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Article

Barrel- and Crown-Shaped Dodecanuclear Copper(II) Cages Built from Phosphonate, Pyrazole, and Hydroxide Ligands

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The reaction of $Cu(ClO_4)_2 \cdot 6H_2O$ with *t*-BuP(O)$(OH)_2$ and 3,5-$(CF_3)_2$PzH in the presence of triethylamine afforded the dodecanuclear cage $\{[Et_3NH]_2[Cu_{12}(\mu\text{-}3,5\text{-}(CF_3)_2Pz)_6(\mu_3\text{-}OH)_6(\mu\text{-}OH)_3(\mu_3\text{-}t\text{-}BuPO_3)_2(\mu_6\text{-}t\text{-}BuPO_3)_3][t\text{-}BuPO_2OH]\text{-}[C_6H_5CH_3]_2\}$ (**2**). The molecular structure of this cage revealed that it possesses a barrel-shaped architechture. The cage structure is built by the cumulative coordination action of phosphonate, hydroxide, and pyrazolyl ligands. A similar reaction involving $Cu(NO_3)_2 \cdot 3H_2O$, *t*-BuP(O)$(OH)_2$, 3,5-dimethylpyrazole, and triethylamine afforded another dodecanuclear cage $[Cu_{12}(\mu\text{-DMPz})_8(\eta^1\text{-DMPzH})_2(\mu_4\text{-O})_2(\mu_3\text{-OH})_4(\mu_3\text{-}t\text{-BuPO}_3)_4] \cdot 3MeOH$ (**3**). The latter is crown-shaped and is built by the coordination of pyrazole, pyrazolyl, phosphonate, hydroxide, oxide, and methanol ligands. Both of the dodecanuclear cages are efficient nucleases in the presence of magnesium monoperoxyphthalate.

Introduction

The recent spurt in research on molecular phosphonates containing transition- and main-group-metal ions can be traced to the advent of new synthetic methodologies that have allowed the assembly of these compounds.[1] Although, many transition-metal phosphonates are known, these are quite insoluble and possess extended structures.[2] The use of sterically hindered phosphonic acids along with suitable ancillary ligands has allowed the isolation of discrete molecular phosphonate complexes.[3] Previously, we have reported the preparation of a neutral dodecanuclear copper(II) phosphonate $[Cu_{12}(\mu_4\text{-Cl})_4(\mu_3\text{-Cl})_2(\eta^1\text{-DMPzH})_6(\mu\text{-DMPz})_4(\mu_3\text{-}t\text{-BuPO}_3)_4(\mu\text{-}t\text{-BuPO}_3)_2(\mu\text{-}t\text{-BuPO}_2OH)_2]$ (**1**) in a reaction involving $CuCl_2$, 3,5-dimethylpyrazole (DMPzH), and *tert*-butylphosphonic acid.[4] Subsequently, we have been able to modulate the nuclearity of the copper(II) cages by variation of the coligand.[3a,5] In view of the versatile coordination behavior of 3,5-bis(trifluoromethyl)pyrazole [3,5-$(CF_3)_2$-PzH],[6] we were interested in utilizing it as an ancillary ligand. Also, our experience in organotin oxide−hydroxides[7] has prompted us to explore the utility of the hydroxide ligand in

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copper phosphonate cages. Accordingly, herein, we report two unprecedented dodecanuclear copper(II) cages (**2** and **3**) possessing barrel-and crown-shaped architectures, respectively.

Many copper complexes have been investigated for their nuclease activity. However, most of these studies are limited to mononuclear complexes.[8] Recently, there has been an interest in evaluating the nuclease activity of multinuclear copper complexes because of their high propensity for oxygen and water activation and also its selective binding to specific nucleic acid conformations.[9] Some polynuclear copper complexes have been studied with regard to their ability to cleave DNA. Recently, we have reported the nuclease activity of a series of tetranuclear copper(II) phosphonates.[5c,d] In view of this interest, we have examined the plasmid modification behavior of **2** and **3**. These results are also reported herein.

