Synthesis of *cis, cis*-1,3,5-trisubstituted cyclohexane based chelators with polyfunctional pendant arms

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Some novel organic compounds of the type: *cis,cis*-1,3,5-tris(X)cyclohexane, where X= $-CONH(CH_2)_2NH_2$, $-CONH(CH_2)_3NH_2$, $-CONH(CH_2)_2NCH-C_6H_4OH$, $CONH(CH_2)_3NCHC_6H_4OH$, which are expected to function as potential polydentate chelators have been synthesised from 1,3,5-benzenetricarboxylic acid through multi-steps reactions. 1,3,5-benzenetricarboxylic acid was reduced to *cis,cis*-1,3,5-tris(ethylcarboxylate)cyclohexane, which on reaction with excess of 1,2-diaminoethane and 1,2-diaminopropane afforded two new compounds. Condensation of the obtained derivatives with three equivalents of salicylaldehyde resulted the formation of two new Schiff base compounds. All the compounds were characterised by a combination of elemental analysis, mass, IR, UV-Vis, ^1H NMR and ^{13}C NMR spectroscopy.

Keywords: *cis, cis*-1,3,5-trisubstituted cyclohexane based chelators, polyfunctional sites

Presence of macrocyclic and polyfunctional sites in the chelating unit of natural occurring biomolecules such as proteins and enzymes has stimulated interest among the synthetic chemists to design and synthesise of such compounds, which mimic the biological systems. Some macrocycles or ligands with multi-functionalities exhibit interesting coordination behaviour where the absence of twisting and folding possibilities, as well as steric restrictions, is likely to slow down the normal rates and introduce mechanistic novelties. Undoubtedly, the interest in this area has been stimulated by biological overtones. Also, owing to the clinical importance of trivalent metal ions there is a need to synthesise chelating agents, which are specifically designed for such applications.[1] Enterobactin (Ent), a representative tricatecholate siderophore, serves as biologically active iron(III) carrier mainly due to its high iron(III) binding efficiency and binding selectivity. It plays a vital role in the treatment of iron-overload diseases, there is a critical need for effective chelation.[2] Thus, more recently, the design and synthesis of Ent analogous have attracted considerable attention of bioinorganic chemists. To probe the design features of Ent, many synthetic tricatecholamide analogues based on tripodal[3] and macrocyclic[4] skeletons have been synthesised. Amide based chelators are usually pH dependent and show interesting binding property in different pH range. It has been reported that in more acidic condition complexes can be formed in which one or no proton are released from the amide nitrogen atoms. Similar observation has also been documented for some copper(II) complexes where metal prefers binding through amide oxygen at low pH while through deprotonated amide nitrogen at high pH range.[5-12] Keeping the above facts in view, it is thought of designing some new face capping ligands with amide functionality, which can enhance the coordination behaviour of metal ion. Herein, the syntheses and characterisation of a series of compounds (**IV**–**VII**, have been reported in which the tripodal topology of Ent has been retained but with a different backbone of cyclohexane. Compounds **IV** and **V** are expected to behave as hexadentate chelating agent that can coordinate either through N_3 (amine-N) or O_3 amide and N_3 (imine-N) donor sites. Compound VI and VII each contains three pendant arms consisting of a phenolate, amido and azomethine subunit. These compounds with a number of coordination sites are expected to exhibit an enhanced coordination property not only with the transition metal but also with lanthanide and actinide ions in different chemical environment.

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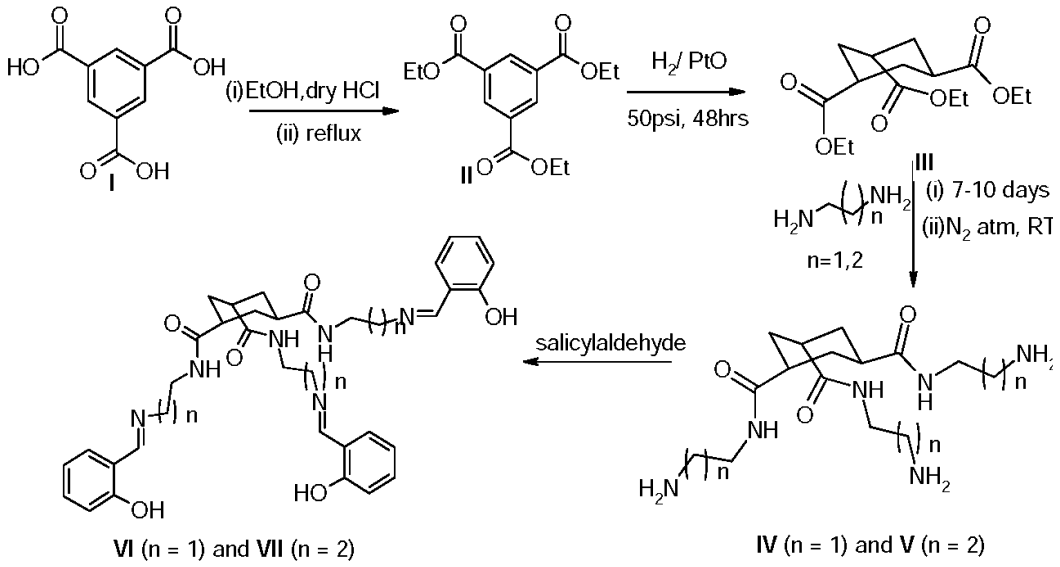
Results and discussion

