

Structural Properties of Cyclopentanone-Bridged Bis-Macrocyclic Ligand Dicopper(II) Complexes in the Solid and in Solution: A Successful Test of the MM-EPR Method

Peter Comba,^{*,†} Marion Kerscher,[†] Yaroslav D. Lampeka,^{*,‡} Lutz Lötzbeyer,[†] Hans Pritzkow,[†] and Lyudmyla V. Tsymbal[‡]

Anorganisch-Chemisches Institut der Universität Heidelberg, INF 270, D-69120 Heidelberg, Germany, and National Academy of Sciences of the Ukraine L. V. Piszarshevsky Institute of Physical Chemistry, Kiev, Ukraine

Received December 13, 2002

The copper(II)-assisted condensation of 2,3,2-tet (3,7-diazanonane-1,9-diamine) with formaldehyde and cyclopentanone yields the mono- and bis-macrocyclic Mannich condensation products L^1 and L^2 , as well as the Schiff-base product L^3 , all with cyclam-type tetraaza macrocycles, coordinated to copper(II). The combination of molecular mechanics and EPR spectroscopy (MM-EPR) reveals that all three isomers of $[Cu_2(L^i)(OH_2)_n]^{2+}$ ($n = 0-4$), with the expected trans-III (R,R,S,S) configuration of the 14-membered tetraaza macrocycles, are of similar stability, and that the isomer whose structure is solved by X-ray crystallography has a different structure in solution.

The theory to simulate EPR spectra of dipole–dipole-coupled dicopper(II) compounds has been known since the 1970s,¹ and EPR constrained molecular mechanics (MM-EPR)² was developed a decade ago to solve solution structures of dipole–dipole-coupled paramagnetic centers. Stochastic searching of the conformational space of coordination complexes³ and the new EPR simulation technology XSophe,^{4,5} which allows the simulation of spectra with spin Hamiltonian parameters which represent the chromophore alone (i.e., the electronic parameters for structurally conserved mono- and dinuclear sites are identical), have greatly enhanced the power of MM-EPR.⁶ In all examples where MM-EPR was used so far, the crystal and solution structures

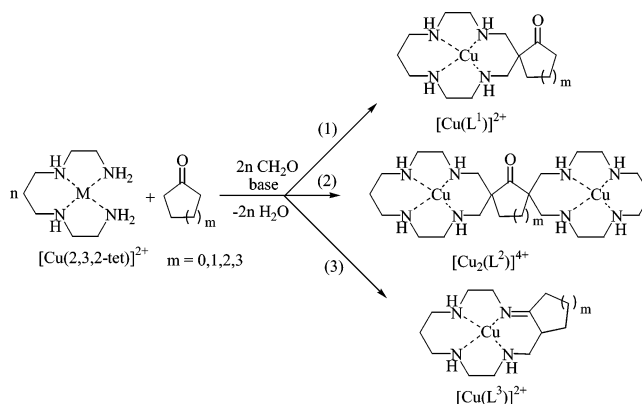
* Authors to whom correspondence should be addressed. P.C.: comba@akcomba.oci.uni-heidelberg.de (e-mail); (fax) ++49-6221-546617.

[†] Anorganisch-Chemisches Institut der Universität Heidelberg.

[‡] National Academy of Sciences of the Ukraine L. V. Piszarshevsky Institute of Physical Chemistry.

- (1) Smith, T. D.; Pilbrow, J. R. *Coord. Chem. Rev.* **1974**, *13*, 173.
- (2) Bernhardt, P. V.; Comba, P.; Hambley, T. W.; Massoud, S. S.; Stebler, S. *Inorg. Chem.* **1992**, *31*, 2644.
- (3) Bartol, J.; Comba, P.; Melter, M.; Zimmer, M. *J. Comput. Chem.* **1999**, *20*, 1549.
- (4) Wang, D.; Hanson, G. R. *J. Magn. Reson. A* **1995**, *117*, 1.
- (5) Wang, D.; Hanson, G. R. *Appl. Magn. Reson.* **1996**, *11*, 401.
- (6) Bernhardt, P. V.; Comba, P.; Fairlie, D. P.; Gahan, L. A.; Hanson, G. R.; Lötzbeyer, L. *Chem. Eur. J.* **2002**, *8*, 1527.