Experimental Section

Materials and General Methods. Solvents and other general reagents used in this work were purified according to standard procedures.[10a] $Cu(ClO_4)_2 \cdot 6H_2O$ (Fluka, Buchs, Switzerland) and $Cu(NO_3)_2 \cdot 3H_2O$ (NICE Chemicals, Cochin, India) were used as obtained. *tert*-Butylphosphonic acid (*t*-$BuPO_3H_2$),[10b] 3,5-bis(trifluoromethyl)pyrazole [3,5-$(CF_3)_2$PzH],[10c] and 3,5-dimethylpyrazole[10d] (DMPzH) were prepared according to published procedures. Supercoiled plasmid DNA (pBR322) was purchased from Bangalore Genei. Ethidium bromide was purchased from Sigma Aldrich Ltd. Magnesium monoperoxyphthalate hexahydrate (MMPP; Lancaster, U.K.) and sodium cacodylate buffer (SRL, Mumbai, India) were used as supplied. Ethylenediaminetetraacetic acid (EDTA), dimethyl sulfoxide (DMSO), *tert*-butanol, and D-mannitol were purchased from S.D. Fine Chemicals, Mumbai, India. All buffer solutions were prepared using Millipore water. IR spectra were recorded as KBr pellets on a Bruker Vector 22 FTIR spectrophotometer operating from 400 to 4000 cm^{-1}. Electronic spectra were recorded on a Perkin-Elmer Lambda 20 UV−vis spectrometer and on a Shimadzu UV-160 spectrometer using dichloromethane and methanol as the solvent for compounds **2** and **3**, respectively. Thermogravimetric analysis and differential scanning calorimetry were carried out on a Perkin-Elmer Pyris 6 thermogravimetric analyzer. Electrospray ionization mass spectrometry (ESI-MS) spectra were recorded on a MICROMASS QUATTRO II triple-quadrupole mass spectrometer. The following ionization protocols were used. For compound **2**: *electrospray in negative-ion full-scan mode* using acetonitrile and 20% formic acid (0.1%) as the solvent and nitrogen gas for desolvation. The capillary voltage was maintained at 2.6 kV and the cone voltage was kept at 35 V. For (**3**): *electrospray in positive-ion full-scan mode* using methanol as the solvent and nitrogen gas for desolvation. The capillary voltage was maintained at 2.7 kV, and the cone voltage was kept at 41.0 V. For compound **2**, magnetic susceptibility measurements were obtained with the use of a Quantum Design SQUID magnetometer MPMS-XL. This magnetometer works between 1.8 and 400 K for direct current applied fields ranging from −7 to 7 T. Measurements were performed on a finely ground crystalline sample of 29.53 mg. *M* vs *H* measurements have been performed at 100 K to check for the presence of ferromagnetic impurities, which were found to be absent. The magnetic data were corrected for the sample holder and the diamagnetic contribution. For compound **3**, magnetic characterization was done using a vibrating sample magnetometer (VSM model EV 7; ADE Technologies, Westwood, MA) with the field applied up to 2.2 T. This magnetometer works between 100 and 673 K; ADE Magnetics DMS Easy VSM software (version 9.01d) were used for the data analysis. Measurements were performed on a finely ground crystalline sample of 57.2 mg. *M* vs *H* measurements have been performed at 293 K to check for the presence of ferromagnetic impurities, which were found to be absent.

Synthesis of $\{[Et_3NH]_2[Cu_{12}(\mu\text{-}3,5\text{-}(CF_3)_2Pz)_6(\mu_3\text{-}OH)_6(\mu\text{-}OH)_3(\mu_3\text{-}t\text{-}BuPO_3)_2(\mu_6\text{-}t\text{-}BuPO_3)_3][t\text{-}BuPO_2OH][C_6H_5CH_3]_2\}$ (2). $Cu(ClO)_4 \cdot 6H_2O$ (0.213 g, 0.575 mmol) was taken in dichloromethane (30 mL), to which was added a solution of 3,5-$(CF_3)_2$PzH (0.053 g, 0.383 mmol) and *tert*-butylphosphonic acid (0.079 g, 0.383 mmol) and triethylamine (0.167 g, 1.20 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at room temperature for 20 h and filtered and the solvent removed in vacuo. The resultant blue solid was recrystallized from a dichloromethane/toluene mixture (1:1) to afford a dark-blue crystals of **2**. Yield: 80%. Anal. Calcd for $C_{80}H_{118}Cu_{12}F_{36}N_{14}O_{27}P_6$ (**2**, 3340.77): C, 28.77; H, 3.56; N, 5.87. Found: C, 30.15; H, 3.92; N, 6.05. IR (KBr, ν, cm^{-1}): 3685(s), 3591(s), 3447(br), 2952(m), 2869(s), 2678(s), 2491(s), 1537(s), 1502(s), 1478(s), 1395(s), 1365(s), 1264(s), 1140(s), 1108(s), 1082(s), 1024(s), 988(s), 903(s), 868(s), 816(s), 759(s), 661(s), 630(s), 576(s), 539(s), 504(s), 465(s), 417(s). UV−vis {CH_2Cl_2 [λ_{max}/nm (ε_{max}/ M^{-1} cm^{-1})]}: 707.0 (553.82). ESI-MS: $[M - \{[t\text{-}BuPO_2OH][C_6H_5CH_3]_2[Et_3NH]_2\} - 1]^-$ 2814.15.

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Table 1. Crystallographic Data and Structure Refinement Details of **2** and **3**

	2	**3**
empirical formula	$C_{80}H_{118}Cu_{12}F_{36}N_{14}O_{27}P_6$	$C_{69}H_{124}\ Cu_{12}\ N_{20}\ O_{21}\ P_4$
fw	3340.18	2456.24
temperature (K)	153(2)	153(2)
wavelength (Mo Kα) (Å)	0.710 73	0.710 73
cryst syst	triclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$
unit cell dimens		
a (Å)	15.4107(9)	16.0202 (8)
b (Å)	20.9924(13)	16.4860(7)
c (Å)	22.0690(13)	20.6953(15)
α (deg)	63.4210(10)	95.156(5)
β (deg)	78.5820(10)	97.146(5)
γ (deg)	87.2410(10)	108.988(4)
volume (Å^3)	6251.9(6)	5078.5(5)
Z, density (calcd) (mg/m^3)	2, 1.774	2, 1.606
abs coeff (mm^{-1})	2.195	2.589
F(000)	3348	2508
cryst size (mm)	0.20 × 0.10 × 0.10	0.07 × 0.04 × 0.02
θ range for data collection (deg)	1.89−26.00	2.20−25.00
limiting indices	$-18 \le h \le 19$, $-25 \le k \le 25$, $-27 \le l \le 16$	$-18 \le h \le 19$, $-19 \le k \le 8$, $-24 \le l \le 24$
reflns collected/unique	35 284/23 981 [*R*(int) = 0.0218]	28 514/17 401 [*R*(int) = 0.0546]
completeness to *θ*	97.7% (*θ* = 26.00°)	97.3% (*θ* = 25.00°)
data/restraints/param	23 981/0/1689	17 401/0/1165
GOF on F^2	1.046	0.677
final *R* indices [$I > 2\sigma(I)$]	R1 = 0.0385, wR2 = 0.1081	R1 = 0.0551, wR2 = 0.1042
R indices (all data)	R1 = 0.0476, wR2 = 0.1174	R1 = 0.1485, wR2 = 0.1147
largest diff peak and hole (e/Å^3)	0.819 and −0.562	0.983 and −0.505
refinement method	full-matrix block least squares on F^2	full-matrix least squares on F^2

