Synthesis and Interaction with Copper(II) Cations of Cyano- and Aminoresorcin[4]arenes[1]

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Following our studies on resorcin[4]arenes, we synthesized new macrocycles containing cyanomethyl and aminomethyl side chains. Three stereoisomers (**2a−c**) of the former were obtained by $BF_3 \cdot Et_2O$ tetramerization of the corresponding *trans*-cinnamic acid derivative and were shown to be in the 1,2-alternate, cone, and 1,3-alternate conformations. Conversely, the tetraamino derivative **6a** in the cone conformation was prepared from the corresponding tetrabromide **3a**. The interactions with Cu^{II} cations of the new compounds were analyzed by measurements of ^1H NMR and EPR spectra in parallel with molecular modeling calculations.

Introduction

Since we obtained *C*-alkylresorcin[4]arene octamethyl ethers by $BF_3 \cdot Et_2O$ tetramerization of cinnamic acid esters,[2] we directed our research toward two main targets:

The first target is the versatility of the reaction, that is the investigation of how many and different substrates may undergo the tetramerization. For example, simple and chiral amido resorcin[4]arenes were prepared from the corresponding monomer.[3] The second target is the complexation properties of the new compounds obtained. The aromatic upper rim of resorcin[4]arenes octamethyl ethers, for instance, was shown to interact with Fe^{III} ions in chloroform either in the cone or the 1,2-alternate forms as well as in the rigidified 1,3-alternate conformation.[4]

Starting from the adequate trans monomer, we synthesized resorcin[4]arenes containing in the side chains cyano groups, which were expected to enhance the salt-complexing capabilities of the macrocycle.[5] Our studies were extended to the synthesis of a resorcin[4]arene with four amino groups, which was considered the best candidate for metal ion complexation, as shown in previous papers.[6] The interactions of Cu^{II} cations with the above compounds have been analyzed by measurements of ^1H NMR and EPR spectra flanked by molecular modeling calculations.

When calixarenes act as receptors and carriers of transition metal cations,[7−10] two well-separated main coordination regions are generally identified in their structure: the so-called "upper rim", a π-basic cavity corresponding to the wide side of the aromatic rings system, and the "lower rim", localized at the narrow side among the substituents. The shape and the conformation of the essentially apolar upper rim determine the ability of including cations, which usually interact with the π electrons of the aromatic nuclei in a binding mode rationalized as a "cation−π interaction".[11]

In the case of cations like Ag^+, Cs^+, and K^+,[6,12,13] it has been reported that their complexes with calix[4]arene ionophores are stabilized by cation−π interaction.

The lower rim corresponds to a pseudocavity created by the side chain polar functions, such as carbonyl and amino groups, that cooperatively converge on the cation.[14]

Results and Discussion

Synthesis and Characterization of Resorcin[4]arenes. The cyanomethyl macrocycle was prepared from

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(1) Part 7 in the series Synthesis of *C*-Alkylcalix[4]arenes. For part 6, see ref 4.

(2) Botta, B.; Iacomacci, P.; Di Giovanni, M. C.; Delle Monache, G.; Gacs-Baitz, E.; Botta, M.; Tafi, A.; Corelli, F.; Misiti, D. *J. Org. Chem.* **1992**, *57*, 3259.

(3) Botta, B.; Delle Monache, G. Salvatore, P. Gasparrini F., Villani, C. Botta, M. Tafi, A. Corelli, Gacs-Baitz E., Santini, A.. Carvalho, C. F.; Misiti, D. *J. Org. Chem.* **1997**, *62*, 932.

(4) Botta, B.; Delle Monache, G.; Ricciardi, P.; Zappia, G.; Seri, C.; Gacs-Baitz, E.; Csokasi, P.; Misiti, D. *Eur. J. Org. Chem.* **2000**, 841.

(5) Paek, K.; Knobler, C. B.; Maverik, E. F.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 8662.

(6) Ikeda, A.; Tsudera, T.; Shinkai, S. *J. Org. Chem.* **1997**, *62*, 3568.

(7) Gutsche, C. D.; Chu Nam, K. *J. Am. Chem. Soc.* **1988**, *110*, 6153.

(8) Molenveld, P.; Engbersen, J. F. J.; Kooijman, H.; Spek, A. L.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1998**, *120*, 6726.

(9) Bodenant, B.; Weil, T.; Businelli-Pourcel, M.; Fages. F.; Barbe, B.; Pianet, I.; Laguerre, M. *J. Org. Chem.* **1999**, *64*, 7034.

(10) Paciello, R.; Siggel, L.; Röper, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1920.

(11) Ikeda, A. Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713−34.

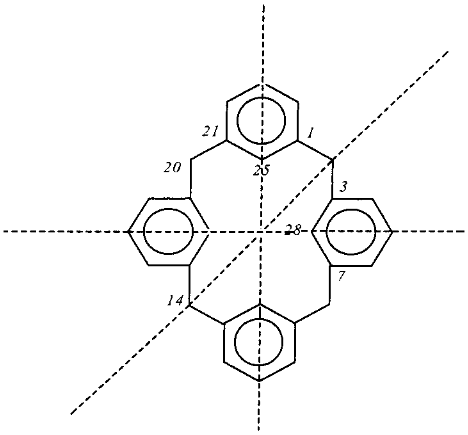
(12) Lamare, V.; Dozol, J.-F.; Ugozzoli, F.; Casnati, A.; Ungaro, R. *Eur. J. Org. Chem.* **1998**, 1559.

