O)_n + nL \rightleftharpoons ML_n + nH_2O$ $\quad \beta_n = \dfrac{[ML_n]}{[M(H_2O)_n][L]^n}$

$\beta_n = K_1 \cdot K_2 \cdot \ldots \cdot K_n$

Overall stability constants

Coordination chemistry: basic principles

Groups of complexes

a/ ***parent complexes*** : only one ligand MA, MA_2, MA_3 ....

MA_N (N: coordination number)

b/ ***mixed-ligand complexes***: two or several ligands

$$M + A + B \rightleftharpoons MAB \quad \text{or}$$

$$MA_2 + MB_2 \rightleftharpoons 2\ MAB$$

c/ ***protonated complexes***: protonation of the non-coordinated donors of the ligand

$$M + H_nA \rightleftharpoons M(AH) + n–1\ H^+$$

Coordination chemistry: basic principles

Groups of complexes

d/ ***deprotonated complexes***: de-protonation and coordination of the ligand

$M + A \rightleftharpoons M(AH_{-1}) + H^+$

– for example alcoholate, amid-group)

– deprotonation of coordinated water

$MA(H_2O)_n \rightleftharpoons MA(H_2O)_{n-1}(OH) + H^+$

e/ *polynuclear complexes:* $nM + mA \rightleftharpoons M_nA_m$

A is a bridging ligand with one or two donor group(s)

Infuence of the charge of the metal ions on stability:

- +3 ions have higher stability compared to +2

- +2 cations in the 3d transition metal block follow the Irving-Williams series:

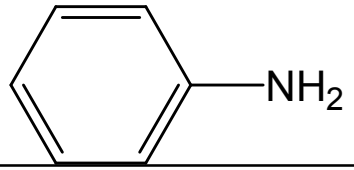
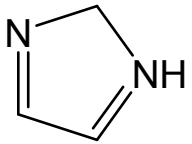
  Mn(II) < Fe(II) < Co(II) < Ni(II) < Cu(II) > Zn(II)

  (i.e. it does not follow the change in size)

Hard –soft theory of Lewis acids and bases

hard acids (metal ions)	**hard bases (ligands)**
H^+, Na^+, K^+ Mg^{2+}, Ca^{2+}, Mn^{2+}, VO^{2+} Al^{3+}, Co^{3+}, Cr^{3+}, Ga^{3+}, Fe^{3+}, Ln^{3+}, Th^{4+} etc.	*O-donor ligands*: H_2O, CO_3^{2-}, NO_3^-, PO_4^{3-}, $ROPO_3^{2-}$, $(RO)_2PO_3^-$, CH_3COO^-, OH^-, RO^-, R_2O, crown ethers *N-donor ligands*: NH_3, N_2H_4, RNH_2, F^-, Cl^-

Coordination chemistry of transition metals

Borderline acids (metal ions)	**Borderline bases (ligands)**
Fe^{2+}, Ni^{2+}, Zn^{2+}, Co^{2+}, Cu^{2+}, Pb^{2+}, Sn^{2+}, Ru^{2+}, Au^{3+} Tl^{+}	Br^{-}, SO_3^{2-}, *N-donor ligands:* NO_2^{-}, N_3^{-}, N_2,  
soft acids (metal ions)	**soft bases (ligands)**
Cu^{+}, Au^{+}, Tl^{3+}, Ag^{+}, Hg_2^{2+} Pt^{2+}, (Pb^{2+}), Hg^{2+}, (Cd^{2+}), Pd^{2+}, (Pt^{4+})	*S-donor ligands:* S^{2-}, RSH, RS^{-}, R_2S, $S_2O_3^{2-}$ R_3P, $(RS)_2PO_2^{-}$, $(RO)_2P(O)S^{-}$, RNC, CN^{-}, CO, R^{-}, H^{-}, I^{-}

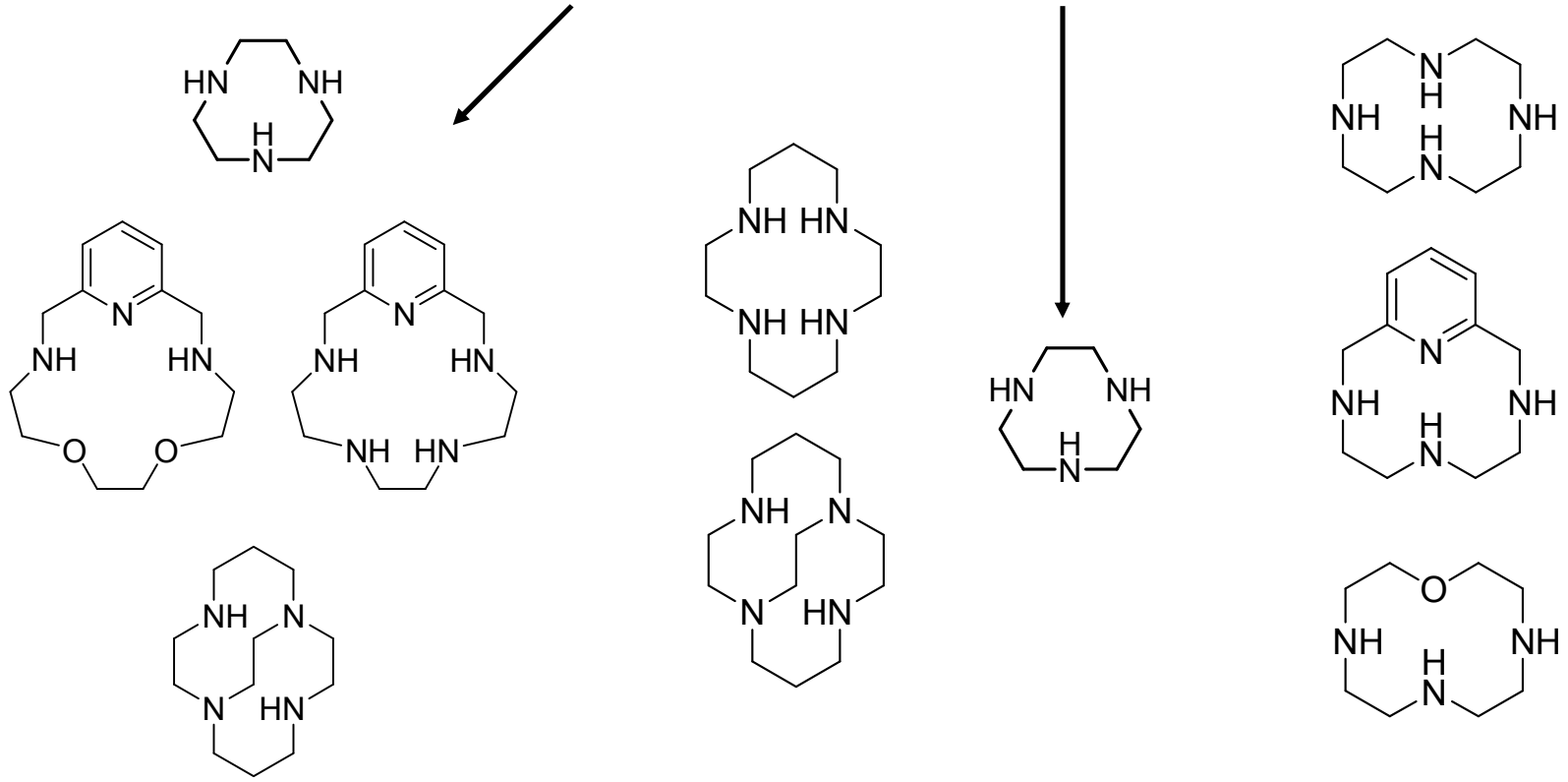
Coordination chemistry: basic principles

Influence of the ligand on the stability of complexes

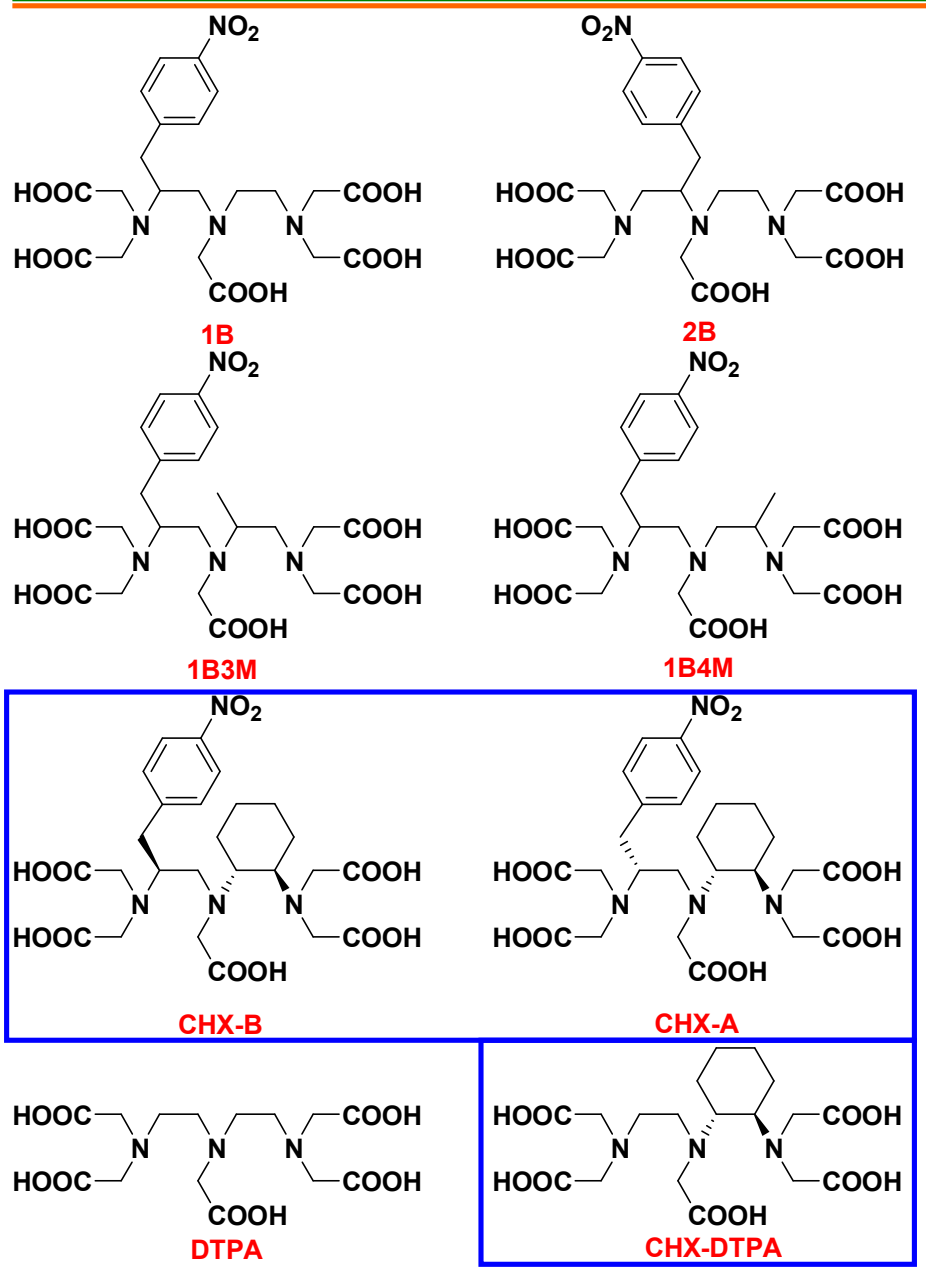
- hard-soft character of donor atoms
- charge
- denticity
- overall basicity
- chelate effect (entropy contribution)
    - chelate ring size (5 is preferred)
- macrocycle effect/ encapsulating ligands
    - cavity size
    - rigidity of the MC

Mathing the size of the metal ion and the cavity

Property	Mn	Cu	Ga	In	Gd
Ionic radius M^{III} or M^{II} (CN=6) (pm)	58 (ls) 64,5 (hs)	73	62	80	93,8
Coordination Number	II – 6(7)	II – 6(4)	III – 6	III – 8(9)	III – 8(9)



Properties of some Y^{3+}complexes formed with DTPA type ligands



Ligand	Σ log K_i^H (log K_1^H)	log K_{YL}	k_D^* (s^{-1})
CHX-A	32.92 **(12.3)**	**24.7**	**0.462**
CHX-B	31.47 **(12.3)**	**24.4**	**0.047**
1B4M	30.39 (11.31)	22.5	6.62
1B3M	30.60 (11.46)	22.5	13.5
2B	29.24 (10.75)	21.7	41.8
1B	29.18 (11.16)	21.5	37.4
CHX-DTPA	32.27 **(12.3)**	**24.2**	**0.75**
DTPA	28.00 (10.48)	22.4	144

* The rates of acid catalyzed dissociation were measured with the use f ArIII ([YL]=10^{-5} mol/dm^3 and [AAIII]=10^{-5} mol/dm^3).

T. J. McMurry, C. G. Pippin, C. Wu, K. A. Deal, M. W. Brechbiel, S. Mirzadeh, O. A. Gansow, *J. Med. Chem.* **1998,** *41,* 3546

Some general requirements to the complexes to be used in medicine

✓Good water solubility (easy to administer)

✓Low osmolality and preferably no (or negative) charge

✓Non-toxicity

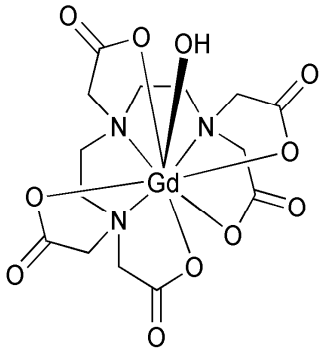
✓High thermodynamic stability and kinetic inertness

✓Possible quick complex formation

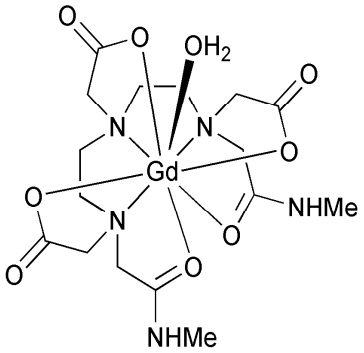
✓Organ specificity (when injected the media concentrates in area(s) required or bifunctional ligands)

✓The production of the ligand and the complex should be cost effective.

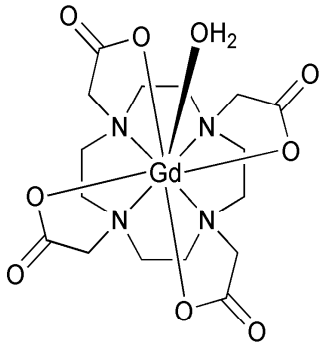
Clinically approved, commercially available Gd-based contrast agents (q=1)



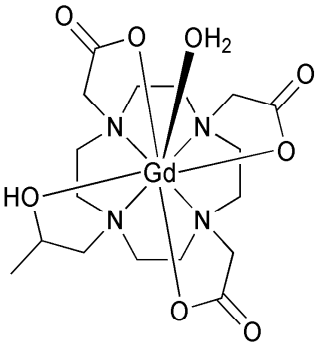
$GdDTPA^{2-}$
Magnavist



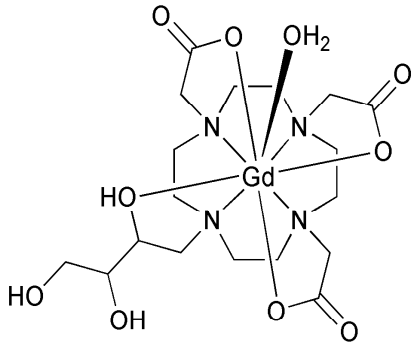
GdDTPA-BMA
Omniscan



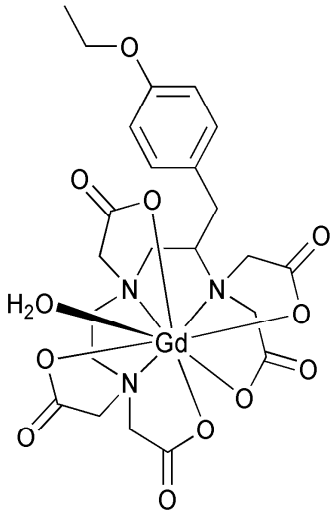
$GdDOTA^{-}$
Dotarem



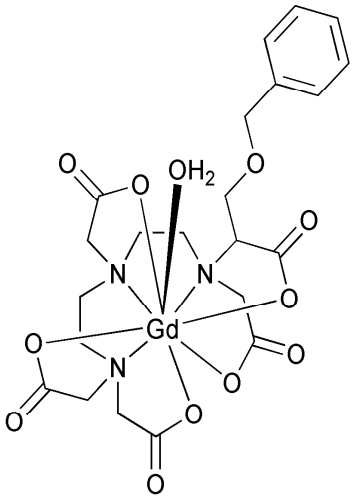
GdHP-DO3A
ProHance



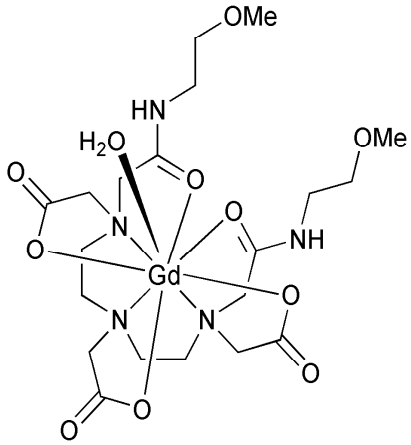
GdDO3A-Butrol
Gadovist



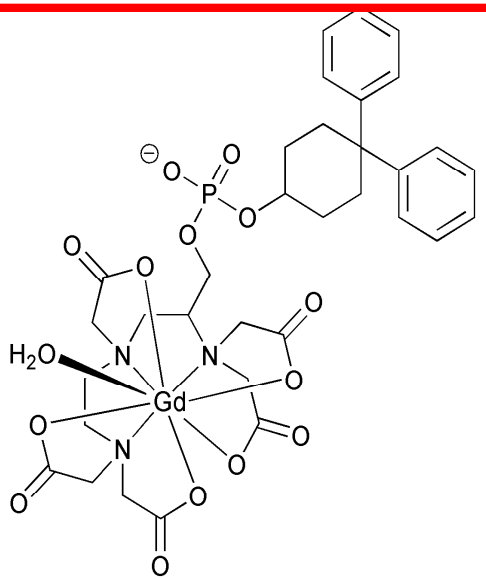
$GdDTPA\text{-}EOB^{2-}$
Eovist



$GdBOPTA^{2-}$
Multihance



GdDTPA-BMEA
Optimark



MS-325
Vasovist

Table 1 General characteristics of currently marketed gadolinium chelates used for magnetic resonance imaging (Idée et al. 2006; Caravan et al. 1999; Brücher and Sherry 2001)

Name	Acronym Generic Name Trade Name	Gd-DTPA Gadopentetate dimeglumine Magnevist®	Gd-DTPA-BMA Gadodiamide Omniscan®	Gd-DTPA-BMEA Gadoversetamide OptiMARK®	Gd-BOPTA Gadobenate dimeglumine MultiHance®	Gd-EOB-DTPA Gadoxetic acid disodium salt Primovist®	MS325 Gadofosveset trisodium salt Vasovist®	Gd-DOTA Gadoterate meglumine Dotarem®	Gd-HP-DO3A Gadoteridol ProHance®	Gd-BT-DO3A Gadobutrol Gadovist®
Company		Bayer-Schering	GE-Healthcare	Covidien	Bracco	Bayer-Schering	Bayer-Schering	Guerbet	Bracco	Bayer-Schering
Chemical structure		Open-chain	Open-chain	Open-chain	Open-chain	Open-chain	Open-chain	Macrocyclic	Macrocyclic	Macrocyclic
Charge		Di-ionic	Nonionic	Nonionic	Di-ionic	Di-ionic	Tri-ionic	Ionic	Nonionic	Nonionic
Dissociated particles per molecule		3	1	1	3	3	4	2	1	1
Log *P* BuOH/H_2O		−3.16	−2.13	ND	−2.33	−2.11	−2.11	−2.87	−1.98	−2
Concentration (M)		0.5	0.5	0.5	0.5	0.25	0.25	0.5	0.5	1.0
Standard dose (mmol/kg)		0.1	0.1	0.1	0.1[a]	0.025	0.03	0.1	0.1	0.1
Osmolality at 37°C (mOsm/kg H_2O)		1960	789	1110	1970	688	825	1350	630	1603
Osmotic load[b] (mOsmol/l)		2	0.67	0.67	2	0.5	0.8	1.33	0.67	0.67
Relaxivity (r_1/r_2) $mM^{-1}s^{-1}$ at 37°C, 1.5 T in water[c]		3.3/3.9	3.3/3.9	3.6/4.1	3.8/4.4	4.6/5.3	5.0/5.9	3.0/3.5	2.9/3.4	3.3/3.9
Viscosity (mPa.s) at 37°C		2.9	1.4	2.0	5.3	1.19	2.1[e]	2.0	1.3	4.96
Formulation		Free DTPA 0.2% (1 mmol/l)	Ca-DTPA-BMA (Na^+ salt) 5% (25 mmol/l)	Ca-DTPA-BMEA (Na^+ salt) (50 mmol/l)	No formulation	Ca-EOB-DTPA (trisodium salt)[d]	Fosvest ligand (0.325 mmol/l)[e]	No formulation	[Ca-HP-DO3A]$_2$ (Ca^{2+} salt) 0.1% (0.5 mmol/l)	Ca-BT-DO3A (Na^+ salt) (1 mmol/l)
Log K_{therm}		22.1	16.9	16.6	22.6	23.46	22.1[f]	25.6[g]	23.8	21.8
Log K_{cond}		17.7	14.9	15.0	18.4[h]	18.7[i]	18.9[f]	19.3[g]	17.1	14.7[j]

