

Crystal and Molecular Structure of the [6-Deoxy-6-[(2-(4-imidazolyl)ethyl)amino]-cyclomaltoheptaose]copper(II) Ternary Complex with L-Tryptophanate. Role of Weak Forces in the Chiral Recognition Process Assisted by a Metallocyclodextrin

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The ternary copper(II) complex of 6-deoxy-6-[(2-(4-imidazolyl)ethyl)amino]cyclomaltoheptaose (CDhm) and L-tryptophanate (L-TrpO⁻) was characterized by ESR and X-ray diffraction. The solid state structure of [Cu(CDhm)(L-TrpO)]⁺ shows that the aromatic side chain of TrpO⁻ is outside the cavity and that the two amino nitrogen atoms, one from the histamine molecule and one from the amino acidate, are in a cis disposition. The two amino nitrogens, the imidazole nitrogen, and the carboxylate oxygen atoms form the base of a square pyramid, which surrounds the copper(II) ion, a water molecule occupying an apical position. Atomic distances suggest for this complex that π - π and d- π interactions could occur in the solid state. Moreover, the [Cu(CDhm)(L-TrpO)]⁺ has a self-assembled structure in which a CDhm molecule behaves as host and as guest. The imidazole and the indole ring are directed into the cavity of an adjacent CDhm molecule from the wider cyclodextrin rim, thus forming a polymeric column structure. ESR spectra were run on the copper(II) ternary complexes with L- or D-tryptophanate and L- or D-alanine in frozen aqueous solution and on the former pair of enantiomers in the solid state, as well. While in the case of the ternary complex with L- or D-alanine no differences are observed in their frozen solution spectra, in the case of complexes with TrpO⁻ subtle differences are found. These differences, which disappear when excess methanol is used, are ascribed to the presence of weak forces, such as hydrophobic or d- π interactions.

Introduction

The appreciation of the influence of intermolecular weak forces (i.e. hydrogen bonding, van der Waals attractive forces, electrostatic, hydrophobic, or stacking interactions)^{1–3} on the chemical reactivity of a wide variety of systems has rapidly increased. In particular, current interest lies in the molecular recognition factors which are responsible for the extraordinary selectivity and catalytic power of enzymes.^{4–7} Stereochemical features are the most sensitive structural details used by molecules to “see” each other as they come together to form complexes and transition states. Unfortunately, the process by which intermolecular forces act together to discriminate between enantiomers has not yet been satisfactorily established.

Cyclodextrins (CDs) are cyclic oligomers of (1 \rightarrow 4) linked α -D-glucose monomers. α -, β -, and γ -cyclodextrins contain six,

seven, and eight units, respectively, and have a toroidal shape with a hydrophobic cavity. These natural macromolecules which may include racemic mixtures may form two diastereoisomeric complexes of different thermodynamic stabilities.^{8–11} The following requirements have been used to explain the enantioselectivity and chiral resolution ability of CDs:^{12,13} (i) a supramolecular species must form with the tight fit of the included species in the host cavity; (ii) the stereogenic center should be able to give rise to hydrogen bonds with the hydroxyl groups of the CD cavity entrance; (iii) the unidirectional 2- or 3-secondary hydroxyl groups of the macrocycle seem to be particularly important for the chiral recognition.

Recently, the enantioselective formation of metal complexes with L- and D-amino acids and monosubstituted- β CDs in aqueous solution was reported.^{14–21} By means of a concerted thermodynamic and spectroscopic approach, the chiral recognition process was rationalized by invoking a preferential cis disposition of amino nitrogens.^{17,18,21} This disposition was thought to assist the preferential inclusion of the aromatic

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- (1) Righy, M.; Smith, E. B.; Wakeham, W. A.; Maitland, G. C. *The Forces Between Molecules*; Oxford Science Publications, Clarendon Press: Oxford, U.K., 1986.
- (2) Tanford, C. *The Hydrophobic Effect*; Wiley: New York, 1980.
- (3) Sinanoglu, O. *Int. J. Quantum Chem.* **1980**, *18*, 381.
- (4) Breslow, R. *Pure Appl. Chem.* **1990**, *62*, 1859.
- (5) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1304.
- (6) Ikeura, Y.; Kurihara, K.; Kunitake, T. *J. Am. Chem. Soc.* **1991**, *113*, 7342.
- (7) Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245.