(13) Lamare, V.; Dozol, J.-F.; Fuangswasdi, S.; Arnaud-Neu, F.; Thuèry, P.; Nierlich, M.; Asfari, Z. Vicens, J. *J. Chem. Soc., Perkin Trans. 2* **1999**, 271.

(14) Guilbaud, P. Varnek, A. Wipff, G. *J. Am. Chem. Soc.* **1993**, *115*, 8298 and references therein.

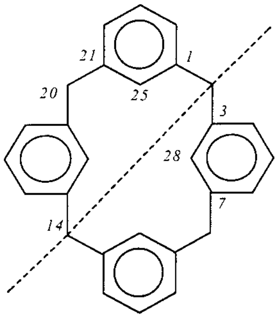
10.1021/jo010844g CCC: $22.00

Table 1. NMR Spectral Data for Compound 2a



posn	δ_C	δ_H
4, 6, 10, 12, 16, 18, 22, 24	156.78	
25, 26, 27, 28	126.00	6.67 s
1, 3, 7, 9, 13, 15, 19, 21	121.85	
CN	119.12	
5, 11, 17, 23	96.16	6.36 s
OMe	55.68	3.72 s
2, 8, 14, 20	33.18	4.89 t (7)
CH_2	21.87	2.92 d (7)

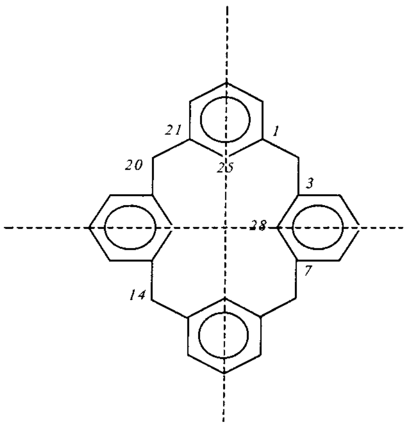
Table 2. NMR Spectral Data for Compound 2b



posn	δ_C	δ_H
4, 24; 6, 22; 10, 18; 12, 16	156.72; 155.66 × 3	
26, 27	127.03	6.45[a] s
25, 28	125.81	7.34 s
1, 3; 7, 21	121.83; 121.76	
9, 19; 13, 15	121.23; 121.09	
CN	119.84 × 2 119.08; 118.85	
11, 17	95.82	6.45[a] s
5, 23	95.63	6.42 s
Ome	56.01; 55.80 55.74; 55.62	3.88; 3.86 3.82; 3.73
8, 20	32.81 × 2	4.24 dd (8.5, 5.5)
14	31.24	5.08 t (8)
2	30.07	5.40 t (8)
2-CH_2	23.90	2.38 d (8)
14-CH_2	23.36	2.94 d (8)
8-, 20-CH_2	21.66 × 2	3.18 dd (17, 8.5) 2.91 dd (17, 5.5)

[a] Coincident.

Table 3. NMR Spectral Data for Compound 2c



posn	δ_C	δ_H
4, 6, 16, 18	156.96	
10, 12, 22, 24	156.34	
25, 27	126.70	6.22 s
26, 28	124.66	7.03 s
1, 9, 13, 21	122.57	
3, 7, 15, 19	120.04	
CN	119.14	
5, 17	96.74	6.52
11, 23	94.93	6.39
OMe	55.83	3.85 3.63
2, 8, 14, 20	32.95	4.90 t (7)
CH_2	21.72	2.81 d (7)

the corresponding monomer **1**, which in turn was obtained by Wittig–Hörner[15] reaction of 2,4-dimethoxybenzaldehyde with diethyl (cyanomethyl)phosphonate/K_2CO_3 in absolute EtOH. Since the obtained (*E*/*Z*)-pair (3:2) of **1** gave a complex mixture with $BF_3{\cdot}Et_2O$, only the (*E*)-isomer was used for a tetramerization reaction, which afforded the cone (**2a**, 40%), the 1,2-alternate (**2b**, 15%), and the 1,3-alternate stereoisomers (**2c**, 12%). The stereostructures (not shown) were assigned on the basis of the similarity of ^1H and ^{13}C NMR spectra with those of the corresponding esters.[2,16] Therefore, the cone conformer **2a**, with a C_{4v} symmetry (Table 1), showed only one signal for each type of proton or carbon. Conversely, in the 1,2-alternate stereoisomer **2b** (Table 2) the symmetry plane passing through C-2 and C-14 carbons determined a 1:1 distribution pattern for the signals of the aromatic carbons (one signal for each pair of carbons), whereas the methine and the side-chain carbons gave signals with 1:2:1 relative intensity, C-2 and C-14 being not equivalent. Finally, in the NMR spectra of the 1,3-alternate stereoisomer **2c** (Table 3), one signal for the methine and side-chain carbons, four signals for protonated aromatic carbons, and four signals for quaternary aromatic carbons require the existence of two symmetry planes passing through opposite aromatic rings (D_{2d} symmetry). The distribution pattern of the signals in the NMR spectra would be compatible also with a chair conformation featuring an r–t–t–c distribution of the side chains, but we preferred the 1,3-alternate form, which was suggested by molecular modeling studies.[2] On the other hand, in the case of amido resorcinarenes we obtained, besides the three described forms, two chairlike structures with less symmetrical arrangements, and the presence of a third chair seems to be unlikely.[3]

