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Equilibrium and solution structural study of the interaction of tri- and tetra-dentate polyimidazole ligands with transition metal ions†

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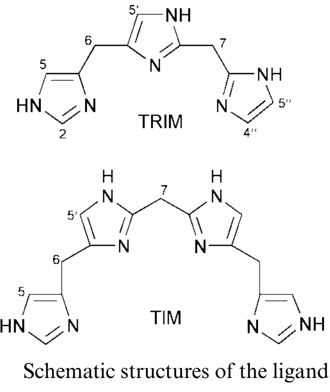
Copper(II) and zinc(II) complexes of two polyimidazole derivatives, 4-(imidazol-4-ylmethyl)-2-(imidazol-2-ylmethyl)-imidazole (TRIM) and bis[4-(imidazol-4-ylmethyl)-imidazol-2-yl]methane (TIM), containing three and four methylene-linked imidazole rings as donor groups, have been studied by potentiometry, UV–VIS, EPR and NMR spectroscopic methods. The data revealed that both ligands form extremely stable and varied complexes with zinc(II) and copper(II). In equimolar solutions of the metal ions and TRIM, two and three imidazole co-ordinated MAH and MA species were formed. The complex Zn(TRIM) probably has tetrahedral geometry. The formation of bis-complexes has also been detected with the ligand in excess. The data revealed 6N and 5N co-ordinated central ions in ZnA_2 and CuA_2, respectively. In MA complexes of TIM, the ligand is co-ordinated to the metal ions *via* all the four imidazole units. Formation of bis-complexes has only been found in the zinc(II) containing system. Ternary systems of zinc(II)–TRIM and –TIM have also been studied with L-cysteine as a second ligand. The potentiometric and NMR results established the formation of ternary complexes with different protonation states in relatively high amount, in spite of the high stability of the parent complexes.

Introduction

The investigation of the metal binding properties of imidazole based ligands, owing to the extremely broad biological presence of imidazole moiety, is one of the main topics of bioco-ordination chemistry. The presence of this particular moiety in the active sites of metalloproteins or enzymes is related to a great variety of metabolic processes.[1] During the last three decades, many efforts have been made to characterise the active centres of these metalloproteins. The use of low molecular weight model compounds of these biological macromolecules has proved to be very useful, and in some cases the only possible way to better understand the structure and function of their active sites.

Following our earlier studies on the co-ordination behaviour of the imidazole ring toward transition metal ions,[2–8] here we report equilibrium and solution structural studies of two imidazole-based ligands, 4-(imidazol-4-ylmethyl)-2-(imidazol-2-ylmethyl)imidazole (TRIM) and bis[4-(imidazol-4-ylmethyl)-imidazol-2-yl]methane (TIM) (Scheme 1) containing three and four fused imidazole units as donor groups, respectively. Metal complexes of several polyimidazole derivatives have already been studied from both structural and equilibrium points of view.[7–14] In such ligands, however, other nitrogen- and/or oxygen-donors were also present besides imidazole units, except for some compounds containing two imidazole rings [2,2′-biimidazole[7,14] and bis(imidazol-2-yl)methane[9]]. The additional N/O donor groups have been found to alter strongly the metal-binding properties of the ligand in question. By contrast, TRIM and TIM offer the possibility to study the intrinsic co-ordination properties of multiimidazole environments. The recently reported crystal structures of the CuA complexes of TRIM and TIM revealed square pyramidal structure for both complexes with $\{N_3OCl\}$ and $\{N_4O\}$ co-ordination, respectively.[15] The ligand in the [CuCl(TRIM)(MeOH)]Cl complex was found to be nearly planar, while the tetraimidazole derivative strongly deviated from planarity in $[Cu(ClO_4)(TIM)]ClO_4$.



Scheme 1 Schematic structures of the ligands studied.

Besides establishing the solution chemical behaviour of TRIM and TIM complexes, the aim of this work was to develop new copper(II) and zinc(II) complexes able to efficiently hydrolyse phosphoester bonds by means of their hydroxo mixed-ligand complexes. Unfortunately, the formation of the parent complexes is followed by precipitation and probably by redox reactions above pH 8 for both ligands, which prevented the investigation of the hydrolytic properties of these complexes.

