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Template Synthesis of a Tetraaza Macrocycle Which Involves Benzaldehyde Rather Than Formaldehyde as a Building Block. Isolation and Structure Determination of the Open-Chain Schiff Base Intermediate Complex

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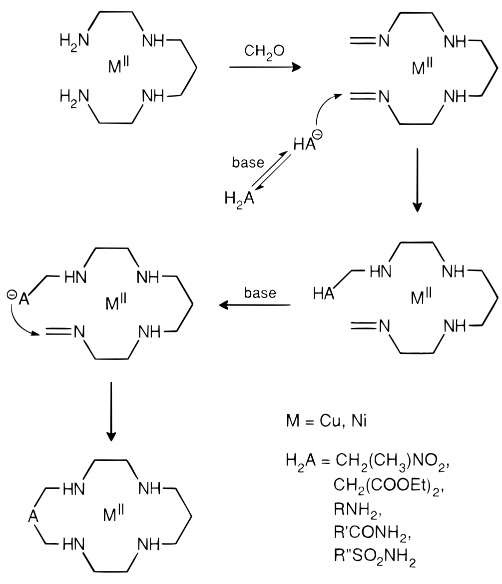
The classical formaldehyde building block has been replaced by the bulkier benzaldehyde in the Cu^{II} template synthesis of the cyclam-like tetraaza macrocycle of type **1**, in which nitroethane operated as locking fragment. The synthetic pathway involves three distinct steps: (i) Schiff base condensation of the metal-free open-chain tetramine; (ii) Cu^{II} coordination and preorientation of the Schiff base; (iii) nucleophilic attack by the deprotonated nitroethane fragment and formation of the macrocyclic complex. Both the Schiff base Cu^{II} complex and the Cu^{II} macrocyclic complex were isolated in a crystalline form and their molecular structures were determined: {*N*-[2-((*E*)-benzylideneamino)ethyl]-*N*′-[2-((*Z*)-benzylideneamino)ethyl]propane-1,3-diamine}copper(II) nitrate: triclinic, space group $P\bar{1}$, with $a = 12.296(5)$ Å, $b = 10.787(6)$ Å, $c = 10.547(7)$ Å, $V = 1161(1)$ Å^3, and $Z = 2$ ($R = 0.055$, $R_w = 0.061$); [(5*R*,6*S*,7*S*)-6-methyl-6-nitro-5,7-diphenyl-1,4,8,11-tetraazacyclotetradecane]copper(II) perchlorate: monoclinic, space group $P2_1/n$, with $a = 15.246(5)$ Å, $b = 23240(7)$ Å, $c = 8.540(4)$ Å, $V = 2980(2)$ Å^3, and $Z = 4$ (R $= 0.095$, $R_w = 0.095$). This allowed us to define mechanistic details of the macrocyclization process. It is suggested that the same three-step pathway takes place in the much easier and faster one-pot template syntheses of cyclam-like macrocyles, which involve formaldehyde as a building block.

Introduction

Template reactions lie at the heart of macrocyclic chemistry. In particular, the rich and lively topic of the coordination chemistry of synthetic macrocycles originated during the 1960s with the high-yield syntheses of cyclic tetraaza ligands, in which the Ni^{II} ion was employed as a templating agent.[1,2] Ni^{II} was chosen as, in its low-spin form, it imposes a square coordinative arrangement and preorientates the parent open-chain polyamine prior to the cyclization process, whose crucial step is a Schiff base condensation between a primary amine group and a carbonyl fragment. Also the Cu^{II} ion can act as a template in this type of reactions. However, Ni^{II} was usually preferred as, in contrast to Cu^{II}, it is not reduced during the subsequent hydrogenation of the C═N double bonds formed on cyclization and is also prone to a clean demetalation process by cyanide (if the free fully saturated macrocycle is desired).[3] In the following decade, many other template processes were discovered that made available a remarkable number of polyaza macrocycles of varying denticity and ring size.[4] During the 1980s, a further very versatile metal template preparation of tetraaza macrocycles was introduced,[5,6] whose pathway is illustrated in Scheme 1.

Scheme 1



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Like most template reactions of macrocyclic chemistry, the cyclization process shown in Scheme 1 is a one-pot procedure, which gives in good yield the metal complex. The templating ion can be either Cu^{II} or Ni^{II}, which preorientates the linear tetramine *N*,*N*′-bis(2-aminoethyl)propane-1,3-diamine (2.3.2-tet; homologous tetraamines 2.2.2-tet[6] and 3.2.3-tet[7] can be also used) according to a square coordinative arrangement. Following the proposed mechanism, first formaldehyde reacts with the terminal primary amine groups of the coordinated ligand.

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Then, an AH_2 fragment, which has a diprotic acid nature, undergoes stepwise deprotonation and gives consecutive nucleophilic attacks on the two C═N double bonds.[7-9] The first $\mathbf{AH_2}$ fragment employed was nitroethane, $CH_3\mathbf{CH_2}NO_2$,[5,6] a carbon acid of well-documented acidic tendencies ($pK_{A_1} = 8.6$).[10] Diethylmalonate, $C_2H_5OOC\mathbf{CH_2}COOC_2H_5$ ($pK_{A_1} = 13.3$)[10] was also successfully used.[7] As the AH_2 fragment firmly locks a chain encircling a (not too precious) object (the metal ion), it was named *padlock*. Further efficient *padlocks* include the following: primary amines ($R\mathbf{NH_2}$)[8,11] and primary amides (both carboxamides, $RCO\mathbf{NH_2}$, and sulfonamides, $RSO_2\mathbf{NH_2}$).[9,12] Noticeably, amine and amide locking fragments give rise to a pentaaza macrocycle. However, the added tertiary nitrogen atom does not show any coordinating tendency and plays a merely structural role within a cyclam-like four-coordinating framework. Kinetic studies have shown that the rate and the efficiency of the *padlock* decrease along the series nitroethane > sulfonamides > carboxamides > amines > diethyl malonate, which parallels the decreasing acidic tendencies.[9] Moreover, template procedures involving amide *padlocks* present a very useful feature: any functional group R can be appended to the quadridentate macrocyclic framework, provided that its RSO_2NH_2 or $RCONH_2$ derivative can be obtained. Following this approach, redox-active moieties (e.g. ferrocene)[13] or further ligating subunits (e.g. pyridine[14] or phenanthroline,[15] to give multimetal supramolecular coordination compounds) were prepared.

At this stage, we considered that a further functionalization of the tetraaza ring **1** could be achieved by using other aldehydes than formaldehyde. In particular, aromatic aldehydes may offer the opportunity to build up further versatile functionalization. We report here the high yield synthesis of a tetraaza ring of type **1**, in which Cu^{II} was used as a template, nitroethane was used as a *padlock*, and benzaldehyde was used as a condensating fragment. The determination of the crystal and molecular structures of both the open-chain Schiff base intermediate metal complex and of the macrocyclic compound allowed us to elucidate the mechanistic details of the cyclization process.

Experimental Section

Unless otherwise stated, commercial grade chemicals were used without further purification. Acetonitrile was distilled from CaH_2 under dinitrogen and stored over molecular sieves.