Scheme 1



were within the error limit identical^{2,7,8} or the solid state structures were unknown.^{6,9,10} We now present an example where the solution structure is strikingly different from that determined by single-crystal X-ray diffraction. Moreover, the dinuclear complex presented here exists in three stable configurations, and it was only due to the frozen solution EPR spectra that these were detected. MM-EPR allowed the unambiguous determination of all three solution structures.

Cyclic alkanones are attractive substrates for the metal-assisted synthesis of tetraazamacrocyclic ligands since, under similar conditions, with cis-disposed coordinated primary amines and in the presence of formaldehyde and base, they produce mono- (L^1) and bis-macrocyclic (L^2) Mannich-type condensation products, as well as Schiff-base (L^3) complexes (Scheme 1). The total yield of macrocyclic ligand products is up to approximately 40%. The ratio of products based on L^1 , L^2 , L^3 depends primarily on the cycloalkanone precursor

- (7) Comba, P.; Hilfenhaus, P. *J. Chem. Soc., Dalton Trans.* **1995**, 3269.
- (8) Comba, P.; Gavriš, S. P.; Hay, R. W.; Hilfenhaus, P.; Lampeka, Y. D.; Lightfoot, P.; Peters, A. *Inorg. Chem.* **1999**, *38*, 1416.
- (9) Comba, P.; Hambley, T. W.; Hilfenhaus, P.; Richens, D. T. *J. Chem. Soc., Dalton Trans.* **1996**, 533.
- (10) Comba, P.; Cusack, R.; Fairlie, D. P.; Gahan, L. R.; Hanson, G. R.; Kazmaier, U.; Ramlow, A. *Inorg. Chem.* **1998**, *37*, 6721.

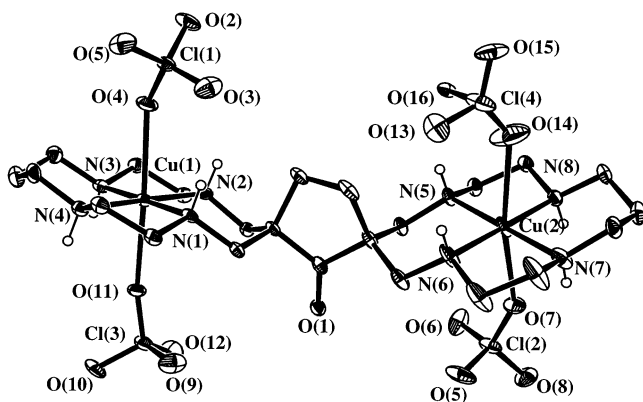


Figure 1. ORTEP¹⁵ plot of $[\text{Cu}_2(\text{L}^{2,m=1})(\text{ClO}_3)_4] \cdot 2\text{H}_2\text{O}$: Cu(1)–N(1) 2.013(3), Cu(1)–N(2) 2.027(4), Cu(1)–N(3) 2.014(3), Cu(1)–N(4) 2.020(4), Cu(2)–N(5) 2.012(4), Cu(2)–N(6) 2.018(4), Cu(2)–N(7) 2.012(5), Cu(2)–N(8) 2.013(4), Cu(1)–O(4) 2.496(4), Cu(1)–O(11) 2.490(4), Cu(2)–O(7) 2.414(5), Cu(2)–O(14) 2.643(5), Cu(1)···Cu(2) 9.19, Å.

Table 1. Structural Parameters of the Four Stable Isomers of $[\text{Cu}_2(\text{L}^2)(\text{X})_m]^{m+}$

structure ^a	$r,^{b,c}$ Å	chi1/2, ^{b,c} deg	rho1/2, ^{b,c} deg	rho2, ^{b,c} deg
b	9.2 (9.2; 9.2)	– (90; 88)	– (49; 49)	– (14; 19)
c	8.9 (8.9; –)	72 (72; –)	48 (44; –)	39.5 (34; –)
d	7.5 (7.95; –)	58 (58; –)	47 (44; –)	68.5 (67; –)
e	7.7 (7.7; –)	75 (76; –)	50 (49; –)	88 (64; –) ^d

^a See Figure 2. ^b MM-EPR (MM; X-ray). ^c r is the distance between Cu1 and Cu2; chi1/2 is the angle between the z -axis of Cu1 and the Cu1–Cu2 vector; rho1/2 is the angle between the x -axis of Cu1 and the Cu1–Cu2 vector, transformed to the x,y -plane of Cu1; rho2 is the angle between the two x,y -planes of Cu1, Cu2. ^d The other Euler angles of the second site (chi2, tau) are -4.5° , -0.1° .