In order to determine the binding ability of thiol containing ligands to zinc(II)–polyimidazole complexes, ternary systems of

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† Electronic supplementary information (ESI) available: Schematic views of tridentate TIM conformations in tetrahedral and octahedral geometry and regions of ^1H NMR spectra measured in the TIM–zinc(II) system. See http://www.rsc.org/suppdata/dt/b0/b001648i/

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TRIM and TIM with L-cysteine and zinc(II) have also been studied. Such mixed-ligand co-ordination may be interesting with respect to zinc-finger-proteins and some ferric uptake proteins where the structural zinc(II) sites are surrounded by three imidazole units and two cysteines.[16]

Experimental

Materials

Copper(II) and zinc(II) perchlorate (Fluka) solutions were standardised complexometrically. pH metric titrations were performed using NaOH (Fluka) solution. The two ligands TRIM and TIM were synthesised as described earlier.[17] The purity of the ligands was checked by pH-metry, elemental analysis [TRIM: found (calc.): C, 57.63 (57.89); H, 5.46 (5.26); N, 36.61 (36.84)%, TIM: found (calc.): C, 47.69 (47.36); H, 6.34 (6.31); N, 29.14 (29.47)%] and ^{1}H NMR spectroscopy (only peaks belonging to the ligands were observed). L-cysteine hydrochloride hydrate was obtained from Aldrich and used without further purification.

pH-Metric measurements

The protonation and co-ordination equilibria were investigated by potentiometric titration in aqueous solution [$I = 0.1$ mol dm^{-3} (NaClO$_4$) and $T = 298 \pm 0.1$ K] in an automatic titration set including a Dosimat 665 (Metrohm) autoburette, an Orion 710A precision digital pH-meter and an IBM-compatible PC. The Orion 8103BN semimicro pH glass electrode was calibrated[18] *via* the modified Nernst equation (1):

$$E = E_0 + K\log[\mathrm{H}^+] + J_\mathrm{H}[\mathrm{H}^+] + \frac{J_\mathrm{OH}K_\mathrm{w}}{[\mathrm{H}^+]} \qquad (1)$$

where J_H and J_OH are fitting parameters in acidic and alkaline media for the correction of experimental errors, mainly due to the liquid junction and to the alkaline and acidic errors of the glass electrode; $K_\mathrm{W} = 10^{-13.75}$ mol^2 dm^{-6} is the autoprotolysis constant of water.[19] The parameters were calculated by a non-linear least squares method. The species formed in the systems were characterized by the general equilibrium process (2) where

$$p\mathrm{M} + q\mathrm{A} + r\mathrm{B} + s\mathrm{H} \xrightleftharpoons{\beta_{\mathrm{M}_p\mathrm{A}_q\mathrm{B}_r\mathrm{H}_s}} \mathrm{M}_p\mathrm{A}_q\mathrm{B}_r\mathrm{H}_s \qquad (2)$$

$$\beta_{\mathrm{M}_p\mathrm{A}_q\mathrm{B}_r\mathrm{H}_s} = \frac{[\mathrm{M}_p\mathrm{A}_q\mathrm{B}_r\mathrm{H}_s]}{[\mathrm{M}]^p[\mathrm{A}]^q[\mathrm{B}]^r[\mathrm{H}]^s} \qquad (3)$$

M denotes the metal ion and A and B the non-protonated ligand molecules. Charges are omitted for simplicity, but can be easily calculated if the composition of the fully protonated ligands TRIM, TIM and Cys are described as $\mathrm{LH_3}^{3+}$, $\mathrm{LH_4}^{4+}$ and $\mathrm{LH_3}^{+}$, respectively. The formation constants ($\beta_{\mathrm{M}_p\mathrm{A}_q\mathrm{B}_r\mathrm{H}_s} \equiv \beta_{pqrs}$) were calculated by means of the computer program PSEQUAD.[20]

The protonation and the complex formation constants were calculated from 4 and 5–6 independent titrations (50–80 data points per titration), respectively. The metal-to-ligand ratios varied between 1 : 1 and 1 : 3, with the metal ion concentration between 9×10^{-4} and 4×10^{-3} mol dm^{-3}.