[a] Dose for liver imaging: 0.05 mmol/kg

[b] osmotic load (mOsm/l) $= \frac{\text{dose(mmol/kg)} * 70}{\text{V}_{\text{distribution}}(l)} *$ number dissociated ions (values are calculated on the assumption that the agents distribute homogeneously in the interstitial space (10.5 l for a patient weighing 70 kg)

[c] Guerbet measurement on commercial solution; Incertainty on relaxometric measurement: ±0.3 $mM^{-1}\,s^{-1}$ for relaxicity measurements

[d] (concentration not disclosed)

[e] Steger-Hartmann et al. (2006)

[f] Caravan et al. (2001)

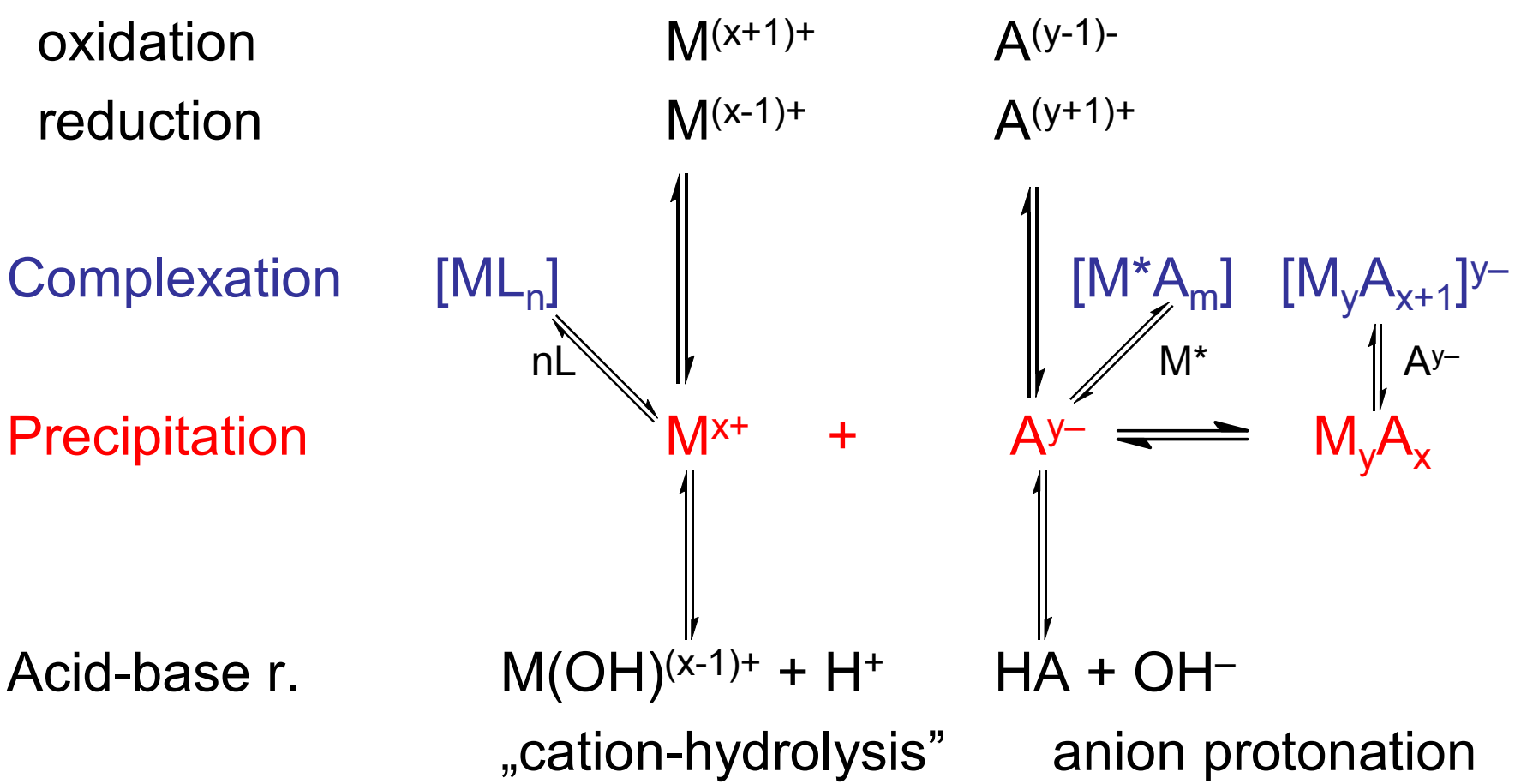
[g] Moreau et al. (2004) and Guerbet calculations

[h] Uggeri et al. (1995)

[i] Schmitt-Willich et al. (1999)

[j] Bellin et al. (2003)

Coupled equilibria (simultaneous equilibria)



Conditional stability constants

There is a definite need to consider the „side reactions” of the metal ion and the ligand

The most important parameter (in clean systems) is pH:

H^+ could protonate the (week base) ligand

OH- could form hydroxo-complexes/hydroxide precipitate with the metal ion

Endogenous metal ions and ligands in „real systems”: almost unlimited number of competitors

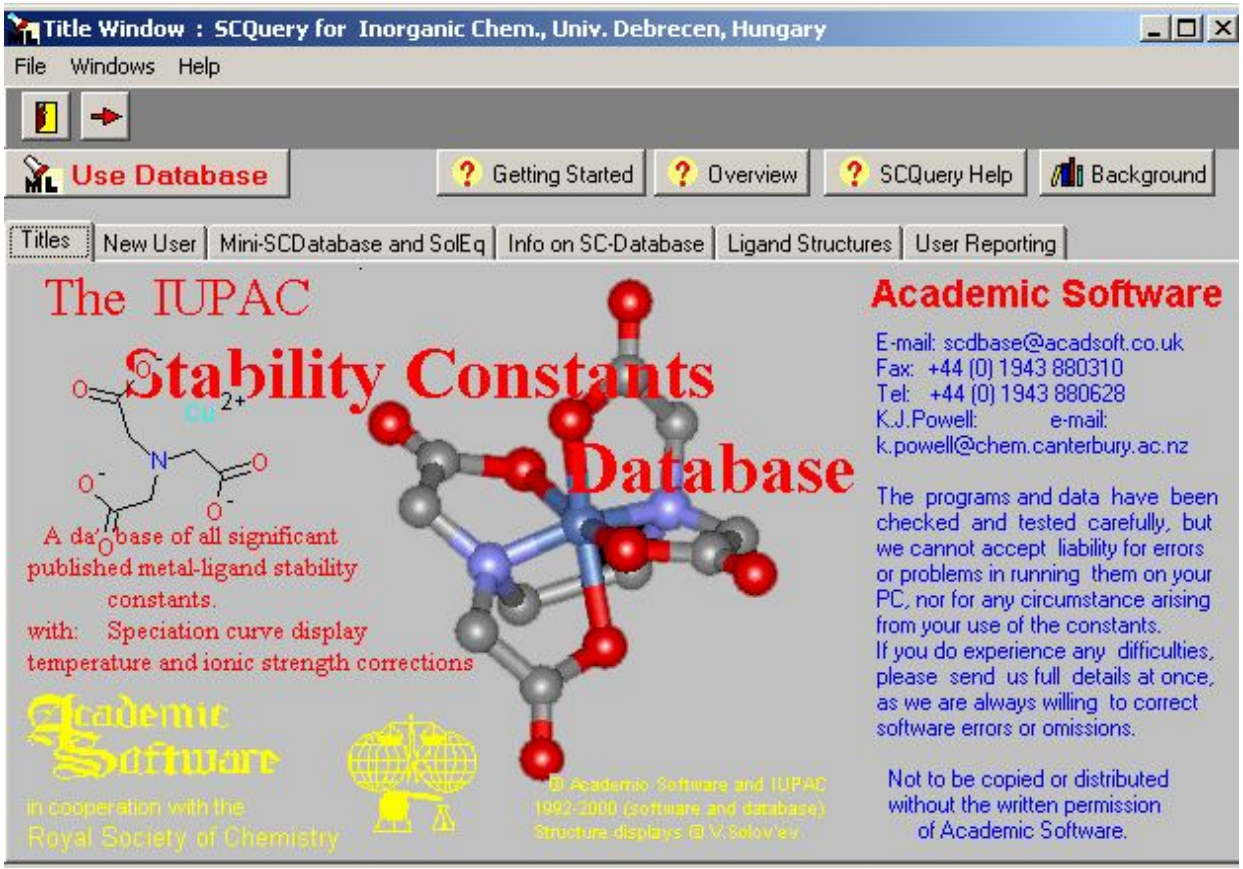
One can not calculate conditional constants by hand

Model calculations need suitable data ($\log\beta_{ML}$, $\log\beta_{HL,}$

pL (solubility product), pH, pE, temperature

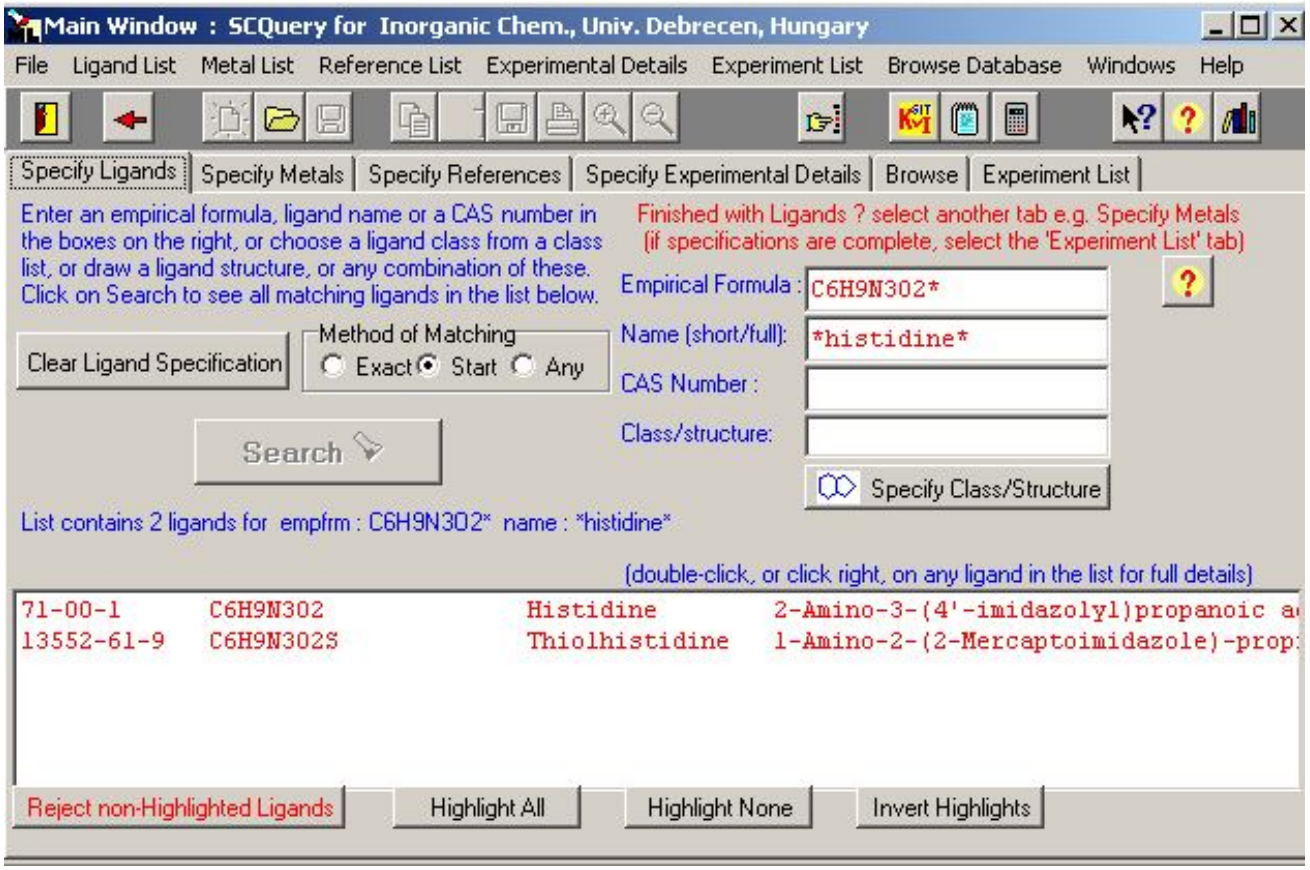
(Could be good for planing experiments also!)

Modelling



(Stability Constants Databases - NIST and IUPAC)

Modelling


Main Window : SCQuery for Inorganic Chem., Univ. Debrecen, Hungary
File Ligand List Metal List Reference List Experimental Details Experiment List Browse Database Windows Help
Specify Ligands Specify Metals Specify References Specify Experimental Details Browse Experiment List
Enter an empirical formula, ligand name or a CAS number in the boxes on the right, or choose a ligand class from a class list, or draw a ligand structure, or any combination of these. Click on Search to see all matching ligands in the list below.
Finished with Ligands ? select another tab e.g. Specify Metals (if specifications are complete, select the 'Experiment List' tab)
Empirical Formula : C6H9N3O2*
Name (short/full): *histidine*
CAS Number :
Class/structure:
Clear Ligand Specification
Method of Matching Exact Start Any
Search
Specify Class/Structure
List contains 2 ligands for empfrm : C6H9N3O2* name : *histidine*
(double-click, or click right, on any ligand in the list for full details)
71-00-1 C6H9N3O2 Histidine 2-Amino-3-(4'-imidazolyl)propanoic a
13552-61-9 C6H9N3O2S Thiolhistidine 1-Amino-2-(2-Mercaptoimidazole)-prop
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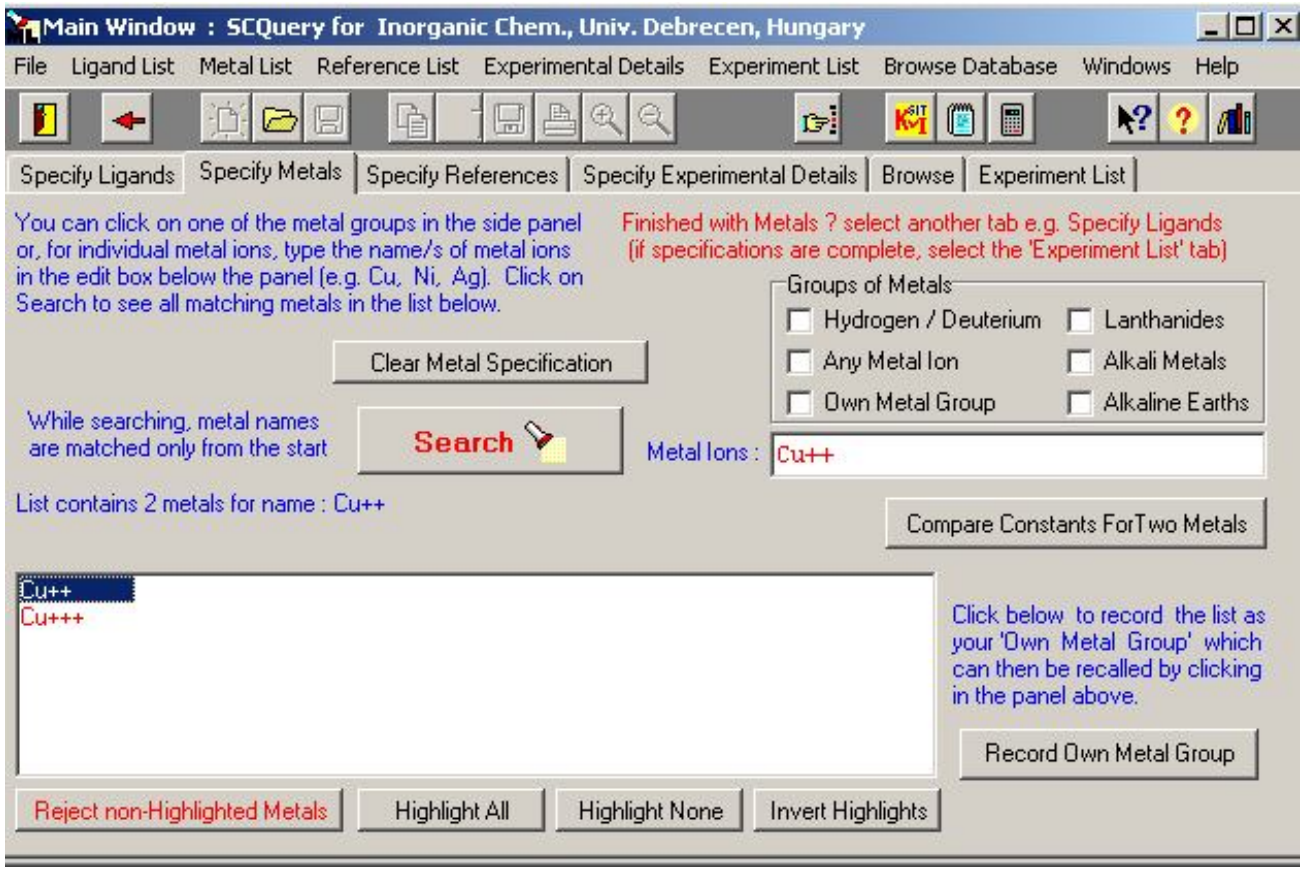
Modelling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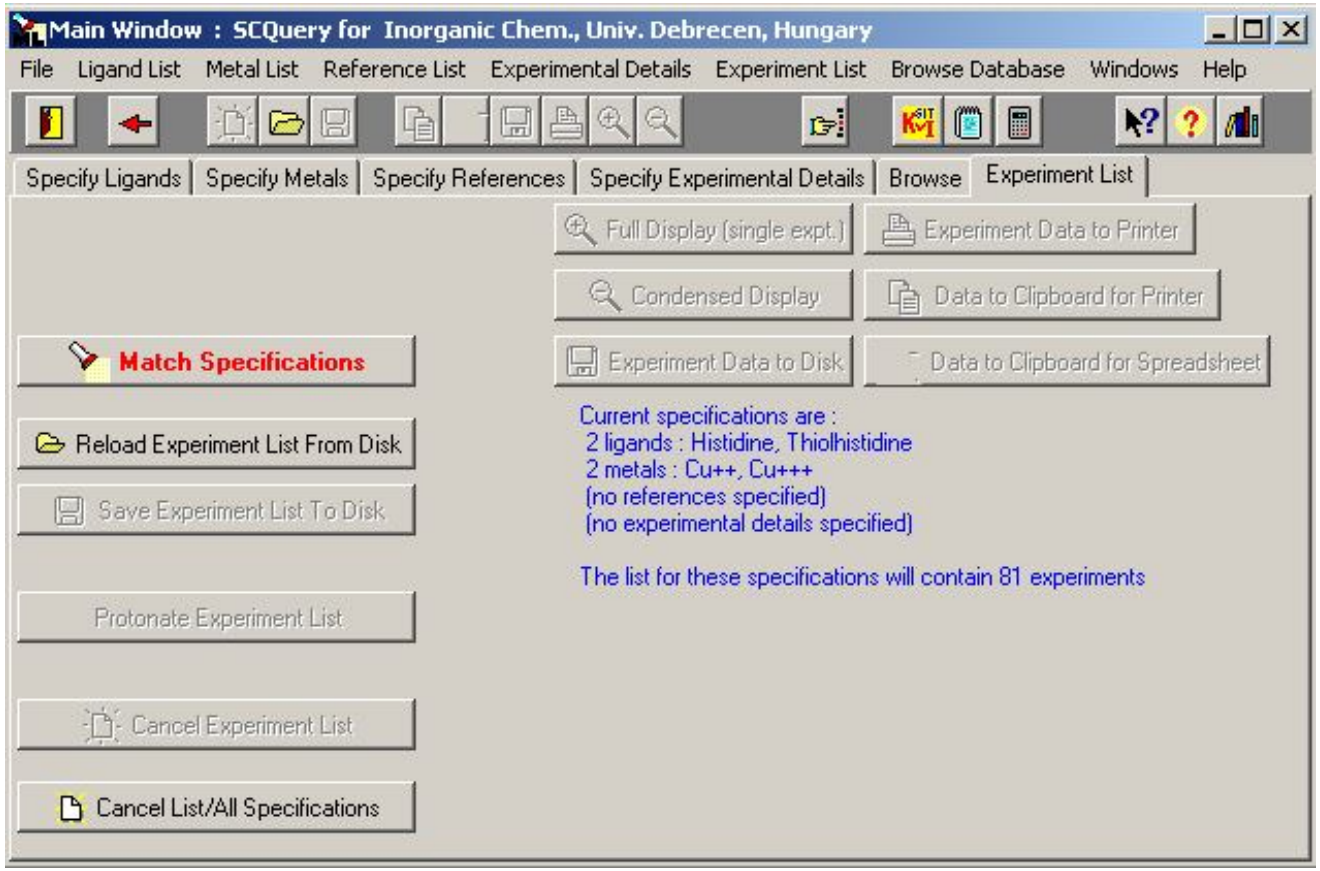
Experiment List
You can click on one of the metal groups in the side panel or, for individual metal ions, type the name/s of metal ions in the edit box below the panel (e.g. Cu, Ni, Ag). Click on Search to see all matching metals in the list below.
Finished with Metals ? select another tab e.g. Specify Ligands (if specifications are complete, select the 'Experiment List' tab)
Groups of Metals
Hydrogen / Deuterium
Lanthanides
Any Metal Ion
Alkali Metals
Own Metal Group
Alkaline Earths
Clear Metal Specification
While searching, metal names are matched only from the start
Search
Metal Ions :
Cu++
List contains 2 metals for name : Cu++
Compare Constants ForTwo Metals
Cu++
Cu+++
Click below to record the list as your 'Own Metal Group' which can then be recalled by clicking in the panel above.
Record Own Metal Group
Reject non-Highlighted Metals
Highlight All
Highlight None
Invert Highlights