Synthesis of $[Cu_{12}(\mu\text{-DMPz})_8(\eta^1\text{-DMPzH})_2(\mu_4\text{-O})_2(\mu_3\text{-OH})_4(\mu_3\text{-}t\text{-BuPO}_3)_4]\cdot 3\text{MeOH}$ (3). $Cu(NO_3)_2\cdot 3H_2O$ (0.178 g, 0.738 mmol) was taken in methanol (30 mL), to which was added a solution of DMPzH (0.142 g, 1.475 mmol) and *tert*-butylphosphonic acid (0.079 g, 0.369 mmol) and triethylamine (0.25 mL, 1.844 mmol) in methanol (20 mL). The reaction mixture was stirred at room temperature for 20 h. The resulting clear blue solution was filtered. Removal of solvent in vacuo afforded a blue-green solid, which was recrystallized from a methanol/petroleum ether (40−60 °C) mixture (1:1) to afford blue crystals of **3**. Yield: 45%. Anal. Calcd for $C_{69}H_{124}Cu_{12}N_{20}O_{21}P_4$ (**3**, 2456.29): C, 33.74; H, 5.09; N, 11.41. Found: C, 33.54; H, 4.92; N, 11.78. IR (KBr, *ν*, cm^{-1}): 3250.18(s), 2976.61(s), 2939.21(s), 2739.67(s), 2678.82(s), 2491.86(s), 1763.78(s), 1577.90(s), 1475.54(s), 1378.79(br), 1170.62(s), 1099.00(s), 1071.19(s), 1034.84(s), 1006.02(s), 969.10(s), 907.53(s), 849.00(s), 826.22(s), 804.11(s), 741.05(s), 653.91(s), 524.10(s), 496.31(s), 469.17(s), 453.23(s). UV−vis {MeOH, [λ_{max}/nm(ε_{max}/M^{-1} cm^{-1})]}: 752.8 (158.46). ESI-MS: $[M + 1]^+$ 2457.77.

X-ray Crystallography. Single-crystal X-ray structural studies were performed on a CCD Bruker SMART APEX diffractometer equipped with an Oxford Instruments low-temperature attachment. Data were collected at 153(2) K using graphite-monochromated Mo Kα radiation (λ_α = 0.710 73 Å). No decomposition of the crystal occurred during data collection. Data collection, structure solution, and refinement were performed using *SMART*,[11a] *SAINT*,[11a] and *SHELXTL*[11b] programs, respectively. All calculations for data reduction were done using the Bruker *SADABS*[11b] program. All non-hydrogen atoms of **2** were anisotropically refined using a full-matrix block least-squares procedure. All hydrogen atoms (except the O−H of hydroxides) were included in idealized positions, using a riding model. The O−H hydrogen atoms were located from the difference Fourier map and refined isotropically. C76, C77, C78, and C81 are disordered over two positions with occupancies of 0.5 (C76A, C77A, C78A, and C81A) and refined anisotropically. C51 and C81 were disordered over three positions with occupancies of 0.33 (C51A, C51B, C80A, and C80B) and refined isotropically. For compound **3**, the crystals obtained from the mother liquor were very small (0.07 × 0.04 × 0.02 mm^3) and weakly diffracting, due to which the data were truncated to 2θ = 50.00°. All of the non-hydrogen atoms were refined anisotropically using a full-matrix least-squares procedure, and all of the hydrogen atoms except the N−H of pyrazole and the O−H of hydroxides were included in idealized positions and a riding model was used. The O−H and N−H hydrogen atoms were not clearly visible from the difference Fourier map because of the poor data quality. Figures and bonding parameters were obtained from the *DIAMOND* 3.1f package.[11c] The crystal and refinement data of **2** and **3** are summarized in Table 1, and selected distances and angles of compounds **2** and **3** are shown in Tables S3 and S4 (see the Supporting Information). Crystallographic data (atom coordinates, thermal parameters, and full tables of bond lengths and angles) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 675588 and 681946). Copies of this information can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. Fax +44(1223) 336-033, e-mail deposit@ccdc.cam.ac.uk, or http://www.ccdc.cam.ac.uk.

pBR322 Cleavage Assay. Plasmid cleavage reactions were performed in a sodium cacodylate buffer (10 mM, pH 7.5, 32 °C), containing pBR322 (8 ng/μL; Bangalore Genei), a solution of the complexes **2** and **3** (1 mM) in distilled methanol, and activating agent MMPP (100 μM). For each cleavage reaction, 16−18 μL of pBR322 supercoiled DNA and 2 μL of complexes **2** and **3** were used, and they were initiated by adding 2 μL of MMPP in an Eppendorf tube. For scavenger experiments, concentrations used were 100 mM. All cleavage reactions were quenched with 5 μL of loading buffer containing 100 mM EDTA and 50% glycerol in Tris-HCl (pH 8.0), and the samples were loaded onto 0.7% agarose gel (Biozym) containing ethidium bromide (1 μg/mL). Electrophoresis was done for 1 h at a constant current (80 mA) in a 0.5 M TBE buffer. Gels were imaged with a PC-interfaced Bio-Rad Gel Documentation System 2000.

