Indian Journal of Chemistry
Vol. 48A, January 2009, pp. 9-14

Synthesis, crystal structure and DNA cleavage activity of (aqua)bis(dipyridophenazine)copper(II) complex

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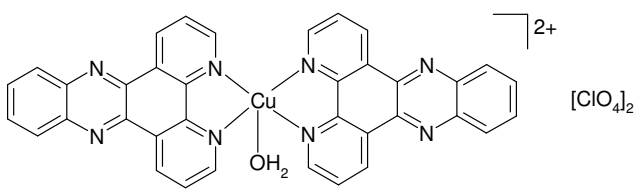
Received 7 November 2008; accepted 3 December 2008

A copper(II) complex of dipyridophenazine, viz., $[Cu(dppz)_2(H_2O)](ClO_4)_2$ (**1**), has been prepared and structurally characterized by X-ray crystallography. The crystal structure of the complex shows a five-coordinate structure in which two N,N-donor dipyridophenazine (dppz) and one aqua ligand bind to the copper(II) center giving Cu-O and Cu-N bond distances in the range of 1.981(6) to 2.043(6) Å. The ESI-MS spectrum of **1** in MeCN shows a peak at *m*/*z* value of 313 (100%) indicating the dissociation of the aqua ligand in the solution phase. The complex is one-electron paramagnetic (μ_{eff}, 1.86 μ_B). It displays a quasi-reversible Cu(II)/Cu(I) redox process at 0.096 V. The complex is an avid binder to CT DNA giving a binding constant value of 3.5×10^5 M^{-1}. It shows significant hydrolytic cleavage of supercoiled pUC19 DNA in dark in the absence of any external agents. The complex exhibits chemical nuclease activity on treatment with 3-mercaptopropionic acid as a reducing agent forming hydroxyl radicals. Complex **1** is a model synthetic nuclease and hydrolase showing both modes of DNA cleavage under different reaction conditions. The DNA cleavage activity of **1** is significantly better than its phen analogue but similar to that of the bis-dpq complex.

Keywords: Bioinorganic chemistry, Hydrolytic cleavage, DNA cleavage, DNA binding, Crystal structure, Copper

IPC code: Int. Cl.[8] C07F1/08; C12N15/00

Metallointercalators having planar phenanthroline bases are known to show DNA cleavage activity and such complexes are of importance in nucleic acids chemistry for their applications as foot printing and sequence specific DNA binding agents, as synthetic models of restriction enzymes, new structural probes and as therapeutic agents[1-10]. DNA cleavage may take place via hydrolytic or oxidative pathways. Hydrolytic cleavage of DNA causes hydrolysis of the phosphodiester bond forming DNA fragments that could be rejoined. Synthetic hydrolases model the activity of restriction enzymes. The oxidative cleavage of DNA results in the oxidation of the sugar moiety or the base. This process is suitable for foot printing and therapeutic studies. Planar phenanthroline bases are known to be excellent binders to DNA. The copper complex of 1,10-phenanthroline, viz., $[Cu(phen)_2(H_2O)]^{2+}$ is the first synthetic chemical nuclease reported by Sigman and coworkers[1]. We have shown that dipyridoquinoxaline (dpq) complex of copper like $[Cu(dpq)_2(H_2O)]^{2+}$ is a model chemical nuclease and synthetic hydrolase[11,12]. In addition, this complex shows metal-assisted red light-induced DNA cleavage activity[13]. Our subsequent report has shown that a copper(II) complex of dipyridophenazine (dppz), viz., $[Cu(dppz)_2Cl]Cl$, is also active in cleaving DNA by hydrolytic and oxidative pathways[14]. The nucleic acids chemistry of dpq and dppz ligands is of importance since the DNA intercalator quinoxalines that are present in antitumor antibiotics like echinomycin or triostin have been extensively used in designing metallointercalators[9,10,15-20]. The present work stems from our interest to synthesize the dppz complex of copper(II) that has molecular structure similar to that of its dpq and phen analogues for a comparative study of their DNA cleavage activity. Herein, we present the synthesis, crystal structure, DNA binding and DNA cleavage activity of $[Cu(dppz)_2(H_2O)](ClO_4)_2$ (**1**).