(cyclobutanone, -pentanone, -hexanone, and -heptanone have been used so far¹¹) and on the ratio of the copper(II) tetraamine and cycloalkanone substrates. The product complexes obtained with the cyclopentanone capping group ($m = 1$ in Scheme 1) were used for the structural studies presented here (see Supporting Information for details).

The single-crystal molecular structure of $[\text{Cu}(\text{L}^1)(\text{solvent})_2] \cdot 2\text{H}_2\text{O}$ is shown in Figure 1. The macrocyclic subunits are in the expected trans-III configuration (R,R,S,S), with all six-membered chelate rings in chair and the five-membered chelates in $\lambda\delta$ conformations (molecular mechanics, for details see Supporting Information). All four amine protons of the two bridged six-membered rings are oriented anti to the cyclopentanone carbonyl group. The structural parameters of the chromophore are as expected,¹² and the two CuN_4 least squares planes ($\text{rms} \leq 0.01$ Å) are nearly coplanar ($\phi = 19.1^\circ$, angle between the two planes) with a $\text{Cu} \cdots \text{Cu}$ distance of 9.19 Å.

The frozen solution EPR spectrum of $[\text{Cu}(\text{L}^1)(\text{solvent})_2]^{2+}$ was recorded to determine the g and A parameters of the $\text{Cu}^{\text{II}}(\text{L}^{1,2})$ chromophores. The spectrum and its simulation are presented in Figure 2a (g and A values in the figure caption). Also shown in Figure 2a is the calculated structure (molecular mechanics, see Supporting Information for details) of $[\text{Cu}(\text{L}^1)(\text{OH}_2)_2]^{2+}$ (note that this is one of several