N,*N*′-Bis(2-aminoethyl)propane-1,3-diamine (2.3.2-tet) was prepared as described for the analogous tetramine 3.2.3-tet,[3] distilled at reduced pressure (125 °C; 5×10^{-2} Torr) and stored over NaOH in the refrigerator.

UV−vis spectra were taken on a Hewlett-Packard 8452A diode array spectrophotometer.

***N*,*N*′-Bis(2-(benzylideneamino)ethyl)propane-1,3-diamine, 5**, and ***N*,*N*′-bis[2-(2-nitrobenzylideneamino)ethyl]propane-1,3-diamine, 6.** The aromatic aldehyde (benzaldehyde or 2-nitrobenzaldehyde, 0.1 mol) was slowly added to a magnetically stirred solution of 2.3.2-tet (0.05 mol) in ethanol (30 cm^3). After 2 h, the solvent was distilled off under reduced pressure to obtain a viscous residue which was dried in a vacuum oven at 75 °C and used without further purification.

{*N*-[2-((*E*)-Benzylideneamino)ethyl]-*N*′-[2-((Z)-benzylideneamino)ethyl]propane-1,3-diamine}copper(II) Nitrate, $\mathbf{7(NO_3)_2}$. Triethylorthoformate (0.3 mol) and $Cu(NO_3)_2 \cdot 3H_2O$ (0.05 mol) were dissolved in dry acetonitrile (50 cm^3). The resulting solution was refluxed for 2 h and cooled to room temperature before adding ligand **5** (0.05 mol). The resulting mixture was first stirred for a few minutes, allowing complete dissolution, and then was left standing for 1 week during which the crystalline product precipitated; it was rapidly filtered at the pump, washed with diethyl ether, and dried in a vacuum oven at 50 °C. More product was obtained after reducing the volume of the mother liquor. Overall yield: 70%. Anal. Calcd for $C_{21}H_{28}CuN_6O_6$ (M_r 524.04): C, 48.13; H, 5.39; N, 16.04. Found: C, 48.28; H, 5.55; N, 16.19. UV−vis (MeCN, nm): 552 ($\epsilon = 117$).

[*N*,*N*′-Bis[2-(2-nitrobenzylideneamino)ethyl]propane-1,3-diamine]copper(II) Nitrate, $\mathbf{8(NO_3)_2}$. The complex was prepared as described for the analogous $\mathbf{7}(NO_3)_2$, using the diimino−diamine **6**. Yield: 57%. Anal. Calcd for $C_{21}H_{26}CuN_8O_{10}$ (M_r 582.03): C, 43.34; H, 4.5; N, 19.25. Found: C, 43.28; H, 4.55, N, 18.91.

[(5*R*,6*S*,7*S*)-6-Methyl-6-nitro-5,7-diphenyl-1,4,8,11-tetraazacyclotetradecane]copper(II) perchlorate, $\mathbf{3(ClO_4)_2}$. Nitroethane (0.02 mol), triethylamine (0.02 mol), and $\mathbf{7}(NO_3)_2$ (0.01 mol) were dissolved in dry acetonitrile (50 cm^3) in a stoppered bottle which was warmed in a thermostated bath at 50 °C for 2 h. After cooling to room temperature, the reaction mixture was treated with 1 M aqueous $HClO_4$ (50−100 cm^3) and the resulting red solution transferred into a wide beaker. Red needles formed on slow evaporation after a few days. The product was filtered by suction, washed with water and dried *in vacuo*. Yield: 76%. Anal. Calcd for $C_{23}H_{33}Cl_2CuN_5O_{10}$ (M_r 673.99): C, 40.99; H, 4.94; N, 10.39. Found: C, 40.57; H, 4.96; N, 10.12. UV−vis (DMF, nm): 528 ($\epsilon = 125$).

[6-Methyl-6-nitro-5,7-bis(2-nitrophenyl)-1,4,8,11-tetraaazacyclotetradecane]copper(II) Perchlorate, $\mathbf{4(ClO_4)_2}$. The complex was prepared according to the synthetic method described for the analogous $\mathbf{3}(ClO_4)_2$, using $\mathbf{8}(NO_3)_2$ as starting material. Yield: 20%. Anal. Calcd for $C_{23}H_{31}Cl_2CuN_7O_{14}$ (M_r 763.99): C, 36.16; H, 4.09; N, 12.83. Found: C, 36.48; H, 4.39; N, 13.09.

Safety Note. *Caution*! *Perchlorate salts are potentially explosive and should be handled with care. In particular, they should never be heated as solids.*[16]

Crystal Structure Determination of $\mathbf{7(NO_3)_2}$ and $\mathbf{3(ClO_4)_2}$. Crystals suitable for X-ray diffraction analysis were obtained by recrystallization from dry MeCN ([$\mathbf{7}(NO_3)_2$]) and from DMF/acetone ($\mathbf{3}(ClO_4)_2$). Single crystals of approximate dimensions 0.2 × 0.1 × 0.3 mm [$\mathbf{7}(NO_3)_2$] and 0.3 × 0.3 × 0.2 mm [$\mathbf{3}(ClO_4)_2$] suitable for X-ray diffraction measurements were mounted on glass fibers without protection from the air. The crystal data for both compounds are reported in Table 1 together with the most relevant experimental parameters used in the X-ray diffraction measurements and in the crystal structure analyses.

All the intensities were determined by profile analysis according to the Lehmann and Larsen procedure[17] and corrected for Lorentz and polarization effects. Data for the complex $\mathbf{3}(ClO_4)_2$ were corrected for absorption effects using ABSORB[18] after the last stage of the isotropic refinement. For each compound one standard reflection, collected every 100 reflections, showed no significant fluctuations.

The two structures were solved by Patterson method with SHELX86[19] and completed by successive Fourier syntheses using SHELX76.[20] In compound $\mathbf{3}(ClO_4)_2$, in addition to the two expected perchlorate anions, half of a DMF solvent molecule was also found for each cation unit. One of the two perchlorate anions was found statistically disordered over two different orientations with the chlorine atom in common. The DMF solvent molecule is statistically disordered, lying on a crystal-

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Table 1. Experimental Data for the X-ray Diffraction Studies

	7	**3**
formula	$C_{21}H_{28}CuN_6O_6$	$C_{24.5}H_{36.5}CuCl_2N_{5.5}O_{10.5}$
cryst syst	triclinic	monoclinic
space group	$P\bar{1}$	$P2_1/n$
cell params at 295K[a]		
a, Å	12.296(5)	15.246(5)
b, Å	10.787(6)	23.240(7)
c, Å	10.547(7)	8.540(4)
α, deg	108.59(2)	90.
β, deg	75.55(2)	99.97(2)
γ, deg	118.13(2)	90.
V, Å^3	1161(1)	2980(2)
Z	2	4
D_{calcd}, g cm^{-3}	1.499	1.584
mol wt	524.04	710.54
linear abs coeff, cm^{-1}	17.64	32.64
$F(000)$	546	1476
diffractometer	Siemens AED	Siemens AED
diffraction geometry	equatorial	equatorial
scan type	$\theta/2\theta$	$\theta/2\theta$
scan speed, deg/min	3−12	3−12
scan width, deg	*b*	*b*
radiation	Cu-Kα (1.54178 Å)	Cu-Kα (1.54178 Å)
2θ range, deg	6÷140	6÷140
reflcns measd	±h,±k,l	±h,k,l
tot. no. of data measd	4649	6237
criterion for obsn	$I \geq 4\sigma(I)$	$I \geq 2\sigma(I)$
no. of obsd data measd	3980	4789
no. of unique obsd data	3672	4469
agreement between equivalent obsd reflcns	0.08	0.04
no. of variables	419	438
max Δ/σ on last cycle	0.8	0.8
$R = \sum\lvert\Delta F\rvert/\sum\lvert F_o\rvert$	0.055	0.095
$R_w = \sum w^{1/2}\lvert\Delta F\rvert/\sum w^{1/2}\lvert F_o\rvert$	0.061	0.095
GOF = $[\sum w\lvert\Delta F\rvert^2/(\mathrm{NO} - \mathrm{NV})]^{1/2}$	2.6	2.8