$[Cu(dppz)_2(H_2O)](ClO_4)_2$ (**1**)

Materials and Methods

All the solvents and chemicals were purchased from commercial sources. Supercoiled (SC) pUC19 DNA (cesium chloride purified) and calf thymus (CT) DNA were purchased from Bangalore Genei (India). Agarose (molecular biology grade), distamycin and ethidium bromide (EB) were obtained from Sigma-Aldrich. Dipyridophenazine (dppz) was prepared by a reported procedure[21]. The elemental analysis was performed on Perkin-Elmer EA 2000 series analyzer. ESI-MS mass spectrometric analysis was performed on a Hewlett Packard Series 1100 MSD mass spectrometer. The electronic, infrared and fluorescence spectral measurements were made on Perkin-Elmer Spectrum one 55, Perkin-Elmer Lambda 35 and Perkin-Elmer LS 50B spectrometers respectively. DNA melting experiments were conducted on a Cary 300 Bio UV-visible spectrophotometer provided with Cary temperature controller. Cyclic voltammetric studies were done at 25°C on a EG&G PAR (model 253) VersaStat potentiostat/galvanostat with electrochemical analysis software 270 using glassy carbon working, platinum wire auxiliary and saturated calomel (SCE) reference electrodes and tetrabutylammonium perchlorate (TBAP, 0.1*M*) as a supporting electrolyte in DMF. Room temperature magnetic susceptibility data were obtained using Lewis-coil-force magnetometer (model 300) of George Associates Inc. $Hg[Co(NCS)_4]$ was used as a standard. Diamagnetic correction was made in the susceptibility data[22].

Preparation of complex(1)

$Cu(ClO_4)_2.6H_2O$ (0.37 g, 1 mmol) in aqueous methanol (1:6 *v*/*v*, 35 mL) was treated with dppz (0.56 g, 2 mmol) in methanol (20 mL), followed by addition of water (2 mL) and subsequent stirring at 60 ºC for 3h. The precipitate thus obtained was filtered and washed with ethanol (Yield: 94%, crude solid). Green single crystals of complex **1** were obtained on crystallization of the solid from acetonitrile solution of the complex. Anal.: Calculated for $CuC_{36}H_{22}N_8O_9Cl_2$: C, 51.2; H, 2.6; N, 13.3%. Found: C, 51.5; H, 2.5; N, 13.1. ESI-MS in MeCN: 313.5 (100% $[M^{2+} - H_2O]/2$). IR (KBr disc), ν (cm^{-1}): 3431br, 1606w, 1581w, 1499m, 1424m, 1096vs (ClO_4^-), 1077vs (ClO_4^-), 1041s, 777m, 724m, 621m, 424m (br, broad; w, weak; m, medium; s, strong; vs, very strong). UV-visible in DMF [λ, nm (ε, M^{-1} cm^{-1})]: 689 (80), 447 (3400), 379 (32000) and 361 (32000). $E_{1/2}$, V (Δ*E*p, mV) in DMF-0.1 *M* TBAP at 50 mV s^{-1}: 0.096 (160). μ_{eff} : 1.86 μ_B at 298 K.

X-ray studies of complex(1)

The unit cell parameters and the intensity data of a green crystal of **1**, mounted on a glass fiber using epoxy cement, were obtained using an automated Bruker SMART APEX CCD diffractometer, equipped with a fine focus 1.75 kW sealed tube Mo-Kα X-ray source (λ = 0.71073 Å). The data reduction and absorption correction were done using SAINT and SADABS software programs[23]. The structure was solved and refined using SHELX system of programs[24]. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were fixed at their calculated positions and refined using a riding model. Selected crystallographic data are listed in Table 1.

DNA binding/cleavage activity of complex(1)

The binding of complex **1** to CT DNA was investigated by emission, UV-visible absorption spectroscopy and thermal denaturation (DNA melting) method. The concentration of CT DNA used for emission and absorption spectroscopic

Table 1—Selected crystallographic data and structure refinement for $[Cu(dppz)_2(H_2O)](ClO_4)_2$ (**1**)