Four new compounds (**IV**–**VII**) reported here were synthesised as per Scheme 1. 1,3,5-Benzenetriethylcarboxylate(**II**) was obtained in quantitative yield from 1,3,5-benzenetricarboxylic acid(**I**) by reaction of latter with ethanol in dry HCl gas, which was reduced to *cis,cis*-1,3,5-tris(ethylcarboxylate)cyclohexane(**III**) with Adam's catalyst and hydrogen at room temperature.[13-14] Compounds **IV** and **V** were obtained after seven days by the reaction of *cis,cis*-1,3,5-tris(ethylcarboxylate)cyclohexane (**III**) and appropriate diamines under N_2 atmosphere and room temperature. Condensation of **IV** and **V** with three equivalents of salicylaldehyde in ethanol yielded the compounds **VI** and **VII** respectively. All the compounds reported here are air sensitive and absorb moisture on exposure to atmosphere. **IV** and **V** are highly water soluble, while **VI** and **VII** are only partially soluble in water and insoluble in common non-polar solvents; however, they produced a good proton NMR spectrum in D_2O and DCl mixture, in which both the compounds are fairly soluble. Compounds **IV** and **V** melted completely at 250 and 260 °C respectively, but before that, they decomposed (220 °C: **IV**, 240 °C: **V**), whereas their corresponding Schiff base derivatives did not decompose and melted at 252–254 °C and 262–264 °C respectively.

The FT-IR spectra of all the compounds were obtained as KBr disc. The C=O stretching vibration of amides (amide I) was observed at a lower range ~1640cm^{-1} than the carbonyl absorption band (at ~1723cm^{-1}). This can be explained due to resonance effect in the amide functional group[15]. The amide II band caused by N–H bending vibration for a secondary amide is usually observed between 1515 and 1570 cm^{-1}.[16] In the present case amide II bands appeared at ~1550–1560, υNH at 3275 and 3170 cm^{-1}. Bands due to υ_{C-H} (aliphatic) for symmetry and asymmetric vibration appeared at ~2850 and ~2923 cm^{-1} respectively in all compounds. In **IV** and **V** $-NH_2$ stretching vibration was observed at ~3618 cm^{-1}. Additional peaks appeared in Schiff base compounds at ~1622($\upsilon_{C=N}$), ~1496 and ~1463 ($\upsilon_{C=C}$), ~1375($\upsilon_{C=O}$) and ~1270(δ_{O-H}) and ~771 cm^{-1} (δ_{Ar-H}), while peaks due to υ_{NH2} were missing.

The *cis*- and *trans*- isomers of cyclohexane are easily distinguished through ^1H NMR and ^{13}C NMR spectra. Proton NMR spectra of all compounds gave characteristics peaks for *cis,cis*-1,3,5-trisubstituted cyclohexane ring protons where the substituents occupy the equatorial position. There was slight downfield shifting which may be due to the replacement of ester with amide group. Besides the peaks for cyclohexane ring protons, compound (**IV**), gave two new peaks(δ) at 3.12–3.16 (t, 6H) and 2.59–2.63ppm (t, 6H) for CH_2 adjacent to –CONH and $-NH_2$ group respectively. Compound (**V**) gave three additional peaks(δ) for methylene groups which



Scheme 1

were observed at 3.15–3.20(t, 6H), 2.59–2.65(t, 6H) and 1.58–1.64 ppm(quintet, 6H). Both the Schiff base compounds containing salicylaldehyde exhibited peaks for aromatic and methine protons respectively at ~6.50 (t, 6H:VI; q,6H:VII), ~7.04 ppm (t,6H) and ~8.20ppm (s,3H). A slight upfield shift was observed for cyclohexane ring protons, while noticeable downfield shift occured for others after the condensation with salicylaldehyde takes place, which may be due to the insertion of conjugation through azomethine linkage to the system. Chelating ability of the synthesised compounds with some transition metal ions is under being carried out.