- (8) Cooper, A.; MacNicol, D. D. *J. Am. Chem. Soc., Perkin Trans. 2* **1978**, 760.
- (9) Brown, S. E.; Coates, J. H.; Lincoln, S. F.; Coghlan, D. R.; Easton, C. J. *J. Chem. Soc., Faraday Trans.* **1991**, *87*, 2699.
- (10) Brown, S. E.; Coates, J. H.; Duckworth, P. A.; Lincoln, S. F.; Easton, C. J. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 1035.
- (11) Colquham, I. J.; Goodfellow, B. J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1803.
- (12) Word, T. J.; Armstrong, D. W. *J. Liq. Chromatogr.* **1986**, *9*, 407.
- (13) Lipkowitz, K. B.; Raghthama, S.; Yang, J. *J. Am. Chem. Soc.* **1992**, *114*, 1554.

residues of one amino acid enantiomer into the cyclodextrin cavity. In contrast, the side chain of the other coordinated amino acid enantiomer was proposed to protrude out of the cavity.^{16–18} In particular, for the formation of $[\text{Cu}(\text{CDhm})(\text{L-TrpO})]^+$ and $[\text{Cu}(\text{CDhm})(\text{D-TrpO})]^+$ the following thermodynamic parameters were determined: $-\Delta H^\circ = 15.5(3)$ kcal/mol, $-\Delta H^\circ = 17.5(3)$ kcal/mol, $\Delta S^\circ = 22(1)$ cal/(mol deg), $\Delta S^\circ = 17(1)$ cal/(mol deg), respectively.¹⁸

We report here the crystal and molecular structure of the ternary complex $[\text{Cu}(\text{CDhm})(\text{L-TrpO})\text{H}_2\text{O}]\text{NO}_3$, where CDhm = 6-deoxy-6-[(2-(4-imidazolyl)ethyl)amino]cyclomaltoheptaose and L-TrpO⁻ = L-tryptophanate. The structure details and the ESR parameters of the diastereoisomeric complexes $[\text{Cu}(\text{CDhm})(\text{AaO})]^+$ in aqueous solution and in the solid state (AaO⁻ = L- or D-alanine and L- or D-tryptophanate) allowed us to provide a deeper explanation of the different forces involved in the thermodynamic stereoselectivity of the formation of the diastereoisomeric complexes and of the previously found chiral recognition process.¹⁸

Experimental Section

Preparation of Complexes and Crystals. An aqueous solution containing equimolar amounts of copper(II) nitrate hexahydrate, CDhm, and L-tryptophanate at pH about 6.0 was left to evaporate. After 2–3 weeks, small dark blue crystals formed. They were left in the liquor in order to obtain suitable larger crystals for the diffractometric study.

Copper(II) complexes in aqueous solution and in the solid state for the ESR study were prepared by using isotopically pure ⁶³Cu-(NO₃)₂·6H₂O. Aqueous 4.5 mM solutions were prepared by mixing together ⁶³Cu²⁺, CDhm, and the appropriate amino acidate in a 1:1:1 ratio and adjusting the pH to about 6 by KOH. Solid copper(II) ternary complexes with L- or D-TrpO⁻ only were obtained by evaporating their aqueous solutions to small volumes, filtering off the blue solid, dissolving it in methanol, and evaporating to dryness. This last procedure was repeated at least three times, in order to obtain microcrystalline powders.

Structure Determination and Refinement. X-ray studies were performed on a CAD4 Enraf/Nonius Turbo diffractometer equipped with a MicroVax 3100 Server computer at the Centro di Studio di Biocristallografia del CNR, University of Naples.

Preliminary oscillation and Weissenberg photographs were taken to establish the crystal symmetry and the preliminary space group. Cell constants were obtained by a least-squares procedure applied to the angular parameters of 25 reflections in the θ range 21–29°. A summary of the crystallographic data is given in Table 1.