FABMS spectra of **2a**–**c** showed a molecular peak at 779, [M + Na]$^+$, and a base peak at 716 mu, corresponding to the loss of one side chain CH_2CN, in accord with our previous observations.[16] Attempts to convert **2a** into the corresponding amino derivative with several reducing agents, like $LiAlH_4$,[17] $NaBH_4/CoCl_2$[18] in MeOH, $B_2H_6{\cdot}$

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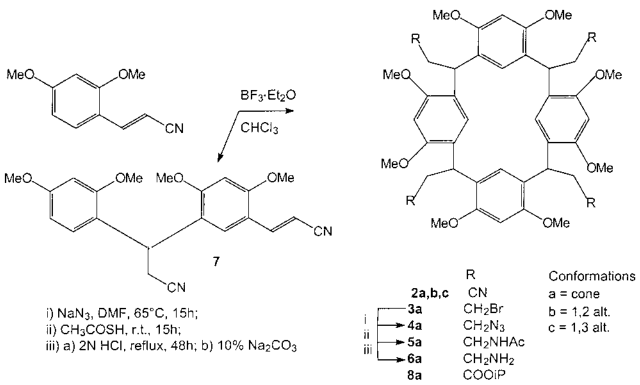
(15) (a) Pettit, G. R.; Dias, J. R. *J. Org. Chem.* **1971**, *36*, 3207. (b) Walsworth, F. C. *Org. React.* **1984**, *25*, 73–253.

(16) Botta, B.; Di Giovanni, M. C.; Delle Monache, G.; De Rosa, M. C.; Gacs-Baitz, E.; Botta, M. Corelli, F.; Tafi, A.; Santini, A.; Benedetti, E.; Pedone, C.; Misiti, D. *J. Org. Chem.* **1994**, *59*, 1532.

Scheme 1



i) NaN$_3$, DMF, 65°C, 15h;
ii) CH$_3$COSH, r.t., 15h;
iii) a) 2N HCl, reflux, 48h; b) 10% Na$_2$CO$_3$

Table 4. Chemical Shift Variations[a] by Effect of CuCl$_2$ in 3 and 4a

	H$_i$	H$_e$	CH	OMe	CH$_2$
7	−0.8	−1.0	−0.3	+0.2	−3.4
2a	−3.0	−3.8	−21.4	+2.3	+35.3; +13.6
2b	−2.4	−0.9	−2.9	+1.6	−4.7

[a] A positive value corresponds to a downfield shift. Average values among the different signals are reported for **2b**.

SMe$_2$/THF,[19]or H$_2$ and Pd/C,[20]were unsuccessful, and we turned to the synthetic route presented in Scheme 1.

Treatment of the tetrabromide **3a**, previously obtained by us,[4] with an excess (6:1) of NaN$_3$[20] in DMF at 65 °C for 15 h gave the corresponding tetraazide derivative **4a** (60% yield). Compound **4a**, very slightly soluble in the most organic solvents, was dissolved in a large excess of thioacetic acid and the solution was kept under stirring at rt (room temperature) overnight.[21] From the reaction mixture the tetraaminoacetyl derivative **5a** was isolated in 40% yield. **6a**·HCl was obtained after heating **5a** with 2N HCl under reflux for 2 days, whereas the free base **6a** was isolated after stirring overnight the hydrochloride with 10% aqueous Na$_2$CO$_3$ and CHCl$_3$.

^{1}H and ^{13}C NMR spectra of compounds **4a**, **5a**, and **6a** showed the same distribution pattern of signals as for **3a**, the only significant difference being the chemical shifts of the methylene in α to the modified function. Analogously, the molecular and the base peak (M − chain) in the FABMS spectra reflected the functionality changes.[16]

Spectroscopic and Molecular Modeling Studies. Tetranitrile 2a. Resorcinarenes are generally insoluble in the solvents where CuCl$_2$ and other copper salts are soluble. The use of two different solvents in a ^{1}H NMR titration may lead to misleading results: e.g. comparable chemical shift variations were obtained for the macrocycle **8a** in CDCl$_3$ by the addition of either a CuCl$_2$ solution in CD$_3$CN or the pure solvent.

