Journal of Inclusion Phenomena and Macrocyclic Chemistry **39:** 241–245, 2001.

Synthesis of New Macrocyclic Polyaza Compounds Containing 1-Methylpyrazole

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(Received: 7 March 2000; in final form: 16 June 2000)

Key words: polyaza compounds, 1-methylpyrazole, silver, copper, complexes, extraction

Abstract

New macrocyclic polyaza compounds containing the 1-methylpyrazole moiety are synthesized in high yield by [2+2]dipodal condensation and reduction. The ring contracted structure of the Schiff base has been elucidated by NMR. Two of these macrocycles form dinuclear complexes with copper and silver. Macrocyclic Schiff base **5a** extracts 74.5% silver from aqueous to organic phase.

Introduction

The interest in the study of new polyaza compounds has increased enormously owing to the analogy of their transition metal complexes with the active site of metalloproteins and metalloenzymes [1, 2].

Previously, one of us has reported the synthesis of different series of polyaza macrocycles and macrobicycles containing two or three 3,5-disubstituted pyrazole units linked to the polyamine chains by imines or amine bonds [3, 4]. In basic medium, these ligands formed di- or tripyrazolate sodium salts from which di- and or tetra-nuclear Zn (II) and Cu (II) complexes were formed [4, 5]. The acid base behaviour of these polyamines have also been reported recently [6]. Now, we have synthesized new macrocyclic Schiff bases and polyamines containing the 1-methylpyrazole moiety and studied the complexing behaviour of two of these compounds towards copper and silver ions.

Experimental section

^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker Ac 200 MHz spectrometer using TMS as an internal standard and $CDCl_3/D_2O$ as solvent. FAB mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer using xenon (6KV, 10 mA) as the FAB gas. Infrared spectra were recorded on a Pye Unicam SP3-300 infrared spectrophotometer by using KBr (solid) as medium. UV spectra were recorrded on a Shimadzu UV-240 spectrophotometer. Dimethyl-3,5-pyrazoledicarboxylate was prepared by the reported method [7].

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Preparation of pyrazole precursors

Dimethyl-1-methyl-3,5-pyrazoledicarboxylate **1**. Methyl iodide (15.3 g, 108 mmol) was added dropwise over a period of 30 minutes to a solution of dimethyl-3,5-pyrazole dicarboxylate (20 g, 108 mmol) in acetone. After the completion of the reaction (tlc, 4 hr), the solvent was removed under reduced pressure and the residue in water was extracted with 3 × 100 mL portions of chloroform. The organic layer was dried over anhydrous Na_2SO_4, filtered and distilled to yield compound **1**. Yield 65%, m.p. 80°C (benzene). ^{1}H NMR ($CDCl_3$) δ3.91 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.26 (s, 3H, NCH_3), 7.35 (s, 1H, PzH); m/z 198 (M^+).

1-Methyl-3,5-bis (hydroxymethyl)pyrazole **2**. A solution of dimethyl-1-methyl-3,5-pyrazoledicarboxylate (3.72 g, 20 mmol) in 200 mL of dry ether was added dropwise under nitrogen to a suspension of 3.08 g (80 mmol) of $LiAlH_4$ in 200 mL of the same solvent. After the addition was complete (2 hr) the reaction was allowed to reflux for 24 hr. The excess of $LiAlH_4$ was hydrolysed by slow and consecutive addition of 25 mL of MeOH and 100 mL of saturated aqueous NH_4Cl solution. After separation of the solid in suspension by filtration and by evaporation of solvents a oily residue was obtained. The water was removed from this residue azeotropically with ethanol to yield the title compound in 60% yield. ^{1}H NMR (D_2O): δ 3.63 (s, 3H, NCH_3), 4.36 (s, 3H, CH_2OH), 4.46 (s, 4H, CH_2OH), 6.16 (s, 1H, PzH); m/z 142 (M^+).