Data were acquired using graphite-monochromated and Cu K α radiation ($\lambda = 1.54178$ Å). The ω -2 θ scan technique was used with a variable scan rate up to 4° min⁻¹. All reflections were corrected for Lorentz and polarization effects. In a range of 1–70°, 8143 reflections were collected, 5418 of which having a net intensity greater than 3.0 $\sigma(I)$

Table 1. Crystal Data for the Ternary Complex of CDhm, Copper(II), and L-Tryptophanate

mol formula	C ₄₇ H ₇₇ N ₃ O ₃₄ ·[C ₁₁ H ₁₁ N ₂ O ₂] ⁻ ·Cu ²⁺ [NO ₃] ⁻ ·15H ₂ O
mol wt	1827.13
crystal system	monoclinic
space group	P2 ₁
Z, molecules/unit cell	2
a (Å)	15.145(3)
b (Å)	17.296(7)
c (Å)	16.420(4)
β (deg)	105.19(2)
V (Å ³)	4151(2)
D _{calc} (g/cm ³)	1.461
radiation (λ (Å))	Cu K α (1.5418)
no. of meas reflns	8143
no. of obs reflns (with $I > 3\sigma(I)$)	5418
R	0.057
R _w	0.059
no. of params refined	1072
temp (K)	293
solvent of crystallzn	water

were considered observed and were used for further calculation. No decline in intensity was observed during the data collection.

The space group symmetry and unit cell dimensions suggested the presence in the cell of the ternary complex of CDhm, copper(II) nitrate, and L-tryptophanate in a ratio of 1:1:1 as an independent unit and a number of water molecules.

The structure was solved by the straightforward application of direct methods, as programmed in SIR92;²² all non-hydrogen atoms were located in the E map corresponding to the highest figure of merit. Subsequent difference Fourier analysis revealed the positions of the nitrate ion and 15 water molecules. The hydrogen atoms were introduced into their stereochemically expected positions with isotropic temperature factors equal to the B_{eq} values of the heavy atoms to which they were linked. Their parameters were kept fixed. Full-matrix least-squares procedures were used and converged to a final R factor of 0.057 and an R_w of 0.059 using anisotropic temperature factors for the non-hydrogen atoms. All refinements were carried out using the SDP package.²³ Scattering factors for all atomic species were calculated from the values of Cromer and Waber.²⁴ In Table 2 are reported the final atomic parameters for all non-hydrogen atoms; the numbering of atoms follows the recommendations of the IUPAC–IUB Commission.

Spectroscopic Measurements. Aqueous frozen solution and solid powder ESR spectra were acquired by a Bruker ER 200 D X-band spectrometer driven by a Bruker ESP 3220 data system and equipped with a standard low-temperature apparatus. All spectra were recorded at 150 K by using quartz tubes with 4 mm inner diameters. Microwave frequency was standardized against the DPPH radical ($g = 2.0036$), and the magnetic field was also monitored by a Bruker ER 035 M gauss meter.

Methanol addition up to 10% was made to the aqueous solutions containing the copper(II) ternary complexes to increase spectral resolution and up to 50% to estimate variations in the magnetic parameters upon the addition of an organic solvent. In the case of frozen solution spectra, parallel spin Hamiltonian parameters were obtained directly from the experimental spectra recorded on an enlarged scale. Their perpendicular parameters were calculated with a previously described procedure which made use of the extra-peak field.²⁵ The ESR spectra of solid powdered complexes revealed that a sufficient magnetic dilution was achieved, since the parallel hyperfine coupling constants were clearly resolved. Their magnetic parameters were computed by slightly changing a simulation procedure substantially

- (14) Impellizzeri, G.; Maccarrone, G.; Rizzarelli, E.; Vecchio, G.; Corradini, R.; Marchelli, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1348.
- (15) Impellizzeri, G.; Maccarrone, G.; Rizzarelli, E.; Vecchio, G.; Corradini, R.; Marchelli, R. In *Chemistry and Properties of Biomolecular Systems*; Rizzarelli, E.; Theophanides, T., Eds.; Kluwer: Dordrecht, The Netherlands, 1991; pp 209–221.
- (16) Cucinotta, V.; D'Alessandro, F.; Impellizzeri, G.; Vecchio, G. *J. Chem. Soc., Chem. Commun.* **1992**, 1743.
- (17) Bonomo, R. P.; Cucinotta, V.; D'Alessandro, F.; Impellizzeri, G.; Maccarrone, G.; Rizzarelli, E.; Vecchio, G. *J. Inclusion Phenom.* **1993**, *15*, 167.
- (18) Corradini, R.; Dossena, A.; Impellizzeri, G.; Maccarrone, G.; Marchelli, R.; Rizzarelli, E.; Sartor, G.; Vecchio, G. *J. Am. Chem. Soc.* **1994**, *116*, 10267.
- (19) Brown, S. E.; Coates, J. H.; Easton, C. J.; Lincoln, S. F. *J. Chem. Soc., Chem. Commun.* **1994**, 47.
- (20) Brown, S. E.; Coates, J. H.; Easton, C. J.; Lincoln, S. F. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 739.
- (21) Maccarrone, G.; Rizzarelli, E.; Vecchio, G. In *Transition Metals in Supramolecular Chemistry*; Fabbri, L., Poggi, A., Eds.; Kluwer: Dordrecht, The Netherlands, 1994; pp 351–370.