However, **2a** gave well-resolved ^{1}H NMR spectra of in CD$_3$CN at 70 °C before and after the addition of aliquots of a CD$_3$CN solution of CuCl$_2$. In Table 4 the chemical shift variations for the addition of an equimolar quantity of CuCl$_2$ are reported. The titration curve (not reported) did not show any significant variation in the slope, but the difference in sign and magnitude for the α-methylene signal suggested an interaction of the cyano group with the metal; notably, the methylene protons became unequivalent and underwent quite different shifts. These data were attributed to the interaction between the ligand and the cation, the signal shown in the NMR spectra being the result of the average values between the free and the "complexed" forms.[4] According to these results the interaction site appears to be confined among the cyano groups in the side chains of the macrocycle. As a confirmation, the dimer **7**, isolated in the tetramerization reaction (see Experimental Section), was titrated under the same conditions and with the same Cu^{II} solution: after the addition of an equimolar quantity of the metal, the corresponding signals showed minimal variations for all the signals (Table 4).

Moreover, the FAB MS spectrum of the sample **2a**/CuCl$_2$ showed the two most prominent peaks at *m*/*z* 821 and 819, corresponding to [M + ^{65}Cu]$^+$ and [M + ^{63}Cu]$^+$, respectively. The intensity ratio (ca. 1:2) between the two peaks is in agreement with the isotopic abundance (ca. 1:3), when we consider the contribution of *m*/*z* 820 and 819 to the intensity of the *m*/*z* 821 peak.

When the titration with CuCl$_2$ in CD$_3$CN at 70 °C was repeated on **2b**, only slight variations were observed for all signals; in Table 4 the average values (per type of signal) are compared with those obtained for **2a**. Notably, the chemical shift variations for the methylene adjacent to the cyano group were −7 Hz (C-8 and C-20 chains), −6 Hz (C-2 chain), and −2 Hz (C-14 chain), respectively. These findings suggest that in the interaction of **2a** with Cu^{II} cations are involved all the four cis group.

The cyano derivative **2c** was insoluble either in CD$_3$CN or in CD$_3$CN/CDCl$_3$ mixtures that could dissolve also CuCl$_2$, and no titration was performed.

In parallel studies we examined by computer calculations the possibility of complexation of Cu^{II} by **2a**. Molecular mechanics (MM) and molecular dynamics (MD) modeling have been applied recently to study the features of metal complexes[22]or metallocalixarenes[12,13] in a qualitative approach addressed to the prediction of reasonable coordination geometries and the exclusion of the forbidden ones.

To model the coordination compounds between Cu^{II} cation and the *C*-alkylcalixresorc[4]arene **2a** we applied the ionic method (IM)[22] of molecular mechanics. In this method the geometry and the energy of the coordination complex are calculated by taking into account only van der Waals and electrostatic interactions of the ligands with the metal cation. The approach does not require the explicit definition of bonds between metal and ligands and recognizes different potential complexation geometries during a single calculation. On the other hand, the IM requires an accurate calibration of both electrostatic and van der Waals parameters to find the proper balance between the different nonbonded interactions that mainly determine the structural aspects of the calculated coordination geometries.[22] To test the accuracy and reproducibility of the method, two X-ray structures of Cu^{II} complexes[23,24]were superimposed to the corresponding

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(17) Cimino, G.; Gavagnin, M.; Sodano, G.; Spinella, A.; Strazzullo, G.*J. Org. Chem.* **1987**, *52*, 2301.

(18) Obsy, J. O. Heinzman, S. W.; Ganem, B. *J. Am. Chem.* **1986**, *108*, 67.

(19) Brown, H. C.; Chai, Y. M..; Narasimhan, S. *Synthesis* **1981**, 605.

(20) Larock, R. C. Ed. In *Comprehensive Organic Transformations*; VCH Publishers: New York, 1989.

(21) Rosen, T.; Lico, I. M.; Chu, D. T. W. *J. Org. Chem.* **1988**, *53*, 1580.

(22) Hay, B. P. *Coord. Chem. Rev.* **1993**, *126*, 177−236.

(23) Castro, I.; Faus, J.; Julve, M. *Transition Met. Chem.* **1992**, *17*, 344.

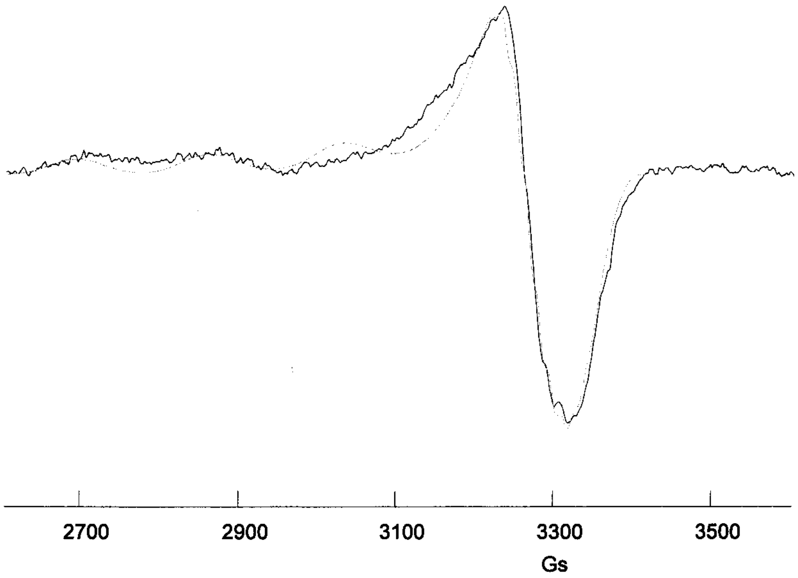

Figure 1. Low-temperature (120 K) EPR spectrum of the Cu$-$(**6a**)$_2$ complex, paired with its best simulation ($\nu = 9.4406$ GHz).