Modelling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Experimental Details
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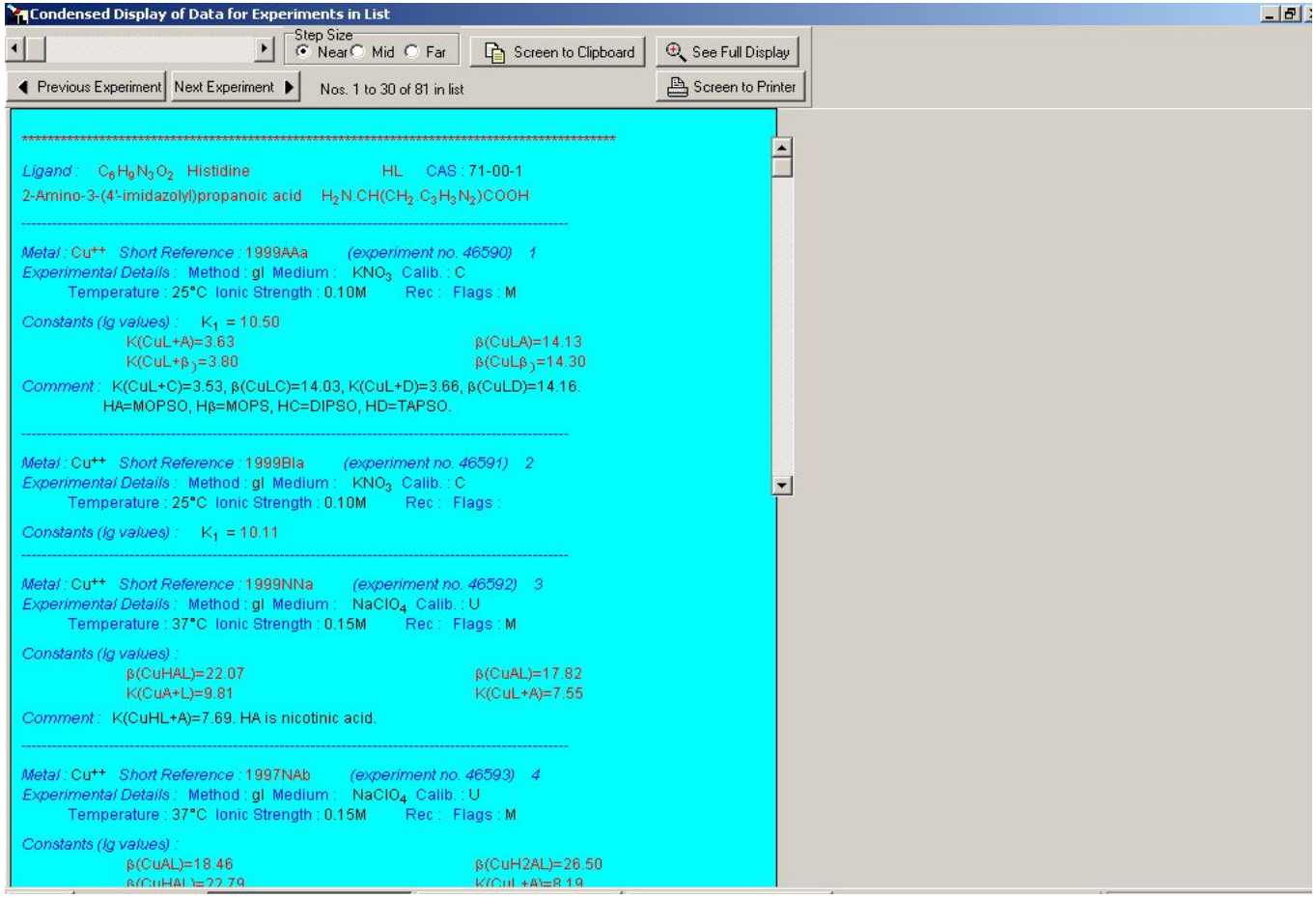
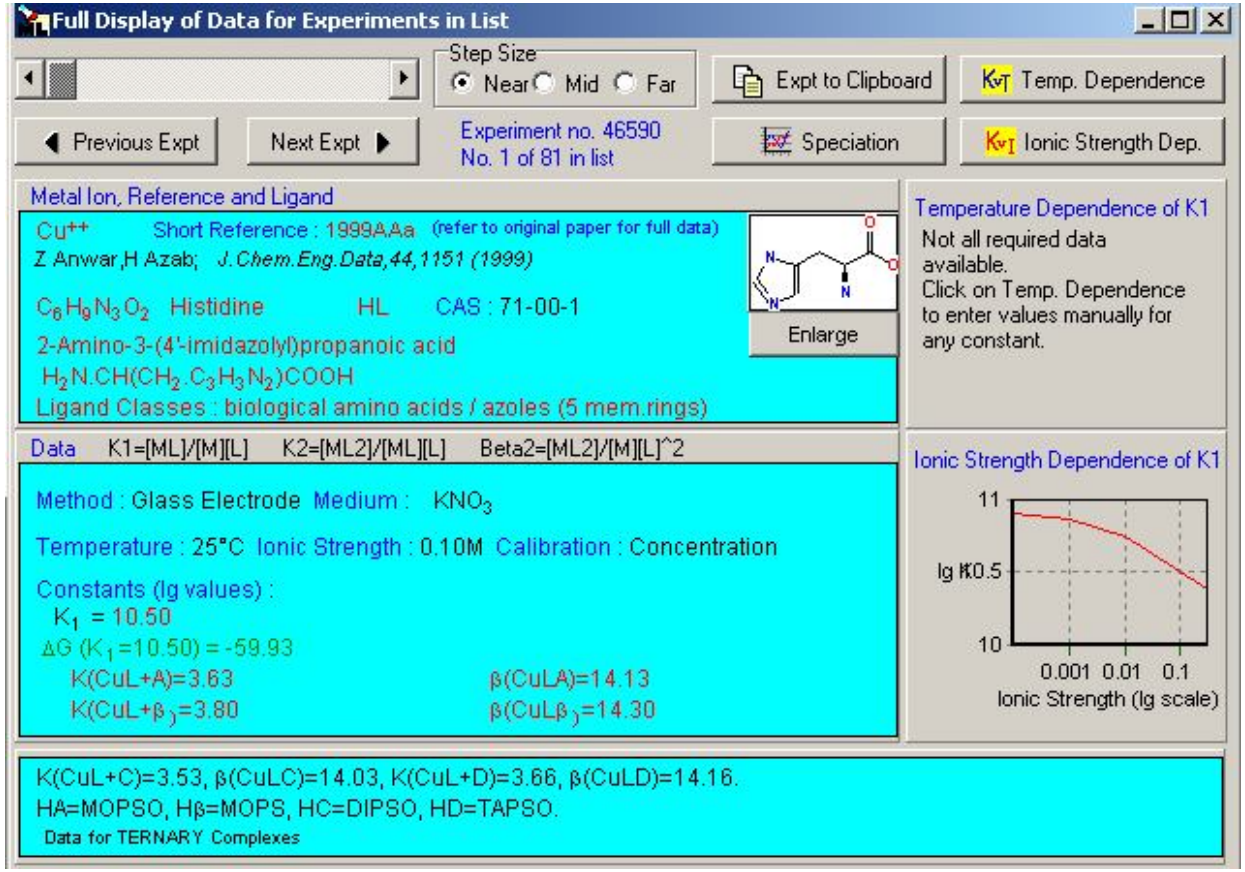
Specify Experimental Details
Browse
Experiment List
Full Display (single expt.)
Experiment Data to Printer
Condensed Display
Data to Clipboard for Printer
Match Specifications
Experiment Data to Disk
Data to Clipboard for Spreadsheet
Reload Experiment List From Disk
Save Experiment List To Disk
Current specifications are :
2 ligands : Histidine, Thiolhistidine
2 metals : Cu++, Cu+++
(no references specified)
(no experimental details specified)
The list for these specifications will contain 81 experiments
Protonate Experiment List
Cancel Experiment List
Cancel List/All Specifications

Modelling


Condensed Display of Data for Experiments in List
Step Size
Near
Mid
Far
Screen to Clipboard
See Full Display
Previous Experiment
Next Experiment
Nos. 1 to 30 of 81 in list
Screen to Printer
Ligand : $C_6H_9N_3O_2$ Histidine HL CAS : 71-00-1
2-Amino-3-(4'-imidazolyl)propanoic acid $H_2N.CH(CH_2.C_3H_3N_2)COOH$
Metal : Cu++ Short Reference : 1999AAa (experiment no. 46590) 1
Experimental Details : Method : gl Medium : KNO_3 Calib. : C
Temperature : 25°C Ionic Strength : 0.10M Rec : Flags : M
Constants (lg values) : K_1 = 10.50
K(CuL+A)=3.63 β(CuLA)=14.13
K(CuL+$β_)$=3.80 β(CuL$β_)$=14.30
Comment : K(CuL+C)=3.53, β(CuLC)=14.03, K(CuL+D)=3.66, β(CuLD)=14.16.
HA=MOPSO, Hβ=MOPS, HC=DIPSO, HD=TAPSO.
Metal : Cu++ Short Reference : 1999Bla (experiment no. 46591) 2
Experimental Details : Method : gl Medium : KNO_3 Calib. : C
Temperature : 25°C Ionic Strength : 0.10M Rec : Flags :
Constants (lg values) : K_1 = 10.11
Metal : Cu++ Short Reference : 1999NNa (experiment no. 46592) 3
Experimental Details : Method : gl Medium : $NaClO_4$ Calib. : U
Temperature : 37°C Ionic Strength : 0.15M Rec : Flags : M
Constants (lg values) :
β(CuHAL)=22.07 β(CuAL)=17.82
K(CuA+L)=9.81 K(CuL+A)=7.55
Comment : K(CuHL+A)=7.69. HA is nicotinic acid.
Metal : Cu++ Short Reference : 1997NAb (experiment no. 46593) 4
Experimental Details : Method : gl Medium : $NaClO_4$ Calib. : U
Temperature : 37°C Ionic Strength : 0.15M Rec : Flags : M
Constants (lg values) :
β(CuAL)=18.46 β(CuH2AL)=26.50

Modelling


Full Display of Data for Experiments in List
Step Size
Near
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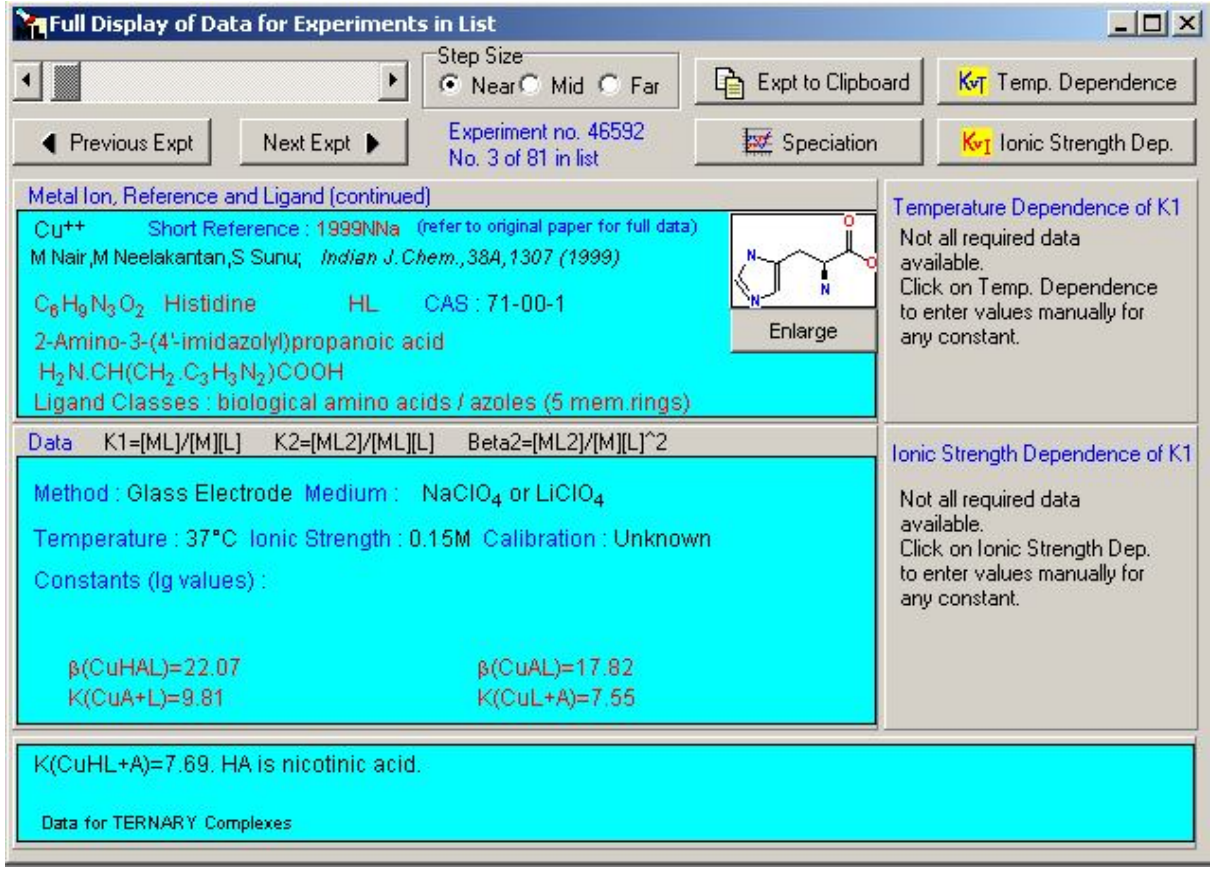
Expt to Clipboard
Temp. Dependence
Previous Expt
Next Expt
Experiment no. 46590
No. 1 of 81 in list
Speciation
Ionic Strength Dep.
Metal Ion, Reference and Ligand
Cu++ Short Reference : 1999AAa (refer to original paper for full data)
Z Anwar,H Azab; J.Chem.Eng.Data,44,1151 (1999)
C6H9N3O2 Histidine HL CAS : 71-00-1
2-Amino-3-(4'-imidazolyl)propanoic acid
H2N.CH(CH2.C3H3N2)COOH
Ligand Classes : biological amino acids / azoles (5 mem.rings)
Enlarge
Temperature Dependence of K1
Not all required data available.
Click on Temp. Dependence to enter values manually for any constant.
Data K1=[ML]/[M][L] K2=[ML2]/[ML][L] Beta2=[ML2]/[M][L]^2
Method : Glass Electrode Medium : KNO3
Temperature : 25°C Ionic Strength : 0.10M Calibration : Concentration
Constants (lg values) :
K1 = 10.50
ΔG (K1=10.50) = -59.93
K(CuL+A)=3.63
β(CuLA)=14.13
K(CuL+β)=3.80
β(CuLβ)=14.30
Ionic Strength Dependence of K1
11
lg K0.5
10
0.001 0.01 0.1
Ionic Strength (lg scale)
K(CuL+C)=3.53, β(CuLC)=14.03, K(CuL+D)=3.66, β(CuLD)=14.16.
HA=MOPSO, Hβ=MOPS, HC=DIPSO, HD=TAPSO.
Data for TERNARY Complexes

Modelling


Full Display of Data for Experiments in List
Step Size
Near
Mid
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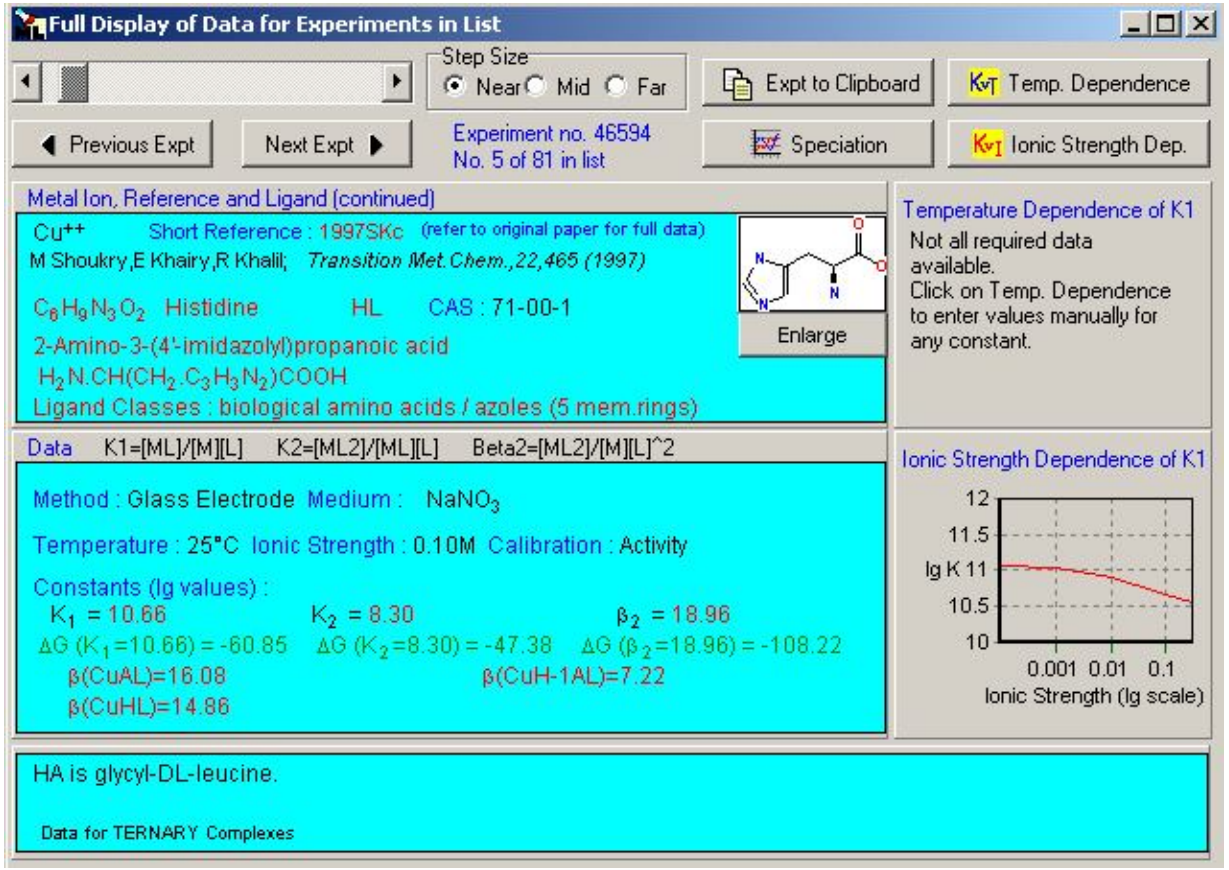
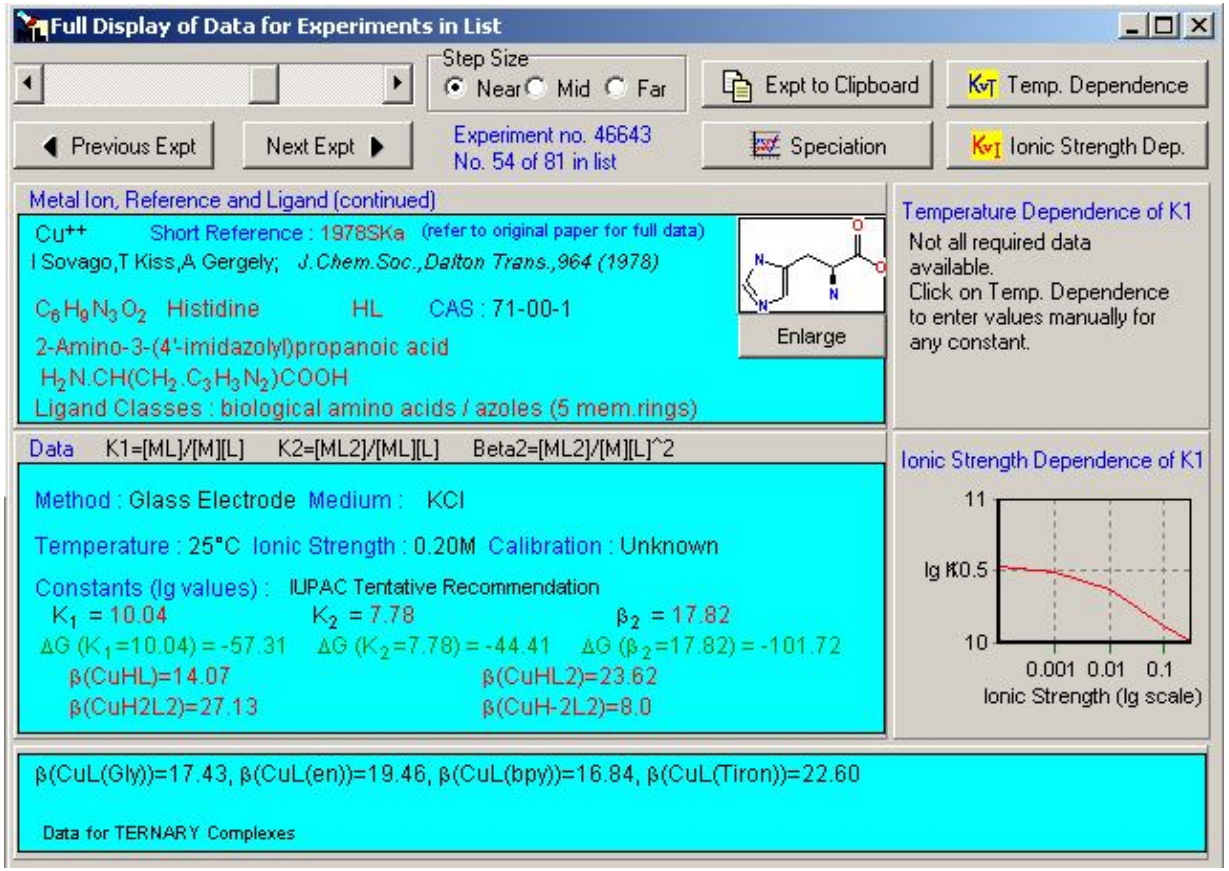
Expt to Clipboard
Temp. Dependence
Previous Expt
Next Expt
Experiment no. 46592
No. 3 of 81 in list
Speciation
Ionic Strength Dep.
Metal Ion, Reference and Ligand (continued)
Cu++ Short Reference : 1999NNa (refer to original paper for full data)
M Nair,M Neelakantan,S Sunu; Indian J.Chem.,38A,1307 (1999)
C6H9N3O2 Histidine HL CAS : 71-00-1
2-Amino-3-(4'-imidazolyl)propanoic acid
H2N.CH(CH2.C3H3N2)COOH
Ligand Classes : biological amino acids / azoles (5 mem.rings)
Enlarge
Temperature Dependence of K1
Not all required data available.
Click on Temp. Dependence to enter values manually for any constant.
Data K1=[ML]/[M][L] K2=[ML2]/[ML][L] Beta2=[ML2]/[M][L]^2
Method : Glass Electrode Medium : NaClO4 or LiClO4
Temperature : 37°C Ionic Strength : 0.15M Calibration : Unknown
Constants (lg values) :
β(CuHAL)=22.07
β(CuAL)=17.82
K(CuA+L)=9.81
K(CuL+A)=7.55
Ionic Strength Dependence of K1
Not all required data available.
Click on Ionic Strength Dep. to enter values manually for any constant.
K(CuHL+A)=7.69. HA is nicotinic acid.
Data for TERNARY Complexes