Electronic absorption, EPR and NMR measurements

UV–VIS spectra were measured on a Hewlett Packard 8452A diode array spectrophotometer. The individual spectra of the copper(II) complexes formed were calculated by the above-mentioned PSEQUAD computer program. The EPR spectra were recorded on a JEOL-JES-FE 3X spectrometer in the X-band region at 298 and 77 K with 100 kHz field modulation. Manganese(II)-doped MgO powder was used as field standard. The concentration of copper(II) was 4–5 × 10^{-3} mol dm^{-3}. The EPR parameters were calculated by a recently developed computer program able to handle four (but preferably two) coexisting species.[21] ^{1}H NMR measurements were performed on Bruker AM-360 and Bruker Avance DRX 500 spectrometers. The chemical shifts δ were measured with respect to dioxane as an internal reference and converted relative to SiMe$_4$, using $\delta_\mathrm{dioxane} = 3.70$. The zinc(II) and ligand concentrations were 0.005 and 0.005–0.01 mol dm^{-3}, respectively. Measurements were generally made in H$_2$O–D$_2$O (9 : 1).

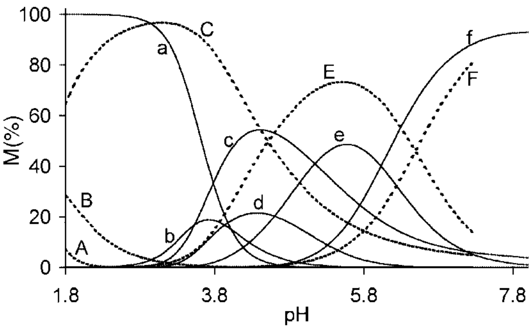

Fig. 1 Species distribution in the TRIM–copper(II) (2 : 1) (dashed lines, upper case letters) and TRIM–zinc(II) (2 : 1) (continuous lines, lower case letters) systems. ([Cu^{2+}] and [Zn^{2+}] = 0.005 mol dm^{-3}, $T = 298$ K, $I = 0.1$ mol dm^{-3} NaClO$_4$). M (A,a), MLH (B,b), ML (C,c), ML$_2$H$_2$ (d), ML$_2$H (E,e) and ML$_2$ (F,f).

Results and discussion

Protonation of ligands

The protonation constants of the studied ligands are collected in Table 1. The pK values of both ligands indicate strongly overlapped, *i.e.* microscopic deprotonation processes. Nevertheless, pK_3 for TRIM and pK_3, pK_4 for TIM can be primarily attributed to the 4-substituted imidazole rings (Scheme 1), based on the pH dependence of the C(2)H signals in the ^{1}H NMR spectra. Consequently, pK_1 and pK_2 are attributed to the 2-substituted imidazole rings. The rather low pK_1 values are in good agreement with those of other 2,2′-linked imidazoles,[7,9] and are due to the strong H–bonding interaction between the 2-substituted imidazole rings in TRIMH$_2$ and TIMH$_3$ species.

Complexes of TRIM

In both TRIM containing systems pH-metric titrations were performed between pH 1.8 and 7.3, since above this pH precipitation occurred. The determined stability constants, together with some calculated data, are listed in Table 1. In the TRIM–copper(II) system differently protonated parent complexes are formed. The CuA species is present in the whole pH range studied in the equimolar system. When the ligand is in excess, bis-complexes (CuA$_2$H and CuA$_2$) are also formed above pH 4 (Fig. 1). The large difference between logK_1 and logK_2 values [log(K_1/K_2) = 10.06, Table 1] strongly suggests different co-ordination modes of the two ligands. To study the structures of the complexes formed in solution, electronic absorption and EPR measurements were performed and the obtained spectral parameters are listed in Table 2. The data reported for the CuA complex are in excellent agreement with the co-ordination of three imidazole nitrogens as found in solid state.[15] The two bis-complexes have identical spectral parameters and their formation from CuA leads to an increase of A and decrease of g values (Fig. 2A, B) and a blue shift of the d–d band. The EPR data reported in Table 2 and computer analysis of the superhyperfine patterns suggest 4N co-ordination in the equatorial plane of copper(II) in both CuA$_2$H and CuA$_2$. However, a question may arise as to axial co-ordination of the second ligand, since EPR parameters are not sensitive to this type of

Table 1 Protonation constants of TRIM and TIM and formation constants of their copper(II) and zinc(II) complexes (as their logarithms), $I = 0.1$ M $NaClO_4$, $T = 298$ K