Experimental

All the reagents used were of AnalR grade. The reagents used for synthesis of ligands *viz* 1,3,5-benzenetricarboxylic acid, PtO_2, ethanol, 1,2-diaminoethane and 1,3-diaminopropane, salicylaldehyde were of Aldrich and 99.9%. All reactions were performed in oven-dried glasswares under an atmosphere of dry nitrogen. ^1H and ^{13}C NMR spectra in $CDCl_3$, D_2O and D_2O–DCl mixture were recorded on a Bruker DPX 300 NMR spectrometer and chemical shifts were reported relative to Me_4Si as internal standard. Elemental analyses were performed for C, H and N using the Exeter Analytical CE 440. Melting points were determined on a capillary melting point apparatus and are uncorrected. IR spectra were obtained in solid state as KBr pallet on a Perkin Elmer model RX-1 FT-IR spectrophotometer and UV-VIS spectra were recorded on Agilent Diode array spectrophotometer. Mass spectra were taken with Kratos MS 80 spectrometer.

Synthesis of cis,cis-1,3,5-tris(ethylcarboxylate)cyclohexane (**III**): Compound (**I**) was synthesised from 1,3,5-benzenetricarboxylic acid as per literature.[13,14] A transparent oil was obtained quantitatively which was slowly solidified to white crystals at room temperature. yield=91.4%; m.p.=36–38 °C; ^1H NMR: (δ in ppm) 1.17–1.29 (t, 9H, CH_3), 1.47–1.62 (q, 3H, CH_2 axial), 2.20–2.31 (d, 3H, CH_2 equatorial), 2.32–2.47 (t, 3H, CH axial), 4.05–4.21(q, 6H, CH_2 of ester); ^{13}C NMR: (δ=ppm) 14.46 (CH_3), 30.74 (ring CH_2), 41.65 (ring CH), 60.65 (CH_2 of ester) 177.31(carbonyl).

Synthesis of cis,cis-1,3,5-tris(–CONH–(CH$_2$)$_2$–NH$_2$)cyclohexane (**IV**): Excess freshly distilled 1,2-diaminoethane(50ml) and 1.5g(0.049mol) of *cis,cis*-1,3,5-tris(ethylcarboxylate)cyclohexane (**III**) was stirred under N_2 atmosphere at room temperature. White turbidity appeared after 48 h of stirring. The mixture was continued stirred for 7 days while more white precipitate formed. The excess 1,2-diaminoethane was removed by Rota evaporator leaving a white sticky solid mass. 25ml of ethanol-diethyl ether mixture was added and filtered under N_2 atmosphere. The process was repeated (five times) till the residue became powder. The product was washed with ether and dried *in vacuuo* to gave a air-sensitive non-sticky pure white solids. yield=94%; M.p.=220 °C (decomposed) and 250 °C (melt completely); ^1H NMR(δ in ppm) 1.35–1.47 (q, 3H, axial ring CH_2), 1.82–1.86 (d, 3H, equatorial CH_2), 2.30–2.38 (t, 3H, axial CH), 2.59–2.63 (t, 6H, CH_2–NH_2), 3.12–3.16 (t, 6H, CH_2–NHCO); ^{13}NMR (δ in ppm) 31.20 (CH_2 ring), 40.26 (CH_2NH_2), 41.59 (CH_2NHCO); 43.42 (CH ring), 178.23(carbonyl); CHN (%): found (Calc.) C=52.15 (52.61), H= 8.62(8.83), N= 24.02(24.54); Mass spec. (CI/EI): *m/z*,343 Calc. 342.24; IR(ν cm^{-1}): 1643(s), 3618(m), 3275(m), 2947(w) and 2850(w).