computer-generated models, obtaining a good overall matching (rms 0.18 and 0.33 Å).

In previous studies[25] the possibility that Cu^{II} might be included in the upper rim of the resorcin[4]arene **8a**, in the cone conformation with ester side chains, had been ruled out by computer simulations. DelPhy calculations had evidenced however a negative potential area suitable for Cu^{II} coordination in the lower rim for a conformation, in which the four carbonyl groups of the side chains had been forced mechanically toward a central point. When the cation was included and the coordination was analyzed by energy minimization of the input complex, the calculations revealed a geometry-optimized complex with an unusual square-planar array.

Albeit the Cu$-$O$_{(CO)}$ distances were very similar to those of the X-ray structure of a Cu$^{II}-$calixarene complex,[26] the geometry of the macrocycle was severely distorted; in confirmation, the steric energy for the structure depleted of the cation resulted ca. 30 kcal/mol higher than for the input conformation.

Similar results were obtained when the complexation of one Cu^{II} at the lower rim of compound **2a** was modeled along the same procedure:[25] the simulations calculated coordination geometries that excluded again the existence of a stable 1:1 complex of the metal with the macrocycles, mainly because of the conformational rigidity of the resorcin[4]arenes.

Tetraamine 6a. The low solubility of the tetraamino derivative **6a** in CD$_3$CN suggested us to analyze directly by an EPR spectrum the interaction of the macrocycle with a copper salt.

In Figure 1 the EPR spectrum of the complex **6a**/Cu^{II} at low temperature is presented. The spectrum is paired with the simulation that actually gave the best fit obtained with the spin-Hamiltonian EPR parameters reported in Table 5. The spectrum appears to be axial or nearly axial and allows the parallel components of the spin-Hamiltonian parameters, $g_{||}$ ($=g_{zz}$) and $A_{||}$ ($=A_{zz}$) to be determined.

Table 5. Spin-Hamiltonian EPR Parameters for the Complex Cu(calix-NH$_2$)$_2$[a]

$g_{\|\|}$[b]	$g_{\perp}$[b]	$A_{\|\|}$[c]	$A_{\perp}$[c]	no. of N[d]	$a_{N\|\|}$[e]	$a_{N\perp}$[e]	f[f]
2.275	2.067	173	3	4	19	14	131

[a] Coupling constants are given in cm^{-1} and multiplied by a factor 10^4. [b] Estimated error ±0.001. [c] Estimated error $\pm 1 \times 10^{-4}$ cm^{-1}. [d] The number of equatorial nitrogen donor atoms. [e] Estimated error $\pm 0.5 \times 10^{-4}$ cm^{-1}. [f] The parameter f is given by $g_{||}/A_{||}$ cm.

Table 6. van der Waals Parameters Readjusted To Describe the Interactions between Ligands and Cu^{II}

atom	A (kcal × Å^{12}/mol)	B (kcal × Å^6/mol)
Cu[a]	1826.0174	19.11030
N[b]	653892.4	409.73

[a] Parameter taken from AMBER force field. [b] Parameter taken from ESFF force field (MSI Inc.).

In the low-field end of the spectrum the parallel components are broadened by the presence of nitrogens in the first coordination sphere of copper and by the presence of the two isotopes of copper (^{63}Cu/^{65}Cu). On the other hand the analysis of the $g_{\perp}$ part of the spectrum (at the high-field end) is usually difficult at X-band because of the overlap of parallel and perpendicular component of copper, the nitrogen interaction, and the "extra absorption" lines.[27]However, the good fit in the $g_{\perp}$ part of the spectrum reported (Figure 1) made us confident that the spin-Hamiltonian parameters and the coordination of four nitrogens are reliable (Table 5).

The spin-Hamiltonian parameters, mainly $g_{||}$ and $A_{||}$, are related to the coordination geometry around the cation and vary in accord with the degree of distortion from planarity of the coordination core (and with the core's charge).[28] It was noticed that $g_{||}$ tends increase and $A_{||}$ tends to decrease as the tetrahedral distortion worsen.[29]

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(24) Panneerselvam, K.; Lu, T. H.; Chi, Y. *Acta Crystallogr.* **1998**, *C54*, 25.

(25) Masignani, V. Application of computational methodologies to the study of enzyme models: calixarenes as synthetic receptors. Thesis, University of Siena, 1994−1995.