[a] Unit cell parameters were obtained by least-squares analysis of the setting angles of 29 (**7**) and 30 (**3**) carefully centered reflections found in a random search on the reciprocal space. [b] $(\theta - 0.6) - [\theta + (0.6 + \Delta\theta)]°$; $\Delta\theta = (\lambda\alpha_2 - \lambda\alpha_1)\lambda^{-1} \tan\theta$.

lographic center of inversion which coincides with the midpoint of the NC(O) bond. The best fit of the disorder was obtained with three independent atoms treated as nitrogens.

The two structures were refined by full-matrix least-squares methods, first with isotropic and then with anisotropic atomic displacement parameters for all the non-hydrogen atoms. In **7**$(NO_3)_2$ all the hydrogen atoms were found in the final Fourier ΔF map and refined with isotropic displacement parameters. In **3**$(ClO_4)_2$, 20 hydrogen atoms of the complex cation were located in the final Fourier ΔF map and refined with a common isotropic displacement parameter whereas the remaining 13 ones were positioned on geometrical grounds (CH 0.96 Å) and refined "riding" on their corresponding C atoms with a common displacement parameter. The atomic fractional coordinates for compounds **7**$(NO_3)_2$ and **3**$(ClO_4)_2$ are listed in Tables 2 and 3, respectively.

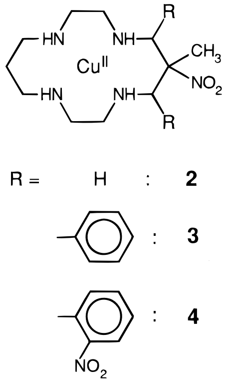
The atomic scattering factors of the non-hydrogen atoms were taken from Cromer and Waber,[21] the values of $\Delta f'$ and $\Delta f''$ were those of Cromer.[22] The geometrical calculations were obtained by PARST.[23]

All the crystallographic calculations were performed on the Gould Encore91 of the Centro di Studio per la Strutturistica Diffrattometrica del CNR Parma, Italy.

Results and Discussion

1. Using Formaldehyde as a Building Block.

Reaction of equimolar amounts of 2.3.2-tet, nitroethane, $Cu(NO_3)_2$ and a 10−20-fold excess of formaldehyde in methanolic solution at 50 °C, in presence of triethylamine as base, gives the macrocyclic complex **2** in good yield. Changing the solvent (water, MeCN, DMF) or operating at room temperature does not substantially change the yield of the reaction.



The reaction is typically carried out according to a one-pot mode. Reactants can be also added stepwise: notice that, in this case, the order of the addition is relevant. A favorable sequence involves the following: (i) dissolution (e.g. in water) of 2.3.2-tet and HCHO; (ii) addition of aqueous $Cu(NO_3)_2$ (the solution in a few minutes takes a blue color, $\lambda = 560$ nm, which corresponds to the Cu^{II} complex with the preformed Schiff base of 2.3.2-tet: $CH_2{=}N(CH_2)_2NH(CH_2)_3NH(CH_2)_2N{=}CH_2$); (iii) addition of nitroethane and triethylamine and heating at 50 °C for 48 h (the solution takes the red color, $\lambda = 524$ nm, of the tetraazamacrocyclic complex, which precipitates in good yield on addition of HNO_3 or on concentration.) A different order of addition prevents cyclization. In particular, if $Cu(NO_3)_2$ and 2.3.2-tet are added first, the solution takes the violet color ($\lambda =$ 535 nm) of the $[Cu^{II}(2.3.2\text{-tet})]^{2+}$ complex. Then, addition of

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Table 2. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters ($Å^2 \times 10^4$) with Esd's in Parentheses for the Non-Hydrogen Atoms of Compound **7**

	x/a	y/b	z/c	$U_{eq}{}^{a}$
Cu	2480(1)	2107(1)	2424(1)	504(2)
C(2)	3229(3)	4281(4)	5140(3)	541(15)
N(3)	2811(2)	3005(3)	4378(3)	496(12)
C(4)	2485(4)	1804(4)	4988(4)	560(16)
C(5)	3012(4)	802(4)	4028(4)	603(17)
N(6)	2562(3)	380(3)	2699(3)	548(13)
C(7)	3193(4)	−424(4)	1621(4)	691(21)
C(8)	2739(5)	−840(5)	273(5)	774(23)
C(9)	3093(4)	407(5)	−317(4)	679(20)
N(10)	2398(3)	1291(3)	446(3)	553(13)
C(11)	2753(4)	2560(5)	−85(4)	618(18)
C(12)	1863(4)	3216(5)	653(4)	617(19)
N(13)	1791(3)	3342(3)	2102(3)	493(12)
C(14)	1241(3)	4048(4)	2995(3)	519(14)
C(15)	3623(3)	5612(4)	4725(3)	520(14)
C(16)	3370(4)	6735(4)	5703(4)	657(17)
C(17)	3669(4)	7997(4)	5350(5)	736(20)
C(18)	4224(4)	8174(4)	4071(5)	730(20)
C(19)	4496(4)	7095(4)	3131(5)	694(19)
C(20)	4192(3)	5818(4)	3461(4)	592(16)
C(21)	620(3)	4856(4)	2818(3)	519(14)
C(22)	−123(4)	4391(5)	1811(4)	689(20)
C(23)	−680(5)	5187(6)	1710(4)	816(26)
C(24)	−466(4)	6519(5)	2596(5)	780(25)
C(25)	237(4)	6996(4)	3626(5)	708(19)
C(26)	775(3)	6164(4)	3751(4)	605(16)
N(1A)	5854(3)	3778(3)	1180(3)	605(15)
O(1A)	6578(3)	5024(4)	1664(3)	992(19)
O(2A)	4940(3)	3055(3)	1916(3)	819(16)
O(3A)	6083(5)	3269(5)	−17(4)	1356(30)
N(1B)	−572(3)	409(3)	2672(3)	620(14)
O(1B)	155(3)	546(3)	3381(3)	750(15)
O(2B)	−1461(4)	673(6)	3185(4)	1148(29)
O(3B)	−375(3)	34(5)	1431(4)	1215(24)

[a] Equivalent isotropic U defined as one-third of the trace of the orthogonalized $\mathbf{U}_{ij}$ tensor.

a 10−20-fold excess of formaldehyde does not induce any color change, indicating that the Schiff base condensation at the terminal primary amine groups of coordinated 2.3.2-tet does not occur. On further addition of base and nitroethane, the cyclization process does not take place. The described behavior does not fit the general reaction scheme outlined in Scheme 1 and would indicate that the amine−carbonyl condensation takes place on the uncomplexed tetramine and that the metal center binds and orientates the performed Schiff base in a conformation favorable to the attack by nitroethane. Unfortunately, we were not able to isolate and characterize any of the postulated intermediates (the Schiff base and/or its Cu^{II} complex). However, the above described findings give valuable insights on the reaction mechanism, which will be useful for the design of cyclization process, when aromatic aldehydes are involved.