Plasmid Cleavage under Anaerobic Conditions. Oxygen-free nitrogen was bubbled through a cacodylate buffer, which was then subjected to four freeze−thaw cycles. All reagents were transferred

Chart 1. Schematic Structure of the Dodecanuclear Copper(II) Assembly of **2** and the Different Binding Modes of the Ligands (Harris Notation) in **2**

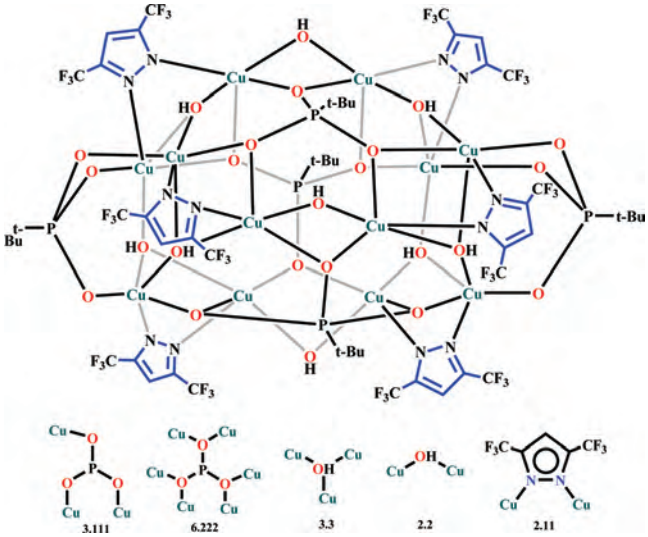
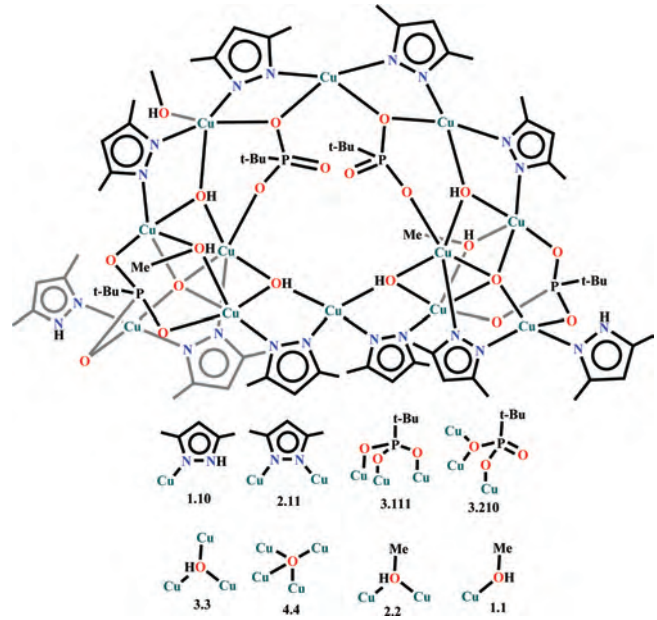


Chart 2. Schematic Structure of the Dodecanuclear Copper(II) Assembly of **3** and the Different Binding Modes of the Ligands (Harris Notation) in **3**



in argon-filled glovebags, and Eppendorf tubes were tightly sealed with parafilm in the argon atmosphere. Reactions were quenched with a loading buffer, and efforts were made to ensure strict anaerobic conditions during irradiation and quenching.

Results and Discussion

Synthesis, Magnetism, and Thermal Analysis. The reaction of $Cu(ClO_4)_2 \cdot 6H_2O$ with [3,5-$(CF_3)_2$PzH] and *tert*-butylphosphonic acid in 3:2:2 stoichiometry in the presence of a slight excess of triethylamine in a dichloromethane solvent afforded a blue solid, which was recrystallized from a 1:1 mixture of dichloromethane and toluene. Dark-blue crystals of **2** were isolated in about 80% yield (Chart 1). On the other hand, the reaction of $Cu(NO_3)_2 \cdot 3H_2O$ with 3,5-Me_2PzH and *t*-BuP(O)$(OH)_2$ in a 2:4:1 stoichiometry in the presence of a small excess of triethylamine in a methanol solvent afforded a greenish-blue solid, which was recrystallized from a methanol/petroleum ether (40−60 °C) mixture (1:1) to afford blue crystals of **3** (Chart 2) in about 45% yield. Unlike the dodecanuclear cage **1**, compounds **2** and **3** represent hydroxide-rich cages. Previously, copper(II) macrocycles containing hydroxide bridges were described.[12] In addition to the experiments that led to the isolation of **2** and **3**, we tried many other variations of reaction conditions such as changing the stoichiometry of the reactants. We were unable to isolate pure products under such conditions.

ESI-MS spectra of **2** and **3** were recorded under negative- and positive-ion modes, respectively. While **2** showed a peak at 2814.15 corresponding to $[M - \{[t\text{-}BuPO_2\text{-}OH][C_6H_5CH_3]_2[Et_3NH]_2\} - 1]^-$ (see the Supporting Information), **3** showed a peak at 2457.77, which corresponds to $[M + 1]^+$ (see the Supporting Information), indicating that under these conditions the dodecanuclear cage structures of **2** and **3** (vide infra) are retained in solution.