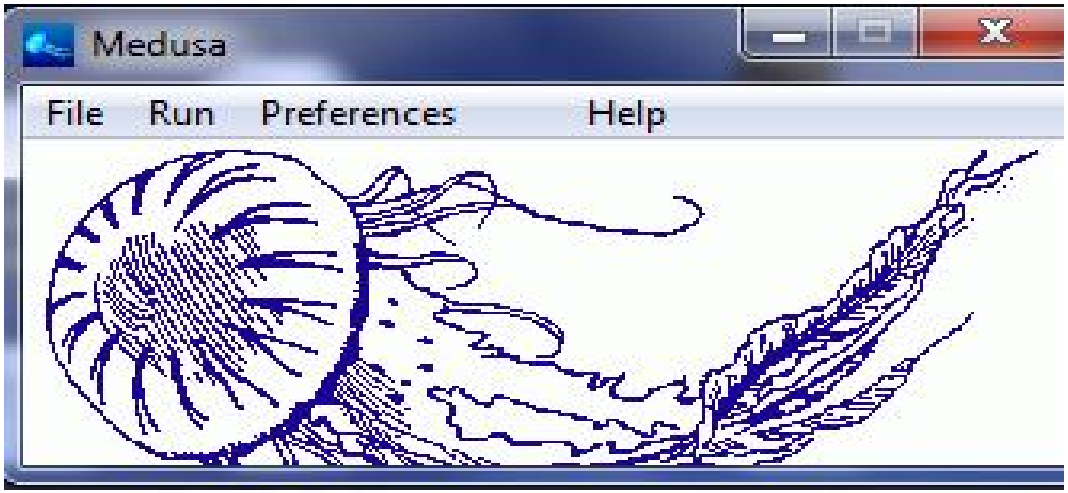
Modelling


Full Display of Data for Experiments in List
Step Size
Near
Mid
Far
Expt to Clipboard
Temp. Dependence
Previous Expt
Next Expt
Experiment no. 46594
No. 5 of 81 in list
Speciation
Ionic Strength Dep.
Metal Ion, Reference and Ligand (continued)
Cu++ Short Reference : 1997SKc (refer to original paper for full data)
M Shoukry,E Khairy,R Khalil; Transition Met.Chem.,22,465 (1997)
C6H9N3O2 Histidine HL CAS : 71-00-1
2-Amino-3-(4'-imidazolyl)propanoic acid
H2N.CH(CH2.C3H3N2)COOH
Ligand Classes : biological amino acids / azoles (5 mem.rings)
Enlarge
Temperature Dependence of K1
Not all required data available.
Click on Temp. Dependence to enter values manually for any constant.
Data K1=[ML]/[M][L] K2=[ML2]/[ML][L] Beta2=[ML2]/[M][L]^2
Method : Glass Electrode Medium : NaNO3
Temperature : 25°C Ionic Strength : 0.10M Calibration : Activity
Constants (lg values) :
K1 = 10.66 K2 = 8.30 β2 = 18.96
ΔG (K1=10.66) = -60.85 ΔG (K2=8.30) = -47.38 ΔG (β2=18.96) = -108.22
β(CuAL)=16.08 β(CuH-1AL)=7.22
β(CuHL)=14.86
Ionic Strength Dependence of K1
12
11.5
lg K 11
10.5
10
0.001 0.01 0.1
Ionic Strength (lg scale)
HA is glycyl-DL-leucine.
Data for TERNARY Complexes

Modelling

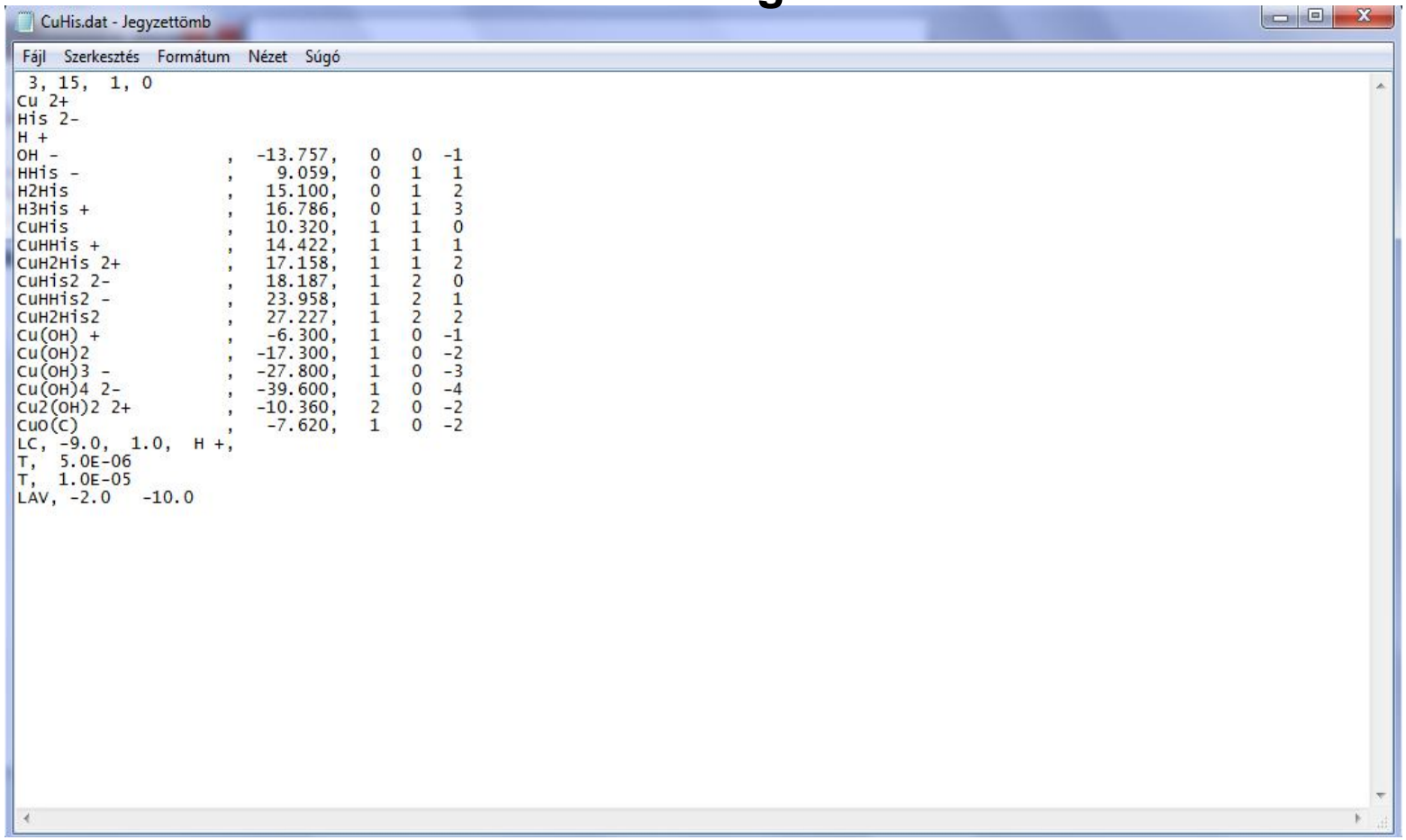

Full Display of Data for Experiments in List
Step Size
Near
Mid
Far
Expt to Clipboard
Temp. Dependence
Previous Expt
Next Expt
Experiment no. 46643
No. 54 of 81 in list
Speciation
Ionic Strength Dep.
Metal Ion, Reference and Ligand (continued)
Cu++ Short Reference : 1978SKa (refer to original paper for full data)
I Sovago,T Kiss,A Gergely; J.Chem.Soc.,Dalton Trans.,964 (1978)
C6H9N3O2 Histidine HL CAS : 71-00-1
2-Amino-3-(4'-imidazolyl)propanoic acid
H2N.CH(CH2.C3H3N2)COOH
Ligand Classes : biological amino acids / azoles (5 mem.rings)
Enlarge
Temperature Dependence of K1
Not all required data available.
Click on Temp. Dependence to enter values manually for any constant.
Data K1=[ML]/[M][L] K2=[ML2]/[ML][L] Beta2=[ML2]/[M][L]^2
Method : Glass Electrode Medium : KCl
Temperature : 25°C Ionic Strength : 0.20M Calibration : Unknown
Constants (lg values) : IUPAC Tentative Recommendation
K1 = 10.04 K2 = 7.78 β2 = 17.82
ΔG (K1=10.04) = -57.31 ΔG (K2=7.78) = -44.41 ΔG (β2=17.82) = -101.72
β(CuHL)=14.07 β(CuHL2)=23.62
β(CuH2L2)=27.13 β(CuH-2L2)=8.0
Ionic Strength Dependence of K1
11
lg K0.5
10
0.001 0.01 0.1
Ionic Strength (lg scale)
β(CuL(Gly))=17.43, β(CuL(en))=19.46, β(CuL(bpy))=16.84, β(CuL(Tiron))=22.60
Data for TERNARY Complexes

Modelling



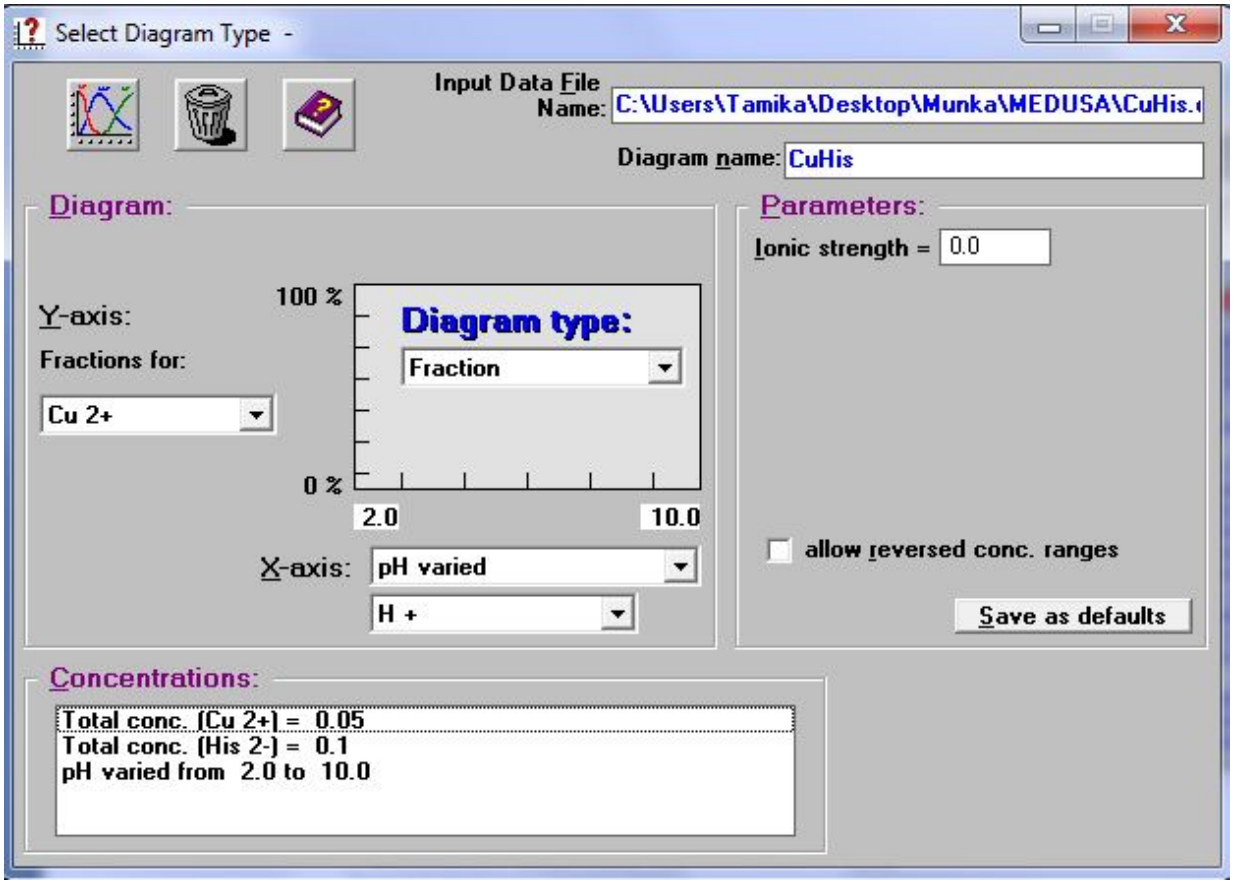
Medusa developed by Ignasi Puigdomenech at the Royal Institute of Technology (KTH), Stockholm, Sweden. (I.Puigdomenech (2000) "Windows software for the graphical presentation of chemical speciation", in: *219th ACS National Meeting. Abstracts of Papers*, Vol.1. Amer. Chem. Soc., San Francisco, Ca, March 26-30, 2000. Abstract I&EC-248. http://www.kemi.kth.se/medusa). This program is free, it can be down loaded from the web-site of the KTH or I. Puigdomenech

Modelling

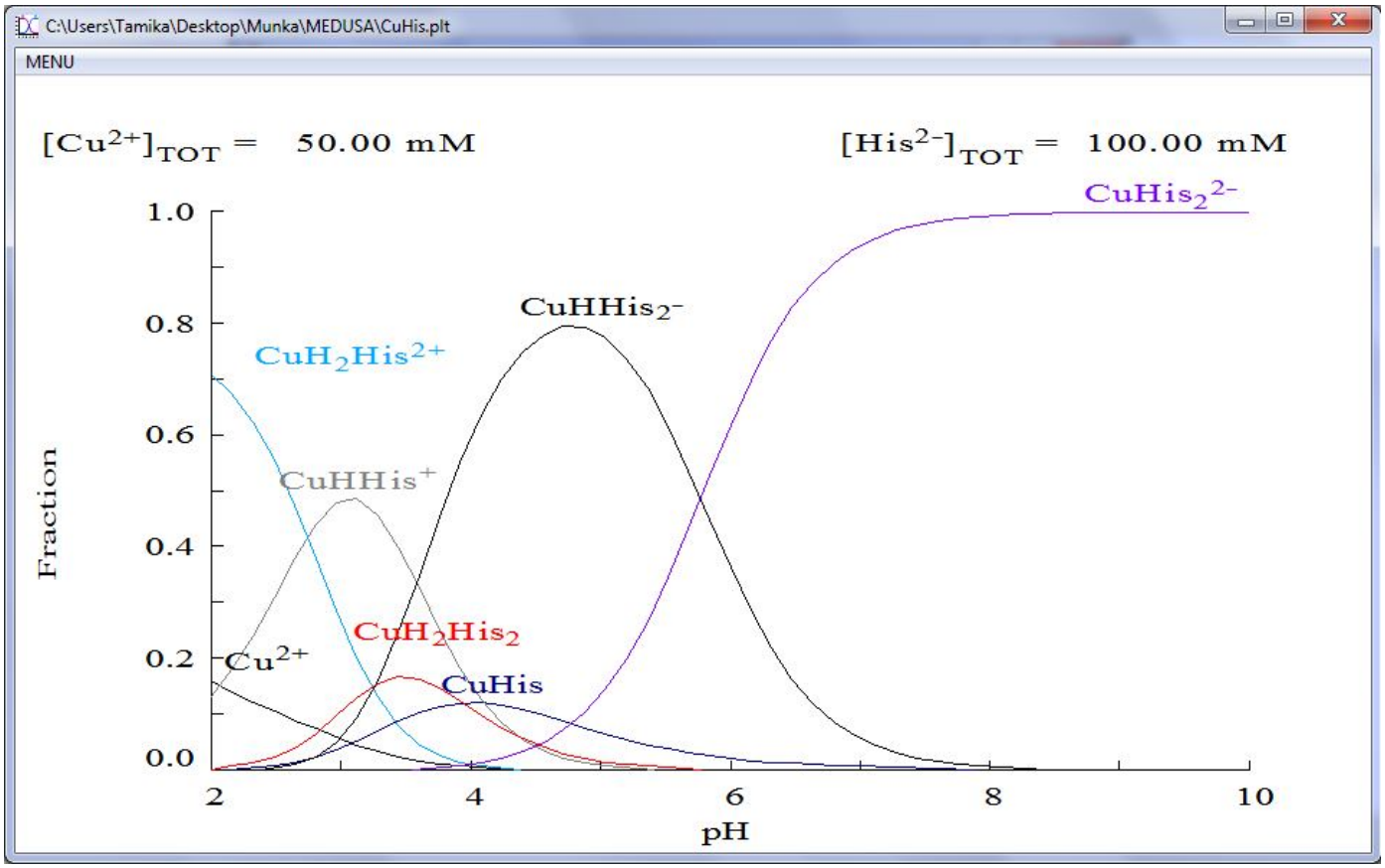


The matrix and the constants are defined by selected components and the equilibrium reaction being considered!