Preparation of 1-methyl-3,5- (1H-pyrazole)dicarbaldehyde **3**. To a refluxing solution of 1-methyl-3,5-bis (hydroxymethyl)pyrazole (5.6 g, 40 mmol) in dioxane was added solid MnO_2 (40 g, 460 mmol) portionwise. The refluxing

was then continued, the reaction was complete after four hours. Insoluble material was then removed by filtration through a celite bed and washed with hot dioxane. The solution was decolourized with charcoal and after filtration, evaporated to dryness to yield the title compound in 70% yield m.p. 70°C. I.R. (KBr) 1675 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 4.26 (s, 3H, NCH_3), 7.4 (s, 1H, PzH), 9.92 (s, 1H, CHO), 10.00 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 40.54 (NCH_3), 114.05 (C_4), 179.85, 185.40 (CO); m/z 138 (M^+); Anal Calcd for $C_6H_4N_2O_2$: C, 52.17; H, 4.35; N, 20.28. Found 51.94; H, 4.07; N, 20.08.

Preparation of macrocyclic ligands

Compound **4**. A solution of 1-methyl-3,5-pyrazoledicarbaldehyde **3** (276 mg, 2.0 mmol) in 20 mL of MeCN was added dropwise to a stirring solution of *m*-xylylenediamine (276 mg, 2.0 mmol) in 20 mL of the same solvent. After the mixture was stirred overnight the desired compound separated as a thick oil, which solidified after scratching to give a white solid which was isolated by filtration, washed with MeCN and Et_2O dried under vacuum to yield the title compound. Yield 30%, m.p. 95 °C. I.R. (KBr) 1639 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$) δ 4.14 (s, 6H, 2xNCH_3), 4.78 (s, 8H, 4xNCH_2), 6.96 (s, 2H, 2x$PzCH_2$), 7.22–7.39 (m, 4xArH), 8.35 (s, 2H, 2xCH=N); ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ 37.64 (NCH_3), 63.97 (Ph-CH_2), 64.42 (Ph-CH_2), 107.67 (C_4), 125.76 (Ar), 126.02 (Ar), 127.79 (Ar), 137.60 (Ar), 138.57 (C_5), 147.71 (C_3), 150.08 (N=C_6), 156.92 (N=C_2); m/z 477 (M^++1); Anal. Calcd. for $C_{28}H_{28}N_8$: C, 70.58; H, 5.38; N, 23.52. Found: C, 70.84; H5.58; N, 23.71.

Compound **5a**. This compound was prepared as described for **4** using diethylenetriamine (206 mg, 2.0 mmol). The desired compound separated as a white solid. Yield 70%, m.p. 122 °C. I.R. (KBr) 1650 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$) δ 8.32 (s, H_2), 8.26 (s, $H_{2'}$), 7.64 (s, H_4), 7.04 (s, $H_{4'}$), 4.30 (s, NCH_3), 4.24 (s, NCH_3), 3.91 (s, $H_{6'}$), 3.97 (s, H_6), 2.44–3.74 (m, rest of the H's); ^{13}C NMR ($CDCl_3$) δ 36.83, 37.08 (NCH_3), 52.37, 53.04 [$C_{\beta-5}$ (Imidazolidine ring)], 45.10, 45.80[$C_{\alpha-5}$ (Imidazolidine ring)], 54.06, 54.52 ($C_{\beta-3}$), 59.20, 59.73 ($C_{\alpha-3}$), 75.04, 74.80 [C6 < (Imidazolidine ring)], 155.46, 155.29 (N=C_2), 105.36, 104.74 (C_4), 145.31, 144.17 (C_5), 149.55, 149.37 (C_3),; m/z 411 (M^+ + 1); Anal. Calcd. for $C_{20}H_{30}N_{10}$: C, 58.53; H, 7.31; N, 34.14. Found: C, 58.33; H, 7.19; N, 33.94.

Compound **5b**. This compound was prepared as described for compound **5a** using *N*- (3-aminopropyl)1,3-propanediamine (262 mg, 2.0 mmol). The desired compound separated as a white solid. Yield 70%, m.p. 125 °C. I.R. 1640 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$) δ 7.94 (s, H_2), 7.92 (s, $H_{2'}$), 6.56 (s, H_4), 6.47 (s, $H_{4'}$), 4.10 (s, NCH_3), 4.03 (s, NCH_3), 3.97 (s, $H_{6'}$), 3.91 (s, H_6), 1.57–3.52 (m, rest of the H's); m/z 467 (M^++1); Anal. Calcd. for $C_{24}H_{38}N_{10}$: C, 61.30; H, 8.15; N, 30.04. Found: C, 61.58; H, 8.37; N, 30.32.