Detailed magnetic studies carried out on **2** between 300 and 1.8 K on a SQUID magnetometer revealed a paramagnetic behavior in the whole range of temperature studied (see the Supporting Information). At room temperature, the $\chi_m T$ product is around 1.45 $cm^3 \cdot K/mol$ and then decreases very rapidly at lower temperatures to reach a constant value of around 0.25 $cm^3 \cdot K/mol$ at 1.8 K. This behavior reveals the presence of dominant and strong antiferromagnetic interactions between the various copper(II) centers. Because of the complex topology of the $[Cu_{12}]$ core and the multiple interaction pathways, it is difficult to go further in the magnetic analysis of the data. Magnetic studies on **3** carried out between 300 K ($\chi_m T = 1.71$ $cm^3 \cdot K/mol$ at 1 T) and the lowest temperature available, 100 K ($\chi_m T = 1.43$ $cm^3 \cdot K/mol$ at 1 T), on a VSM also revealed paramagnetic behavior (see the Supporting Information) in the temperature range studied. In view of the molecular structure of **3**, dominant antiferromagnetic interactions are also expected for this compound at very low temperatures.

Thermogravimetric analysis of **2** showed an initial weight loss of 16% (197 °C) corresponding to the loss of toluene, triethylamine, and *t*-BuP$O(OH)_2$. Further weight loss of 20% (252 °C) corresponds to the loss of P_4O_{10}. At 900 °C, a char residue of 28% is still present (see the Supporting Information). Thermal analysis of **3** shows a more rapid weight loss (45%, 200 °C) corresponding to the loss of 10 dimethylpyrazole molecules. The char residue of **3** is 16% at 450 °C (see the Supporting Information).

Molecular Structures of 2 and 3. Compound **2** crystallizes in the triclinic $P\bar{1}$ space group. The asymmetric unit consists of a monoanionic dodecanuclear copper(II) cage, a monoanionic *t*-$BuPO_2(OH)$ unit, two triethylammonium cations, and two toluene solvent molecules. Two of the

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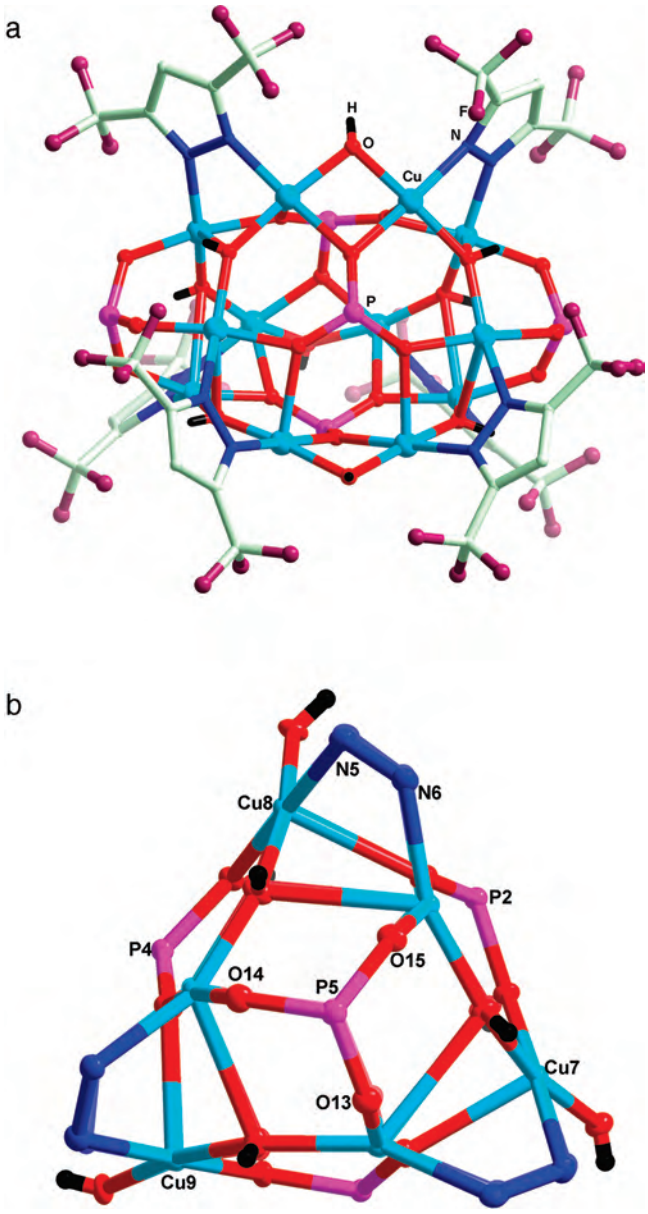

Figure 1. (a) Molecular structure of **2** (*tert*-butyl groups have been removed for clarity). (b) Core of **2**. View showing its D_3 symmetry.

oxygen atoms of the $[t\text{-BuPO}_2\text{OH}]^-$ anion interact with the triethylammonium cations by strong N−H····O contacts (see the Supporting Information).