Table 3. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters ($Å^2 \times 10^4$) with E.s.d.'s in Parentheses for the Non-Hydrogen Atoms of Compound **3**

	x/a	y/b	z/c	$U_{eq}{}^{a}$
Cu	2698(1)	2868(1)	1927(1)	402(3)
C(1)	1702(5)	4181(3)	1340(9)	466(25)
C(2)	2714(5)	4145(3)	1265(9)	445(24)
N(3)	2970(4)	3582(2)	705(7)	388(18)
C(4)	3942(5)	3552(4)	637(10)	467(26)
C(5)	4171(5)	2938(4)	368(10)	497(26)
N(6)	3905(4)	2586(3)	1672(7)	445(20)
C(7)	4028(6)	1963(3)	1434(11)	562(30)
C(8)	3755(7)	1616(4)	2760(13)	675(36)
C(9)	2760(7)	1605(4)	2776(13)	644(36)
N(10)	2433(4)	2175(3)	3197(8)	519(22)
C(11)	1462(5)	2175(4)	3143(11)	595(31)
C(12)	1154(6)	2782(4)	3392(11)	563(30)
N(13)	1477(4)	3163(3)	2189(7)	432(20)
C(14)	1434(5)	3785(3)	2630(9)	467(25)
C(15)	3055(6)	4650(4)	351(13)	647(35)
C(16)	2933(7)	4656(5)	−1294(14)	812(42)
C(17)	3275(9)	5110(7)	−2059(20)	1265(74)
C(18)	3721(11)	5552(7)	−1195(30)	1557(113)
C(19)	3875(11)	5533(6)	508(27)	1488(98)
C(20)	3522(7)	5099(4)	1211(17)	937(51)
C(21)	527(5)	3937(3)	3086(10)	499(27)
C(22)	524(6)	4183(3)	4565(11)	626(33)
C(23)	−274(8)	4324(4)	5031(14)	781(44)
C(24)	−1070(8)	4232(4)	4012(15)	822(46)
C(25)	−1065(7)	3978(6)	2622(14)	947(51)
C(26)	−271(6)	3821(5)	2118(12)	800(42)
C(27)	1108(6)	4130(4)	−280(10)	633(31)
N(28)	1587(5)	4791(3)	1993(11)	686(32)
O(29)	2025(5)	4904(3)	3297(10)	844(30)
O(3)	1081(6)	5118(3)	1218(11)	1072(38)
Cl(1)	3703(2)	3233(1)	5982(3)	760(9)
O(1A)	3735(8)	2631(4)	6096(10)	1381(52)
O(2A)	3532(5)	3395(3)	4372(7)	896(31)
O(3A)	4427(5)	3482(4)	6923(8)	1015(35)
O(4A)	2934(7)	3423(5)	6645(13)	1468(55)
Cl(2)	1393(2)	2343(2)	−1634(3)	988(13)
O(1B)	2163(5)	2233(5)	−424(10)	744(40)
O(2B)	605(5)	2369(6)	−880(13)	879(44)
O(3B)	1292(8)	1914(5)	−2849(13)	1422(71)
O(4B)	1500(9)	2909(4)	−2334(16)	1380(67)
O(1*)[b]	1166(10)	1778(4)	−1213(20)	2040(115)
O(2*)	733(7)	2718(6)	−1270(18)	1462(75)
O(3*)	2210(4)	2489(5)	−726(12)	663(34)
O(4*)	1420(9)	2354(8)	−3246(6)	1438(72)
N(1G)[c]	60(8)	215(3)	−550(8)	2523(77)
N(2G)	516(13)	719(4)	45(26)	2523(77)
N(3G)	173(26)	36(11)	−2096(19)	2593(77)

[a] Equivalent Isotropic U defined as one-third of the trace of the orthogonalized $\mathbf{U}_{ij}$ tensor. [b] Starred atoms are involved in static disorder. [c] Symmetry independent atoms of the disordered DMF solvent molecule.

2. Synthesis of the Cu^{II} Complex of the Schiff Base Derivative of 2.3.2-tet. We tried to replace formaldehyde with benzaldehyde in the cyclization reaction, following the one-pot approach. Mixing equimolar amounts of Cu^{2+}, 2.3.2-tet, nitroethane, and varying excesses of benzaldehyde and triethylamine in different solvents (methanol, MeCN, DMF), in the 20−60 °C temperature range, did not give rise to any cyclization process. In particular, the violet color ($\lambda = 530-540$ nm) of the $[Cu^{II}(2.3.2\text{-tet})]^{2+}$ complex persisted. Moreover, no improvement was obtained by extending the reaction time to days and weeks or by adding the reactants according to a consecutive mode and changing the addition sequence in any possible way. Thus, we not only decided to follow the stepwise approach outlined in the previous Section (Schiff base condensation of the free tetramine, binding to Cu^{II}, cyclization), but we tried also to isolate the intermediates (the Schiff base, its Cu^{II} complex) in a pure form and to characterize them.

First, on reaction of 2.3.2-tet with benzaldehyde in ethanol, the Schiff base **5** was obtained in good yield. It should be noted that **5** derivative could exist in three isomeric forms (*EE*, *EZ*, and *ZZ*; see Figure 1), but molecular mechanics modeling indicates that *EE* isomer is expected to form because of its higher stability. As the second step, we isolated the complex of the Schiff base, $\mathbf{7}(NO_3)_2$. Such a preparation had to be carried out under strictly anhydrous conditions. In particular, an MeCN solution of the hydrated metal salt, $Cu(NO_3)_2{\cdot}3H_2O$, was dehydrated by refluxing in presence of a 3-fold excess of triethyl orthoformate. Alternatively, a water free MeCN solution of $Cu(NO_3)_2$ could be obtained from anhydrous $CuBr_2$ and $AgNO_3$. Nitrate is required as counterion as it favors the precipitation of the complex salt. The complex $\mathbf{7}(NO_3)_2$ precipitated in good yield from a solution containing equimolar amounts of $Cu(NO_3)_2$

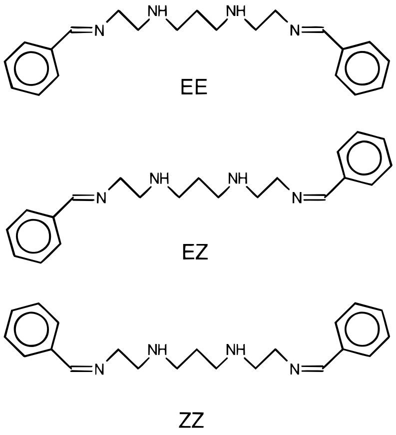

Figure 1. Three isomeric forms of **5**.