Compound **6a**. To a stirred suspension of Schiff base imidazolidine **5a** (410 mg, 1.0 mmol) in 10 mL of ethanol was added solid $NaBH_4$ (151 mg, 4.0 mmol) portionwise. After stirring for 2 h at room temperature, the solvent was evaporated and 10 mL of water was added to the residue. The solution was extracted with 3 × 25 mL of chloroform and the organic layer was dried over anhydrous Na_2SO_4 to yield a thick liquid. Yield 80%. ^{1}H NMR ($CDCl_3$) 2.02 (br, s, 6H, NH_2), 2.75 (br, s, 16H, 8xNCH_2), 3.74 (s, 6H, NCH_3), 3.76 (s, 4H, $PzCH_2$), 3.83 (s, 4H, $PzCH_2$), 6.10, 6.12 (s, 2H, PzH); ^{13}C NMR/DEPT ($CDCl_3$): 36.09/+ve phase (CH_3), 44.47/−ve phase (C_6), 47.17/−ve phase (C_2), 48.94/−ve phase ($C_{\alpha-3}$ and ($C_{\alpha-5}$), 49.10/−ve phase ($C_{\beta-3}$ & $C_{\beta-5}$), 104.06/+ve phase (C_4), 141.71/absent (C_5), 149.61/absent (C_3); m/z 419 (M^++1).

Compound **6b**. This compound was prepared from Schiff base imidazolidine **5b** (466 mg, 1.0 mmol) and $NaBH_4$ (150 mg, 4.0 mmol) as described for **6a**. The title compound was thus isolated as the hydrochloride salt by treating the residue with 10mL of 36% HCl and 100 mL of ethanol. Yield 85%. ^{1}H NMR (D_2O): 1.80–2.00 (m, 8H, CH2), 2.93–3.02 (m, 16H, 8xNCH_2), 3.70 (s, 6H, NCH_3), 4.07 (s, 4H, Pz–CH_2), 4.25 (s, 4H, Pz–CH_2),6.53 (s, 2H, PzC-4); m/z 475 (M^+ + 1).

Synthesis of dinuclear silver complexes

To a solution of 1-methyl-3,5-pyrazoledicarbaldehyde **3** (138 mg, 1 mmol) in methanol (50 mL) was added silver nitrate (170 mg, 1 mmol) and solution stirred at room temperature. A solution of diethylenetriamine/*N*-(3-aminopropyl)1,3-propanediamine (1 mmol) was added slowly over a period of 20 minutes. The solution turned yellow and became turbid. The solution was filtered through celite and the filtrate treated with $NaClO_4$ (3 mmol) in methanol. A pure yellow solid separated which was filtered washed with methanol and dried under vacuum over $CaCl_2$.

5a. $Ag_2(ClO_4)_2$. Yield 60%, m.p. > 250°C. I.R. 1647 cm^{-1} (-CN). Anal. Calcd. for $C_{20}H_{30}N_{10}Ag_2$ $(ClO_4)_2$: C, 23.09; H, 3.63; N, 16.36. Found: C, 23.45; H, 3.88; N, 16.64.

5b. $Ag_2(ClO_4)_2$. Yield 50%, m.p. > 250°C. I.R. 1647 cm^{-1} (–CN). Anal. Calcd. for $C_{24}H_{38}N_{10}Ag_2$ $(ClO_4)_2$: C, 32.69; H, 4.31; N, 15.39. Found: C, 33.05; H, 4.64; N, 15.74.

Synthesis of dinuclear copper complexes

Compound **5a/5b** (0.1 mmol) was dissolved in methanol (10mL). $Cu(ClO_4)_2 \cdot 6H_2O$ (0.2 mmol) dissolved in methanol (5 mL) was added to the above solution. A blue colour developed and precipitates were formed immediately. The precipitates were filtered and dried over $CaCl_2$.