Synthesis of cis,cis-1,3,5–tris(CONH-(CH$_2$)$_3$–NH$_2$)cyclohexane (**V**): Synthesis of compound **V** is similar to **IV**. Freshly distilled 1,3-diaminopropane was used in place of 1,2-diaminoethane. Continuous stirring under N_2 atmosphere at room temperature for 10 days gave a sticky white solid after repeatedly washing with ethanol and ether mixture. The product was purified completely under high vacuum line at 40°C oil bath. A white, dry solid was obtained which is highly hygroscopic and water-soluble. yield=95%; m.p.=240(d) –260 °C (m); ^1H NMR (δ in ppm) δ=1.39–1.47.(q, 3H, axial ring CH_2), δ=1.84–1.96 (d, 3H, equatorial ring CH_2), δ=2.31–2.42 (t, 3H, axial ring CH), δ=2.59–2.64 (t, 6H, CH_2NH_2), δ=3.14–3.20.(t, 6H, CH_2–NHCO); =1.55–1.65(q, 6H, middle CH_2 of 1,3-diaminopropane); ^{13}C NMR(δ in ppm) δ=31.16 (ring CH_2), δ=31.26 (middle CH_2 of 1,3-diaminopropane) δ=37.03 (C of CH_2NH_2), δ=38.13 (C of CH_2NHCO); δ=43.47 (ring CH), δ=177.90 (carbonyl); CHN (%)found (Calc.): C=56.48 (56.23), H=9.15(9.44), N=22.09(21.86); Mass spec. (CI/EI): *m/z*, 385 Calc. 384.28; IR: (ν cm^{-1})1644(s), 3618(m), 3286(m),2937(w) and 2850.

Synthesis of cis,cis-1,3,5-tris(CONH–(CH$_2$)$_2$–N=CH–C$_6$H$_4$OH) cyclohexane (**VI**): A fine suspension of (**IV**) was taken in hot ethanol to which 3-equivalents of salicylaldehyde in 15 cm^3 of ethanol was added slowly with continuous stirring under N_2 atmosphere. A yellow solid was separated out immediately which was warmed in water bath (~40°C) for 1h. After cooling, it was filtered under N_2 atmosphere, washed with ethanol till filtrate became colourless and then was dried *in vacuo*. It was an air sensitive yellow solid becoming sticky and orange on exposure to air. M.p.=252–254 °C; Yield=92 % ^1H NMR (δ in ppm) δ=0.95–1.15.(q, 3H, axial ring CH_2), δ=1.45–1.55 (d, 3H, equatorial ring CH_2), δ=2.19–2.38 (t, 3H, axial ring CH), δ=3.19–3.55 (t, 6H, CH_2–NHCO), δ=3.45–3.65 (t, 6H, CH_2-N=CH–); δ=6.50–6.80 (t, 6H) and 7.04–7.20 (t, 6H) for aromatic H; 8.30 (s,3H,–CH=N–); CHN (%): found (Calc.) C=66.4 (66.04), H=6.43(6.47), N=13.13(12.84); Mass spec.(CI/EI): *m/z*, 654 Calc. 654.32; IR: 1646), 3350–3600(br), 3324(w), 2947(w), 2864(w), 1624(s), 1592(s), 1497(s), 1464(s), 1386(s), 1276(s) and 771(s).

Synthesis of cis,cis-1,3,5-tris(CONH–(CH$_2$)$_3$–N=CH–C$_6$H$_4$OH) cyclohexane (**VII**): The same method as for the synthesis of compound (**VI**), except taking the ethanolic suspension of compound (**V**), a bright yellow residue was obtained which was washed repeatedly with ethanol and dried *in vacuuo*. Yield=89%; m.p.=262–264 °C; ^1H NMR (δ in ppm) δ=1.34–1.52.(q, 3H, axial ring CH_2), δ=1.70–1.90 (d, 3H, equatorial ring CH_2), δ=2.50–2.69 (t, 3H, axial ring CH), δ=2.98–3.19 (t, 6H, CH_2-NHCO), δ=3.33–3.51.(t, 6H, CH_2–N=CH); 1.6 or 1.75 (q, 6H, middle CH_2 of 1,3-diamine propane) δ=6.50–6.68 (q, 6H) and 7.05–7.22(t, 6H) f, aromatic CH; δ=8.21–8.40 (s,3H,

–CH=N-); CHN analysis (%): found (Calc.) C=66.88 (67.22), H=6.96(6.94), N=12.13(12.06); Mass spec.(CI/EI): *m*/*z*, 696 Calc. 696.36; IR (n cm^{-1}): 3300–3600(br), 3289(w), 2947(w), 2812(w), 1638(s), 1590(s), 1498(s), 1460(s), 1384(s), 1278(s) and 764(s).

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