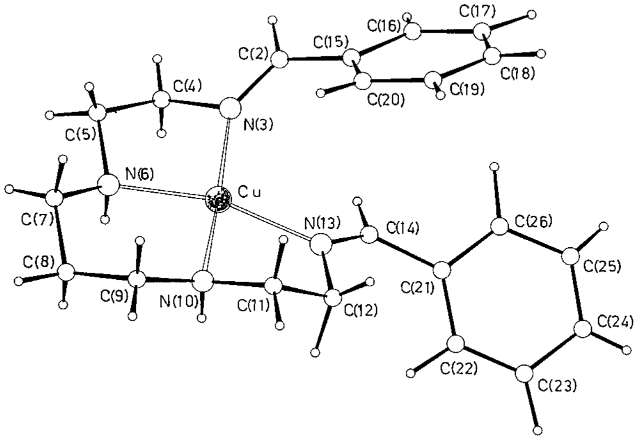

Figure 2. Perspective view of the complex cation **7**.

and of **5**, left at room temperature for 1 week. **7**$(NO_3)_2$ represents the first isolated and fully characterized complex of the Schiff base derivative of an open-chain tetramine.

3. Molecular Structure of the Cu^{II} Complex of the Schiff Base Derivative of 2.3.2-tet, 7$(NO_3)_2$. A perspective view of complex **7** is shown in Figure 2. The most significant bond distances and angles are given in Table 4. The table also reports significant structural parameters for the corresponding Cu^{II} tetraaza macrocyclic complex, to be discussed later. Complex **7** shows a planar coordinative arrangement, with a small tetrahedral distortion, as shown by the N–Cu–N angles. Noticeably, the N(3)–Cu–N(6) and N(6)–Cu–N(10) bond angles [85.0(1) and 93.4(1)°] are quite comparable with those found in the five- and six-membered rings, respectively, of the $[Cu^{II}(cyclam)]^{2+}$ complex,[24] which displays a regular square planar stereochemistry. On the other hand, the N(10)–Cu–N(13) bond angle of the other five-membered ring is significantly reduced [81.9(1)°]. The deviation of the N(3)–Cu–N(13) angle [102.1(1)°] from the theoretical value (90°) seems imposed by the steric hindrance of the bulky substituents of the imine nitrogen atoms, which also force the N–Cu–N angles involving opposite nitrogen atoms to the 160.5(1) and 172.3(1)° values. Also the Cu–N bond distances seem affected by a significant strain. In fact, in related macrocyclic systems containing both amine and imine nitrogen atoms, the M–N(amine) distance is always distinctly higher than the M–N(imine) distance.[25] On the contrary, in complex **7**, the Cu–N(10) bond [1.997(3) Å], which involves an sp^3 nitrogen atom, is remarkably shorter than all the other Cu–N distances, all closely comparable each other [2.025(1)–2.031(3) Å]. The two nitrate counterions are not coordinated to the metal center, as the long contacts Cu···O(2A) = 2.665(4) Å and Cu···O(1B) = 2.671(3) Å cannot be considered as bonding.

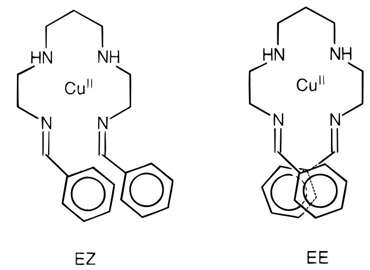

Figure 3. Sketch of complex **7** and of its hypothetical isomer in which the ligand **5** has maintained the EE configuration.

The six-membered ring adopts a flattened chair conformation, whereas *gauche* conformations are observed for both five-membered rings. However, the chelate ring containing the N(10) and N(13) atoms is remarkably more strained than that involving N(3) and N(6) atoms. Moreover, the two NH hydrogen atoms of each six-membered ring are *cis* with respect to each other, whereas the N(3)–C(2) and N(13)–C(14) bonds are *trans*. Indeed, because of their bulkiness, the two benzylidene groups are pushed to the opposite sides, with respect to the roughly planar N_4 donor set [C(2) and C(14) are almost symmetrically disposed above (by +0.634(4) Å) and below (by −0.790(4) Å) the N4 least-squares plane] and almost orthogonal to each other. In particular, the dihedral angle between the least-squares planes passing through the C(15)-to-C(20) and the C(21)-to-C(26) rings is 72.4(2)°.

Quite interestingly, one of the two phenyl rings, C(15)-to-C(20), lies in front of the coordinated ligand cavity, acting as an umbrella on the C(14)–N(13) double bond and perhaps exerting a sort of shielding effect on it. The other phenyl ring, C(21)-to-C(26), points out of the coordinating cavity and seems to play a role only in the molecular packing.

It should be finally noted that the Schiff base derivative **5**, when coordinated to the Cu^{II} center, exhibites an *EZ* configurates, and not the *EE* configuration which had been hypothesized on the basis of molecular mechanics evidence. On the other hand, molecular models suggest that the *EE* isomer would experience serious steric repulsive effects, when coordinated to a metal center according to a planar stereochemistry (as sketched in Figure 3).

It is possible that the thermodynamically favored *EE* to *EZ* configurational change takes place according to the mechanism illustrated in Figure 4, which involves the deprotonation of the imine nitrogen atom, followed by a tautomeric rearrangement. Such an acidic behavior, very disfavored for the uncomplexed derivative **5**, is enhanced by metal coordination. Moreover, the secondary amine nitrogen atoms of the metal-free ligand may act as basic sites and help the proton release.[26]

The complex **7**$(NO_3)_2$ is stable in anhydrous media (CH_2Cl_2, DMF, MeCN), as indicated by the persistence of the d–d absorption band centered at 550–560 nm, but undergoes rapid hydrolytic decomposition in solvents which had not been carefully dehydrated (alcohols, MeCN). In particular, in such media, the d–d band centered at 550–560 nm shifts to 530–540 nm, a band corresponding to the $[Cu^{II}(2.3.2\text{-tet})]^{2+}$ complex,

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(24) Tasker, P. A.; Sklar, L. *J. Cryst. Mol. Struct.* **1975**, *5*, 329.

(25) Heeg, M. J.; Endicott, J. F.; Glick, M. D.; Khalifa, M. A. *Acta Crystallogr.* **1982**, *B38*, 730.

(26) An alternative mechanism for the conversion of the *EE* isomer to the *EZ*, as suggested by one of the reviewers, could involve nucleophilic addition to the imine, followed by rotation about the N–C bond and subsequent elimination of nucleophile. It should be also considered the possibility that the various isomers are in rapid equilibrium in solution and that the *EZ* isomer is isolated because it forms the most stable solid.

