Selective synthesis of novel multiimidazole ligands

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Novel ligands containing di- to tetra-imidazole rings have been synthesised. 2,2'-Biimidazole was chosen as a dimeric analogue of imidazole which extended the range of ligands.

Keywords: selective synthesis, mulitimidazole ligand, 2,2'-biimidazole

In the last two decades, a large number of binuclear copper complexes have been reported as model compounds for the active sites of type 3 copper proteins like hemocyanin and tyrosinase.[1-10] The most important reaction characterising tyrosinase models is the *o*-hydroxylation of exogenous phenols. However, the artificial tyrosinase has not yet overtaken the natural high efficiency and selectivity. The reason, may be that few models[1,11] have imidazole (**Im**) or multiimidazole ligands present. Commonly, aliphatic amines or imines; or pyridine, pyrazole and benzimidazole (**Bim**) are used.

The **Im** of histamine is a ubiquitous ligand, which is present in various types of copper active sites. It is also known that structural modulation of copper complexes by subtle structural perturbation of ligands dramatically affects the copper(I)-dioxygen reactivity. This shows that functions of **Im** cannot be replaced completely by other heterocycles or heteroatom molecules. **Im**-based ligends and macrocycles have received increasing attention in coordination chemistry, host–guest chemistry and biomimetic chemistry.

Our work has been focused on synthesis and application of **Im**, imidazolium and their derivatives.[12-16]

In order to extend the scope, we have explored novel spacers, binding groups and some variation of the molecular backbones. Here 2,2'-Biimidazole (**Biim**) is chosen as the component. New macrocycles with four nitrogen donors can be used as multidentate ligands to bind transition metal ions or other guest molecules. The synthetic scheme is outlined as follows (Scheme 1).

Results and discussion

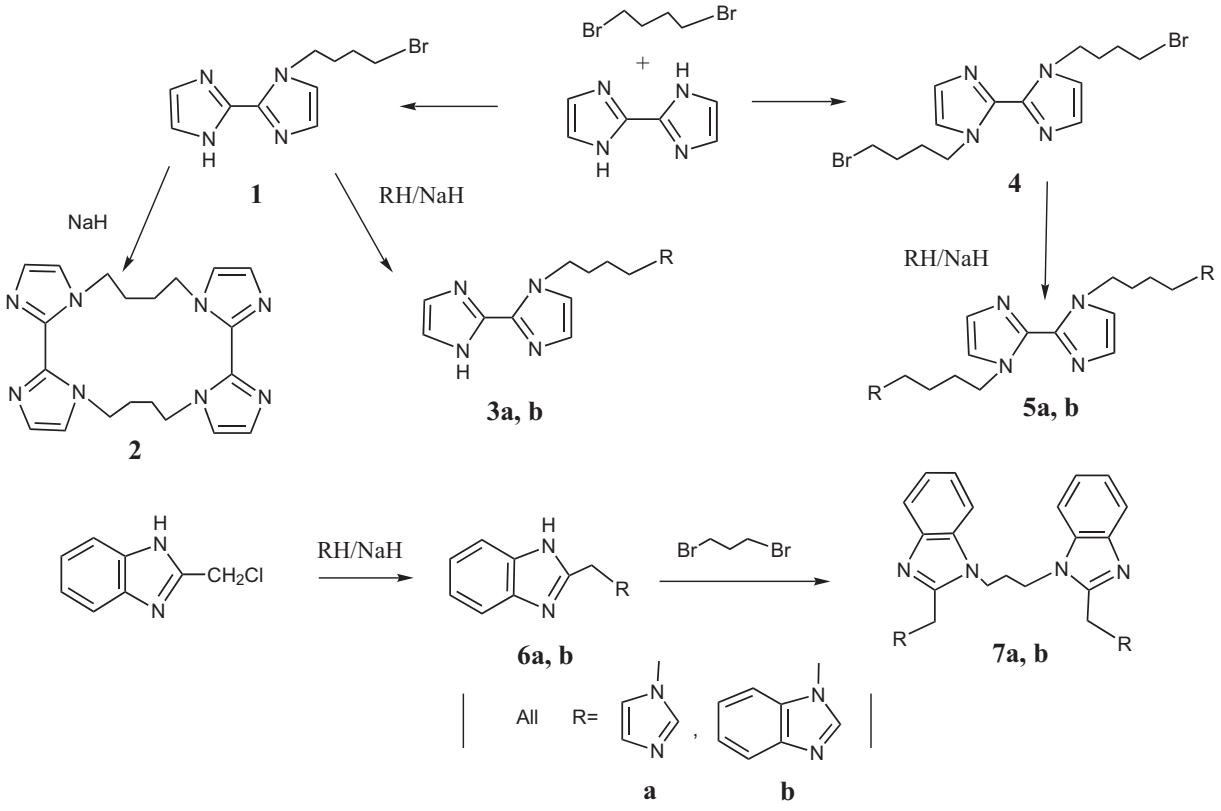
Design of ligands

Im can serve as proton donor–acceptor, general acid–base, nucleophile and selective binding group. The nature of **Biim** is characterised by its greater chemical stability and that it has a nearly planar structure. More importantly, **Biim** possesses bidentate chelating sites and might function as a bridging ligand. The incorporation of pendant groups provides additional binding sites.