Formula	$C_{36}H_{22}Cl_2CuN_8O_9$
FW(g/mol)	845.06
Space group	Pī
a (Å)	8.4602(10)
b (Å)	13.8262(17)
c (Å)	15.4394(19)
α (°)	72.222(2)
β (°)	79.781(2)
γ (°)	85.759(2)
V ($Å^3$)	1692.1(4)
Z	2
T (K)	293(2)
λ (Å) (MoKα)	0.71073
μ(Mo–K_α) (mm^{-1})	0.876
ρ_{calc} (g cm^{-3})	1.659
F(000)	858
Parameters	505
Goodness-of-fit on F^2	1.129
Unique reflections	6619
Obs. reflns [$I > 2\sigma(I)$]	2755
*R*1 (obs) (*R*1, all data)[a]	0.088 (0.2118)
*wR*2 (*wR*2, all data)[b]	0.1482 (0.1789)

[a]$R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, [b]$wR=\{\Sigma[w(F_o^2-F_c^2)^2]/\ \Sigma[w(F_o)^2]\}^{½}$, where $w = 1/[\sigma^2(F_o^2) + (0.0500P)^2 + 0.0P]$ and $P = (F_o^2 + 2F_c^2)/3$.

measurements was 387 μ*M* and was determined by absorption spectroscopy using the known molar absorption coefficient (ε) value of 6600 M^{-1} cm^{-1} for CT DNA at 260 nm. The apparent binding constant (K_{app}) was determined by ethidium bromide displacement assay[25]. Absorption titration experiments were conducted to determine the intrinsic binding constant (K_b). The metal complex concentration was maintained at 25 μ*M*. Equal quantity of DNA pretreated with the metal complex and DNA in tris-HCl buffer was added to the sample solution and the reference solution, respectively. The intrinsic binding constant (K_b) and the DNA binding site size (s) were obtained following reported procedures[25–27]. The CT-DNA binding was studied by thermal denaturation experiment. The interaction of the copper(II) complex with DNA was investigated by monitoring the absorbance of CT DNA (120 μ*M*) in phosphate buffer (Na_2HPO_4, 5 m*M*; NaH_2PO_4, 5 m*M*; Na_2EDTA, 1m*M* and NaCl, 5 m*M*; pH, 7.4) at 260 nm over a range of temperatures (40 – 90 °C) in the presence and absence of complex **1** (30 μ*M*) (ref. 28). The temperature of the solution was increased by 1 °C per minute and a delay period of 2 min was maintained for all of the samples. The hydrolytic and oxidative cleavage activity of the complex (55 μ*M*) was studied using supercoiled pUC19 DNA (33.3 μ*M*, 0.2 μg) by agarose gel electrophoresis following procedures as described previously[25].

Results and Discussion

Complex $[Cu(dppz)_2(H_2O)](ClO_4)_2$ (**1**) has been prepared from a reaction of $Cu(ClO_4)_2.6H_2O$ with dppz (dipyridophenazine) in aqueous methanol. The complex has been characterized from analytical and spectral data (Table 2). The infrared spectrum of **1** shows a broad band around 3431 cm^{-1} for the coordinated water and two characteristic bands at 1096 and 1077 cm^{-1} for the perchlorate anions in possibly different structural environments. The ESI-MS spectrum in MeCN shows a peak at *m*/*z* value of 313 that corresponds to the dicationic complex with the loss of bound aqua ligand. This is an important observation since the presence of labile aqua ligand is known to augment the hydrolase activity of a complex[4-6,12]. Complex **1** is one-electron paramagnetic. It exhibits a *d-d* band at 689 nm in DMF. The complex also shows a visible band at 447 nm. The complex is redox active showing a Cu(II)-Cu(I) quasi-reversible couple at 0.096 V. The $E_{1/2}$ value of **1** is lower than that of $[Cu(dppz)_2Cl]Cl$ but comparable to that of $[Cu(dpq)_2(H_2O)](ClO_4)_2$[14]. The dppz ligand reduction is observed at -0.995 V with an ΔE_p value of 116 mV at 50 mV s^{-1} scan rate.

Table 2—Physicochemical and DNA binding data for $[Cu(dppz)_2(H_2O)](ClO_4)_2$ (**1**)

λ_{max}, nm (ε, $M^{-1}cm^{-1}$)[a] (visible data)	689 (80); 447 (3400)
ESI-MS in MeCN	313.5 (100%, M^{2+}- H_2O)/2)
$E_{1/2}$, V (ΔE_p, mV)[b]	0.096 (160)
μ_{eff} [c](μ_B)	1.86
K_{app} [d], M^{-1}	3.5×10^5
K_b [e], M^{-1} ([s])[f]	$7(\pm1) \times 10^5$ [0.29]
ΔT_m, °C[g]	2

[a] In DMF; [b] Cu(II)-Cu(I) couple in DMF-0.1*M* TBAP vs. SCE. Scan rate = 50 mV s^{-1}; [c]Magnetic moment at 298 K;
[d] Apparent CT DNA binding constant;
[e] Intrinsic CT DNA binding constant; [f]Binding site size (s);
[g] Change in DNA melting temperature.