5a. $Cu_2(ClO_4)_2$. Yield 50%, m.p. > 250°C. I.R.1640 cm^{-1} (–CN). Anal. Calcd. for $C_{20}H_{30}N_{10}Cu_2$ $(ClO_4)_2$: C, 32.50; H, 4.07; N, 19.02. Found: C, 32.77; H, 4.39; N, 19.40.

Table 1. Extraction (%) profile for compound **5a**

Compound	Li^+	Na^+	K^+	Tl^+	Ag^+	Ba^{2+}	Mg^2	Ca^{2+}	Sr^{2+}
5a	0.00	0.53	0.53	2.94	74.5	0.44	0.70	0.42	0.64

Table 2. Selectivity of Ag^+ against alkali and alkaline earth metals

$Ag+/Na^+$	$Ag+/K^+$	$Ag+/Ba^{2+}$	$Ag+/Mg^{2+}$	$Ag+/Ca^{2+}$	$Ag+/Sr^{2+}$
140.5	140.5	169.3	106.4	177.3	116.4

5b. $Cu_2(ClO_4)_2$. Yield 60%, m.p. > 250°C. I.R. 1640 cm^{-1} (-CN). Anal. Calcd. for $C_{24}H_{38}N_{10}Ag_2$ $(ClO_4)_2$: C, 36.36; H, 4.79; N, 17.67. Found: C, 36.59; H, 5.10; N, 18.06.

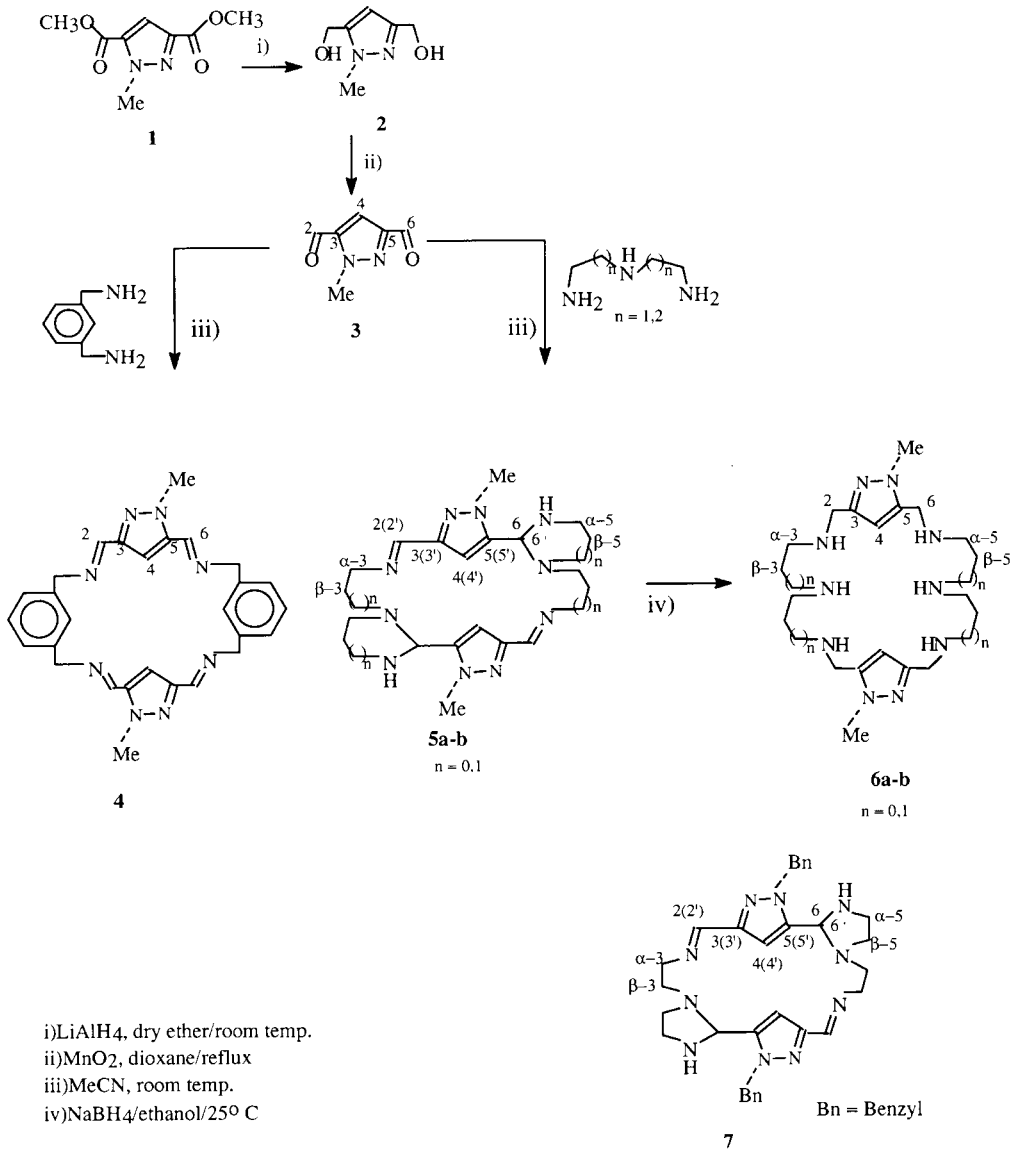
Extraction measurements [15]