	TRIM		TIM	
Species	copper(II)	zinc(II)	copper(II)	zinc(II)
pK_1[a]	3.94(1)		3.58(1)	
pK_2[a]	6.15(1)		5.43(1)	
pK_3[a]	7.26(1)		6.66(1)	
pK_4[a]	—		7.49(1)	
MAH_2	—	—	—	18.05(8)
MAH	16.61(4)	11.98(3)	21.40(2)	14.85(2)
MA	15.17(1)	8.45(1)	19.61(1)	11.18(1)
MAH_{-1}	6.9(1)	0.23(7)	9.57(4)	1.7(1)
MA_2H_2	—	24.05(8)	—	27.7(1)
MA_2H	26.77(3)	19.45(2)	—	21.45(7)
MA_2	20.28(3)	13.42(2)	—	14.66(4)
$\log K_2$	5.11	4.97	—	3.48
$\log(K_1/K_2)$	10.06	3.48	—	7.70
$pK_{ML_2H_2}$[b]	—	4.60	—	6.25
pK_{ML_2H}[b]	6.49	6.03	—	6.79
$\log K_1^{corr}$	−2.17	−8.89	−3.54	−11.97
Number of exptl. points	216	219	299	273
Fitting parameter/cm³	0.005	0.003	0.004	0.005

[a] For free ligand. [b] $pK_{ML_2H_n} = \log\beta_{ML_2H_n} - \log\beta_{ML_2H_{n-1}}$, $\log K_1^{corr} = \log\beta_{ML} - \log\beta_{H_nL}$ ($n = 3$ and 4 for TRIM and TIM, respectively).

Table 2 Spectroscopic data for the copper(II) complexes of the ligands studied ($T = 298$ K)

Ligand	Complex	g_0	A_0/G	$a_{N,0}$/G	$g_\perp$	$g_\parallel$	$A_\perp$/G	$A_\parallel$/G	$a_{N,\perp}$/G	λ_{max}/nm (ε/M^{-1} cm^{-1})
TRIM	MA	2.133	61.4	13.4	2.067	2.272	15.3	168.5	14.1	626 (42) 305 (117)
	MA_2H	2.125	66.7	13.6	2.056	2.244	14.0	180.0	15.5	602 (64) 295 (207)
	MA_2	2.125	66.7	13.4	2.057	2.247	15.0	180.6	15.0	601 (70) 298 (193)
TIM	MA	2.118	70.3	13.6	2.062	2.234	16.0	179.4	15.5	610 (93) 324 (181)

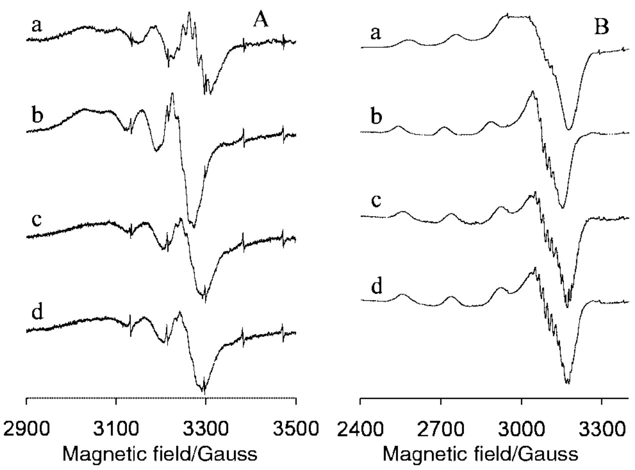

Fig. 2 EPR spectra measured in TRIM–copper(II) and TIM–copper(II) systems at 298 K (A) and 77 K (B). a: $[Cu^{2+}] = [TIM] = 0.005$ mol dm^{-3}, pH = 5.72, b: $[Cu^{2+}] = [TRIM] = 0.005$ mol dm^{-3}, pH = 5.81, c: $[Cu^{2+}] = 0.005$ mol dm^{-3}, $[TRIM] = 0.015$ mol dm^{-3}, pH = 5.34, d: $[Cu^{2+}] = 0.005$ mol dm^{-3}, $[TRIM] = 0.015$ mol dm^{-3}, pH = 7.5.

binding. The pH range of the formation of CuA_2H complex is about 2 pH units lower than that of the non-coordinated AH species and is *ca.* 0.8 pH units lower than that of the ZnA_2H complex (Fig. 1). This suggests metal promoted deprotonation of AH_2 according to the equilibrium $CuA + AH_2 \rightleftharpoons CuA_2H + H^+$ and chelate binding of the second ligand with one equatorial and one axial imidazole ring. Axial coordination is also supported by the red shift of the observed d–d transition ($\lambda^{d-d}_{max} \approx 602$ nm) compared with the theoretical value assuming only four equatorial imidazole rings[22] ($\lambda^{d-d}_{max} \approx 581$ nm) and to the closely related bis[bis(imidazol-2-yl)methane]-copper(II) complex[9] ($\lambda^{d-d}_{max} \approx 578$ nm). During the $CuA_2H \longrightarrow CuA_2 + H^+$ deprotonation no additional metal binding occurs.