Modelling

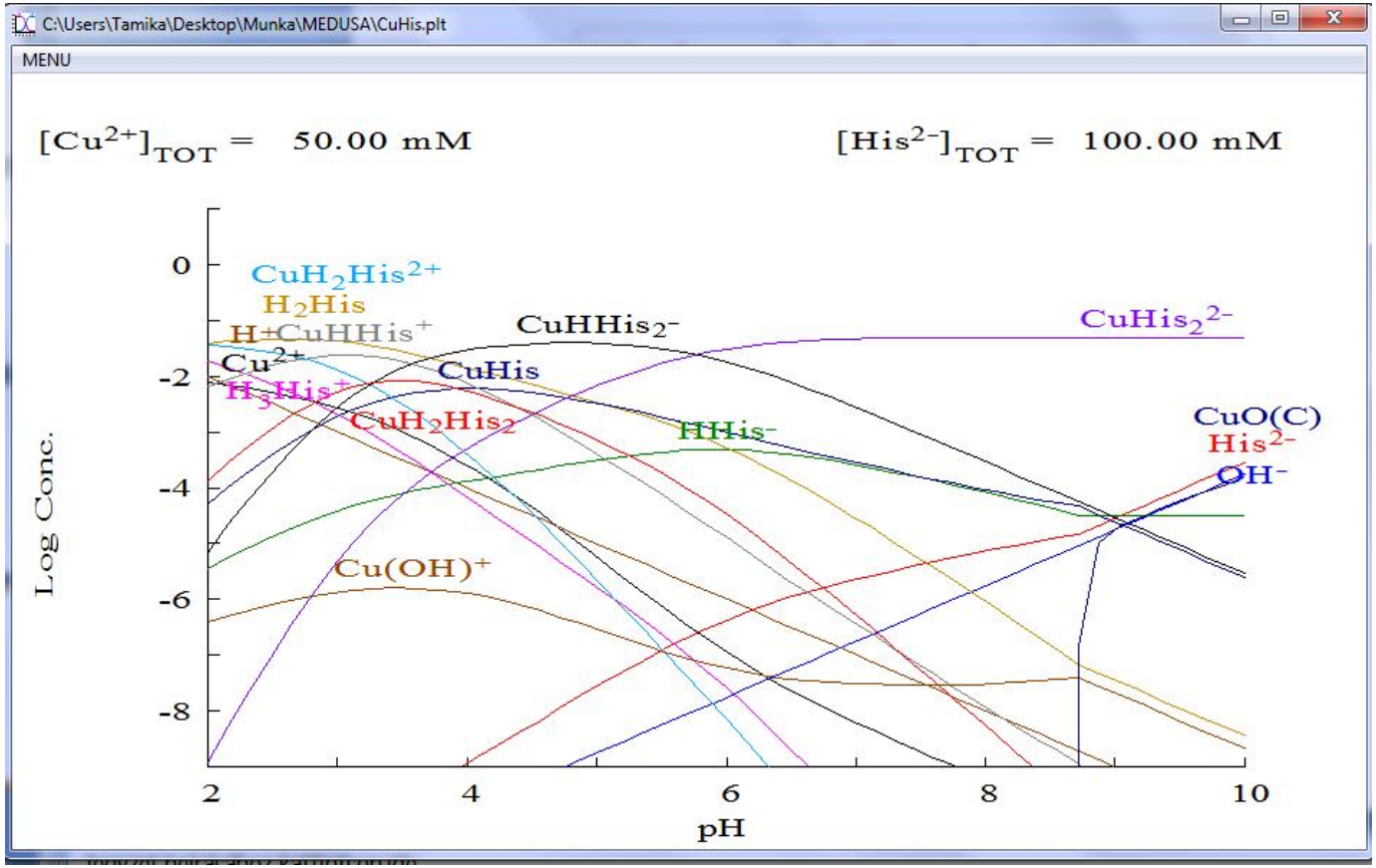

Select Diagram Type -
Input Data File Name:
C:\Users\Tamika\Desktop\Munka\MEDUSA\CuHis.
Diagram name:
CuHis
Diagram:
Parameters:
Ionic strength =
0.0
Y-axis:
Fractions for:
Cu 2+
100 %
0 %
Diagram type:
Fraction
2.0
10.0
X-axis:
pH varied
H +
allow reversed conc. ranges
Save as defaults
Concentrations:
Total conc. (Cu 2+) = 0.05
Total conc. (His 2-) = 0.1
pH varied from 2.0 to 10.0

Modelling



Distribution curves for the major species (e.g. >10 %)

Modelling



Log c – pH showing „all species”. Numerical values are also calculated.

Measuring of stability constants

Step-vice formation of complexes:

$$M + L \rightleftharpoons ML \qquad K_1 = \frac{[ML]}{[M][L]}$$

Mass balance equaitions + measuring at least one equilibrium concentration

$T_M = [M] + [ML]$

$T_L = [L] + [ML]$

Several standard methods are known in case of fast equilibration and moderate stability: [M] / [ML] ~ 1 (0.1 – 10) adjusted by the experimental conditions (pH, concentrations of components etc)

- pH-potentiometric titration (2 <pH >12)
- UV-VIS spectrophotometry
- multinuclear NMR spectroscopy
- 1H-NMR relaxometry
- microcalorimetry

Serious limitations in case of slow equilibration and very large stability

Measuring of (moderate) stability constants by pH-potentiometry: H^+ competition

$$M^{n+} + H_xL \rightleftharpoons ML + xH^+$$

Fast formation and dissociation

Slow formation and dissociation

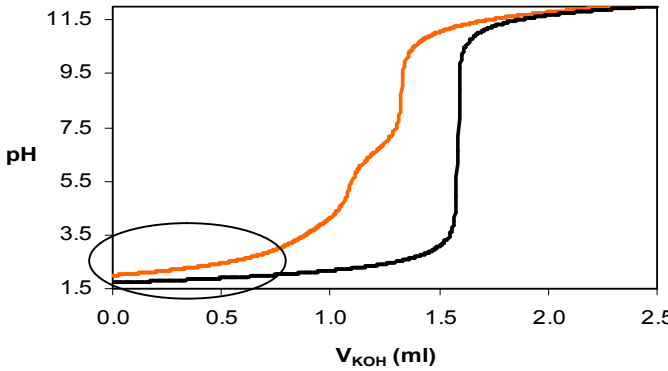
$[H^+]_{TOT}$,

$[L]_{TOT}$,

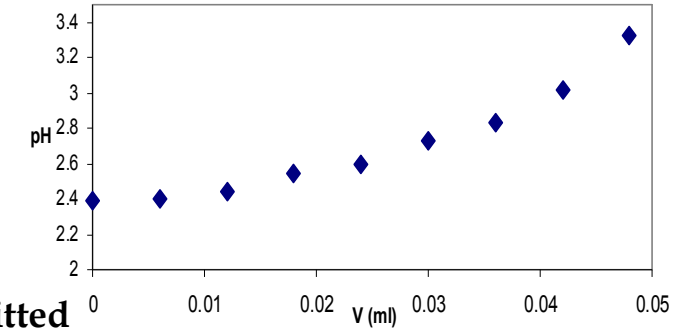
$[M^{n+}]_{TOT}$

are known

Direct titration



"out-of-cell" technique



The titration data is usually fitted with the use of the following softwares:

PSEQUAD

SUPERQUAD

HYPERQUAD

OPIUM

The stability of various complex species can be obtained simultaneously.

$(\log K_{ML}, \log K^{H}_{MH_iL}, \log K^{H}_{ML(OH)_j}, \log K_{M_2L}$ and $\log K_{ML_2})$

In most of the cases the stability constants of the ML complexes can be calculated.

$(\log K_{ML})$

The protonation constant of the complexes have to be determined in a separate (direct) titration

$(\log K_{M_2L}, \log K_{ML_2}, \log K^{H}_{MH_iL}$ and $\log K^{H}_{ML(OH)_j})$

Determination of (high) stability constants : proton + metal ion or ligand competition

$$M^{n+} + H_yA + H_xL \rightleftharpoons ML + MA + x+yH^+$$
$$M^{n+} + Y^{z+} + H_xL \rightleftharpoons ML + YL + xH^+$$

Direct titration when the ligand or the metal exchange reaction is fast

"Out-of-cell" technique when the ligand or the metal exchange reaction is slow

pH-potentiometric titration

Large number of protonation and stability constants must be known ion order to be able to calculate the one that is under question.

$\log K^{H}_{H_jA}, \log K^{H}_{H_jL}, \log K_{MA}, \log K^{H}_{MH_iA}, \log K^{H}_{MA(OH)_j}$

$\log K^{H}_{H_jL}, \log K_{YL}, \log K^{H}_{YH_iL}, \log K^{H}_{YL(OH)_j}$

UV-VIS spectrophotometry

- Fast formation and dissociation: direct titration
- Slow formation and dissociation: "out of cell" method

} Competition reactions (metal or ligand exchange) or Simple complex formation

$A = l \cdot \varepsilon_{ML} \cdot c_{ML} + l \cdot \varepsilon_{MA} \cdot c_{MA} \Longrightarrow$ ligand exchange

$A = l \cdot \varepsilon_{ML} \cdot c_{ML} + l \cdot \varepsilon_{YL} \cdot c_{YL} \Longrightarrow$ metal exchange

Even larger number of constants must be obtained very precisely.

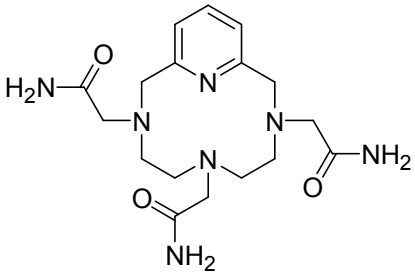
$\log K^{H}_{H_jA}, \log K^{H}_{H_jL}\ \log K_{MA}, \log K^{H}_{MH_iA}, \log K^{H}_{MA(OH)_j}$

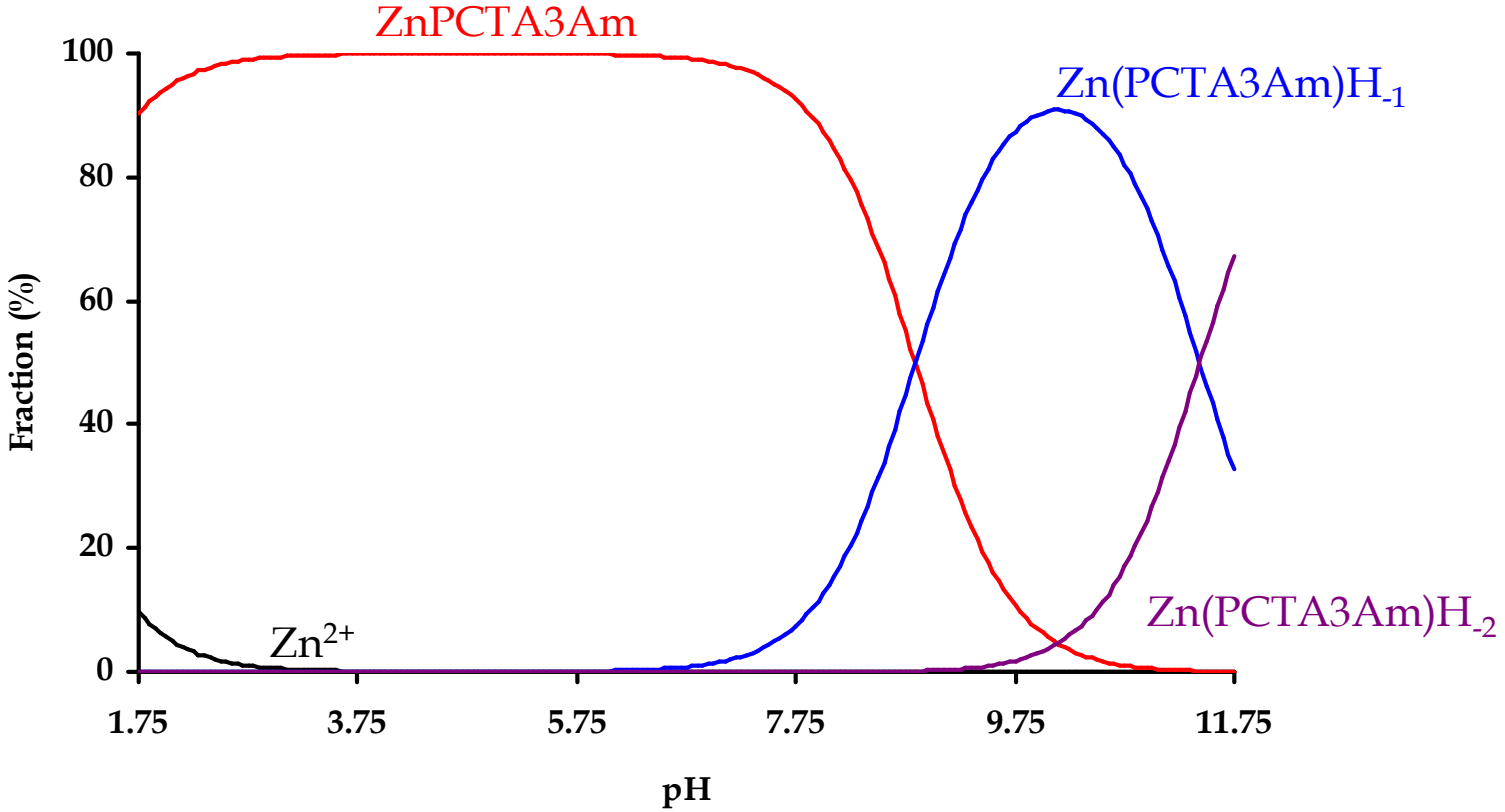
ε_{ML}, ε_{MHL}, $\varepsilon_{ML(OH)}$, ε_{MA}, ε_{MHA}, $\varepsilon_{MA(OH)}$

$\log K^{H}_{H_jL}, \log K_{YL}, \log K^{H}_{YH_iL}, \log K^{H}_{YL(OH)_j}$

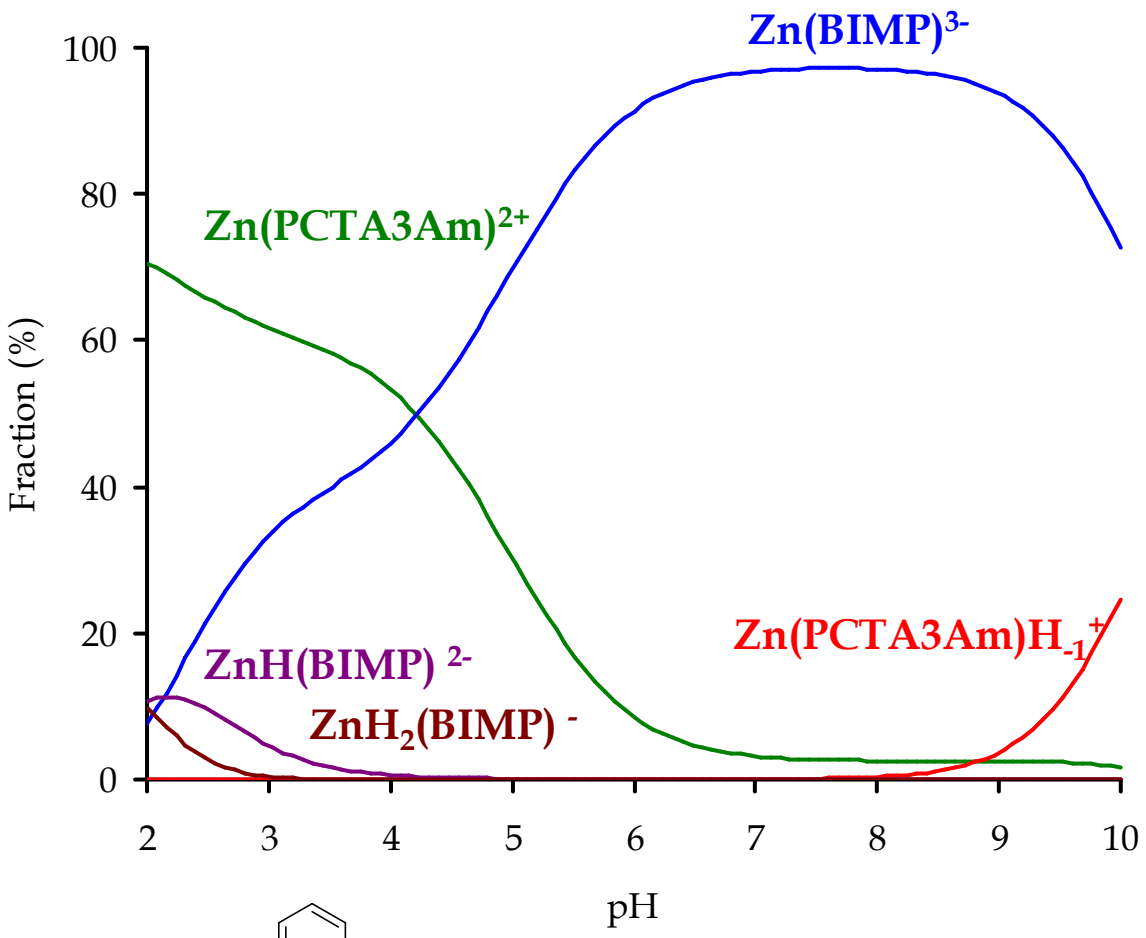
ε_{ML}, ε_{MHL}, $\varepsilon_{ML(OH)}$, ε_{YL}, ε_{YHL}, $\varepsilon_{YL(OH)}$,

Speciation of Zn^{2+}- PCTA3Am - H^{+} system

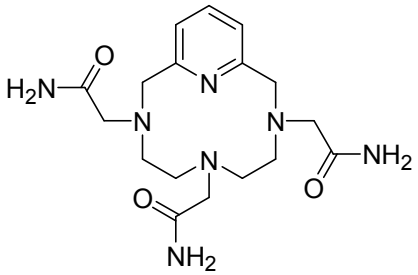




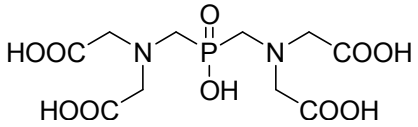
Competiton of PCT3Am and BIMP ligands for Zn^{2+} ions



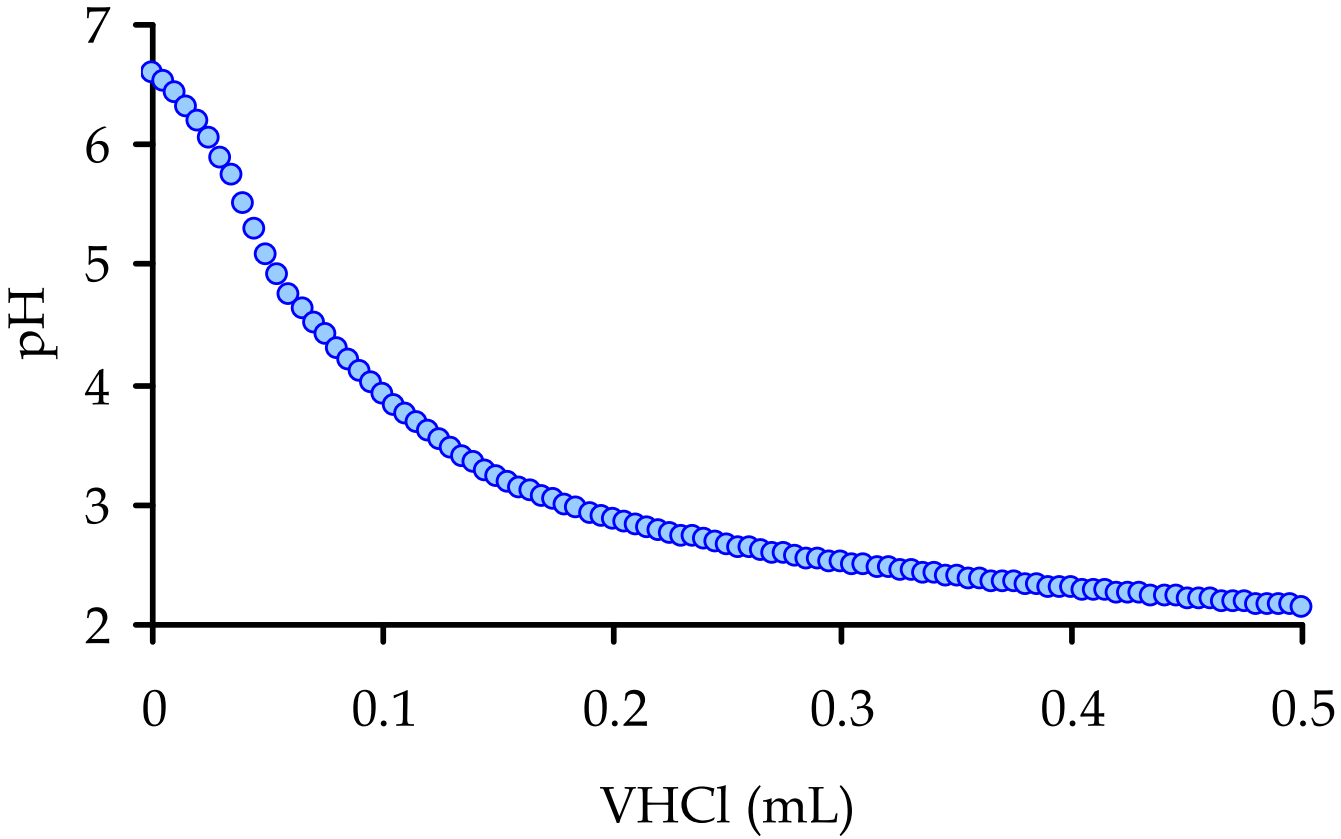
Species	logβ
HPCTA3Am	9.53
H_2PCTA3Am	13.73
HBIMP	9.33
H_2BIMP	15.83
H_3BIMP	18.36
H_4BIMP	20.36
H_5BIMP	21.78
ZnPCTA3Am	14.74
ZnPCTA3AmH_{-1}	5.90
ZnPCTA3AmH_{-2}	-5.54
ZnBIMP	15.94
ZnBIMP	18.08
ZnBIMP	20.04
Zn2BIMP	17.55
OH-	-13.815



vs.