For the extraction experiments, metal picrate solutions were prepared in double distilled water. The solution of compound **5a** (0.001 M) was prepared in chloroform (A.R. grade). The solutions of macrocycle and metal picrates were taken in test tubes with a septum and were shaken for five minutes and kept at constant temperature (27 ± 1 °C) for 4 hr. An aliquot of the chloroform layer was taken and diluted to 10 mL in a measuring flask with acetonitrile. The U.V. absorption was measured at $\lambda_{max.}$ 374 nm. The extraction of metal picrate was calculated as the percentage of metal picrate extracted in the chloroform layer and the values reported here are the mean of three independent measurments which are within ±2% error (Table 1).

Results and discussion

The synthesis of polyaza macrocycles containing heteroaromatic moieties like pyridine, pyrrole, thiophene and furan rings have been reported by [2+2] dipodal condensation of α,ω-diamines with the corresponding dialdehydes followed by hydrogenation of the Schiff bases [8–10]. However, when such α,ω-diamines have NH or OH groups in the middle of the chain then the condensation with dialdehydes gives a product which corresponds to a mixture of the desired tetraimine Schiff base together with an imidazolidine isomer formed by nucleophilic addition of two secondary amine groups of the tetraimine macrocycle across the adjacent imine bonds. Similar processess have been reported in the synthesis of tetraimine Schiff base macrocycles in which Ba (II) [11] and Pb II [12] were used as metal templating agents. In fact, tetraimine dicopper (II) complexes have also been prepared from ring-contracted oxazolidine lead complexes by transmetallation with concomittant expansion of the macrocycle [13]. Furthermore, Martell *et al*. have characterized the structure of the imidazolidine isomer obtained by [2+2] dipodal condensation of diethylenetriamine and *m*-phthaldehyde by X-ray crystallography [14]. In contrast to the above behaviour the [2+2] dipodal condensation of 3,5-pyrazoledicarbaldehyde with diethylenetriamine in methanol at room temperature did not precipitate out the expected Schiff base [6]. The ^1H NMR and ^{13}C NMR spectra of the solution indicated the presence of more than one species which corresponded to a mixture of tetraimine and imidazolidine isomers [6]. Consequently, the mixture was reduced *in situ* with $NaBH_4$ to obtain the hexaamine macrocycle in moderate yield. 3,5- (1-Methylpyrazole)dicarbaldehyde **3** [m.p. 70 °C], which is reported in this paper for the first time, was prepared from 3,5-bis (hydroxymethyl)-1-methylpyrazole by oxidation with MnO_2 in dioxane in 80% yield. Compounds **4** and **5** were prepared by the [2+2] dipodal condensation of 3,5-(1-methylpyrazole)dicarbaldehyde, **3**, with an equimolar amount of *m*-xylylenediamines/diethylenetriamine/*N*-(3-aminopropyl)1,3-propanediamine in acetonitrile at room temperature gave in all three cases stable solids which separated from solution and were identified as Schiff base **4** and the imidazolidine isomers **5a** and **5b** respectively in good yields (Scheme 1). The IR spectra of **4** and **5** show a band at 1639–1645 cm^{-1} which indicates the presence of an imine group. There is no band corresponding to free carbonyl and free amino group which indicates that the cyclization has taken place. A parent ion peak is observed in the mass spectra of compounds **4** and **5**. In the ^1H NMR spectrum of **4** the presence of the 1-methyl substituent breaks the magnetic equivalence of the pyrazole environment. In the ^{13}C NMR spectrum, different signals can be observed for the quaternary carbons labelled as C_3 and C_5 [the pyrazole N = C_3 appears at lower field than C_4=C_5], as well as for those of the imine carbons [the C_2 is more deshielded than C_6].