The complexes formed in the TRIM–zinc(II) system have similar composition to the copper(II) species, except the complex ZnA_2H_2. The corresponding formation and stability constants are also listed in Table 1. The structures of the bis-complexes are likely to differ between copper(II) and zinc(II). In the presence of zinc(II) the binding of the second ligand to the metal ion is much more favoured: $\log(K_1/K_2) = 3.48$. Moreover, the p*K* values of the two successive deprotonations of ZnA_2H_2 are considerably lower than those of the corresponding p*K* values of the free ligand. In addition, the p*K* of MA_2H is 0.5 log units smaller in the zinc(II) containing system relative to copper(II) (Table 2). All these findings indicate tridentate co-ordination of both ligands in an octahedral ZnA_2 species.

Below pH 4.5, the observed ^1H NMR chemical shifts of the equimolar zinc(II)–TRIM system are similar to those of the free ligand at the same pH, but the signals are very broad, probably due to relatively slow mutual exchange between the protonated ligand and the formed zinc(II) complexes. At pH 5.5, where the formation of ZnA is almost 100%, the peaks are narrow and are upfield shifted (Fig. 3, Table 3) compared with the free ligand at the same pH, indicating metal-promoted deprotonation of the imidazole rings. At pH 6.95, only a slight further upfield shift can be observed, but the peaks are broadened again, probably owing to exchange with the hydrolyzed species $ZnLH_{-1}$. In the presence of a two-fold ligand excess, the ^1H NMR spectra are similar to those of the equimolar system up to pH 5.3. However, the formation of the six-coordinate complex ZnA_2 leads to significant changes in the spectra. All peaks, especially those of the C(2)H and C(4″,5″)H protons, undergo substantial shifts relative to the complex ZnA and the non-protonated free ligand

Table 3 ^{1}H NMR chemical shifts (δ) of TRIM and TIM alone as well as those measured for zinc(II) : L (1 : 1) and (1 : 2) systems and the ternary TRIM–Cys–Zn^{II} (1 : 1 : 1) system (T = 298 K). Atom numbering as in Scheme 1. Tentative assignment

System	pH	C(2)H	C(4″,5″)H	C(5)H (C(5′)H)	C(5′)H (C(5)H)	C(7)H$_2$	C(6)H$_2$
TRIM	5.49	8.42	7.25	7.15	6.99	4.41	3.98
TRIM	7.23	7.89	7.03	6.97	6.86	4.18	3.86
TRIM	9.36	7.61	6.97	6.87	6.77	4.10	3.79
TRIM–Zn^{II} (1 : 1)	5.50	7.94	7.16	7.06	6.99	4.29	3.85
TRIM–Zn^{II} (1 : 1)	6.92	7.82	7.09	7.03	6.99	4.26	3.82
TRIM–Zn^{II} (2 : 1)	5.30	7.88	6.98	7.04	6.92	4.30	3.76
TRIM–Zn^{II} (2 : 1)	7.22	7.10	6.60	7.03	6.83	4.06	3.66
TRIM–Cys–Zn^{II} (1 : 1 : 1)	7.45	≈7.45	≈6.85	7.00	6.92	4.17	3.75
TIM	7.75	7.72	—	6.90	6.80	4.07	3.81
TIM	10.30	7.60	—	6.85	6.75	4.03	3.78
TIM–Zn^{II} (1 : 1)	7.75	7.68	—	7.09	6.98	4.25	3.88
TIM–Zn^{II} (2 : 1)	7.76	7.44	—	6.81	6.71	4.11	3.57