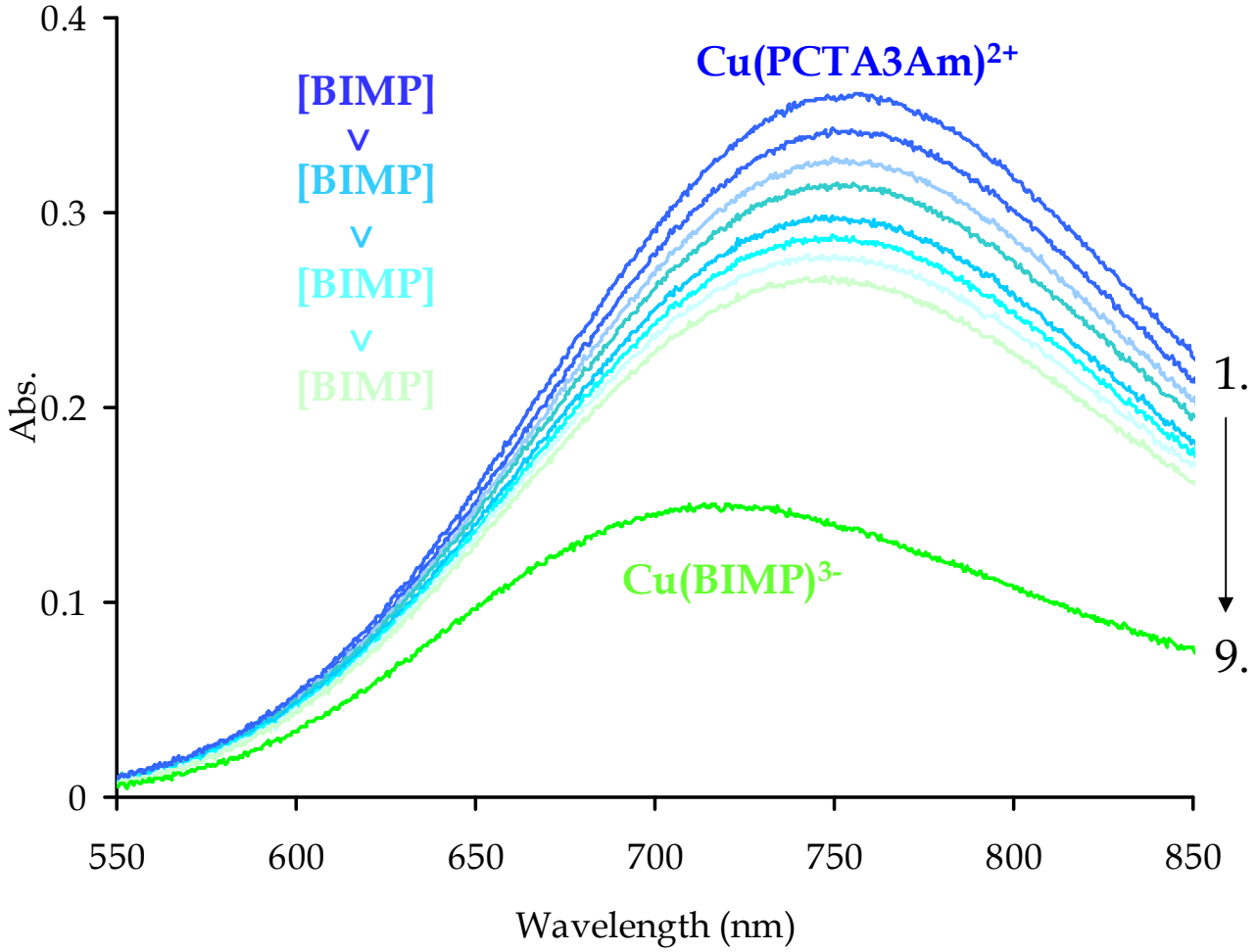


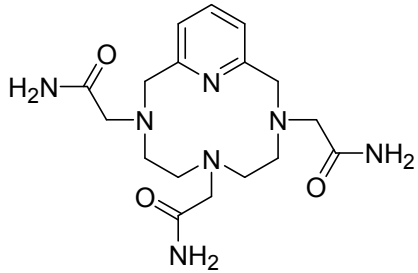
Competiton of PCT3Am and BIMP ligands for Zn^{2+} ions



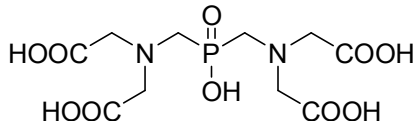
Zn – BIMP – PCTA3Am competition reaction followed by pH-potentiometry $[Zn^{2+}]$ = [PCTA3Am] = 2 mM [BIMP] = 4 mM ([HCl]=0.2188 M).

Competiton of PCT3Am and BIMP ligands for Cu^{2+} ions





vs.



Cu – BIMP – PCTA3Am competition reaction

1. [Cu(PCTA3Am)] (4 mM); **2-8.** [Cu(PCTA3Am)(BIMP)] (**2.** 0,5mM; **3.** 1,0mM; **4.** 1,5mM; **5.** 2,0mM; **6.** 2,5mM; **7.** 3,0mM; **8.** 3,5 mM BIMP) **9.** [Cu(BIMP)] (4 mM)

Optimal Ln-complexes from thermodynamic point of view

- **High (as high as possible) thermodynamic stability**

Tuning stability (as high as possible) playing with

-quality and number of donor atoms

-structure of ligand (open chain or MC)

- basicity

-rigidity etc

One can not forget other requirements as effectiveness, inertness, price etc.

Kinetics: basic principles (Ions in Solution by J. Burgess, Ellis Horwood Ltd. Chicester, 1988).

$$A + B \underset{k_b}{\overset{k_f}{\rightleftharpoons}} C + D \qquad K = \frac{k_f}{k_b}$$

Table 8.1 — Thermodynamic and kinetic data relating to cyanide exchange at cyano-complexes of transition metals

Complex	$\log_{10}\beta_n$	Mean ΔH(M–CN) (kJ mol^{-1})	k(*CN$^-$ exchange) (s^{-1}) fast	slow
$[Mn(CN)_6]^{4-}$		−24	$>10^{-2}$	
$[V(CN)_6]^{4-}$		−33	$>10^{-2}$	
$[Co(CN)_5]^{3-}$	19	−43	$>10^{-2}$	
$[Cr(CN)_6]^{4-}$		−44	$>10^{-2}$	
$[Mn(CN)_6]^{3-}$			2×10^{-4}	
$[Ni(CN)_4]^{2-}$	31	−45	$>10^{-2}$	
$[Cr(CN)_6]^{3-}$				3×10^{-7}
$[Fe(CN)_6]^{4-}$	34	−60		$<10^{-6}$
$[Pt(CN)_4]^{2-}$	35		1.2×10^{-2}	
$[Pd(CN)_4]^{2-}$	42	−96	$>10^{-2}$	
$[Fe(CN)_6]^{3-}$	44	−49		$<10^{-6}$
$[Co(CN)_6]^{3-}$	64			$<10^{-6}$

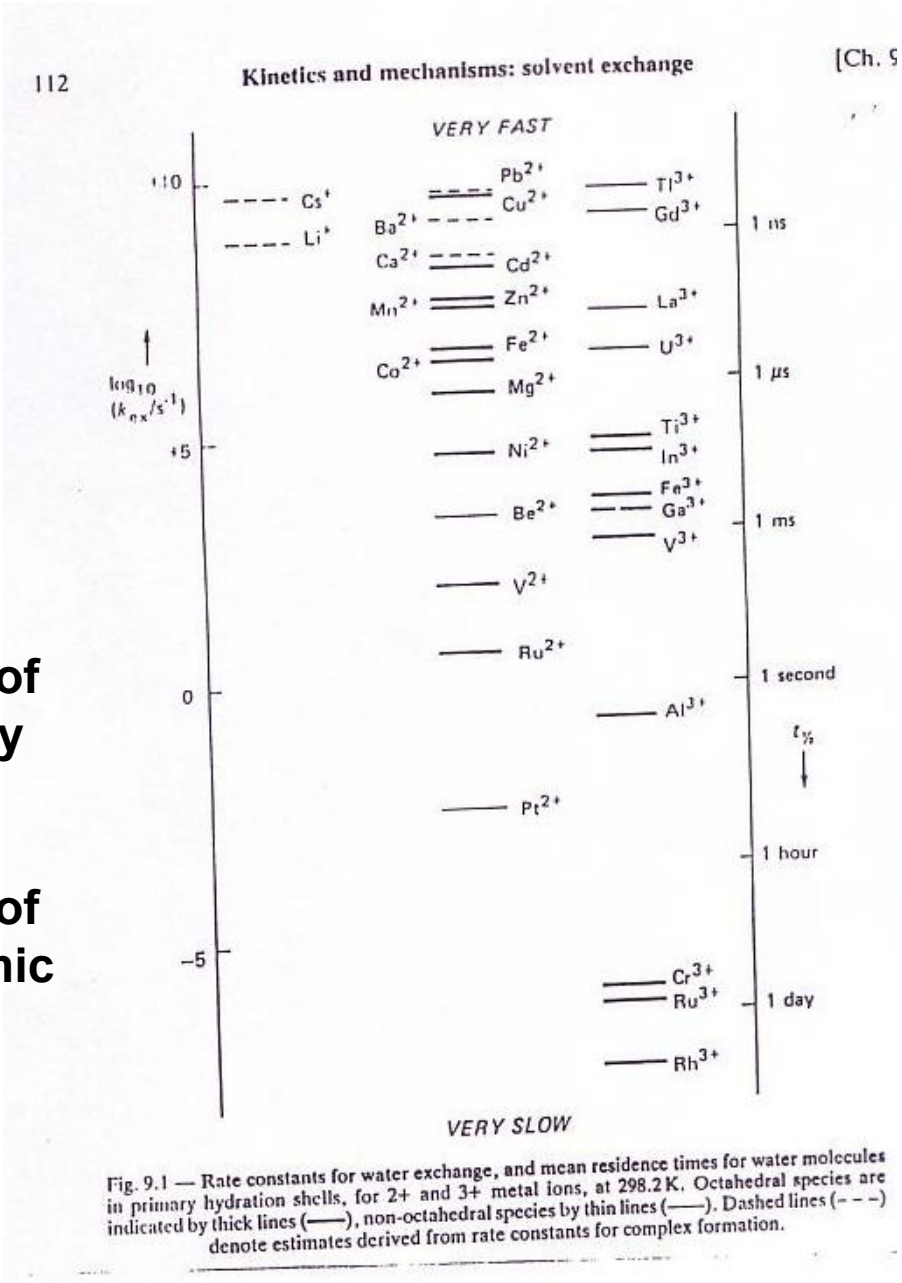
Water exchange

Stable vs. unstable (thermodynamics)

Inert vs. labile (kinetics)

Gd(III) complexes: the importance of kinetic and thermodynamic stability

Should be as:
Gd(III) complexes: the importance of kinetic inertness and thermodynamic stability



Solvent exchange

Table 9.3 — Activation entropies as a guide to solvent exchange mechanisms

Cation	Solvent[a]	$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})	Mechanism
Be^{2+}	TMU	+16	dissociative
	DMSO	−32	associative
	TMP	−54	
Al^{3+}	water	+42	dissociative
	DMSO	+22	
	TMP	+37	
	DMF	+43	
Ga^{3+}	water	+30	dissociative
	DMSO	+ 4	
	DMF	+46	
In^{3+}	water	−96	associative
	TMP	−113	
Sc^{3+}	TMP	−126	associative
	DMA	−132	
	TMU	+48	dissociative
Tm^{3+}	DMF	+10	dissociative
Cr^{3+}	DMSO	−49	associative
	DMF	−42	
Fe^{3+}	water	−54	associative
	MeOH	−31	
	DMSO	−43	
Pd^{2+}	water	−24	associative

[a]Solvent abbreviations as Table 9.3, plus: DMA dimethylacetamide; DMF dimethylformamide.

determined for exchange of a coordinating solvent in an appropriate diluent. The form

Mechanisms of solvent exchange (A. Merbach)

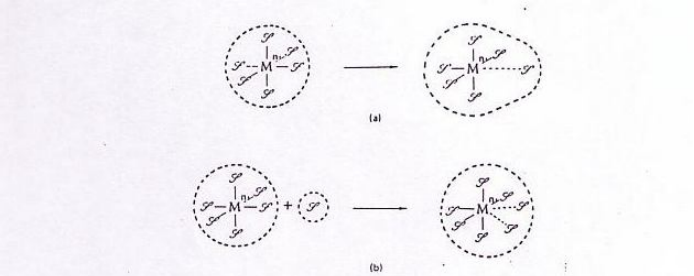
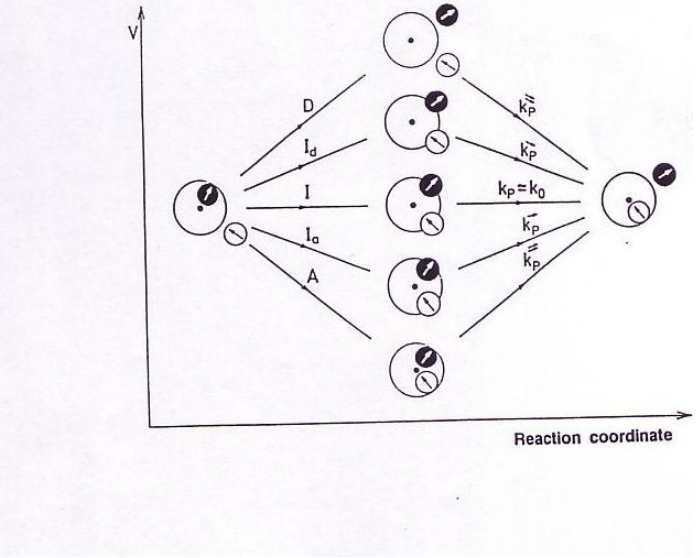


Fig. 9.4 — Volume changes on transition state formation for (a) dissociative and (b) associative solvent exchange.



Kinetics and mechanisms: complex formation

10.1 BACKGROUND

The formation of a metal complex from a solvated metal ion and a ligand is, like solvent exchange, a special case of substitution (Fig. 10.1). It is a special case which is

SUBSTITUTION: GENERAL

$ML_5L' + L'' \rightarrow ML_5L'' + L'$

e.g. $[Fe(CN)_5(NH_3)]^{3-} + py \rightarrow [Fe(CN)_5(py)]^{3-} + NH_3$

SUBSTITUTION: SPECIFIC

Solvent exchange

$MS_6^{n+} + {}^*S \rightarrow MS_5{}^*S^{n+} + S$

e.g. $[Al(OH_2)_6]^{3+} + {}^*OH_2 \rightarrow [Al(OH_2)_5({}^*OH_2)]^{3+} + OH_2$

Complex formation

$MS_6^{n+} + L \rightarrow MS_5L^{n+} + S$

e.g. $[Ni(OH_2)_6]^{2+} + Br^- \rightarrow [Ni(OH_2)_5Br]^+ + OH_2$

Aquation or solvolysis

$ML_5L' + S \rightarrow ML_5S + L'$

e.g. $[Co(NH_3)_5Cl]^{2+} + H_2O \rightarrow [Co(NH_3)_5(OH_2)]^{2+} + Cl^-$

Ligand exchange

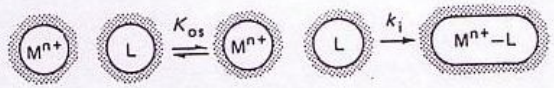
$ML_6^{n+} + {}^*L \rightarrow ML_5{}^*L^{n+} + L$

e.g. $[Fe(CN)_6]^{4-} + {}^*CN^- \rightarrow [Fe(CN)_5({}^*CN)]^{4-} + CN^-$

Fig. 10.1 — Types of substitution reactions at complexes.

Eigen-Wilkins mechanism

Sec. 10.2] **The Eigen–Wilkins mechanism**



$$M(OH_2)_x^{n+} + L \overset{K_{os}}{\rightleftharpoons} M(OH_2)_x^{n+}, L \overset{k_i}{\rightarrow} M(OH_2)_{x-1}\,L^{n+} + H_2O.$$

General rate law:

$$+\frac{d[ML^{n+}]}{dt} = \frac{K_{os}k_i[M^{n+}][L]}{1 + K_{os}[L]}$$

Under usual experimental conditions, $[M^{n+}] \gg [L]$:

$$+\frac{d[ML^{n+}]}{dt} = K_{os}k_i[M^{n+}][L]$$

Whence:

$$k_f = K_{os}k_i$$

Fig. 10.3 — Complex formation: mechanism, equations, and kinetics.

$$K_{os} = \frac{4\pi N_A}{3000}\, e^{-z_1 z_2 e^2/\varepsilon kT \cdot a}$$

a : ionok távolsága $\sim 5 \cdot 10^{-8}$ cm

z_1, z_2 ion töltés

e elektron töltése / $1.6 \cdot 10^{-19} \times 3$

ε diel. állandó / 80 vízv.

k Boltzman

$$K_{os} = 0{,}3 \times e^{-1.4\, z_1 z_2}$$

pl. $+1, +1$ $\quad K_{os} = 1.2$

Eigen-Wilkins mechanism: Ni^{2+} complexes

Table 10.1 — Rate constants and pre-association constants (defined in the text and in Fig. 10.3) for formation of complexes from $Ni^{2+}aq$, in aqueous solution at 298.2 K

Ligand	Measured $10^{-3}k_f(M^{-1}\,s^{-1})$	Estimated K_{os} (molar scale)	Derived $10^{-3}k_i(s^{-1})$
N-Methylimidazole$^+$	0.23	0.02	12
Imidazole H^+	0.3	0.02	15
Ammonia	5	0.15	33
Hydrogen fluoride	3	0.15	20
Imidazole	2.8–6.4	0.15	19–43
1,10-Phenanthroline	4.1	0.15	26
Diglycine	21	0.17	12
Fluoride$^-$	8	1	8
Acetate$^-$	100	3	30
Glycinate$^-$	20	2	10
Oxalate H^-	5	2	3
Oxalate^{2-}	75	13	6
Malonate^{2-}	450	95	5
Methylphosphate^{2-}	290	40[a]	7
Pyrophosphate^{3-}	2100	88	24
Tripolyphosphate^{4-}	6800	570	12
Cf. Water exchange			30

[a] In this favourable case K_{os} was derived from the kinetic results.

SCS mechanism for bidentate ligands

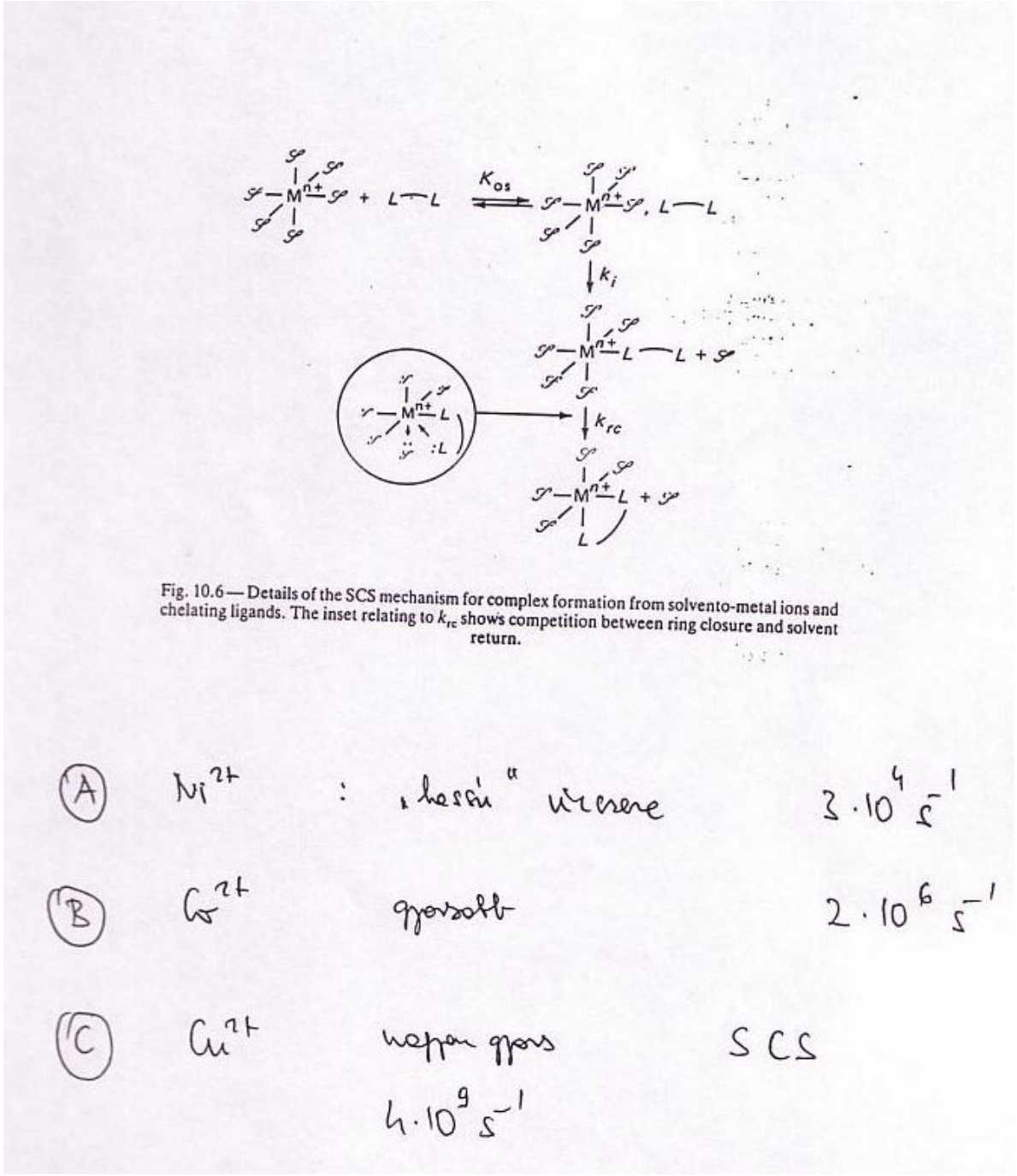


Fig. 10.6 — Details of the SCS mechanism for complex formation from solvento-metal ions and chelating ligands. The inset relating to k_{rc} shows competition between ring closure and solvent return.