(26) Beer, P. D. Drew, M. G. B. Leeson, P. B. Ogden, M. I. *J. Chem. Soc., Dalton Trans.* **1995**, 1273.

(27) Ovchinnikov, I. V.; Konstantinov, V. N. *J. Magn. Reson.* **1978**, *32*, 179.

(28) Peisach, J.; Blumberg, W. E. *Arch. Biochem. Biophys.* **1974**, *165*, 691.

(29) Rosenberg, R. C.; Root, C. A.; Bernstein, P. K.; Gray, H. B. *J. Am. Chem. Soc.* **1975**, *97*, 2092.

Accordingly, the empirical index factor *f* ($f = g_{\|} / A_{\|}$ cm) may be considered an index of tetrahedral distortion. This quotient ranges from ca. 105 to 135 cm for square-planar structures. In our case a value of 131 cm, at the high end of the range, was determined for the *f* factor. Moreover, on the basis of the relationship with the $g_{\|}$ value, the dihedral angle between chelate ring planes for our system was estimated around 60°. EPR data suggested a coordination of four nitrogens in a square planar environment tetrahedrically distorted, but the Cu^{II} ligands are normally arranged in an octahedral environment: four ligands lie close to the copper approximately in a plane including the cation and are strongly bonded;[30] the other two ligands are located on a straight line perpendicular to the plane and including the Cu^{II} ion. These ligands are much more weakly bonded than those in the plane and play only a minor role in both magnetic and optical properties of the copper complexes. We may, therefore, conclude that the complex **6a**−Cu^{II} is in a stoichiometric ratio 2:1 and in octahedral coordination with a tetrahedral distortion.

Molecular modeling studies excluded the existence of a stable 1:1 complex also for compound **6a**, in which steric clashes of the side chains with the flattened aromatic rings[16] caused the distortion of these groups, when the nitrogen atoms were arranged to converge on the cation. Different allowed coordination geometries were not found in this case.

Suggested by the EPR results and by the literature,[31−33] further calculations were performed to explore the possible complexation of one Cu^{II} cation by the functionalities of two resorcin[4]arenes. In vacuo MD simulations followed by energy minimizations on such trimolecular complex produced few possible coordination geometries, mostly octahedral, tetrahedral, and trigonal bipyramidal. In all these geometries the macrocycle **6a** can bind without strain three side chains with the copper ion. The generated structure of the trimolecular complex, in which the Cu^{II} presents a distorted octahedral geometry and four ligand nitrogen atoms are disposed approximately in a plane including the cation (Figure 2), was in accord with the results of EPR. The bond distances between Cu^{II} and the nitrogen atoms spread a range of 0.2 Å around the average value of 2.28 Å while the bond angles are homogeneously distributed between the values 79 and 101°.

Conclusions

The tetramerization with $BF_3 \cdot Et_2O$ of cinnamic acid derivatives was shown to be valid also for nitrile (*E*)-**1**, which gave the resorcin[4]arenes **2a** (cone conformation), **2b** (1,2-alternate conformation), and **2c** (1,3-alternate conformation), as a further demonstration of the versatility of the reaction. Conversely, the tetraamino derivative **6a** was prepared by modifications of the side functions starting from the available **3a**.[4]

The spectroscopic analysis of the interaction with Cu^{II} of calixarenes **2a**−**c** and **6a** was complicated by their low solubility, mainly after we realized that the use of mixtures of solvents (e.g. $CDCl_3$ vs CD_3CN) in NMR spectroscopy may lead to misleading results.

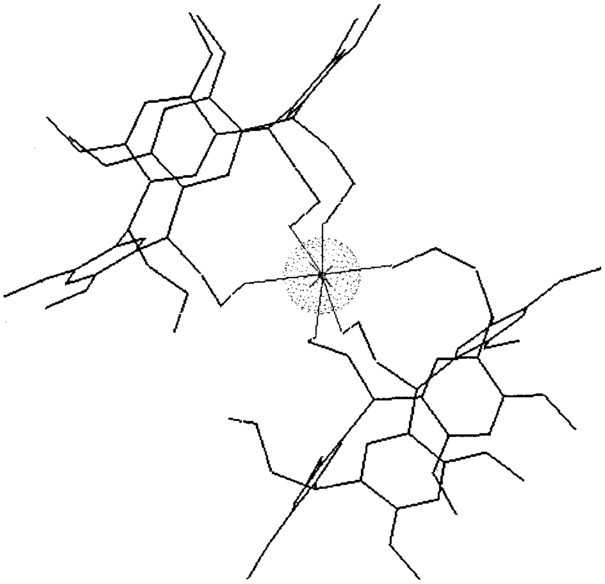

Figure 2. Geometry of the computer-calculated structure of the three-molecular complex of Cu^{II} with two molecules of compound **6a**, in which the ligands use their functionalities at the lower rim to coordinate the ion with distorted octahedral coordination in agreement with the EPR results.

However, diagnostic shifts of the signals for the CH_2-CN methylene in the ^1H NMR spectrum and of the molecular-ion peak in the FAB MS spectrum substantiated a possible interaction among the cyano groups of compound **2a** and the metal but no further information on the geometry of the complex.