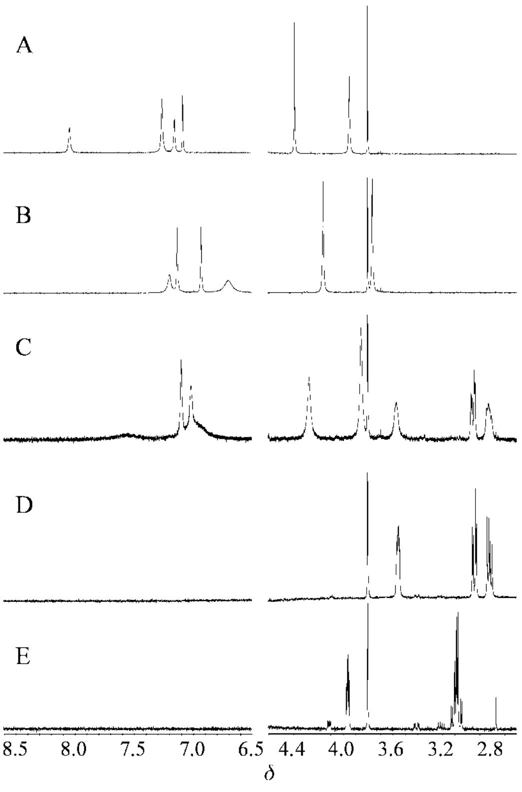

Fig. 3 Parts of the ^{1}H NMR spectra measured in TRIM–zinc(II) (1 : 1) (A), (2 : 1) (B), TRIM–Cys–zinc(II) (1 : 1 : 1) (C), (0 : 2 : 1) (D) and (0 : 1 : 0) (E) systems; pH = 5.50 (A), 7.22 (B), 7.45 (C), 7.48 (D) and 7.52 (E), respectively.

(Fig. 3, Table 3). Additionally, the signals of imidazole protons show some selective line-broadening, which decreases on heating the solution. Such differences in chemical shifts of the mono- and bis-complex [*e.g.* 0.7 ppm for C(2)H] is surprising, since the ligand TRIM is tridentate in both ZnA and ZnA$_2$. To explain these observations, we suggest different conformations for the ligand in the mono- and bis-complexes. Two different conformations of TRIM can bind in a tridentate coordination mode, resulting in different geometries around the metal ions (ESI, Fig. S1).† In the first conformation, both outer imidazole moieties lie to the same side of the plane determined by the central imidazole ring, and the coordinated metal ion would adopt a tetrahedral geometry. In the second conformation, the outer imidazoles lie on opposite sides of the central plane, which allows octahedral coordination around the metal ion. Zinc(II) complexes are known to switch easily between octahedral and tetrahedral geometries and the latter is preferred when several (2–4) imidazole nitrogens are coordinated.[23] Taking into account our NMR results, we propose mostly tetrahedral geometry for the mono-complex ZnA and octahedral geometry for the bis-complex ZnA$_2$.

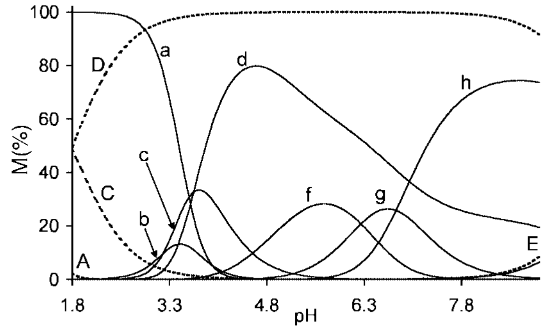

Fig. 4 Species distribution in the TIM–copper(II) (2 : 1) (dashed lines, upper case letters) and TIM–zinc(II) (2 : 1) (continuous lines, lower case letters) systems. ([Cu^{2+}] and [Zn^{2+}] = 0.005 mol dm^{-3}, T = 298 K, I = 0.1 mol dm^{-3} NaClO$_4$). M (A,a), MLH$_2$ (b), MLH (C,c), ML (D,d), MLH$_{-1}$ (E), ML$_2$H$_2$ (f), ML$_2$H (g) and ML$_2$ (h).