- (22) Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Gugliardi, A.; Polidori, G. *J. Appl. Crystallogr.* **1994**, *27*, 435.
- (23) *Enraf-Nonius Structure Determination Package*; Enraf-Nonius: Delft, The Netherlands, 1979.
- (24) Cromer, D. T.; Waber, J. T. *International Tables for X-Ray Crystallography*; The Kynoch Press: Birmingham, England, 1984; Vol. 4, Table 2.2B.
- (25) Bonomo, R. P.; Riggi, F. *Chem. Phys. Lett.* **1982**, *93*, 99.

Table 2. Fractional Atomic Coordinates and Equivalent Isotropic Thermal Parameters for Non-Hydrogen Atoms

atom	x	y	z	B_{eq}^a (Å ²)	atom	x	y	z	B_{eq}^a (Å ²)
C(1)1	-0.0225(5)	0.2123(5)	-0.1749(5)	3.5(2)	O(3)4	0.2745(4)	0.1969(4)	0.6416(4)	5.0(2)
C(2)1	-0.0709(5)	0.2867(6)	-0.1646(5)	4.0(2)	C(4)4	0.2719(5)	0.0871(6)	0.5535(6)	4.3(2)
O(2)1	-0.0100(4)	0.3504(4)	-0.1609(4)	4.8(1)	O(4)4	0.3310(3)	0.1270(4)	0.5104(3)	4.0(1)
C(3)1	-0.1020(5)	0.2826(5)	-0.0844(5)	3.9(2)	C(5)4	0.2136(6)	0.0277(6)	0.4968(7)	5.3(2)
O(3)1	-0.1548(4)	0.3492(4)	-0.0775(4)	5.2(1)	O(5)4	0.1480(4)	-0.0041(4)	0.5356(4)	5.2(2)
C(4)1	-0.1604(5)	0.2104(5)	-0.0866(5)	3.2(2)	C(6)4	0.2733(8)	-0.0434(8)	0.4835(9)	10.0(4)
O(4)1	-0.1799(3)	0.2048(4)	-0.0058(3)	3.7(1)	O(6)4	0.2181(6)	-0.0963(5)	0.4314(8)	12.6(3)
C(5)1	-0.1108(5)	0.1373(5)	-0.1029(5)	3.5(2)	C(1)5	0.4257(5)	0.1134(6)	0.5383(5)	4.1(2)
O(5)1	-0.0799(3)	0.1473(3)	-0.1775(3)	3.4(1)	C(2)5	0.4721(5)	0.1888(5)	0.5391(5)	3.8(2)
C(6)1	-0.1783(6)	0.0694(5)	-0.1227(6)	4.3(2)	O(2)5	0.4440(4)	0.2428(4)	0.5925(4)	5.1(2)
Cu	-0.25149(8)	-0.057	-0.23987(7)	3.43(2)	C(3)5	0.4572(5)	0.2201(5)	0.4491(5)	3.4(2)
N1H	-0.1438(4)	-0.0001(4)	-0.1583(4)	3.5(1)	O(3)5	0.5092(4)	0.2884(4)	0.4485(4)	4.5(1)
C1H	-0.0788(6)	-0.0440(6)	-0.0919(6)	5.3(2)	C(4)5	0.4846(5)	0.1600(5)	0.3934(5)	3.5(2)
C2H	-0.1221(8)	-0.1057(7)	-0.0550(6)	6.1(3)	O(4)5	0.4594(3)	0.1891(4)	0.3087(3)	3.7(1)
C3H	-0.1555(6)	-0.1723(6)	-0.1131(6)	4.5(2)	C(5)5	0.4364(5)	0.0838(5)	0.3985(5)	3.8(2)