To fully characterize compounds **5a** and **5b**, a comparison with **4** is very illustrative, because in this compound the formation of the imidazolidine ring is precluded by the presence of the benzene ring. The ^{13}C NMR spectrum of **5a** is very complex showing 20 different signals. The signals can be arranged in two sets of 10 of similar relative intensities. All of these spectral features suggest that the species formed could be either a unique one with all its carbon nuclei magnetically nonequivalent or a mixture of at least two different species with 2-fold symmetry in almost the same proportion. To decide which one of the two possibilities was the correct one we have compared the ^{13}C NMR spectrum of compound **5a** with the ^{13}C NMR of polyaza compound **7** containing the 1-benzylpyrazole moiety [6]. Compound **7** shows 28 signals which can be arranged in two sets of 14 of similar relative intensities. HMQC and multiple bond HMBC 2D-NMR heteronuclear correlation spectra were used to characterize compound **7**. Based on the comparable spectral features and the fact that the NMR spectra of the Schiff base **4** suggest the existence of only one constitutional isomer it is reasonable to suppose that although the condensation of **3** with either *m*-xylylenediamine or diethylenetriamine or *N*-(3-aminopropyl)1,3-propanediamine could afford a mixture of the two possible constitutional isomers, the most abundant should be the one with 1-methylpyrazole substitutents in the opposing positions and displaying C_2 symmetry. Con-



Scheme 1.

sequently, the saturated polyamines **6a** and **6b** obtained by reduction of **5a** and **5b**, respectively may correspond to the isomers with the same disposition (with the methyl groups in opposing positions). In the ^{1}H NMR spectra of **6a** and **6b** the 1-methyl substituent breaks the magnetic equivalence of the pyrazole environment. The ^{1}H NMR spectrum of **6a** shows two different types of H_4Pz, CH_2NH and NCH_3 proton signals and a broad singlet at 2.75 (NCH_2). The ^{13}C NMR spectrum of **6a** shows that the carbon atoms C_5 and C_6 which are closer to the pyrazole 1-methyl substituent, appear at higher field than C_3 and C_2 which are closer to the pyrazole sp^2 nitrogen.

Complexation studies. The silver complexes were prepared by condensation of equimolar amounts of 1-methyl-3,5-pyrazoledicarbaldehyde and diethylenetriamine/*N*-(3-aminopropyl)1,3-propanediamine in the presence of $AgNO_3$ as templating agent in methanol. The copper complexes were prepared by treating the compound **5a/5b** with copper perchlorate hexahydrate in methanol. The cyclic nature of the ligand was suggested by the presence of strong absorption bands due to –CN at 1640–1647 cm^{-1} and by the absence of bands due to free carbonyl and free amino groups. The molecular formula of the complexes is confirmed by elemental analysis.

For determining the extraction, the ligand solution in chloroform was equilibrated with metal picrate solution in water. The amount of metal picrate extracted into the chloroform layer was determined in accordance with Lambert-Beer's law by measuring the absorbance at $\lambda_{max.}$ 374 nm. It was found that compound **5a** extracts Ag^+ 140.5 times as compared to Na^+ and K^+, 106.4 times as compared to Mg^{2+}, 177.3 times as compared to Ca^{2+}, 116.4 times as compared to Sr^{2+} and 169.3 times as compared to Ba^{2+}. From these obvservations it is concluded that compound **5a** selectively extracts silver over alkali and alkaline earth metal ions.

Acknowledgements

We are thankful to CSIR (New Delhi) for financial assistance and one of us (M.K.) is thankful to Dr. P. Navarro of Instituto de Quimica Medica, CSIC, Madrid, Spain for introducing him to this field of supramolecular chemistry.

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