X-ray studies

The molecular structure of **1** has been determined by X-ray crystallography. The ORTEP[29] view of the complex is shown in Fig. 1. Selected bond distances and angles are given in Table 3. The complex

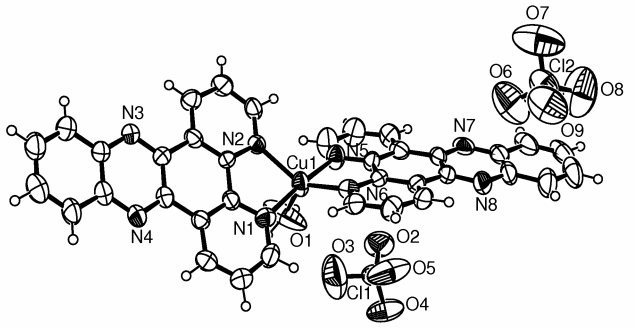


Fig. 1—An ORTEP view of $[Cu(dppz)_2(H_2O)](ClO_4)_2$ (**1**) showing atom numbering scheme for the metal and hetero atoms and thermal ellipsoids at 50% probability level.

Table 3—Selected bond lengths and bond angles in $[Cu(dppz)_2(H_2O)](ClO_4)_2$ (**1**) with esds in parentheses

Bond lengths (Å)		Bond angles (°)	
Cu(1)-O(1)	2.043(6)	N(1)-Cu(1)-N(5)	173.0(3)
Cu(1)-N(1)	1.9816)	N(1)-Cu(1)-N(6)	99.2(2)
Cu(1)-N(2)	2.058(5)	N(5)-Cu(1)-N(6)	81.4(2)
Cu(1)-N(5)	1.985(5)	N(1)-Cu(1)-O(1)	87.9(2)
Cu(1)-N(6)	2.032(5)	N(5)-Cu(1)-O(1)	86.3(2)
		N(6)-Cu(1)-O(1)	128.8(3)
		N(1)-Cu(1)-N(2)	82.2(2)
		N(5)-Cu(1)-N(2)	103.02)
		N(6)-Cu(1)-N(2)	129.1(2)
		O(1)-Cu(1)-N(2)	102.0(3)

crystallizes in the triclinic space group P$\bar{1}$ with two molecules in the unit cell. The structure shows the presence of the complex cation $[Cu(dppz)_2(H_2O)]^{2+}$ and two lattice perchlorate anions. The copper(II) ion is coordinated to four nitrogens from two dppz ligands and an oxygen atom from the aqua ligand in a distorted trigonal bipyramidal (tbp) geometry[30] (τ = 0.7). The tbp structure is axially compressed marginally and the angle formed by two axially coordinated nitrogen atoms with the central copper(II) ion is 172.9(3)º. The equatorial plane is formed by the Cu(1), O(1), N(6), N(2) atoms and the displacement of the Cu(1) from the mean plane is 0.013 Å. The axially coordinated nitrogen atoms N(1) and N(5) are located at distances of 1.968 Å and 1.919 Å, respectively, from the equatorial mean plane. The Cu(1)-N distances are in the range of 1.981 – 2.06 Å. The Cu(1)-O(1) distance is 2.043(6) Å. We have observed intra- and intermolecular hydrogen-bonding interactions in the structure of complex **1**. The intra-molecular H-bonding interaction [O(1)-H(10A)...O(5), 2.859 Å] is observed between O(1) of the coordinated water and O(5) atom of one of the perchlorate anion. The oxygen atom of the coordinated water, an oxygen atom of the other perchlorate ion and a nitrogen atom of one of the phenazine moiety of dppz are involved in intermolecular H-bonding interactions. The intermolecular H-bonding interaction between the nitrogen atoms of one of the dppz ligand is complimented by the location of the planar dppz heterocyclic ring at a distance of ~3.7 Å which could be considered as π-π stacking interaction. The other dppz ligand wherein the nitrogen atoms are not involved in any intermolecular interaction is located at a distance of 6.7 Å.