Complexes of TIM

The pH-metric titrations were evaluated between pH 1.8 and 8–9, depending on the ligand excess. The determined stability constants, together with some derived data, are presented in Table 1. Copper(II) forms an extremely stable CuA complex with TIM (Fig. 4). The complex MAH exists only at low pH, the metal promoted deprotonation of the fourth imidazole nitrogen takes place with pK *ca.* 1.8, indicating 4N co-ordination in the CuA species. Precipitation can be observed parallel to the formation of the CuAH$_{-1}$ complex around pH 9. Because of the tetradentate nature of TIM, no bis-complexes can be detected in the copper(II)–TIM system at any ligand to metal ratio. The spectral data determined for the CuA complex (Table 2) are somewhat different from those expected for the equatorial co-ordination of four imidazole ring, *e.g.* in case of the related bis[bis(imidazol-2-yl)methane]copper(II) complex $\lambda^{d-d}_{max} \approx 578$ nm, $g_{\parallel} = 2.237$ and $A_{\parallel} = 199$ G have been determined.[9] Despite this, both the pH-metric results and computer analysis of the well resolved ^{14}N superhyperfine splitting for the isotropic EPR spectra (Fig. 2A) support 4N co-ordination in the equatorial plane. The crystal structure of [Cu(ClO$_4$)(TIM)]ClO$_4$ indicated considerable distortion from the tetragonal symmetry around the copper(II) due to the strained ligand backbone.[15] The structure of the Cu(TIM) species appears to be distorted in solution as well, which may explain the observed deviation of the spectral parameters. This distortion, however, does not reduce the stability of the Cu(TIM) complex. The basicity corrected stability constant of the bis[bis(imidazol-2-yl)methane]copper(II) complex, which has nearly perfect tetragonal symmetry around the metal ion,[9,15] is considerably lower ($\log\beta_{120} - 2\log\beta_{012} = -6.28$) than the corresponding value of the Cu(TIM) species (-3.54).

Table 4 Formation constants and some derived data of the ternary complexes with cysteine (as their logarithms, the estimated errors are in parentheses), $I = 0.1$ M $NaClO_4$, $T = 298$ K (TRIM, TIM = A, L-cysteine = B)

Complex	Zinc(II)–TRIM–Cys	Zinc(II)–TIM–Cys
$ZnABH_2$	28.79(7)	—
ZnABH	23.06(3)	24.22(2)
ZnAB	15.66(4)	15.98(3)
pK_{ZnABH2}	5.73	—
pK_{ZnABH}	7.40	8.24
$\Delta\log K_{MAB}$	−1.51	−3.92
$\Delta\log\beta_{MAB}$	−0.38	−0.68
Number of exptl. points	293	416
Fitting parameter/cm^3	0.006	0.004

The $\log\beta_{pqr}$ values determined for the zinc(II)–L–cysteine binary complexes are: $\log\beta_{011} = 10.29(1)$, $\log\beta_{012} = 18.45(1)$, $\log\beta_{013} = 20.35(1)$, $\log\beta_{111} = 14.3(1)$, $\log\beta_{110} = 8.72(9)$, $\log\beta_{122} = 30.22(6)$, $\log\beta_{121} = 23.8(1)$, $\log\beta_{120} = 18.06(1)$, $\log\beta_{230} = 30.28(8)$, $\log\beta_{341} = 49.31(4)$, $\log\beta_{340} = 42.83(8)$.

The EPR spectra of both copper(II)–TRIM and –TIM complexes indicate strong superhyperfine coupling (13–15.5 G, Table 2) *i.e.* relatively important delocalisation of the unpaired electron over the imidazole rings.

In the zinc(II)–TIM system, several mono- and bis-complexes are formed having different protonation states. In equimolar solution the 4N co-ordinated ZnA complex is the only species above pH 5. For a two-fold ligand excess, the parent bis-complex ZnA_2 becomes dominant above pH 7 (Fig. 4). This latter species may exist as at least two co-ordination isomers: both TIM ligands can act as tridentate ligands or one of them may bind to the zinc(II) ions in a tetradentate manner, similarly to ZnA, and the second may occupy the fifth and sixth positions in a bidentate manner. In both cases, $\log K_1$ and $\log K_2$ values refer to different processes which may explain their significant difference [$\log(K_1/K_2) = 7.7$].

The ^1H NMR study of the zinc(II)–TIM system gave similar results as observed for the zinc(II)–TRIM complexes. Below pH 4 the peaks are broad and the chemical shifts of the ZnA species are close to those of the non-protonated free ligand (Table 3 and ESI, Fig. S2), whereas the signals of the bis-complex ZnL_2 are fairly substantially upfield shifted. Based on our data, the distinction between coordination isomers is rather difficult, but the analogous ^1H NMR behaviour of the $Zn(TRIM)_2$ and $Zn(TIM)_2$ complexes would suggest tridentate coordination of TIM.