The 1,2-alternate form showed no interaction with copper salts in NMR titration whereas no measurement was possible with the 1,3-alternate stereoisomer.

By contrast, the EPR spectrum showed not only a clear interaction between the macrocycle **6a** and the cation but also suggested an octahedrical geometry for the complex **6a**/Cu^{II}.

Computer calculations discarded the possibility of the formation of a 1:1 complex between Cu^{II} and the lower rim of resorcin[4]arenes, even when functions (CN, NH_2) suitable for the complexation were present. According to the EPR results, a trimolecular complex with a 2:1 stoichiometry in which two macrocycles coordinate the cation with a distorted octahedrical geometry appeared to be the most probable for compound **6a**.

Experimental Section

2-(2,4-Dimethoxyphenyl)acrylonitrile (1). To a solution of 2,4-dimethoxybenzaldehyde (1.0 g, 6 mmol) in absolute EtOH (20 mL) were added diethyl (cyanomethyl)phosphonate (1.27 g, 7.2 mmol) and anhydrous K_2CO_3 (2.5 g, 18 mmol). The reaction mixture was heated at reflux 1 h and poured into ice−water. Standard workup gave a residue, which was purified on silica gel with CH_2Cl_2−EtOAc, 95:5, to give the (*E*)- and the (*Z*)-isomers (ca. 3:2) of the title compound (1.08 g, overall 95% yield).

***r*-2,*c*-8,*c*-14,c-20-Tetrakis(cyanomethyl)pentacyclo[19.3.1.13.7]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19-(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol, Octamethyl Ether (2a)**. To a solution of (*E*)-2-(2,4-dimethoxyphenyl)acrylonitrile (**2**) (192 mg, 1 mmol) in $CHCl_3$ (5 mL) was added $BF_3 \cdot Et_2O$ (0.2 mL, 1.5 mmol), and the mixture was

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(30) Yokoi, H.; Addison, A. W. *Inorg. Chem.* **1977**, *6*, 1341.

(31) Della Lunga, G.; Basosi, R. *J. Magn. Reson. A* **1995**, *112*, 102−105.

(32) Pogni, R.; Della Lunga, G.; Basosi, R. *J. Am. Chem. Soc.* **1993**, *115*, 1546−1550.

(33) Della Lunga, G.; Pogni, R.; Basosi, R. *Mol. Phys.* **1998**, *95*, 1275−1278.

heated at reflux for 30 min, cooled, diluted with MeOH, and dried. The residue was purified on silica gel with CH_2Cl_2−*n*-hexanes−EtOAc, 85:10:5, gave the dimer **3** (12 mg), the isomeric tetramers **2b** (1,2-alternate, 29 mg, 12%) and **2c** (1,3-alternate, 23 mg, 15%), and the title compound **2a** (cone, 77 mg, 40%).

***r*-2,*c*-8,*c*-14,*c*-20-Tetrakis(azidomethyl)pentacyclo[19.3.1.13.7]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19-(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol, Octamethyl Ether (4a)**. To a solution of the tetrabromide **3a**[3] (324 mg, 0.316 mmol) in dry DMF (8 mL) was added NaN_3 (412 mg, 6.32 mmol), and the reaction mixture was stirred overnight at 65 °C, cooled, and added to a saturated aqueous solution of $NaHCO_3$. The solution was extracted with EtOAc (3 × 25 mL), and the combined organic layers were washed with brine and dried. The residue (yellow oil) was purified by silica gel column chromatography (CH_2Cl_2−*n*-hexane, 9:1) to give the title compound **4a** (180 mg, 65%) as a solid (mp: 191−2 °C).

***r*-2,*c*-8,*c*-14,*c*-20-Tetrakis(acetylaminonomethyl)-pentacyclo[19.3.1.13.7]octacosa-1(25),3,5,7(28), 9,11,13-(27),15,17,19(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol, Octamethyl Ether (5a)**. A suspension of compound **4a** (100 mg, 0.11 mmol) in CH_3COSH (0.2 mL) was stirred overnight at room temperature under N_2. The mixture was concentrated under vacuo, and the residue was treated with EtOAc (5 mL) to give a suspension which was filtered. The solid was purified by silica gel column chromatography ($CHCl_3$−MeOH, 95:5) to give the title compound **5a** (45 mg, 40%) as a vitreous solid.

***r*-2,*c*-8,*c*-14,*c*-20-Tetrakis(aminomethyl)pentacyclo-[19.3.1.13.7]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19-(26),21,23-dodecaen-4,6,10,12,16,18,22,24-octol, Octamethyl Ether (6a)**. To a solution of **5a** (25 mg, 0.027 mmol) in MeOH (1.5 mL) was added HCl (2N, 1.5 mL), and the mixture was held under reflux for 48 h. The reaction mixture was cooled and dried under vacuo. The residue was suspended in a 1:1 mixture (5.0 mL) of $CHCl_3$ and 10% Na_2CO_3 and stirred overnight. The organic layer was separated, and the aqueous solution was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried under vacuo to give the title compound **6a** (15 mg, 70%) as vitreous solid.