A stable chain or **Biim** is employed as the spacer so that the complex would not undergo oxygen insertion in the ligand itself[6-7,17] and would therefore be expected to have an appreciable lifetime.

Synthesis of ligands

The multiimidazole compounds are generally considered to be difficult to prepare because several reactive sites exist in the



Scheme 1 The synthetic route of ligands

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reactants, even as **Im**, **Biim** and the intermediate 1,1'-bis(4-bromobutyl)-2,2'-biimidazole[18] (**4**). The reaction conditions have a significant influence on the selectivity. Treatments of **Biim** with 1,4-dibromobutane can provide intermediate **1**, **4**, or *N,N'*-bridged derivative and quaternisation salt,[19] as well as products that **1**, **4** or **Biim** connect inter-molecularly or intra-molecularly.

The *N*-alkylation of **Im** and its derivatives is the usual route.[20] However competing reactions may lead to poor yields. There are many possible substitutions at different sites, such as quaternisation or *N,N'*-bridged cyclisation, 1,1'-disubstitution. By optimising conditions, these competitive reactions can be minimised. Temperature is more important in obtaining **1** or **4** stably. Excessive heating may lead **1** and **4** respectively to becoming 1,1'-tetramethylene-2,2'-biimidazole and 1,1',3,3'-bis(tetramethylene)-2,2'-biimidazolium dibromide.[18] Inter- and intra-molecular annular byproducts of **1** or **4** are easily produced because they are more stable than open-chain **1** or **4** itself.

Under equivalent basicity to **Biim**, only **1** is produced. 1-Substitution of **Biim** proceeds far faster than 1,1'-disubstitution. Once two equivalents of base are used, the mixture of **1**, **4** and 1,1'-tetramethylene-2,2'-biimidazole are formed. It is only by dropping **Biim** disodium salt into excess 1,4-dibromobutane that **4** can be obtained simplex.

It is important to separate **1** or **4** from **Biim** before preparation of 1-[4-(imidazol-1-yl)butyl]-2,2'-biimidazole (**3a**), 1-[4-(benzimidazol-1-yl)butyl]-2,2'-biimidazole (**3b**), 1,1'-bis [4-(imidazol-1-yl)butyl]-2,2'-biimidazole[18] (**5a**) and 1,1'-Bis [4-(benzimidazol-1-yl)butyl]-2,2'-biimidazole (**5b**). Adding **1**, **4** or 2-(chloromethyl)benzimidazole dropwise is an effective method to prevent cross linking. Although **1** and **4** have a high tendency to cyclise **3a**,**b** and **5a**,**b** can be firstly obtained by adding intermediate **1** (or **4**) to excess sodium salt of **Im** or **Bim** under higher temperature and shorter heating times. While **5a**,**b**, 1,3-bis{2-[(imidazol-1-yl)methyl]benzimidazol-1-yl}propane (**7a**) or 1,3-bis{2-[(benzimidazol-1-yl)methyl]benzimidazol-1-yl}propane (**7b**) is prepared by adding intermediate **4** or 1,3-dibromopropane slowly in order to avoid side reactions.

The yields of compounds **1–7a,b** are typically 32–84%.

Table 1 Yields and characterisation of multiimidazole compounds

Compound	Yield/%[a]	M.p./°C	Formula	Elemental analysis/%[b]		
				C	H	N
1	84	208.5-209.4	$C_{10}H_{13}N_4Br$	44.40 (44.63)	4.50 (4.87)	21.01 (20.82)
2	65	185–187	$C_{20}H_{24}N_8$	63.86 (63.81)	6.45 (6.43)	29.28 (29.77)
3a	32	>300	$C_{13}H_{16}N_6$	60.60 (60.92)	5.98 (6.29)	32.84 (32.79)
3b	59	187–188	$C_{17}H_{18}N_6$	66.95 (66.65)	6.31 (5.92)	27.20 (27.43)
5b	49	285–287	$C_{28}H_{30}N_8$	69.99 (70.27)	6.34 (6.32)	23.83 (23.41)
7a	80	238–239	$C_{25}H_{24}N_8{\cdot}C_2H_5OH{\cdot}NaBr$	55.03 (55.39)	4.93 (5.16)	19.18 (19.14)
7b	70	172–173	$C_{33}H_{28}N_8{\cdot}1/2NaBr{\cdot}CH_3OH{\cdot}H_2O$	64.06 (63.99)	5.27 (5.37)	17.54 (17.56)

[a]Yield of isolated is pure products. [b]The data in parentheses are calculated values.