The molecular structure (anionic portion) of **2** is shown in Chart 1 and Figure 1a. A crystallographically imposed D_3 molecular symmetry is seen in the cage (Figure 1b). The dodecanuclear cage is barrel-shaped and is held together by an array of anionic ligands: five $[t\text{-BuPO}_3]^{2-}$, nine $[\text{OH}]^-$, and six $[3,5\text{-}(\text{CF}_3)_2\text{Pz}]^-$. The coordination modes of these ligands (Harris notation)[13] are summarized in Chart 1.

The architecture of the barrel-shaped molecular structure of the cage can be understood by considering the various structural subunits that constitute it. The two ends (Chart 1 and Figure 1a) of the barrel contain a Cu_3O_3 six-membered ring present in a chair conformation. The oxygen atoms of this unit are derived from μ_3-OH ligands. Each such six-membered ring is capped by a tridentate phosphonate ligand (3.111). The bulge of the barrel is a circular rim of three four-membered Cu_2O_2 rings (Chart 1). While one of these oxygen atoms belongs to a phosphonate ligand, the other is obtained from a μ-OH ligand. The central bulge is held together by the coordination action of three phosphonate ligands. The subunits (the two ends and the rim) are joined together by phosphonate and hydroxide ligands. This results in a μ_3 (3.3) coordination from the hydroxides and a remarkable 6.222 coordination by the three phosphonate ligands in the central rim. The cage is completed by the μ_2 (2.11) coordination action of the anionic pyrazolyl ligands. Each pyrazole ligand binds to one copper atom of the end and another of the central rim (Chart 1). The formation of the cage by the cumulative and diverse coordination action of the various ligands results in a remarkable array of 40 cyclic rings that are fused with each other. These comprise of 19 six-membered rings, 12 five-membered rings, and 9 four-membered rings. All of the copper centers in the cage are five-coordinate (4O and 1N) and are present in an approximate square-pyramidal geometry (τ_5 values[14a] representing the extent of deviation from a regular trigonal-bipyramidal geometry range from 0.06 to 0.16; see the Supporting Information).

The metric parameters found in the cage are summarized in the Supporting Information. For the 3.111 mode of phosphonate coordination, the Cu−O distances are nearly equivalent [average 1.905(3) Å]. For the 6.222 mode of coordination, two types of Cu−O distances are found, a shorter distance of 1.927(3) Å (Cu11−O10) and a longer distance of 2.404(3) Å (Cu5−O4). For the 3.3 mode of μ_3-OH, two types of Cu−O distances are found [average values: 1.902(3) and 2.644(2) Å]. For the 2.2 mode of μ_2-OH, the two Cu−O distances are equivalent [average value: 1.898(3) Å]. Finally, for the 2.11 coordination mode of the pyrazole ligand, the Cu−N distances are equivalent [average value: 2.005(3) Å]. Another interesting aspect of **2** is that its periphery is surrounded by 36 lipophilic fluorine atoms. As a result, several C−H···F and O−H···F interactions occur to generate an interesting supramolecular architecture (see the Supporting Information).

In contrast to the anionic nature of **2**, cage **3** is neutral. The assembly of **3** is mediated by a variety of ligands exhibiting diverse coordination modes (Chart 2 and Figure 2). Thus, the following types and numbers of ligands are involved in the formation of **3**. Two neutral pyrazole ligands (1.10 mode), eight anionic pyrazolyl ligands (2.11 mode), four phosphonates, $[t\text{-BuPO}_3]^{2-}$ (two of the 3.111 mode and two of the 3.210 mode), four hydroxide ligands (3.3), three

(13) Harris notation describes the binding mode as $[X.Y_1Y_2Y_3\cdots Y_n]$, where X is the overall number of metals bound by the whole ligand and each value of Y refers to the number of metal atoms attached to the different donor atoms. See: Coxall, R. A.; Harris, S. G.; Henderson, D. K.; Parsons, S.; Tasker, P. A.; Winpenny, R. E. P. *J. Chem. Soc., Dalton Trans.* **2000**, 2349.

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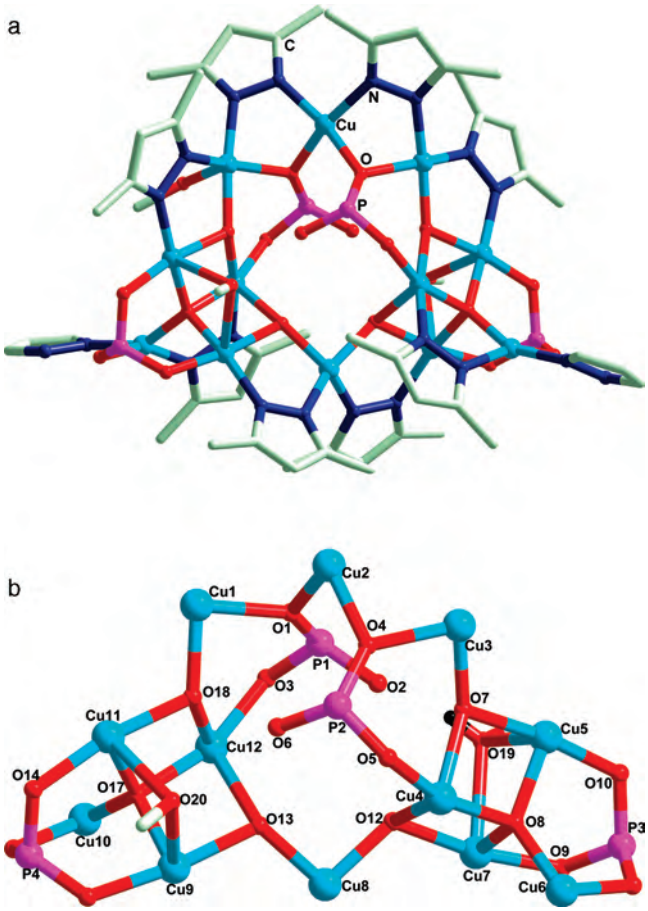