DNA binding and cleavage studies

The DNA binding propensity of **1** has been studied by UV-visible absorption spectroscopy. The binding constant, K_b, and the binding site size (s) values are $7(\pm1) \times 10^5$ M^{-1} and 0.29 respectively (Table 2). The DNA binding propensity of **1** has also been investigated by ethidium bromide displacement assay. Addition of DMF solutions of the complex (25 μ*M*) decreased the emission intensity at 602 nm of the saturated solution of CT-DNA bound to ethidium bromide in tris-HCl buffer (5 m*M*, *p*H 7.2). The plot of the apparent emission intensities (I/I_0) against the complex concentrations gives a K_{app} value of 3.5×10^5 M^{-1}. Thermal denaturation study at 260 nm of CT-DNA on increasing the temperature in the presence and absence of **1** (30 μ*M*) gives a ΔT_m value of 2 ºC, suggesting partial intercalative nature of the complex to CT DNA.

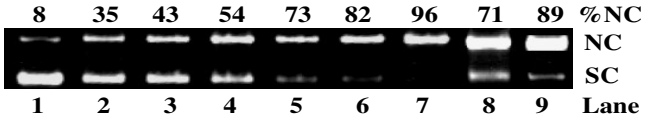


Fig. 2—Gel electrophoresis diagram showing cleavage of SC pUC19 DNA (0.2 μg, 30 μ*M* b.p.) by complex **1** (55 μ*M*) in dark at different incubation time in tris-HCl/NaCl buffer (50 m*M*, *p*H 7.2) containing 10% DMF. [lane 1, DNA control; lane 2, DNA + **1** (5 min); lane 3, DNA + **1** (10 min); lane 4, DNA + **1** (15 min); lane 5, DNA + **1** (20 min); lane 6, DNA + **1** (25 min); lane 7, DNA + **1** (30 min); lane 8, DNA + $[Cu(phen)_2(H_2O)](ClO_4)_2$ (55 μ*M*, 30 min); lane 9, DNA + $[Cu(dpq)_2(H_2O)](ClO_4)_2$ (55 μ*M*, 30 min)].

The hydrolytic cleavage activity of **1** towards SC pUC19 DNA has been investigated in the dark using tris–HCl/NaCl buffer (50 m*M*, *p*H 7.2) containing 10% DMF. The results obtained from agarose gel electrophoresis are shown in Fig. 2. Selected DNA cleavage data are given in Table 4. An essentially complete cleavage of SC DNA is observed after incubation of **1** of 55 μM with SC DNA (33.3 μ*M*) for 30 min. The DNA hydrolase activity of the phen and dpq analogues of **1**, viz., $[Cu(phen)_2(H_2O)](ClO_4)_2$ and $[Cu(dpq)_2(H_2O)](ClO_4)_2$, has also been studied. The DNA hydrolytic cleavage activity follows the order: **1** ≥ $[Cu(dpq)_2(H_2O)](ClO_4)_2$ > $[Cu(phen)_2(H_2O)](ClO_4)_2$.

Table 4—Selected cleavage data of SC pUC19 DNA by the complex **1** in tris-HCl/NaCl buffer

No.	Reaction condition	Cleavage mode (t, min)	NC (%)
1	DNA control	—	8
2	DNA + **1** (55 μ*M*)	Hydrolytic (10)	43
3	DNA + **1** (55 μ*M*)	Hydrolytic (20)	73
4	DNA + **1** (55 μ*M*)	Hydrolytic (30)	96
5	$[Cu(phen)_2(H_2O)](ClO_4)_2$ (55 μ*M*)	Hydrolytic (30)	71
6	$[Cu(dpq)_2(H_2O)](ClO_4)_2$ (55 μ*M*)	Hydrolytic (30)	89
7	DNA + **1** (30 μ*M*) + MPA (5 m*M*)	Oxidative (15)	94
8	DNA + **1** (30 μ*M*) + DMSO (2 μL)+MPA (5 m*M*)	Oxidative (15)	16
9	DNA + **1** (30 μ*M*)+NaN_3 (100 μ*M*) + MPA (5 m*M*)	Oxidative (15)	75
10	DNA + distamycin (100 μ*M*) + **1** (30 μ*M*) + MPA (5 m*M*)	Oxidative (15)	97
11	$[Cu(phen)_2(H_2O)](ClO_4)_2$ (30 μ*M*) + MPA (5 m*M*)	Oxidative (15)	67
12	$[Cu(dpq)_2(H_2O)](ClO_4)_2$ (30 μ*M*) + MPA (5 m*M*)	Oxidative (15)	85