Table 2 Characterisation of multiimidazole compounds

Compd.	MS *m/z* (%)	^{1}H NMR	UV (CH_3OH) λ_{max}
1	EI (70 eV) 270 (M^++1, 17), 188 (M^+-Br, 100), 159 (25), 133 (20), 80 (23), 55 (38)	(D_2O, 400 MHz) δ 1.95 (s, 4H, CH_2), 3.97 (s, 4H, CH_2N, CH_2Br), 7.18 (s, 2H,Biim-5,5'-H), 7.34 (s, 2H, Biim-4,4'-H)	203 nm (Abs 0.367), 248 nm (1.012)
2	ESI 399.0 (M^++Na)	(D_2O, 400 MHz) δ 2.01(s, 8H, CH_2), 4.02 (s, 8H, CH_2N), 7.24 (s, 4H, Biim5-H), 7.40 (s, 4H, Biim4-H)	206 nm (Abs 0.196), 249 nm (0.440)
3a	ESI 279.8 (M^++Na)	(D_2O, 400 MHz) δ 1.77 (bs, 4H, CH_2), 3.83 (br s, 4H, CH_2N), 6.97-7.01 (d, 2H, Im4,5-H), 7.10–7.35 (d, 4H, Biim-H), 7.55 (s, 1H, Im2-H)	209 nm (Abs 0.564), 247 nm (0.353)
3b	EI (70 eV) 307 (M^++1, 17), 261(55), 189 (100), 173 (15), 159 (15), 95 (23), 84 (75), 58 (50).	(D_2O, 400 MHz) δ 1.41–1.51, 1.67–1.78 (d m, 2H, CH_2–CH_2Bim), 1.92–2.01, 2.23–2.35 (d m, 2H, CH_2–CH_2Biim), 3.73–3.85 (d m, 2H, CH_2Bim), 4.05–4.14 (d m, 2H, CH_2Biim), 6.62 (s, 4H, Bim-4,5,6,7-H), 7.54 (s, 4H, Biim-H), 8.08 (s, 1H, Bim2-H)	212 nm (Abs 1.277), 248 nm (0.483)
5b	EI (70 eV) 244 (M^+-2Bim, 100), 203 (10), 188 (95), 136 (40), 119 (90), 91 (15), 80 (20).	(D_2O, 400 MHz) δ 1.41–1.51, 1.67–1.78 (d m, 4H, CH_2–CH_2Bim), 1.92–2.01, 2.23–2.35 (d m, 4H, CH_2–CH_2Biim), 3.41–3.48, 3.88–3.94 (d m, 4H, CH_2Bim), 4.05–4.14, 4.42–4.47 (d m, 4H, CH_2Biim), 6.62 (s, 8H, Bim-4,5,6,7-H), 7.54 (s, 4H, Biim-H), 8.77 (s, 2H, Bim2-H).	205 nm (Abs 0.837)
7a	EI (70 eV) 436 (M^+, 28), 301(20), 289 (28), 239 (38), 198 (25), 131 (78), 81 (43), 68 (100)	(D_2O, 300 MHz) δ 2.36 (t, 2H, *J*=2.2Hz, CH_2–CH_2N), 4.77 (t, 4H, CH_2N), 5.67 (s, 4H, NCH_2N), 7.39, 7.66 (d d, 8H, Bim–H), 8.41, 8.63 (d, 6H, Im-H)	218 nm (Abs 1.54), 254 nm (1.37), 275 nm (1.17), 283 nm (0.98)
7b	EI (70 eV) 537 (M^++1, 17), 408 (28), 277 (90), 248 (28), 145 (47), 131 (100), 117(23), 77 (25).	(DMSO-d_6, 300 MHz) δ 2.53 (t, 2H, *J*=2.2Hz,CH_2–CH_2N), 4.15 (br s, 4H, CH_2N), 5.76–6.02 (m, 4H, NCH_2N), 7.16 (s, 8H, Bim-β-H), 7.68 (s, 8H, Bim-α-H), 8.52 (s, 2H, Bim2-H)	218 nm (Abs 1.54), 250 nm (1.52), 274 nm (1.38), 281 nm (1.20)

Biomimetic studies of target compounds in metal complexes are in progress. More detailed mechanistic studies will improve our understanding of the structure–function relationships.