Figure 2. (a) Molecular structure of **3** (*tert*-butyl groups and two methyl groups have been removed for clarity). (b) Crown-shaped core of **3**.

methanol ligands (2.2 and 1.1), and two oxide ligands (4.4). The overall architechture of **3** is crown-shaped (Figure 2b). In spite of its apparent complexity, the molecular structure of **3** can be understood in terms of three types of building blocks that are joined with each other (Figure 2b). These are (1) two symmetry-related [$Cu_4(\mu_4$-O)] units (Cu4, Cu5, Cu6, Cu7, and O8; Cu9, Cu10, Cu11, Cu12, and O17) and (2) a molecular $Cu(\mu_3\text{-}OH)_2$ unit (Cu8, O12, and O13), and (3) a trinuclear Cu_3 (Cu1, Cu2, and Cu3) unit. Each of the Cu_4O units contains a central oxygen atom, which is attached to four copper atoms in a tetrahedral fashion [average distance: Cu−O8, 1.956(5) Å]. Such tetrahedral Cu_4O structural units are known among copper clusters.[15] It is of interest to note that, in the dodecanuclear copper(II) cage **1** (see the Supporting Information) that we prepared using $CuCl_2$ as the starting material,[4] [$Cu_4(\mu_4$-Cl)] units are present that are structurally similar to the [$Cu_4(\mu_4$-O)] found in the current instance. The [$Cu_4(\mu_4$-O)] core in **3** is completed by the interconnection of the copper atoms by other ligands: $\mu\text{-}\kappa^2$-pyrazole, κ^1-pyrazole, $\mu_3\text{-}\kappa^3\text{-}t\text{-}BuPO_3^{2-}$, μ-MeOH, and μ_3-OH. The two symmetry-related [$Cu_4(\mu_4$-O)] subunits are linked to each other by a putative copper hydroxide, $Cu(OH)_2$ (Cu8). The oxygen atoms involved viz., O13 and O12, bridge Cu8 with Cu12 and Cu9 on one side [average distance: Cu−O13, 2.151(5) Å] and with Cu4 and Cu7 on the other [average distance: Cu−O12, 2.090(5) Å]. The μ_3-bridging action of O13 and O12 is augmented by two $\mu\text{-}\kappa^2$-pyrazolyl ligands generating two Cu_2N_2O ring systems. The dodecanuclear cage assembly is completed by the fusion of the Cu_9 unit described above with a Cu_3 unit. This is accomplished by the following ligands: hydroxides, μ_3-O18 and μ_3-O7; $\mu\text{-}\kappa^2$-pyrazolyl, N19 and N20, N5 and N6; $\mu\text{-}\kappa^2$-phosphonate, O1 and O3, O4 and O5. The three copper atoms of the trinuclear unit Cu1, Cu2, and Cu3 are linked to each other by pyrazolyl and phosphonate ligands. The copper atoms present in the dodecanuclear cage adopt two different geometries. The five-coordinated copper atoms (Cu1, Cu4, Cu5, Cu7, Cu9, Cu11, and Cu12) possess a distorted square-pyramidal geometry (τ_5[14a] 0.055−0.269; see the Supporting Information), while the four-coordinated copper atoms (Cu2, Cu3, Cu6, Cu8, and Cu10) are in a distorted square-planar geometry (τ_4[14b] 0.181−0.444; see the Supporting Information).

Nuclease Activity. In contrast to studies pertaining to the utility of phosphonates in catalysis[16] and as materials,[17] there have been very few attempts to probe their biological applications.[18] Encouraged by our recent studies on the plasmid modification capability of tetranuclear copper(II) cages,[5c,d] we explored the DNA-cleaving capacity of the dodecanuclear cages **2** and **3**. We have found that, even without any external oxidant, **2** and **3** can effect DNA cleavage, albeit to small extents viz., 10 and 5%, respectively (Figures 3a and 4a). However, in the presence of an external oxidant such as MMPP, the conversion of supercoiled pBR322 DNA form I to nick form II occurs rapidly, within 2 min. Keeping in mind that copper-based artificial nucleases

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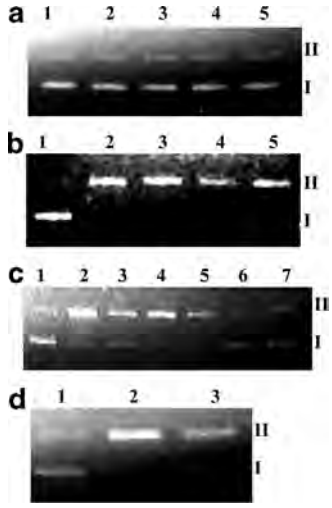