C4H	-0.1380(7)	-0.2482(6)	-0.1051(6)	5.3(2)	O(5)5	0.4535(3)	0.0591(3)	0.4846(4)	3.8(1)
N2H	-0.1879(5)	-0.2836(4)	-0.1785(5)	4.7(2)	C(6)5	0.4703(6)	0.0158(6)	0.3527(6)	4.7(2)
C5H	-0.2310(6)	-0.2244(5)	-0.2271(5)	4.1(2)	O(6)5	0.5638(4)	0.0009(4)	0.3871(4)	4.5(1)
N3H	-0.2135(4)	-0.1581(4)	-0.1923(4)	3.5(1)	C(1)6	0.5269(6)	0.1946(6)	0.2656(5)	4.3(2)
NT	-0.2906(5)	0.0378(4)	-0.3114(5)	4.5(2)	C(2)6	0.5158(6)	0.2713(6)	0.2192(5)	4.3(2)
O1T	-0.3413(4)	-0.1061(3)	-0.3348(3)	4.1(1)	O(2)6	0.5147(5)	0.3340(4)	0.2745(4)	5.4(2)
C ¹ T	-0.3594(5)	-0.0694(5)	-0.4024(5)	3.5(2)	C(3)6	0.4304(5)	0.2714(5)	0.1441(5)	3.8(2)
O2T	-0.4071(4)	-0.0936(4)	-0.4726(4)	4.6(1)	O(3)6	0.4294(4)	0.3395(4)	0.0943(4)	4.7(1)
C ^o T	-0.3213(6)	0.0119(5)	-0.4005(5)	3.8(2)	C(4)6	0.4286(5)	0.2003(5)	0.0912(5)	3.5(2)
C [#] T	-0.2399(7)	0.0133(6)	-0.4401(5)	5.1(2)	O(4)6	0.3424(3)	0.2013(4)	0.0296(3)	3.6(1)
C ^v T	-0.1519(6)	-0.0193(6)	-0.3844(5)	4.8(2)	C(5)6	0.4383(6)	0.1282(6)	0.1426(5)	4.0(2)
C ^{o1} T	-0.0841(7)	0.0239(8)	-0.3366(6)	6.3(3)	O(5)6	0.5251(4)	0.1328(4)	0.2086(4)	4.6(1)
N ¹ T	-0.0164(5)	-0.0202(7)	-0.2902(5)	6.6(3)	C(6)6	0.4419(9)	0.0532(6)	0.0953(7)	7.1(3)
C ² T	-0.0385(6)	-0.0957(8)	-0.3084(6)	5.9(3)	O(6)6	0.5020(6)	0.0547(5)	0.0426(4)	8.2(2)
C ^{o1} T	0.0076(7)	-0.1625(9)	-0.2745(7)	7.8(3)	C(1)7	0.3381(6)	0.1826(6)	-0.0544(6)	4.6(2)
C ^{o2} T	-0.0296(9)	-0.2291(9)	-0.3042(8)	9.0(4)	C(2)7	0.2997(6)	0.2522(6)	-0.1114(5)	4.6(2)
C ^{o3} T	-0.1108(9)	-0.2351(7)	-0.3659(7)	8.1(3)	O(2)7	0.3530(4)	0.3194(4)	-0.0808(4)	5.7(2)
C ^{o2} T	-0.1628(7)	-0.1695(7)	-0.4011(6)	6.0(3)	C(3)7	0.2000(5)	0.2666(6)	-0.1095(5)	3.8(2)
C ^{o2} T	-0.1241(6)	-0.0998(7)	-0.3683(6)	5.2(2)	O(3)7	0.1623(4)	0.3241(4)	-0.1701(4)	4.6(1)
C(1)2	-0.2717(5)	0.1929(6)	-0.0031(5)	4.0(2)	C(4)7	0.1457(5)	0.1913(5)	-0.1273(5)	3.4(2)
C(2)2	-0.2897(6)	0.2532(6)	0.0589(5)	4.2(2)	O(4)7	0.0588(3)	0.2047(3)	-0.1079(3)	3.3(1)
O(2)2	-0.2769(4)	0.3275(4)	0.0305(4)	5.9(2)	C(5)7	0.1922(5)	0.1259(5)	-0.0722(5)	3.6(2)