Table 4. Selected Geometrical Parameters in Compounds **7** and **3**

Bond Distances (Å)

	7	**3**		**7**	**3**
Cu−N(3)	2.031(3)	2.041(5)	N(10)−C(11)	1.477(7)	1.473(10)
Cu−N(6)	2.025(4)	2.000(7)	C(11)−C(12)	1.503(8)	1.513(13)
Cu−N(10)	1.997(3)	2.021(7)	C(12)−N(13)	1.474(6)	1.502(12)
Cu−N(13)	2.026(5)	2.032(7)	N(13)−C(14)	1.279(5)	1.498(10)
C(2)−N(3)	1.280(4)	1.469(9)	C(14)−C(21)	1.476(7)	1.541(11)
C(2)−C(15)	1.458(6)	1.548(13)	C(1)−C(2)		1.558(11)
N(3)−C(4)	1.472(6)	1.495(10)	C(1)−C(14)		1.544(11)
C(4)−C(5)	1.500(6)	1.496(13)	C(1)−C(27)		1.521(11)
C(5)−N(6)	1.490(6)	1.493(11)	C(1)−N(28)		1.544(10)
N(6)−C(7)	1.487(6)	1.479(10)	N(28)−O(29)		1.224(11)
C(7)−C(8)	1.512(8)	1.506(14)	N(28)−O(30)		1.197(11)
C(8)−C(9)	1.494(8)	1.520(15)	Cu−O(2A)		2.561(6)
C(9)−N(10)	1.491(7)	1.481(12)	Cu−O(1B)		2.511(9)

Bond Angles (deg)

	7	**3**		**7**	**3**
N(10)−Cu−N(13)	81.9(1)	86.4(3)	N(10)−C(11)−C(12)	106.8(4)	109.3(7)
N(6)−Cu−N(13)	160.5(1)	179.4(3)	C(11)−C(12)−N(13)	107.6(3)	107.9(7)
N(6)−Cu−N(10)	93.4(1)	94.0(3)	Cu−N(13)−C(12)	111.7(3)	106.9(5)
N(3)−Cu−N(13)	102.1(1)	93.0(3)	C(12)−N(13)−C(14)	121.6(3)	111.3(6)
N(3)−Cu−N(10)	172.3(1)	178.3(2)	Cu−N(13)−C(14)	126.4(3)	115.7(5)
N(3)−Cu−N(6)	85.0(1)	86.5(3)	N(13)−C(14)−C(21)	129.2(4)	111.4(6)
N(3)−C(2)−C(15)	125.2(4)	112.3(6)	C(2)−C(15)−C(20)	124.0(3)	119.1(8)
Cu−N(3)−C(2)	136.7(3)	118.0(4)	C(2)−C(15)−C(16)	116.5(3)	121.4(9)
C(2)−N(3)−C(4)	116.7(3)	112.0(6)	C(14)−C(21)−C(26)	117.3(4)	122.9(7)
Cu−N(3)−C(4)	106.5(2)	105.8(5)	C(14)−C(21)−C(22)	124.6(4)	118.0(7)
N(3)−C(4)−C(5)	108.2(3)	108.0(6)	C(27)−C(1)−N(28)		108.2(7)
C(4)−C(5)−N(6)	108.1(3)	107.9(7)	C(14)−C(1)−N(28)		103.2(6)
Cu−N(6)−C(5)	108.2(2)	106.0(5)	C(14)−C(1)−C(27)		114.4(6)
C(5)−N(6)−C(7)	112.1(3)	112.1(6)	C(2)−C(1)−N(28)		103.8(6)
Cu−N(6)−C(7)	120.3(3)	118.5(5)	C(2)−C(1)−C(27)		113.3(7)
N(6)−C(7)−C(8)	111.8(3)	111.3(6)	C(2)−C(1)−C(14)		112.6(6)
C(7)−C(8)−C(9)	114.5(4)	115.0(9)	C(1)−C(2)−C(15)		113.7(6)
C(8)−C(9)−N(10)	111.6(4)	111.4(8)	C(1)−C(2)−N(3)		112.5(6)
Cu−N(10)−C(9)	119.3(2)	118.4(5)	C(1)−N(28)−O(29)		116.6(7)
C(9)−N(10)−C(11)	113.1(4)	111.8(7)	C(1)−N(28)−O(30)		119.1(7)
Cu−N(10)−C(11)	103.9(2)	106.0(5)	O(29)−N(28)−O(30)		124.4(9)

Intermolecular Hydrogen Bonds (Å and deg)

Compound **7**[a]

N(10)···O(3B)	3.052(5)	H(10)···O(3B)	2.32(5)	N(10)−H(10)−O(3B)	149(5)
N(10)···O(3B^{i})	3.074(6)	H(10)···O(3B^{i})	2.45(6)	N(10)−H(10)−O(3B^{i})	134(5)
C(2)···O(1A^{ii})	3.256(5)	H(2)···O(1A^{ii})	2.29(5)	C(2)−H(2)−O(1A^{ii})	175(4)

Compound **3**[b]

N(6)···O(2B^{i})	3.037(1)	H(6)···O(2B^{i})	2.10(8)	N(6)−H(6)−O(2B^{i})	148(7)
N(10)···O(1A)	3.081(11)	H(10)···O(1A)	2.15(6)	N(10)−H(10)−O(1A)	167(4)
N(13)···O(2*)	3.150(16)	H(13)···O(2*)	2.44(9)	N(13)−H(13)−O(2*)	154(9)

[a] (^{i}) $-x, -y, -z$; (^{ii}) $1 - x, 1 - y, 1 - z$. [b] (^{i}) $^{1}/_{2} + x, ^{1}/_{2} - y, ^{1}/_{2} + z$.

indicating complete hydrolysis of the two C═N double bonds. It is interesting to note that similar hydrolytic tendencies are not observed in the corresponding Cu^{II} complex of the Schiff base derivative of 2.3.2-tet and formaldehyde, which forms and lasts even in aqueous solution, as judged from the persistence of the band centered at 558 nm, but which we were not able to isolate.

4. The Cyclization Process. The diprotic carbon acid nitroethane was chosen as a *padlock* as it had shown the highest efficiency in closing Cu^{II} preoriented tetramines, in presence of formaldehyde building blocks. The cyclization of the fragment **7** was carried out in anhydrous MeCN solution, which contained equivalent amounts of **7**$(NO_3)_2$ and nitroethane and 2 equiv of triethylamine. After the mixture was heated for 2 h at 50 °C, $HClO_4$ was added to the brown solution, which turned immediately red. The red color corresponds to the Cu^{II} macrocyclic complex, which resists well the acid attack, due to the kinetic macrocyclic effect. On the other hand, all the other noncyclized material (the unreacted complex **7** and other unidentified products) is decomposed by the acid. On addition of water, the macrocyclic complex **3**$(NO_3)_2$ precipitates. The cyclization yield was 76%, which gives a total yield for the two step template reaction of 53% (=0.70 × 0.76 × 100). Quite interestingly, the cyclization process was also successfully carried out under phase-transfer conditions. In particular, a CH_2Cl_2 solution containing **7**$(NO_3)_2$, nitroethane and dibenzo-18-crown-6 was equilibrated with KOH pellets. In a few hours, the solution took the red color of the macrocyclic complex and was evaporated to give the **3**$(ClO_4)_2$ complex salt. On the other hand, replacing triethylamine with KOH, in the classical template reaction in presence of formaldehyde in aqueous or methanolic solution, prevents cyclization. Such a contrasting behavior may be ascribed to the fact that the solvated OH^- ion attacks the C═N double bond faster and more effectively than monodeprotonated nitroethane, causing hydrolysis. This effect is surprisingly not observed in the reaction in CH_2Cl_2. It is possible that in this poorly polar medium the OH^- ion is strongly bound to the crowned K^+ ion, which reduces its mobility and activity, preventing any competition with the nitroethane fragment.