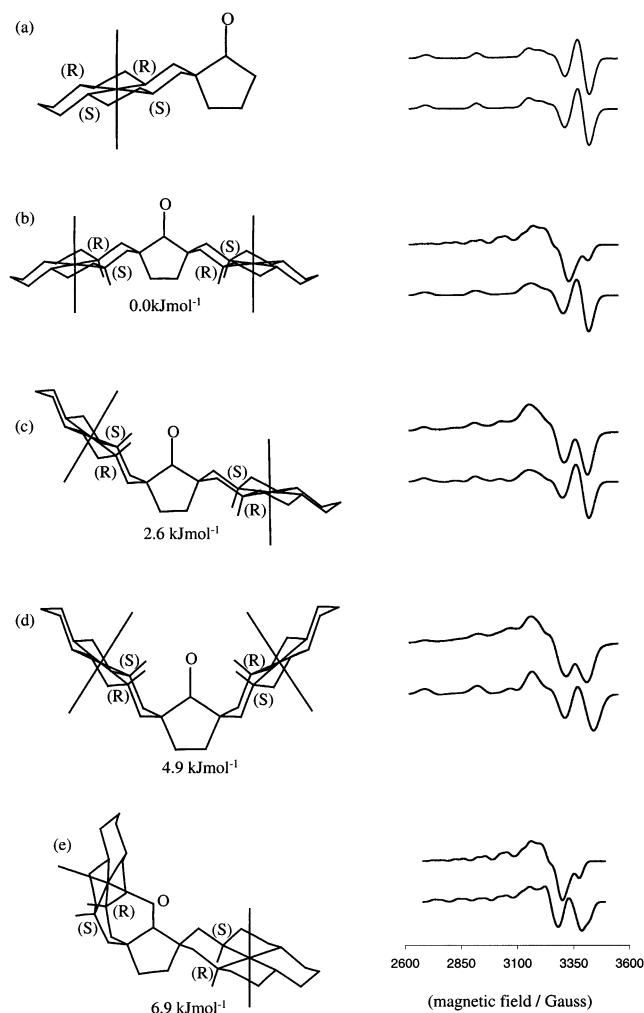


Figure 2. Computed structures and relative strain energies (optimization of the 6-coordinate chromophores, removal of the axial donors, single-point calculation of the resulting structures) of (a) $[\text{Cu}(\text{L}^{1,m=1})(\text{OH}_2)_2]^{2+}$, (b–d) the three possible $(R,R,S,S)_2$ configurations of $[\text{Cu}_2(\text{L}^{2,m=1})(\text{OH}_2)_2]^{4+}$ (most stable conformers; chair/chair, λ/δ), and (e) the corresponding observed (top) and simulated (bottom) EPR spectra ($\text{DMF}/\text{H}_2\text{O} = 2:1$, liq. N_2 , identical magnetic field axis for all spectra; for structural parameters for the simulation, see Table 1, g and A parameters (g_{\perp} , g_{\parallel} , A_{\perp} , A_{\parallel} in 10^{-4} cm^{-1}); microwave frequency in GHz: (a) 2.045, 2.190, 23, 200; 9.473; (b) g and A parameters as in part a; 9.316; (c) g and A parameters as in part a; 9.311; (d) 2.045, 2.185, 23, 205; 9.314; (e) 2.045, 2.185, 23, 205; 2.045, 2.130, 19, 180 (two sites); 9.316; natural isotope distribution, g - and A -strain Gaussian line shape model).

possible isomers, i.e., that derived from the X-ray structure of the dinuclear compound, see below); the structural parameters of the chromophore are close to identical to those of the X-ray crystal structure of $[\text{Cu}_2(\text{L}^2)(\text{OCIO}_3)_4]$ ($\text{Cu}-\text{N}_{\text{MM,av}} = 2.020 \pm 0.002$ Å, $\text{Cu}-\text{N}_{\text{Xray,av}} = 2.016 \pm 0.005$ Å). The well-resolved experimental EPR spectrum of the dinuclear compound (Figure 2b, same fraction as that used for crystallography) is very different from that of the mononuclear complex. However, the simulation of the spectrum, using the g and A values of the parent mononuclear chromophore (see Figure 2a), as well as the structural parameters from the crystal structure (shown in Figure 2b is the computed structure, MM, which is within the error limit identical) does not lead to agreement with the experimental spectrum (small changes of the structural and/or electronic

(11) Comba, P.; Lampeka, Y. D.; Tsybal, L. V. Work in progress.
(12) Boeyens, J. C. A.; Dobson, S. M. In *Stereochemical and Stereophysical Behaviour of Macrocycles*; Bernal, I., Ed.; Elsevier: Amsterdam, New York, 1987; p 1.

parameters do not lead to any notable improvement; note that the “missing” signals at around 2850/3050 G appear with changes of structural parameters but not in the observed intensity ratios, and not as “doublets”). This simulated spectrum is basically identical to that of the mononuclear chromophore (see Figure 2a,b). The experimental EPR spectra of two other fractions of the dinuclear species (fractional crystallization of the eluate from the ion exchange chromatography) are different from that of the X-ray fraction, see Figure 2c,d.

A combination of deterministic and stochastic searching³ was used to find structural models for the simulation of the three dipole–dipole-coupled EPR spectra (4-, 5- and 6-coordinate chromophores were modeled; presented here are the 6-coordinate structures). The three lowest energy optimized structures (see Figure 2b–d and Table 1) all have trans-III configuration of the macrocycles and chair/ $\lambda\delta$ conformation of the chelate rings. These are close to degenerate (other isomers are significantly higher in energy) and should coexist after the template synthesis. They differ by the relative orientation of the amine protons of the capped six-membered chelate rings (syn or anti to the pentanone carbonyl oxygen, see Figure 2b–d). Note that isomer interconversion involves bond breaking and is not expected to occur in neutral aqueous or H₂O/DMF solution (solvent used for the EPR spectra). Simulation of the EPR spectra with g and A values constrained to those of the mononuclear complex and structural parameters of configurations c and d lead to good agreement with the observed spectra of the fractions not analyzed by crystallography (see Figure 2c,d and Table 1).