Experimental

Instrumentation and materials

Melting points were determined on a XSP-I micro-melting point apparatus and uncorrected. Mass spectra (MS) were measured on an EI-MS (electron ionisation) Finnigan Mat 4510 or ESI-MS (electron spray ionisation) Finnigan-LCQ instrument. ^{1}H NMR spectra were recorded on Varian INOVA-400 (400 MHz) or Bruker DPX-300 (300 MHz) spectrometers. UV spectrogram was recorded on TU-1901. Elemental analyses were carried out on a Carlo Erba 1106 analyser.

All reagents and solvents were of commercially available reagent quality unless otherwise stated. Dimethylsulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF) and tetrahydrofuran (THF) were dried over $MgSO_4$ for one day.

Synthesis of ligands

1-(4-Bromobutyl)-2,2'-biimidazole (**1**): A mixture of **Biim** (268 mg, 2.00 mmol) and NaOH (96 mg, 2.40 mmol) in DMF (20 ml) was stirred to a dark green solution at room temperature. 1, 4-Dibromobutane (518 mg, 2.40 mmol) was added and reacted overnight. The solid was filtered and washed with a little absolute ethanol. Combined solution was rotary-evaporated to dryness under a vacuum at 80°C. The residue was purified over a silica gel column (acetone eluting). Yellow flakes of **1** were obtained (450 mg, 84%), m.p. 208.5–209.4°C.

8,9,10,11,20,21,22,23-terahydrotetraimidazo[1,2-a:2',1'-c:1",2"-i:2"', 1"'-k][1,4,9,12]tetraazahexadecine (**2**): To a stirred and warmed (55°C) solution of NaH (144 mg, 6.00 mmol) and THF (10 ml), compound **1** (5.00 mmol) in THF was added dropwise over 5 h. THF was removed and the crude product was purified over a silica column (THF eluting). The colourless blocks were obtained in yield 0.61 g (65%), m.p. 185–187°C.

1-[4-(Imidazol-1-yl)butyl]-2,2'-biimidazole (**3a**) *and 1-[4-(Benzimidazol-1-yl)butyl]-2,2'-biimidazole* (**3b**): **Im** or **Bim** (1.00 mmol) and NaOH (48 mg, 1.20 mmol) in dry DMSO (20 ml) were stirred overnight. To the above warmed (80°C) solution, compound **1** (269 mg, 1.00 mmol) in DMSO (5 ml) was added dropwise over a period of 10 hours. **1** was monitored by thin-layer chromatography until it disappeared. DMSO was evaporated to dryness under a vacuum. The crude product was purified over a silica column with THF/C_2H_5OH (1/2, v/v).

3a: Colourless hygroscopic crystals were obtained (82 mg 32%), m.p.>300°C.

3b: Yellow crystals were obtained (180 mg, 59%), m.p. 187–188°C.

1,1'-Bis[4-(benzimidazol-1-yl)butyl]-2,2'-biimidazole (**5b**): To a stirred and warmed (60°C) suspension of **Im** or **Bim** (1.00 mmol) and NaH (1.20 mmol) in dry DMSO (10 ml), the solution of **4** (0.50 mmol) and dry DMSO (2 ml) was added dropwise for a day. At the same time, one equivalent of KOH solution was added to keep basicity. The mixture was evaporated to dryness under a vacuum. The residue was purified over a silica gel column with THF/C_2H_5OH (1/1, v/v). White crystals were obtained (120 mg, 49%), m.p. 285–287°C.

1,3-Bis{2-[(imidazol-1-yl)methyl]benzimidazol-1-yl}propane (**7a**) *and 1,3-Bis{2-[(benzimidazol-1-yl)methyl]benzimidazol-1-yl}propane* (**7b**): 2-[(imidazol-1-yl)methyl]benzimidazole[21] (**6a**) or and 1,2'-bis(benzimidazol-2-yl)methane[22] (**6b**) (5.00 mmol) was added dropwise to a stirred mixture of NaH (120 mg, 5.00 mmol) and THF (20 ml). To the above warmed solution (60°C), 1,3-dibromopropane (606 mg, 3.00 mmol) was added dropwise over a period of one day. The mixture was concentrated and purified over a silica gel column with THF/C_2H_5OH (1/1, v/v).

7a: A white powder was obtained (1.17 g, 80%), m.p. 238–239°C.

7b: A yellow powder was obtained (1.12 g, 70%), m.p.172–173°C.

The structures of compounds **1–7a,b** were consistent with the data from MS, ^{1}H NMR, UV and element analyses (see Tables 1 and 2).

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