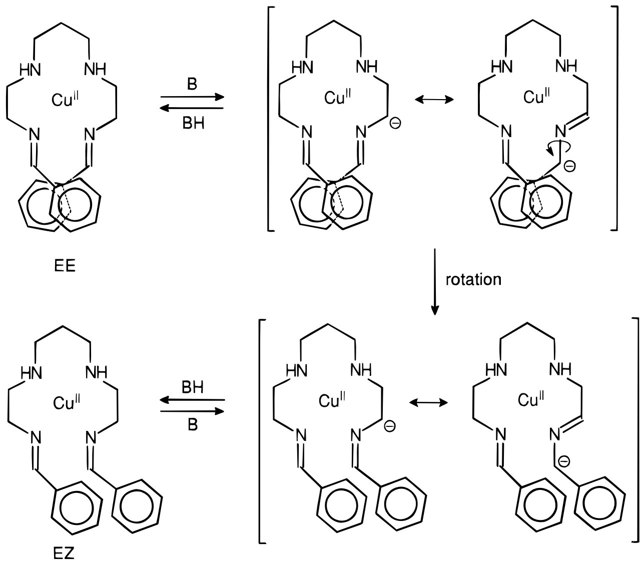


Figure 4. Proposed mechanism of isomerization of **5** from *EE* to *EZ* conformation when complexed to copper(II).

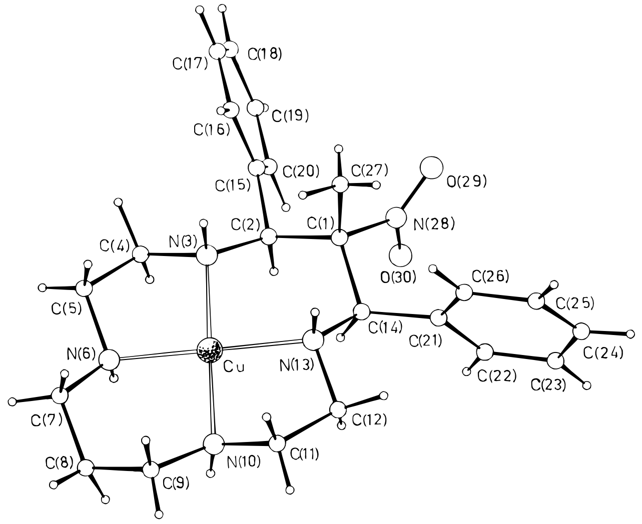
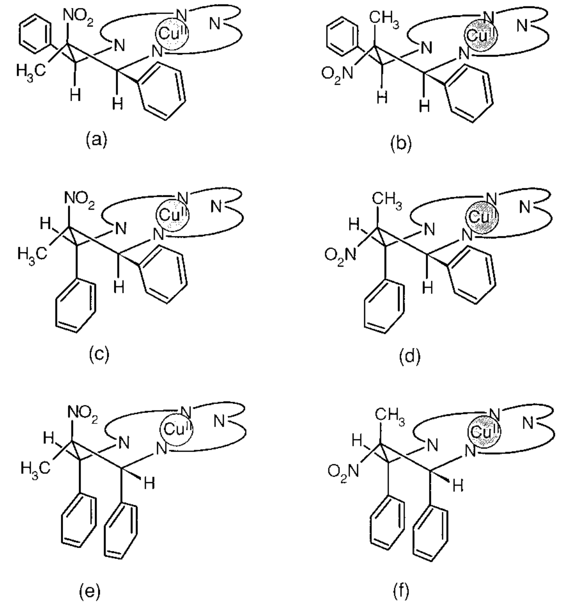


Figure 5. Perspective view of the complex cation **3**.

5. The Molecular Structure of the Macrocyclic Complex 3. The macrocyclic complex was isolated as the perchlorate, **3**$(ClO_4)_2$, through addition of perchloric acid to the reaction mixture. An ORTEP perspective view of the **3** complex is shown in Figure 5. Values of selected bond distances and angles are given in Table 4. The complex cation **3** consists of a cyclam-like system, in which one of the trimethylene chain possesses phenyl (2), methyl, and nitro substituents. The Cu^{II} cation is four-coordinated and lies on the N_4 plane, the deviation from the least-squares plane being only 0.017(1) Å. The average $Cu^{II}-N$ distance, 2.037(7) Å, and the average NCuN angles, 93.5(3) and 86.5(3)° in the six- and five-membered rings, respectively, are quite comparable with the values observed for analogous copper(II) tetramine complexes. If the two long contacts involving the metal center and the two *trans* perchlorate oxygen atoms [Cu−O(2A) = 2.561(6) Å and Cu−O(1B) = 2.511(9) Å] are considered, the Cu atom presents a slightly distorted octahedral geometry, whose axial Cu−O bonds deviate from the mean N_4 donor-set plane by angular values ranging from 3.5 to 7.8°.

Both five-membered rings show a *gauche* conformation, whereas both six-membered rings adopt a *flattened chair* conformation, with the two NH hydrogen atoms of the ring involving the N(6) and N(10) atoms below (as obesred in the corresponding fragment of the open-chain precursor **7**) and the two NH nitrogen atoms of the other ring above, with respect to the N_4 coordination plane. The very slight deformation of the torsion angles in the five- and six-membered chelate rings suggests that the macrocyclic framework of **3** is an unstrained cyclam-like system, very similar to that observed in the corresponding $[Cu^{II}(cyclam)]^{2+}$ complex.[24] More interestingly for mechanistic considerations (*vide infra*), in the substituted six-membered ring, which formed during the cyclization step, the nitro group and the two phenyl groups are all equatorial. The two phenyl groups are bent to each other by 68.3(4)°.

Chart 1



The most relevant differences of the common structural fragments of complexes **7** and **3** concern the benzylidene and the phenyl groups. In particular, the value of the torsion angle Cu−N(13)−C(14)−C(21), −169.9(5)°, in **3** is similar to that observed for the corresponding angle of **7** (−173.9(3)°). However, a remarkably different value is observed for the Cu−N(3)−C(2)−C(15) torsion angle of **3**, 173.5(5)°, to be compared with the 0.6(6)° value observed in **7**. Such a behavior will be fully accounted for, when the ring closure mechanism is discussed.

In Section 3, it has been pointed out that the benzylidene groups sterically disfavored axial coordination by the two nitrate groups in the complex **7**$(NO_3)_2$. On the other hand, in the compound **3**$(ClO_4)_2$, the two phenyl moieties are well away from the Cu^{II} axial coordination sites, making more room to accommodate the two perchlorate ions.

Finally, in both **7**$(NO_3)_2$ and **3**$(ClO_4)_2$ salts, N−H···O hydrogen bonds involving NH hydrogen atoms and oxygen atoms from counterions contribute to the crystal packing. Noticeably, in **7**$(NO_3)_2$ a quite strong C−H···O hydrogen bond involving the imine N(3)−C(2)−H(2) group and a neighboring nitrate oxygen atom has been observed: C(2)−H(2)···O(1A) $(1 - x, 1 - y, 1 = z)$ = 3.26(1) Å and H(2)···O(1A)$(1 - x, 1 - y, 1 - z)$ = 2.29(1) Å and C(2)−H(2)−O(1A)$(1 - x, 1 - y, 1 - z)$ = 175(4)°.