A number of slightly higher energy structures have six-membered chelate rings in the boat conformation, especially when 4- or 5-coordinate copper centers (dissociated axial ligands) are modeled. Structure e in Figure 2 is an example, and this is the result of a simple conformational transformation from structure b (chair/boat transformation of one six-membered chelate ring; one axial water has been removed and replaced by the carbonyl oxygen of cyclopentanone). Simulation of the EPR spectrum of this structure (see Table 2) with the usual electronic parameters leads to a spectrum similar to that observed, see Figure 2e. Admittedly, the agreement between the calculated and experimental spectra is less than perfect. While the positions of the transitions are acceptable, there are some deficiencies with respect to the intensities of some lines. One reason is that in the currently available version of Sophe the parameter adjustment has to be done manually, and this involves (for the asymmetrical structure e) two sets of g and A parameters and the corresponding Euler angles, the Cu···Cu distance, and a set of line shape parameters.¹³ However, the simulated spectrum

e is based on a chemically reasonable structural model and on two sets of g and A parameters which are identical to those of the mononuclear chromophore or deviate from it by small amounts and in the predicted direction (distortion of one of the chromophores). Also, other chemically reasonable sets of structural and electronic parameters do not lead to simulated spectra which are similar to that observed experimentally.

An interesting question is why structure b is transformed to e in solution. The small but significant distortion of one of the copper(II) chromophores suggests that the folding of the structure leads to some strain (6.9 kJ mol⁻¹, based on our molecular mechanics analysis). This is compensated by a favorable entropy term (release of one axial water, which is replaced by the carbonyl oxygen of the pentanone spacer). The question then is why there is no analogous conformational change in the other case, structure c, where a chair–boat flip might lead to a copper–carbonyl–oxygen interaction (the simulated spectrum of this structure is very different from all experimental spectra, see Supporting Information). The corresponding computed structure has a Cu···Cu distance of 5.9 Å (vs 7.7 in structure e). A qualitative calculation of the electrostatic repulsion (charge distribution and partial neutralization by ion-pairing were assumed as before⁷) indicates that the folded structure derived from c is disfavored by at least 10 kJ mol⁻¹ with respect to structure e.

In conclusion, we have presented an example where EPR spectroscopy alone was able to detect three different configurations of a dicopper(II) complex. MM-EPR was used to unambiguously assign them, and to find that the structure of one of these configurations, i.e., that determined by X-ray crystallography, is different in solution and in the solid. The conformation in solution probably is slightly higher in energy; distortion of the planar chromophore and electrostatic repulsion destabilize it. However, it is favored entropically (loss of an axial water, axial coordination of the pentanone carbonyl group). The structural results presented here unequivocally relativate the recent comment on a structure determination by a methodologically similar method (MM-AOM)¹⁴ that “in an ideal world the structure determination by the combination of molecular mechanics with spectroscopy should be proven with an X-ray structure”.

Acknowledgment. Financial support by the German Science Foundation (DFG) and the Department of Fundamental Research of the Ministry for Education and Science of Ukraine is gratefully acknowledged.

Supporting Information Available: Experimental details (syntheses, crystallography, molecular mechanics, as well as the simulated EPR spectrum of the folded form of structure c). This material is available free of charge via the Internet at <http://pubs.acs.org>.

IC026265R

(13) Depending on the line shape model used and the copper isotope distribution, the simulation of a spectrum needs approximately 10–20 min (AMD Athlon 900 MHz processor, 128 MB memory, matrix diagonalization, 25/5 field segments). Also, the structural model with the copper–carbonyl–oxygen interaction is not based on a well-refined force field and, as in other examples using MM-EPR, solvation has not been included.

(14) Comba, P.; Pritzkow, H.; Schiek, W. *Angew. Chem.* **2001**, *113*, 2556.
(15) Johnson, C. K. *ORTEP: A Thermal Ellipsoid Plotting Program*; Oak Ridge National Laboratory: Oak Ridge, TN, 1965.