NMR Titrations. To a solution of **2a** (20 mmol in 0.8 mL) was added a solution of $CuCl_2$ (40 mmol in 1 mL of CD_3CN) portionwise (0.05 mL aliquots), and the ^{1}HNMR spectrum of the mixture was run at 70 °C 5 min after each addition. The procedure was repeated on substrates **2b** and **7**.

EPR Spectrum. The presence of the two isotopes of copper has been adequately taken into account by the simulation computer program.

The **6a**−Cu^{II} complex solution was prepared by starting from the stock solutions of $Cu(ClO_4)_2 \cdot 6H_2O$, 2×10^{-3} M, in THF and **6a,** 1×10^{-3} M, in THF. The starting solution of the ligand was dried and redissolved in the Cu^{II} solution. The metal−ligand molar ratio was 1:2, and the final concentration of the complex resulted as 1×10^{-3} M. Since the solution was turbid, it was dried again and redissolved in CH_2Cl_2 to give a clear yellow solution.

EPR spectrum was obtained with a Bruker 220D SRC X-band spectrometer. Microwave frequency was measured with an XL Microwave model 3120 counter. The spectrometer was interfaced with a PS/2 Technical Instruments Hardware computer, and the data were acquired using the CS-EPR data system produced by Stelar Inc., Mede (PV), Italy. The spectrum was preliminary corrected for baseline drift using a recently developed procedure.[32] The frozen solution EPR spectrum was simulated with program with minimization procedure discussed in previous reports.[33]

Molecular Modeling. All the computational work was carried out on Silicon Graphics workstation (Indigo Entry 4000 and O2). Molecular mechanics (MM) and dynamics (MD) calculations were performed by MSI Inc. softwares (version 95.0) InsightII and Discover. An update of the CVFF force field, successfully developed in our laboratories to model resorcin[4]arene-capped porphyrins and implemented in the 95.0 version of MSI software (unpublished results), was considered as the starting molecular mechanics force field.

The side chains of **8a** and **6a** were manually built by InsightII on the input geometries.[16] The input structure of the trimolecular complex **6a**−Cu^{II} was also manually built in InsightII locating one Cu^{II} ion approximately in the middle of the side chains of two facing local-minimum-energy conformers of the resorc[4]arene and minimized.

Since structures calculated with the IM method are extremely sensitive to the point charges assigned to the atoms, semiempirical molecular orbital calculations (MOPAC program and MNDO-ESP method) were performed on local-minimum-energy geometries of all the studied ligands to obtain accurate partial charges, which were used instead of the original CVFF charges. Conversely, to the Cu cation the full formal charge +2 was assigned, as usual for IM methodology.[22]

The van der Waals parameters of both the coordinating atoms of the ligands and the Cu^{II} cation were carefully readjusted by selecting the best values among those implemented in the force fields at our disposal.

The parameters used to describe the interactions between the Cu^{II} cation and the nitrogen atoms of **6a** are reported in Table 4, while in the case of **8a** default CVFF parameters were employed.

Throughout all calculations a dielectric constant $\epsilon = 1.0$ and a scale factor for the 1−4 vdW and the 1−4 electrostatic interactions were used.

MD simulations were performed at constant temperature (400 K) for 300 ps with a 1.0 fs time step. The high temperature was chosen to enhance the ability of the system to overcome high conformational energy barriers. A total of 150 geometries (one for each 2 ps) of each compound were generated: each geometry was then minimized with the Conjugate Gradients algorithm of MM until convergence (average derivative of 0.001 kcal mol^{-1} A^{-1}). The temperature equilibration time of the system was fixed in 2 ps. During the MD simulations the distances among Cu^{II} and appropriate atoms of the two resorcin[4]arenes were regulated by constraints which restricted the rotation freedom of the ligands and avoided the coordination of the cation by the partially negative charged oxygen atoms at the upper rim.

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Supporting Information Available: ^{1}H and ^{13}C NMR and MS spectral data for compounds **1** (*E*- and *Z*-forms)**, 3a**, **4a**, **5a**, and **6a**, ^{1}H NMR titration data with $CuCl_2$ (in CD_3CN) of resorcinarene **8a** (in $CDCl_3$) (Table S1), details on molecular modeling studies with a comparison between experimental and calculated values for selected geometric features of two Cu^{II} complexes with organic solvents (Table S2), an illustration of the interaction between **8a** and Cu^{II} by computer calculations (Figures S1 and S2 and structure files **8a**_upperrim.pdb and **8a**_lowerrimm.pdb), geometric details of the structure of the 1:1 complex at the lower rim **8a** /Cu^{II} compared with literature data (Table S3), and other geometries obtained from the minimization of the Cu^{II}/**6a** complex (Figure S3 and structure files **6a**_octahedric.pdb, **6a**_tetrahedric.pdb, **6a**_squareplan.pdb, and **6a**_bipitrig.pdb). This material is available free of charge via the Internet at http://pubs.acs.org.

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