6. The Mechanism of the Cyclization Process. It should be noted that the macrocyclic complex **3** can give rise to *six* diastereoisomers (see Chart 1).[27] The crystal structure corresponds to isomer b. The comparison of the molecular structures of the complexes **7** and **3** (see Figures 2 and 5) indicates that some dramatic stereochemical changes take place in the course of the cyclization process. In particular, it appears that the most

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[27] A larger number of diastereoisomers are possible, if one considers the nitrogen stereocenters.

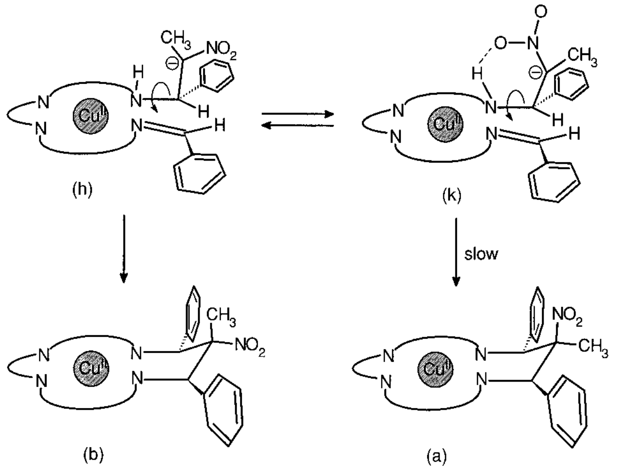
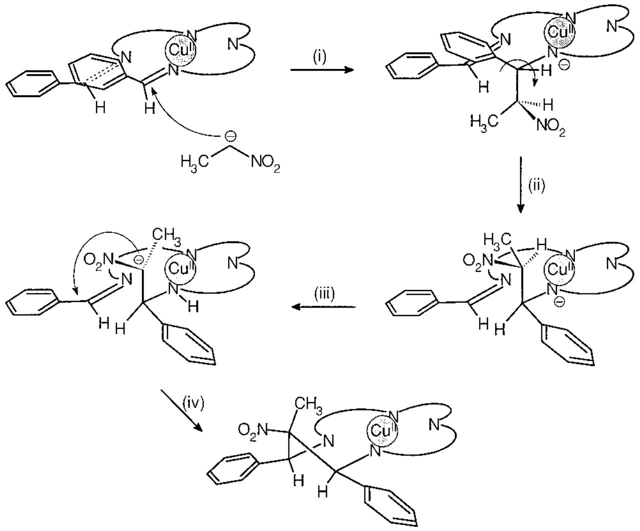


Figure 6. Possible pathways for the second nucleophylic attack from the bound *padlock* on the Schiff-base moiety, leading to different isomers of the macrocyclic complex **3**.

Scheme 2



serious modification has occurred at the benzylidene substituent on the N(3) atom of **7** and that the crucial step, from the point of view of stereochemical consequences, should be the nucleophilic attack of the *padlock* at the C(2)=(N3) double bond of **7**. The mechanistic sequence illustrated in Scheme 2 is proposed. It consists of the following steps: (i) the nucleophilic agent, deprotonated nitroethane, $CH_3\mathbf{CH}^-NO_2$, attacks the C(2) atom, from one side. The attack at the other double bond, C(12)=N(13) is sterically disfavored, as the C=N bond is protected by the C(15)-to-C(20) *umbrella*; (ii) the N(3)−C(2) σ bond rotates to make the bulky phenyl and nitro groups point outward, minimizing the steric repulsions; (iii) an intramolecular proton transfer process takes place from the acidic group of the bound nitroethane fragment to the proximate N(3) atom; (iv) the carbon atom of the attacking fragment now possesses a negative charge and is sp^2 hybridized. In particular, it can exists in two forms, h and k, which can rapidly interconvert (see Figure 6). The nucleophilic attack to the C(14) atom simply involves a further rotation around the N(3)−C(2) σ-bond. Noticeably, rotation of the carbanion fragment in the h form will put the methyl group in the axial position, whereas rotation in the k form will put the methyl group in the equatorial position. The "spherical" methyl group exerts greater sterical repulsions towards the phenyl groups than the planar nitro group. Such repulsions are larger when the substituent is in the equatorial rather than in the axial position. This would probably favor the formation of the isomer b.

The outlined synthetic pathway appears as rather complex and delicate. However, the macrocyclic complex that forms is robust and inert toward demetalation like metal complexes of cyclam analogues. For instance, it lasts intact for days in 96% H_2SO_4, as shown by the persistence of the absorption band centered at 526 nm.

7. Changing Fragments. The synthetic approach involving the preformed tetramine Schiff base was extended to other aldehydes: 4-nitrobenzaldehyde, 9-anthracencarbaldehyde, 1-ferrocenecarbaldehyde. In any case, the reaction of the envisaged aldehyde with 2.3.2-tet, according to a 2:1 stoichiometric ratio, in ethanolic solution, gave the corresponding Schiff base derivative. However, only in the case of the 4-nitrobenzaldehyde derivative we were able to isolate the Cu^{II} complex, which was successfully used to accomplish cyclization, according to the procedure described in the preceding sections. With the other aldehydes, we tried also the one-pot synthesis, using anhydrous reactants and solvents, but all attempts were unsuccessful. Our lack of success may depend on the severe repulsive effects exerted by the bulky substituents, which prevent strong metal coordination and effective template effect and, in any case, disfavor the approach of the nitroethane *padlock*.

Padlocks other than nitroethane were tested for the ring closure of **7**. However, only the other carbon acid diethylmalonate worked well (yield of the cyclization step: 70%, in DMF solution), whereas all the nitrogen containing acids (primary amines, carboxamides, sulfonamides) failed.

Finally, in contrast to analogous reactions involving formaldehyde and to most template reactions, Cu^{II} cannot be replaced by Ni^{II}. Any attempt involving Ni^{II} as a templating agent failed. This behavior may be ascribed to the fact that Ni^{II} forms less stable complexes with the tetramine Schiff base derivative than Cu^{II}, due to its less acidic nature and intrinsically lower binding tendencies.

Conclusions

Replacing the classical condensing fragment formaldehyde makes the synthesis of quadridentate macrocycles of type **1** definitively more difficult. In particular, only the more acidic templating cation (Cu^{II}) and the more efficient *padlocks* (the carbon acids nitroethane and diethylmalonate) give successful cyclization, through several distinct steps, under anhydrous conditions. This behavior should be mainly ascribed to the serious steric effects generated by the bulky aromatic aldehyde, which make the intermediate species less thermodynamically stable and the overall reaction kinetically more difficult (in particular, the nucleophilic attack by the deprotonated *padlock* to the C=N double bond). However, it is just the benzaldehyde bulky nature that favors the isolation of the intermediate species **7** and allows one to *freeze* the synthesis at its crucial point and to detail unequivocally the mechanistic features of the macrocyclization process. It is suggested that the sequence defined in presence of benzaldehyde—(i) Schiff base condensation on the metal-free tetramine, (ii) metal coordination, and (iii) attack by the deprotonated H_2A fragment—should take place, more easily and at a faster rate, also in the one-pot procedure performed in the presence of formaldehyde and in an aqueous medium.

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Supporting Information Available: Lists of the atomic coordinates of the H atoms, complete atomic displacement parameters, and bond distances and angles for **3** and **7** (9 pages). Ordering information is given on any current masthead page.

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