C(3)2	-0.2336(6)	0.2345(5)	0.1466(5)	4.0(2)	O(5)7	0.2838(4)	0.1158(4)	-0.0803(4)	4.5(1)
O(3)2	-0.2607(4)	0.2866(4)	0.2043(4)	5.1(2)	C(6)7	0.1482(7)	0.0473(6)	-0.0937(7)	5.9(3)
C(4)2	-0.2451(5)	0.1528(5)	0.1693(5)	3.5(2)	O(6)7	0.1425(5)	0.0251(4)	-0.1769(5)	6.7(2)
O(4)2	-0.1837(4)	0.1394(4)	0.2503(3)	4.2(1)	Ow1	-0.2132(4)	-0.1647(4)	0.3201(4)	5.1(2)
C(5)2	-0.2269(6)	0.0966(6)	0.1047(5)	4.0(2)	Ow2	-0.3494(4)	-0.0339(4)	-0.1524(4)	6.1(2)
O(5)2	-0.2839(4)	0.1172(4)	0.0225(3)	4.2(1)	Ow3	-0.3685(5)	-0.0735(5)	0.2657(4)	6.4(2)
C(6)2	-0.2429(8)	0.0127(6)	0.1198(6)	6.1(3)	Ow4	0.3064(5)	-0.2324(5)	0.5005(5)	7.2(2)
O(6)2	-0.3328(5)	-0.0002(5)	0.1293(4)	7.1(2)	Ow5	0.0826(6)	-0.1576(5)	0.5344(6)	9.2(3)
C(1)3	-0.2171(6)	0.0972(5)	0.3103(5)	4.0(2)	Ow6	0.2874(7)	-0.0502(7)	-0.1998(7)	12.7(3)
C(2)3	-0.2042(5)	0.1467(5)	0.3882(5)	3.7(2)	Ow7	0.4279(6)	-0.0827(6)	-0.0505(7)	11.8(3)
O(2)3	-0.2457(4)	0.2192(4)	0.3659(4)	5.0(2)	Ow8	-0.411(1)	0.141(2)	-0.242(1)	28.3(8)
C(3)3	-0.1034(6)	0.1548(5)	0.4336(5)	3.9(2)	Ow9	0.251(1)	-0.2968(8)	0.338(1)	24.1(7)
O(3)3	-0.0904(4)	0.1936(4)	0.5135(4)	5.3(2)	Ow10	0.424(1)	-0.0206(9)	-0.287(1)	25.6(7)
C(4)3	-0.0562(5)	0.0773(6)	0.4462(5)	3.8(2)	Ow11	0.485(1)	-0.173(2)	0.142(2)	25.2(8)
O(4)3	0.0414(3)	0.0932(4)	0.4806(3)	3.9(1)	Ow12	-0.307(1)	-0.605(1)	-0.204(1)	27.2(8)
C(5)3	-0.0712(6)	0.0350(6)	0.3631(6)	4.4(2)	Ow13	-0.401(2)	-0.372(2)	0.226(1)	27.4(8)
O(5)3	-0.1705(4)	0.0267(4)	0.3291(4)	4.3(1)	Ow14	-0.522(2)	-0.428(2)	0.119(2)	26.5(8)
C(6)3	-0.0337(6)	-0.0461(6)	0.3710(6)	4.9(2)	Ow15	-0.555(2)	-0.192(2)	0.276(2)	25.7(7)
O(6)3	-0.0699(5)	-0.0925(4)	0.4285(4)	6.0(2)	N1S	-0.874(1)	0.040(1)	0.207(1)	18.0(7)
C(1)4	0.0878(6)	0.0525(6)	0.5534(6)	4.5(2)	O1S	-0.936(1)	0.052(1)	0.134(1)	24.3(8)
C(2)4	0.1427(5)	0.1096(6)	0.6151(5)	4.3(2)	O2S	-0.864(1)	-0.0411(9)	0.251(1)	26.1(6)
O(2)4	0.0829(4)	0.1670(4)	0.6379(4)	5.0(2)	O3S	-0.799(1)	0.0572(8)	0.233(1)	20.7(7)
C(3)4	0.2150(5)	0.1489(6)	0.5809(5)	4.0(2)					