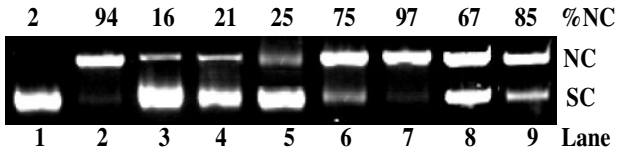


Fig. 3—Gel electrophoresis diagram showing cleavage of SC pUC19 DNA (0.2 μg, 30 μM b.p.) by complex **1** (30 μM) in the presence of MPA (5 m*M*) in the dark in tris-HCl/NaCl buffer (50 m*M*, *p*H 7.2) containing 10% DMF. [lane 1, DNA control; lane 2, DNA + **1** (30 μ*M*, 15 min) + MPA, lane 3, DNA + DMSO + **1** + MPA; lane 4, DNA + KI + **1** + MPA; lane 5, DNA + mannitol + **1** + MPA; lane 6, DNA + NaN_3 + **1** + MPA; lane 7, DNA + distamycin + **1** + MPA; lane 8, DNA + $[Cu(phen)_2(H_2O)](ClO_4)_2$ (30 μ*M*, 15 min) + MPA; lane 9, DNA + $[Cu(dpq)_2(H_2O)](ClO_4)_2$ (30 μ*M*, 15 min) + MPA].

The mechanistic studies using various additives indicate the hydrolytic nature of the cleavage. The addition of hydroxyl radical scavengers DMSO, KI, mannitol and the singlet oxygen quencher, NaN_3, does not show any apparent effect on the DNA cleavage activity indicating non-involvement of hydroxyl and singlet oxygen species in the DNA cleavage reaction. The inhibition by T4 DNA ligase in the formation of the nicked circular (NC) form of DNA supports the hydrolytic nature of the DNA cleavage. The DNA cleavage experiment using DNA minor groove binder distamycin does not show any inhibition in the cleavage activity. This indicates DNA major groove-binding propensity of **1**.

The oxidative cleavage of DNA by **1** in the presence of a reducing agent 3-mercaptopropionic acid (MPA, 5 m*M*) is studied using SC pUC19 DNA in tris-HCl/NaCl buffer. The gel electrophoresis diagram is shown in Fig. 3. Complex **1** (30 μ*M*) shows efficient chemical nuclease activity. A comparison of the oxidative DNA cleavage activity of the phen, dpq and dppz complexes shows that the dpq and dppz complexes are significantly more active than the phen complex (Fig. 3). The dppz complex is a better cleaver of plasmid DNA than its dpq analogue. The mechanistic studies done using various additives reveal that addition of hydroxyl radical scavengers like DMSO, KI or mannitol inhibits the cleavage activity, while singlet oxygen quencher NaN_3 does not show any inhibitory effect. The mechanistic data suggest the formation of hydroxyl radicals in the DNA cleavage reaction in the presence of MPA.

In summary, the hitherto unknown bis-dipyridophenazine complex of copper(II) that is analogous to $[CuB_2(H_2O)]^{2+}$ (B = phen, dpq) has been prepared and structurally characterized by X-ray crystallography. The dppz complex displays good DNA binding propensity and efficient DNA cleavage activity by hydrolytic and oxidative pathways. The dppz complex differs from its phen and dpq analogues by binding to DNA in the major groove with partial intercalation to DNA, while the other phen and dpq analogues bind DNA in the minor groove. The dppz complex shows better DNA cleavage activity than its phen and dpq analogues.

Supplementary Data

CCDC 705759 contains the supplementary crystallographic data that can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44 1223 336 033, Email: deposit@ccdc-cam.ac.uk. www:http://www.ccdc.cam.ac.uk).

Acknowledgement

We thank the Department of Science and Technology (DST) for funding (SR/S5/MBD-02/2007) and the CCD diffractometer facility. MSAB thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, for a fellowship under the Scientist Pool Scheme. SS and AH thank CSIR for research fellowships. ARC thanks DST for JC Bose Fellowship.

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