(A) Ni^{2+} : "hesitant" ligand $3 \cdot 10^4\ s^{-1}$

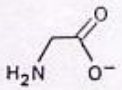
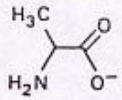
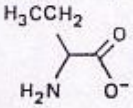
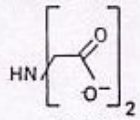
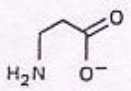
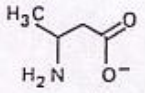
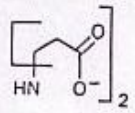
(B) Cr^{2+} groups $2 \cdot 10^6\ s^{-1}$

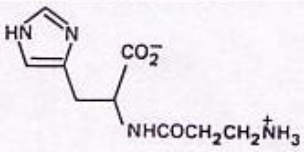
(C) Cu^{2+} weak groups SCS

$4 \cdot 10^9\ s^{-1}$

SCS mechanism for bidentate ligands

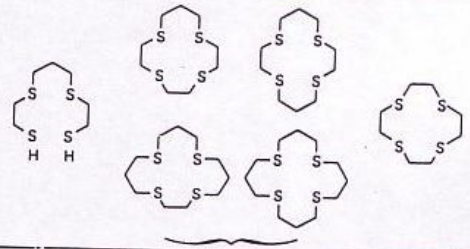
Table 10.7 — Kinetic data relating to the SCS (sterically controlled substitution) mechanism for formation of chelate complexes; all rate constants are in units of $M^{-1}\,s^{-1}$, at 298.2 K in aqueous solution

Cobalt(II)				
	water exchange: 2×10^6			
	complex formation with monodentate ligands: uncharged ~1 to 3×10^5; charge 1− ~1 to 3×10^6			
5-membered rings:	glycinate$^-$  2×10^6	α-alaninate$^-$  2×10^6	α-aminobutyrate$^-$  2.5×10^5	iminodiacetate^{2-}  1×10^7
6-membered rings:	β-alaninate$^-$  1×10^5	β-aminobutyrate$^-$  2×10^4	iminodipropionate^{2-}  3×10^5	
Copper(II)				
	water exchange: 4×10^9			
	reaction with: ammonia, pyridine, imidazole: 2 to 20×10^8			
5-membered-ring: α-alaninate	10×10^8			
6-membered-ring: β-alaninate	2×10^8			
7-membered-ring: L-carnosine[a]	5×10^4			

[a] L-carnosine = 

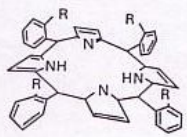
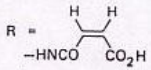
Polydentate and macrocycle ligands

Table 10.10 — Rate constants, k_f ($M^{-1}s^{-1}$), for formation of macrocyclic complexes from $Cu^{2+}aq$ and tetrathiamacrocycles; in 80% methanol at 298.2 K

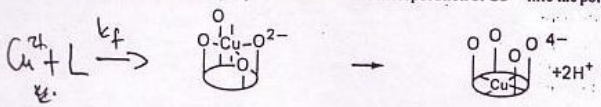
Ligand (LLLL)			
k_f for $Cu^{2+}aq + LLLL$	$\sim 10^6$ [a]	1 to 4×10^4	0.12×10^4

[a] Estimated.

Table 10.11 — Rate constants for formation of copper(II) complexes of rigid macrocyclic ligands; in aqueous solution at 298.2 K

		k_f ($M^{-1}s^{-1}$)
	deuteroporphyrin-2,4-disulphonic acid dimethyl ester $R^1 = R^2 = SO_3H$ $R^3 = R^4 = CH_2CH_2CO_2CH_3$	4.3
	haematoporphyrin IX $R^1 = R^2 = CH(OH)CH_3$ $R^3 = R^4 = CH_2CH_2CO_2H$	~0.01
	meso-tetraphenylporphine (5 derivatives)	0.001 to 0.02
	'picket fence' porphyrin 	5.6[a]

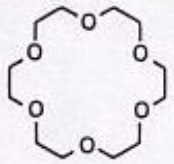
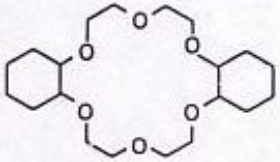
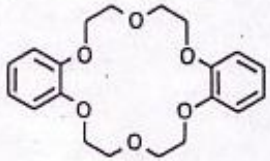
[a] First-order rate constant (s^{-1}) for intramolecular incorporation of Cu^{2+} into the porphyrin ring, i.e. for:



$k_f \simeq 300\ M^{-1}s^{-1}$

Effect of rigidity on rate constants (of the rate determining step)

Table 10.15 — Effects of ligand rigidity on rate constants (k (s^{-1})) for the slower stage[a] in the formation of 18-crown-6 complexes of Na^+, in *NN*-dimethylformamide at 313 K

			
k =	3.5×10^6	2×10^6	$< 1 \times 10^6$

[a]The fast first stage, involving initial bonding of the crown ether to the Na^+, has k_f between 4 and 6×10^8 $M^{-1} s^{-1}$ for these three ligands.

Table 10.16 — Rate constants, k_f ($M^{-1} s^{-1}$), for formation of cryptates of alkali metal cations; in methanol at 298.2 K

	[211]	[221]	[222]
Li^+	4.8×10^5	1.8×10^7	
Na^+	3.1×10^6	1.7×10^8	2.7×10^8
K^+		3.8×10^8	4.7×10^8
Rb^+		4.1×10^8	7.6×10^8
Cs^+		$\sim 5 \times 10^8$	$\sim 9 \times 10^8$

Kinetic studies on Ln(III)-ligand systems

Kinetic studies

Type of the ligand:

	Formation	Metal exchange	Dissociation
open chain	Ø too fast (pH>2)	measurable (pH=4-6)	Ø too fast (pH<2)
macrocyclic	Ø too slow (pH=1-3) measurable (pH=3-7) fast (pH > 7)	Ø measurable (pH=4-6) in the presence of large [LnL] excess	slow (pH>1) measurable (pH<1)

Methods:

- fast → Stopped-flow (UV-VIS); Rapid mixing unit (UV-VIS)
- intermediate → UV-VIS; Luminescence; Relaxometry
- slow → UV-VIS; NMR (relaxometry)

Detection:

- on the metal ion → UV-VIS (Ce^{3+} and Eu^{3+}); Relaxometry (Gd^{3+})
- on the ligand → UV-VIS; NMR

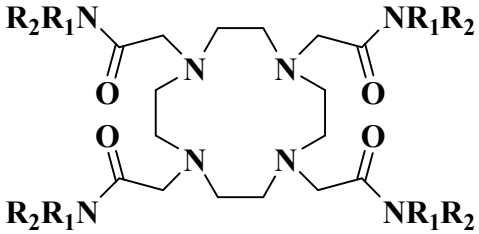
Formation kinetics of the MC complexes

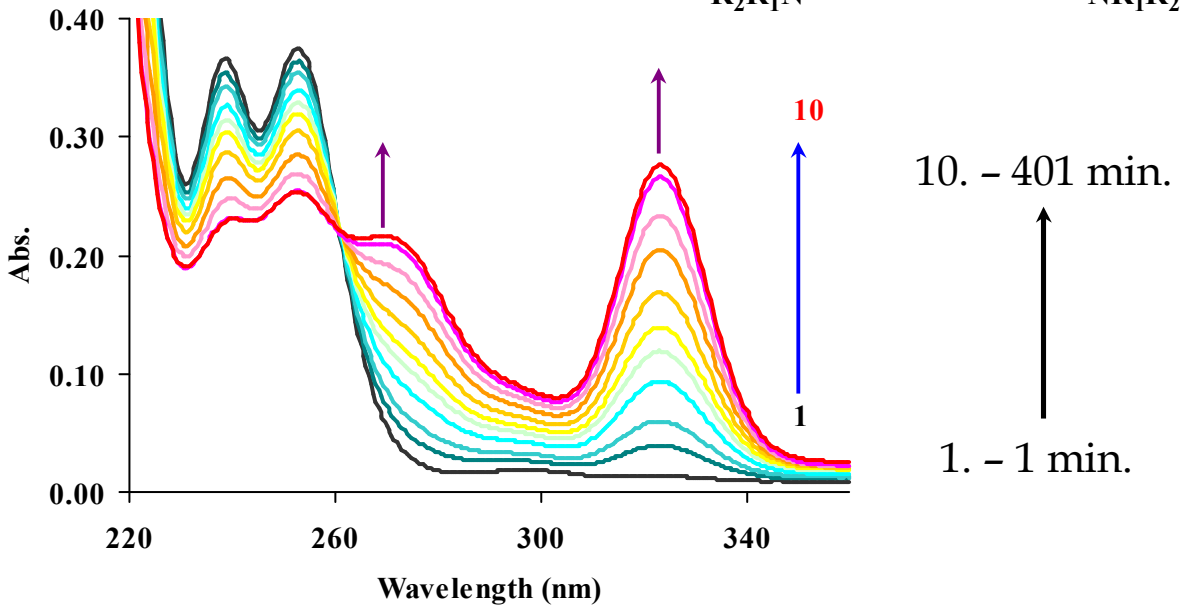
Two cases were observed:

a. Formation of Ln(III) complexes of simple DOTA-tetraamides (e.g. DOTAM, DTMA, …) which is a simple second order reaction between the Ln^{3+} and the deprotonated ligand.

$$Ce^{3+} + DTMA \rightleftharpoons [Ce(DTMA)^{3+}]$$

For the DTMA ligand (R_1 = -CH_3, R_2 = -H)
log K_1^H = 9.56 and log K_2^H = 5.95
log K_{ML} = 12.68 (Ce^{3+}) ÷ 13.91 (Yb^{3+})

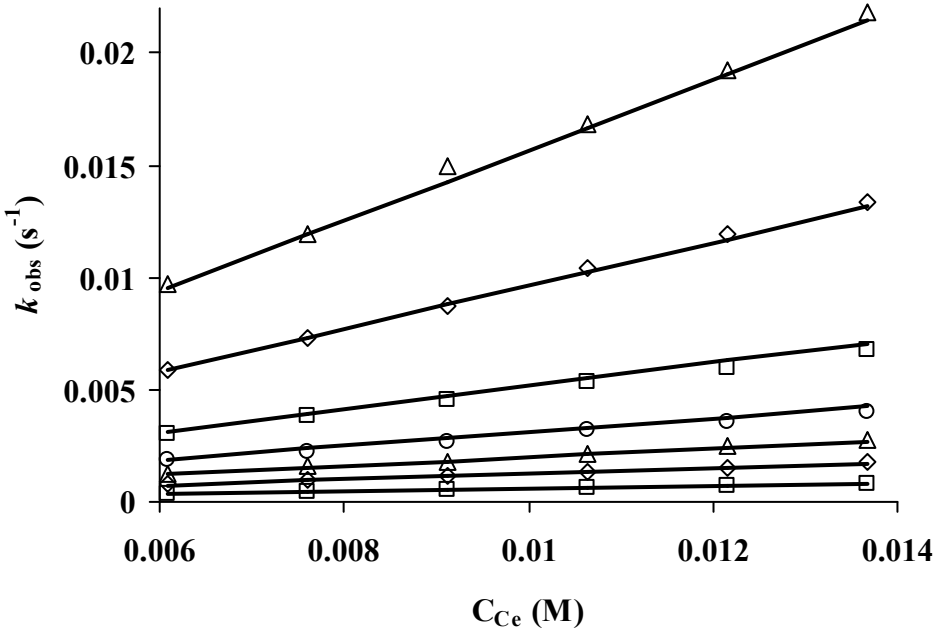




Formation of $[Ce(DTMA)]^{3+}$ as a function of time ($C_{Ce} = C_L = 5\times10^{-4}$ M in NMP buffer ($C_{NMP} = 2.5\times10^{-2}$ M) with pH = 5.26).

Formation kinetics of the complexes

Dependence of the formation rates on the Ln^{3+} ion concentration:



$$v = \frac{d[LnL]_t}{dt} = k_{obs}[L]_t$$

$$\mathrm{v} = k_0[\mathrm{M}][\mathrm{L}] + k_1[\mathrm{M}][\mathrm{HL}] + + k_2[\mathrm{M}][\mathrm{H_2L}]$$

$$k_{\mathrm{obs}} = \frac{[\mathrm{M}](k_0 + k_1 K_1^{\mathrm{H}}[\mathrm{H}^+] + k_2 K_1^{\mathrm{H}} K_2^{\mathrm{H}}[\mathrm{H}^+]^2)}{1 + K_1^{\mathrm{H}}[\mathrm{H}^+] + K_1^{\mathrm{H}} K_2^{\mathrm{H}}[\mathrm{H}^+]^2}$$

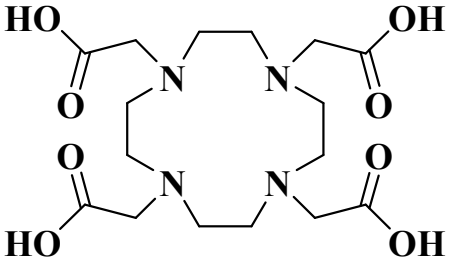
Since the fitting returned negative values for k_1 and k_2 the reaction of HL and H_2L were neglected

$$k_{\mathrm{obs}} = \frac{k_0[\mathrm{M}]}{1 + K_1^{\mathrm{H}}[\mathrm{H}^+] + K_1^{\mathrm{H}} K_2^{\mathrm{H}}[\mathrm{H}^+]^2}$$

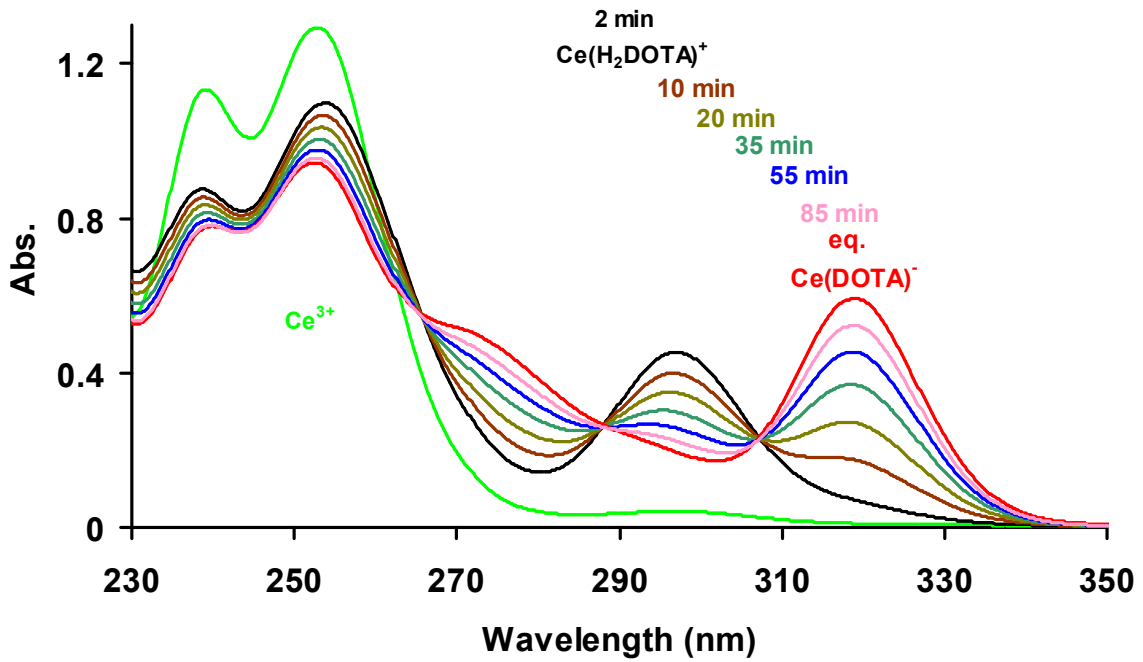
Formation kinetics of the complexes

b. Formation of Ln(III) complexes of macrocyclic ligands bearing negatively charged side arms (e.g. DOTA, DOTP, DOTA-4Gly, DOTA-4AMP …) proceeds via the formation of stable intermediates (protonated complexes).

$$Ce^{3+} + H_xDOTA \rightleftharpoons [Ce(H_2DOTA)^+] + (x-2)H^+ \xrightarrow[-H^+]{} [Ce(HDOTA)] \xrightarrow[-H^+]{} [Ce(DOTA)]^-$$



For the DOTA log K_1^H = 12.6
log K_2^H = 9.70, log K_3^H = 4.5
and log K_4^H = 4.14
log K_{ML} = 23.0 (Ce^{3+}) ÷ 24.
(Yb^{3+})



Formation of $[Ce(DOTA)]^-$ as a function of time ($C_{Ce} = C_L = 5\times10^{-4}$ M in NMP buffer ($C_{NMP} = 5.0\times10^{-2}$ M) with pH = 4.39).

Brücher, E.; Laurenczy, G.; Makra, Zs. *Inorg. Chim. Acta* **1987**, *139*, 141.

Own memories from the last century

Inorg. Chem. **1994,** *33,* 4070–4076

Kinetics of Formation and Dissociation of Lanthanide(III)–DOTA Complexes

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Department of Inorganic and Analytical Chemistry, Lajos Kossuth University, Debrecen H-4010, Hungary

$$Ln^{3+} + H_iDOTA \rightleftharpoons Ln(H_2DOTA)^+ + (i-2)H^+ \quad (3)$$

$$Ln(H_2DOTA)^+ \underset{-H^+}{\overset{\text{slow}}{\rightarrow}} Ln(HDOTA) \underset{-H^+}{\overset{\text{slow}}{\rightarrow}} Ln(DOTA)^- \quad (4)$$

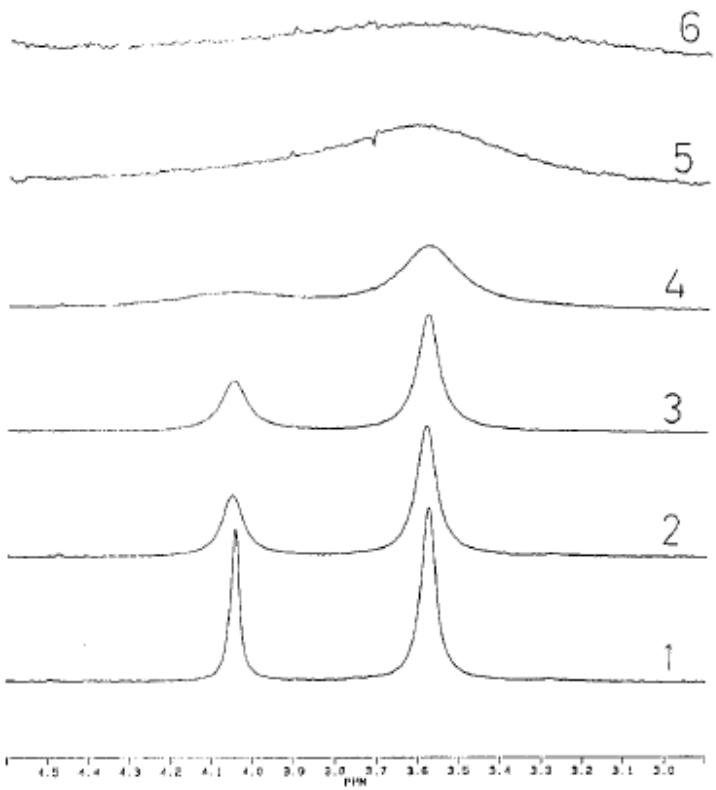
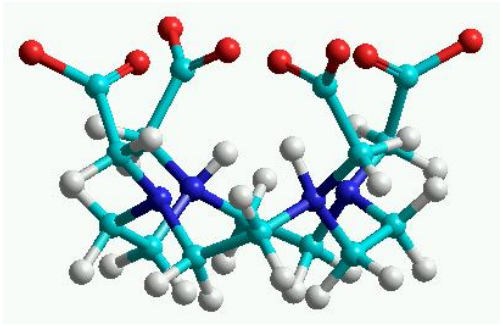


Figure 4. ^{1}H-NMR spectra of DOTA in the presence of Gd^{3+}. c_{DOTA} = 0.02 M; pD = 3.8; c_{Gd} = 0 (1), 5×10^{-5} M (2), 1×10^{-4} M (3), 3×10^{-4} M (4), 1×10^{-3} M (5), and 2×10^{-3} M (6). δ(acetate CH_2) = 4.5 ppm; δ(ring CH_2) = 3.6 ppm.