$$^a B_{\text{eq}} = (8/3)\pi^2 \sum_i U_{ij} a_i^* a_j^* \mathbf{a}_i \mathbf{a}_j$$

devised by Pilbrow et al.²⁶ The fitting procedure revealed a small rhombic component, the difference between g_x and g_y , not exceeding 0.030. For a comparison with the frozen solution spin Hamiltonian parameters, which were typical of axial copper ESR spectra, only mean values ($g_z = g_{\parallel}$, $A_z = A_{\parallel}$, $g_{\perp} = 1/2(g_x + g_y)$, $A_{\perp} = 1/2(A_x + A_y)$) are reported in Table 3. Moreover, in order to obtain a good fit of the experimental spectra, a parallel quadrupolar tensor component of $(4-5) \times 10^{-4} \text{ cm}^{-1}$ needed to be taken into account and line width parameter variation with the copper nuclear quantum number was

allowed by using the expression $W = W + am_l^b$. Figure 1 shows experimental and computed ESR powder spectra of copper(II) ternary complexes containing CDhm and L- or D-TrpO⁻, the parameters for which are reported in Table 4.

Visible optical spectra were recorded on a Hewlett-Packard HP 8452 spectrophotometer by using the same aqueous solutions from the ESR study in 1.0 cm quartz cells.

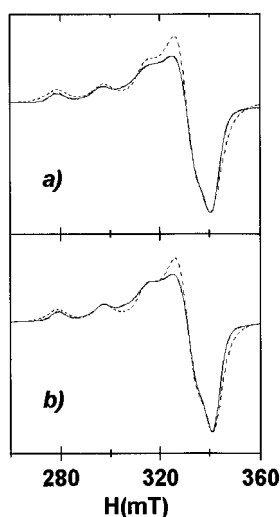
Results and Discussion

Cyclodextrin Molecular Conformation. Figure 2 shows the perspective view of the molecular model of the ternary

Table 3. ESR Magnetic Parameters from Frozen Solution and Solid Powder Spectra of Ternary Copper(II) Complexes with CDhm and L- or D-AlaO⁻, or L- or D-TrpO⁻

amino acid	pH	% CH ₃ OH	λ_{\max} (nm)	ϵ_{\max} (dm ³ mol ⁻¹ cm ⁻¹) ^a	$g_{ }$	$A_{ }$ ^b	g_{\perp}	A_{\perp} ^b
L-AlaO ⁻	6.1	10	620 (87)	2.233(1)	193(1)	2.047(2)	18(2)	
D-AlaO ⁻	6.1	10	620 (87)	2.233(1)	193(1)	2.047(2)	18(2)	
L-AlaO ⁻		50		2.236(1)	191(1)	2.047(2)	17(2)	
D-AlaO ⁻		50		2.234(1)	192(1)	2.046(2)	17(2)	
L-TrpO ⁻	6.0	10	618 (92)	2.238(1)	184(1)	2.046(2)	17(2)	
D-TrpO ⁻	6.0	10	632 (79)	2.227(1)	189(1)	2.043(2)	19(2)	
L-TrpO ⁻		50		2.232(1)	188(1)	2.043(2)	18(2)	
D-TrpO ⁻		50		2.230(1)	187(1)	2.041(2)	17(2)	
L-TrpO ⁻		solid		2.233(1)	184(1)	2.057(2)	15(2)	
D-TrpO ⁻		solid		2.231(1)	185(1)	2.056(2)	15(2)	

^a λ_{\max} in nm; ϵ_{\max} in dm³ mol⁻¹ cm⁻¹. ^b Hyperfine coupling constants are given in units of 10⁴ cm⁻¹. ^c Errors on the last digit in g and A values are given in parentheses.

**Figure 1.** Experimental (—) and simulated (---) ESR powder spectra of (a) [Cu(CDhm)(L-TrpO)]⁺, and (b) [Cu(CDhm)(D-TrpO)]⁺. Instrumental settings: microwave frequency = 9.546 GHz, modulation frequency = 100 kHz, modulation amplitude = 0.149 mT, time constant = 0.327 s, microwave power = 20 mW.

complex with the indication of the numbering of the glucose residues. Geometrical data for the glucose residues are reported in Table 5. All glucose units have a ⁴C₁ chair conformation. The macrocycle structure shows an approximate 7-fold axis, and the presence of the histamine moiety does not significantly affect the structure of each glucose residue. The distances O(4)*n*–O(4)*n*+1 range from 4.30 to 4.46 Å, and the radius of the heptagon is between 4.78 and 5.26 Å. The seven glycosidic O(4) atoms are almost coplanar within 0.3 Å from their least-squares plane and form a heptagon more distorted than that found for the “empty” βCD.²⁷ The dihedral angles (tilt angles) between the above mentioned O(4) plane and the optimum planes of the C(1), C(4), O(4), O(4′) atoms for each glucose residue range from 4.7 to 24.6° with an average of 14.7°. The difference between the narrower and wider rim diameters makes the hydrophobic cavity at the primary hydroxyl site smaller than that shown in other monosubstituted βCD structures.^{28,29} As result, the intramolecular O(2)*n*–O(3)*n*–1 hydrogen bonds that stabilize the structure of the βCD macrocycle are longer and consequently weaker with respect to the range (2.78–2.86 Å)