Figure 3. (a) Complex **2**-mediated pBR322 DNA cleavage experiments at different time intervals. Lane 1: DNA alone. Lanes 2−5: DNA + complex **2** (30, 60, 90, and 120 min, respectively). (b) pBR322 DNA cleavage effected by complex **2** in the presence of MMPP at different time intervals. Lane 1: DNA alone. Lanes 2−5: DNA + complex + MMPP (1, 2, 3, and 4 min, respectively). The data reveal that compound **2** is showing 100% (within 2 min) and 10% (120 min) conversion of DNA form I to nick form II, in the presence and in the absence of the external oxidant MMPP, respectively. (c) pBR322 DNA cleavage experiments assisted by **2** in the presence of free-radical scavengers and singlet oxygen quenchers in a 2 min reaction. Lane 1: DNA alone. Lane 2: pBR322 + **2** + MMPP. Lane 3: pBR322 + **2** + MMPP + DMSO. Lane 4: pBR322 + **2** + MMPP + D-mannitol. Lane 5: pBR322 + **2** + MMPP + *t*-BuOH. Lane 6: pBR322 + **2** + MMPP + EDTA. Lane 7: pBR322 + **2** + MMPP + NaN_3. (d) pBR322 DNA cleavage assisted by **2** in anaerobic conditions at different time intervals. Lane 1: DNA alone. Lanes 2 and 3: DNA + complex **2** + MMPP reaction mixture and DNA + complex + MMPP under anaerobic conditions.

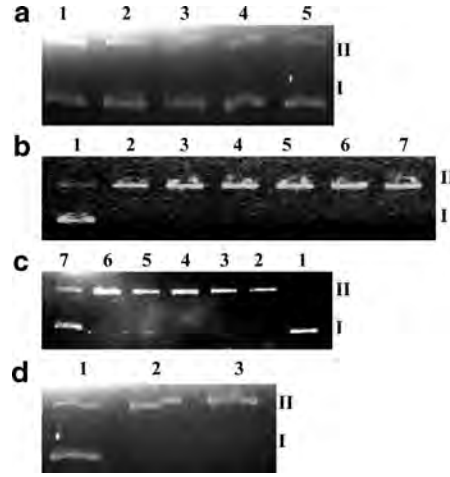

Figure 4. (a) Complex **3**-mediated pBR322 DNA cleavage experiments at different time intervals. Lane 1: DNA alone. Lanes 2−5: DNA + complex **3** (30, 60, 90, and 120 min, respectively). (b) pBR322 DNA cleavage effected by complex **3** in the presence of MMPP at different time intervals. Lane 1: DNA alone. Lanes 2−7: DNA + complex + MMPP (2, 4, 6, 8, 10. and 12 min. respectively). The data reveal that compound **3** shows 100% (within 2 min) and 5% (120 min) conversion of DNA form I to nick form II, in the presence and in the absence of external oxidant MMPP, respectively. (c) pBR322 DNA cleavage experiments assisted by **3** in the presence of free-radical scavengers and singlet oxygen quenchers in a 2 min reaction. Lane 1: DNA alone. Lane 2: pBR322 + **3** + MMPP. Lane 3: pBR322 + **3** + MMPP + DMSO. Lane 4: pBR322 + **3** + MMPP + D-mannitol. Lane 5: pBR322 + **3** + MMPP + *t*-BuOH. Lane 6: pBR322 + **3** + MMPP + NaN_3. Lane 7: pBR322 + **3** + MMPP + EDTA. (d) pBR322 DNA cleavage assisted by **3** under anaerobic conditions at different time intervals. Lane 1: DNA alone. Lanes 2 and 3: DNA + complex + MMPP reaction mixture and DNA + complex + MMPP under anaerobic conditions.

follow hydrolytic[19] and/or oxidative[20] pathways, we probed the mechanism of nuclease activity. We carried out plasmid-modification studies in the presence of hydroxyl radical scavengers such as DMSO, D-mannitol, and *tert*-butyl alcohol as well as in the presence of singlet oxygen quenchers such as NaN_3. We could not detect any inhibition of activity in the presence of hydroxyl radical scavengers. DNA cleavage by compound **2** is completely inhibited in the presence of sodium azide. However, the reactivity of compound **3** is not affected under similar reaction conditions. It was equally important to probe the involvement of coordinated copper for plasmid modification. Accordingly, plasmid-cleavage studies of **3** were studied in the presence of efficient complexing agents such as EDTA. The latter completely inhibited the cleavage reaction, essentially proving the crucial role of coordinated copper metal ions in **2** and **3** for plasmid cleavage. Further, to study the effect of molecular oxygen, the reaction was done under strictly anaerobic conditions. No inhibition of activity was observed for either cage. These cumulative inhibition experiments suggest that cage **2** follows a hydrolytic pathway whereas cage **3** follows multiple reaction pathways involving singlet oxygen as well as hydrolysis pathways. To the best of our knowledge, this is the first instance where copper(II) aggregates larger than tetranuclear ones have been utilized for DNA cleavage.

Conclusion

We have described the synthesis of two dodecanuclear copper(II) cages **2** and **3** by a multicomponent reaction strategy that involved a copper(II) salt, *t*-$BuPO(OH)_2$, an ancillary pyrazole ligand, and triethylamine. The latter acts as a base for deprotonation of the phosphonic acid and pyrazoles as well as presumably the coordinated water molecules around the metal ion. Cages **2** and **3** possess unprecedented structures and have barrel- and crown-shaped architectures, respectively. These cages are built from the coordination action of multiple ligands. Both of these cages

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can be described as hydroxide-rich. The nuclease activity of these cages has been probed and reveals that both of them are effective nucleases in the presence of an external oxidant.

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Supporting Information Available: Experimental details, additional schemes and figures (Figures S1—S13 and Tables S1—S4), and crystal data and CIF files for **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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