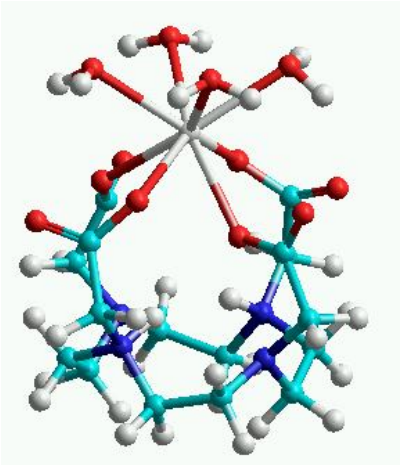
Why do macrocyclic ligands form complexes with metal ions slowly?



H_2DOTA^{2-} (pre-organized)

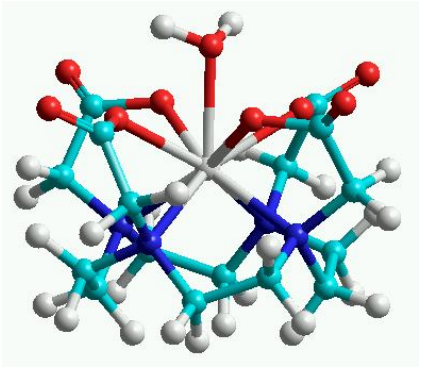
Ln^{3+}_{aq}

fast



Intermediate $Ln(H_2DOTA)^{+}$

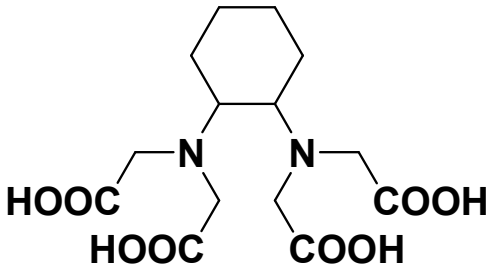
slow step, requires deprotonation and rearrangement



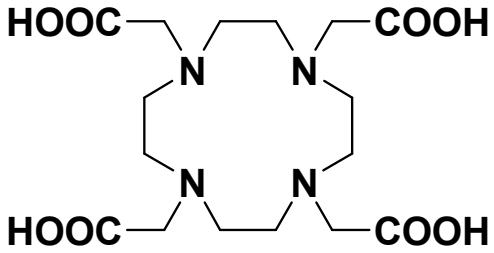
$Ln(DOTA)^{-}$ formed

Approximate half-lifes of the intermediates

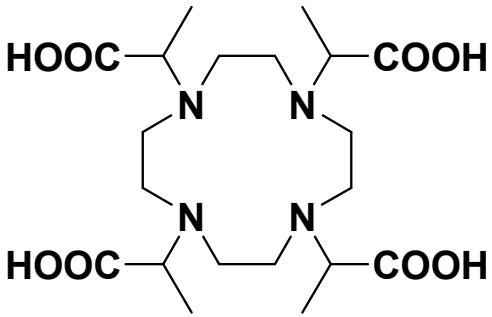
At pH = 4.4 in 0.001 M solution of CeL



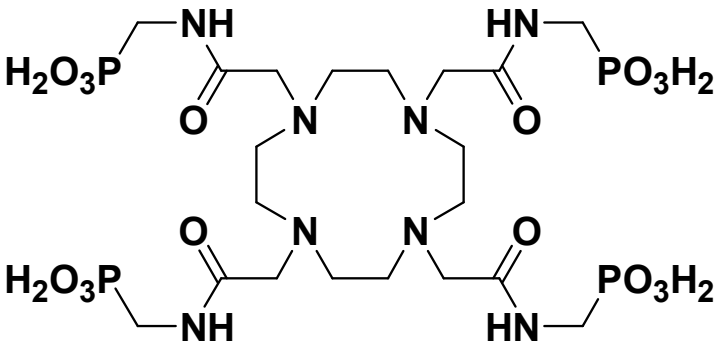
[Ce(CDTA)]$^-$ $t_{1/2} < 0.1$ sec.



[Ce(DOTA)]$^-$ $t_{1/2} \approx 12$ min.

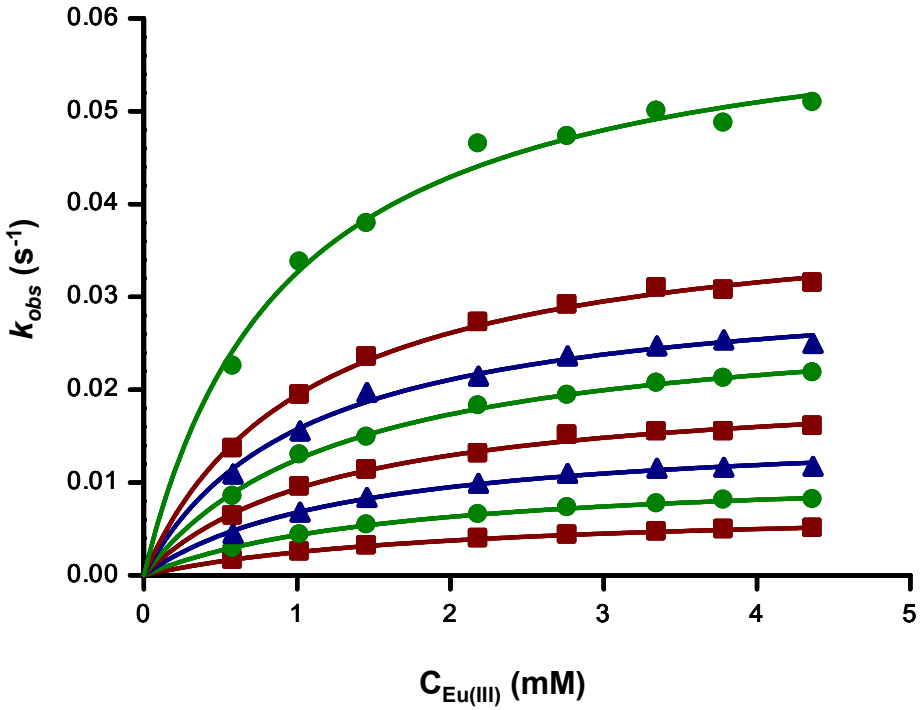


[Ce(DOTMA)]$^-$ $t_{1/2} > 100$ h.



[Ce(DOTA-4AMP)]$^{5-}$
thermodynamically practically
stable under these conditions

Formation kinetics of the complexes



k_{obs} vs. $[Ln^{3+}] \rightarrow$ saturation curve !!!

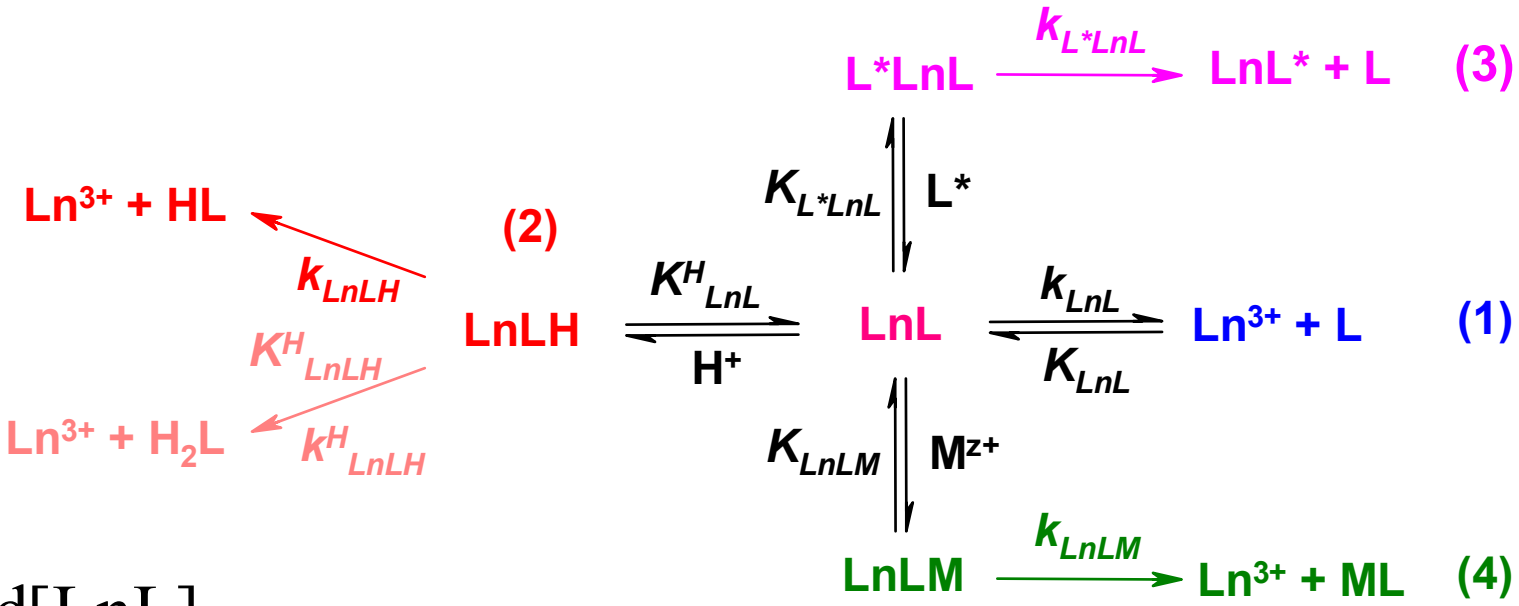
$$\frac{d[LnL]_t}{dt} = k_{obs}[L]_t$$

$$k_{obs} = \frac{k_r K_{Ln}[Ln^{3+}]}{1 + K_{Ln}[Ln^{3+}]}$$

$$k_r = \frac{k_H}{[H^+]} = k_{OH}[OH^-]$$

K_{Ln} is the conditional stability constant of the accumulating intermediate, LnH_yL, and k_r is the formation constant at the given pH.

Dissociation of the complexes



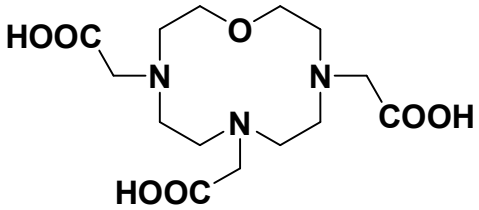
$$-\frac{d[LnL]_t}{dt} = k_d[LnL]_t$$

$$[LnL]_t = [LnL] + [LnHL] + [LnHL][H^+] + [LLnL^*] + [LnLM]$$

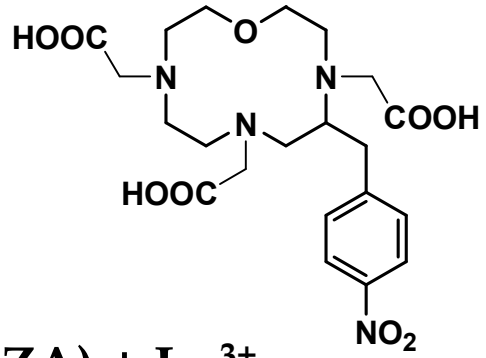
$$-\frac{d[LnL]_t}{dt} = k_d[LnL]_t = k_{LnL}[LnL] + k_{LnLH}[LnHL] +$$

$$+ k^H{}_{LnLH}[LnHL][H^+] + k_{L*LnL}[L*LnL] + k_{LnLM}[LnLM]$$

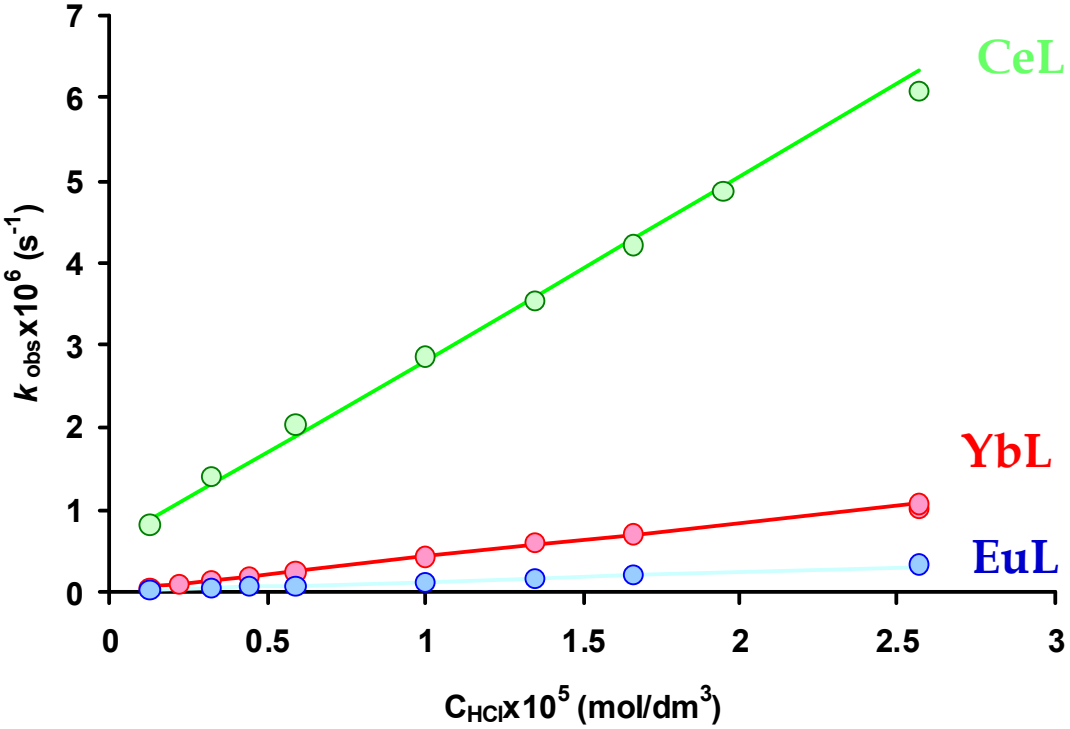
Tuning the kinetic inertness of the complexes by making the ligands more rigid



vs.



$$Ln(OXAAZA) + M^{2+} \rightleftharpoons M(OXAAZA) + Ln^{3+}$$



$$LnL \xrightarrow{k_0} Ln + L$$

$$LnL \rightleftharpoons LnHL \quad (K^{H}_{ML})$$

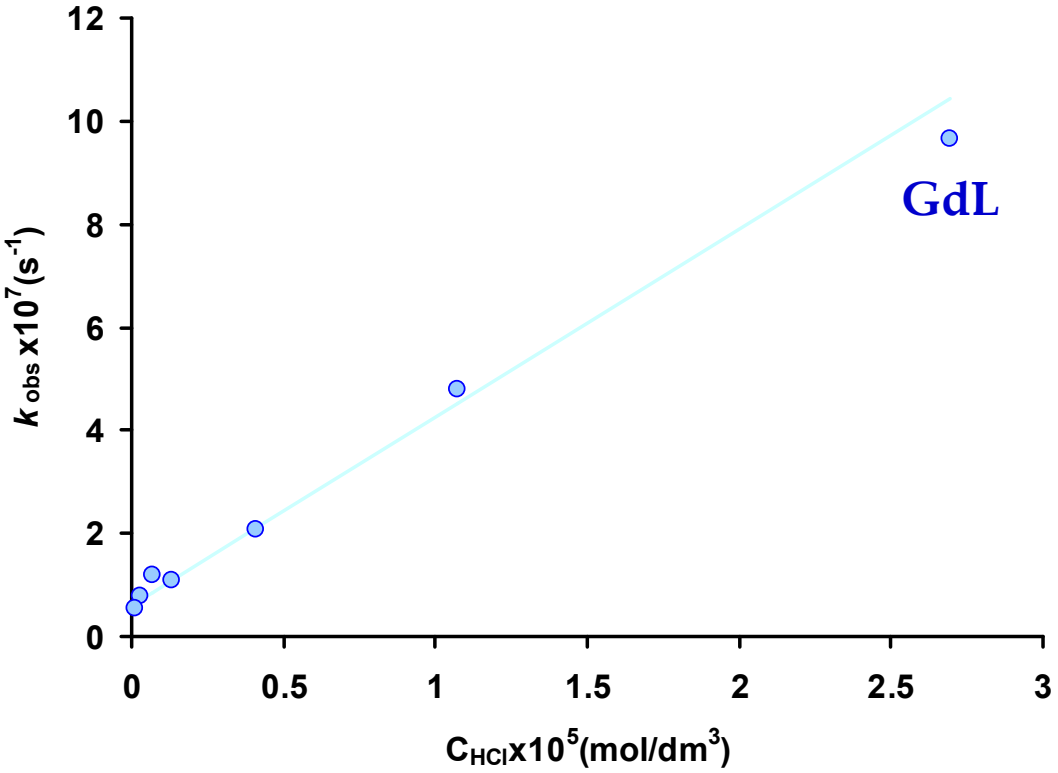
$$LnHL \xrightarrow{k_1} Ln + HL$$

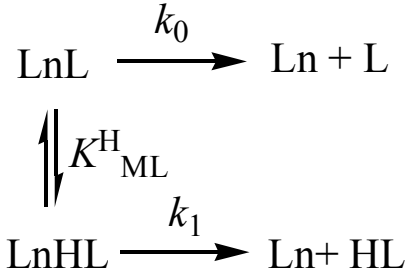
$$-\frac{d[LnL]_t}{dt} = k_d[LnL]_t$$

$$k_d = k_0 + k_1[H^+]$$

Tuning the kinetic inertness of the complexes by making the ligands more rigid

$$Gd(p\text{-}NO_2\text{-}Bz\text{-}OXAAZA) + Zn^{2+} \rightleftharpoons Zn(p\text{-}NO_2\text{-}Bz\text{-}OXAAZA) + Gd^{3+}$$





$$-\frac{d[LnL]_t}{dt} = k_d[LnL]_t$$

$$k_d = k_0 + k_1[H^+]$$

Tuning the kinetic inertness of the complexes by making the ligands more rigid

Ligand	Ln^{3+}	Ce^{3+}	Eu^{3+} or Gd^{3+}	Yb^{3+}
OXAAZA	k_0 s^{-1}	**$(5.9\pm0.4)\times10^{-7}$**	**$(1.4\pm0.3)\times10^{-7}$**	**$(2.0\pm1.2)\times10^{-7}$**
	k_1 $M^{-1}s^{-1}$	**(0.22 ± 0.01)**	**$(1.19\pm0.06)\times10^{-2}$**	**$(4.05\pm0.08)\times10^{-2}$**
p-NO_2-Bz-OXAAZA	k_0 s^{-1}	–	**$(6.1\pm0.7)\times10^{-8}$**	–
	k_1 $M^{-1}s^{-1}$	–	**$(3.7\pm0.4)\times10^{-3}$**	–
DTPA[i]	k_0 s^{-1}	–	not detected	–
	k_1 $M^{-1}s^{-1}$	–	0.58	–
	k_2 $M^{-2}s^{-1}$	–	9.7×10^{-4}	–
	k_3 $M^{-1}s^{-1}$ (k_3^{Eu}, k_3^{Cu} and k_3^{Zn})	–	4.9×10^{-4}, 0.93 and 5.6×10^{-2},	–

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Optimal Ln-complexes from kinetic point of view

- ✓ **Possible quick complex formation**

Engineering point of view (i.e. cheaper for Gd), but essential for some short lived radioisotopes

Easy(er) characterisation of the complex, good for students…

- ✓ **Non-toxicity, i.e. high thermodynamic stability and kinetic inertness (i.e. slow dissociation)**

Ideal case: no any dissociation of LnMC before the complete excretion

Some useful references

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Coordination Chemistry Reviews:
http://www.elsevier.com/wps/find/journaldescription.cws_home/500845/description#description
Pure and Applied Chemistry: http://www.iupac.org/publications/pac/index.html

Who is the expert? / definition of expert

Logos Quotes
<quotation@logosquotes.org
Date: Fri, 01 Sep 2006 18:26:58 +0200
Author - Niels Bohr (1885-1962)

An expert is a man who has made all the mistakes which can be made in a very narrow field.

Bohr and Einstein debating quantum theory at Ehrenfest's home in Leiden (December 1925).

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