Ternary complexes with cysteine

To be able to determine the formation constants in the ternary systems we have re-measured those of the species formed in the L-cysteine–zinc(II) binary system. The model and the determined constants are in good agreement with those found by several authors earlier.[24] These data, together with the formation constants of the ternary complexes, are listed in Table 4. In both TRIM and TIM containing systems, beside the dominant ZnA species, mixed ligand complexes with different protonation states ($ZnABH_2$, ZnABH, ZnAB) are also formed to a considerable extent. The calculated stability constant for the ZnA + BH_2 = $ZnABH_2$ reaction ($\log\beta_{1112} - \log\beta_{1100} - \log\beta_{0012} = 1.89$) suggests monodentate co-ordination of the carboxylate group of L-cysteine to the Zn(TRIM) complex. The pK values of the two successive deprotonations of this mixed ligand complex (pK = 5.73 and 7.40) are remarkably lower than those found for the free L-cysteine. This indicates the stepwise co-ordination of the thiolate and amino groups of L-cysteine (ligand B) to the zinc(II) ion. As a consequence, the value of $\log K_{ZnA+B}$ (=7.21) shows a significant binding ability of the ZnA complex towards L-cysteine, although somewhat less compared with that of the corresponding binary cysteine complex ($\log K_{Zn+B} = 8.72$). Near pH 7, *ca.* half of the metal ions are present in ternary complexes (Fig. 5). The ^1H NMR spectra of the ternary system also indicate the formation of mixed ligand complexes, since both the TRIM and cysteine signals are different from those of the binary systems. Near pH 7, the imidazole protons undergo selective broadening (Fig. 3). The chemical shift of the C(2)H proton (δ 7.45) lies between those for the binary complexes Zn(TRIM) and $Zn(TRIM)_2$. The cysteine protons in the ternary complex are considerably upfield shifted as compared with free cysteine, but nearly identical to the binary Zn(II)–cysteine (1:2) system, in which both the amino and thiolate group are proposed to be coordinated to the metal ion around pH 7. On the other hand, all peaks are sharp for the binary Zn(II)–cysteine system, while the CH and one of the two inequivalent CH_2 proton signals of the cysteine are considerably broadened in the spectra of the ternary system. According to the pH-metric study, the ^1H NMR data also suggest strong, at least bidentate $\{N,S^-\}$, coordination of the cysteine in the complex ZnAB.

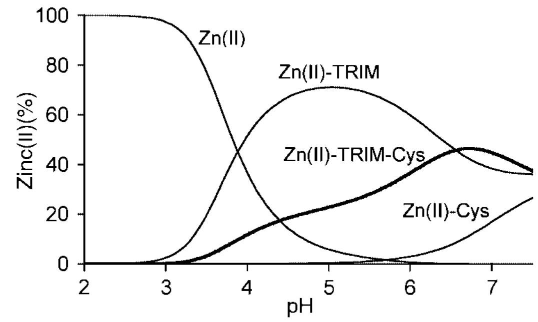

Fig. 5 Predominance diagram of the TRIM–Cys–zinc(II) system at 1:1:1 ligand to metal ratio. ($[Zn^{2+}] = 0.005$ mol dm^{-3}, $T = 298$ K, $I = 0.1$ mol dm^{-3} $NaClO_4$).

The formation of mixed ligand complexes is less favoured for the tetradentate ligand TIM, as indicated by the lower value of the $\log K_{ZnA+B}$ (= 4.80) constant. Nevertheless, the pK of the ZnABH complex of TIM is considerably lower (pK = 8.24) than that of the third pK of cysteine, suggesting chelate co-ordination of cysteine in ZnAB, even in the presence of four imidazole rings. To our knowledge no ternary complexes of zinc(II)–cysteine have been reported so far with (poly)imidazole ligands, although such information may be informative with respect to many biological zinc(II) sites. The formation of the ternary complexes described above is noteworthy, taking into account the high stability of the binary complexes formed in both zinc(II)–TRIM/TIM and zinc(II)–cysteine systems. This suggests preferred formation of $\{N,S^-\}$ co-ordination around the zinc(II) ion, especially in case of the triimidazole derivative TRIM.

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