(27) Lindner, K.; Saenger, W. *Carbohydr. Res.* **1982**, *99*, 103.

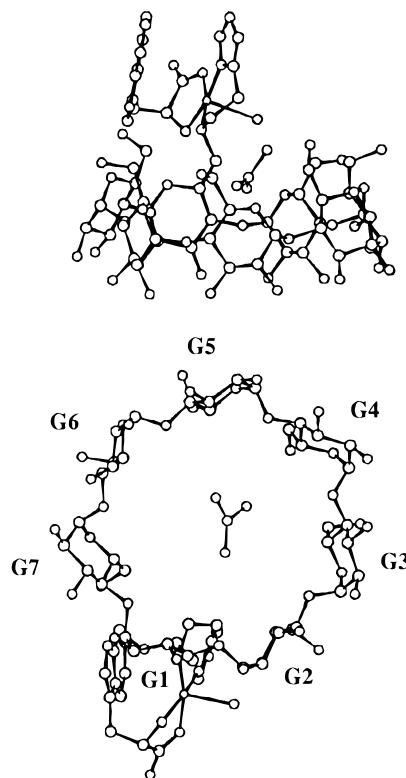
(28) Di Blasio, B.; Pavone, V.; Nastri, F.; Isernia, C.; Saviano, M.; Pedone, C.; Cucinotta, V.; Impellizzeri, G.; Rizzarelli, E.; Vecchio, G. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 7218.

(29) Kamitori, S.; Hirotsu, K.; Fujita, K.; Yamamura, H.; Imoto, T.; Tabushi, I. *J. Chem. Soc., Perkin Trans. 2* **1987**, 10.

Table 4. Spin Hamiltonian Parameters and Conditions for the Simulation of the ESR Powder Spectra of the [Cu(CDhm)(L-TrpO)]⁺ and [Cu(CDhm)(D-TrpO)]⁺ Ternary Complexes

parameters ^a	values	
	[Cu(CDhm)(L-TrpO)] ⁺	[Cu(CDhm)(D-TrpO)] ⁺
no. of nitrogens	3	3
$A_{ }^N$	0.0007	0.0007
A_{\perp}^N	0.0014	0.0014
g_x	2.045	2.041
g_y	2.068	2.071
g_z	2.233	2.231
A_x , cm ⁻¹	0.0020	0.0020
A_y , cm ⁻¹	0.0010	0.0010
A_z , cm ⁻¹	0.0184	0.0185
W_x , mT	4.0	2.8
W_y , mT	4.5	4.5
W_z	4.5 T	4.5 mT
a_x	1.0	1.0
a_y	7.0	7.0
a_z	5.0	1.0
b_x	1.0	1.0
b_y	4.0	4.0
b_z	0.0	0.0
P , cm ⁻¹	0.0004	0.0004

^a A^N : shf constants. g_x, g_y, g_z : g values. A_x, A_y, A_z : hyperfine coupling constants. W_x, W_y, W_z : line width parameters. a_x, a_y, a_z and b_x, b_y, b_z : coefficients and exponents of the expression $W = W + am^p$, respectively. P : quadrupole term.

**Figure 2.** Molecular model of the ternary complex of CDhm, copper(II), and L-tryptophanate, with residue numbers. The nitrate group is shown within the cyclodextrin ring.

of similar distances observed in other βCD crystal structures^{30,31} (Table 6). The torsion angles related to the orientations of C(6)–O(6) bonds show two different types of conformation, gauche-trans for G4 and gauche-gauche for all remaining glucose units. Therefore, six primary hydroxyl groups point

(30) Zabel, V.; Saenger, W.; Maso, S. A. *J. Am. Chem. Soc.* **1986**, *108*, 3663.

(31) Hamilton, T. A.; Chen, L. Y. *J. Am. Chem. Soc.* **1988**, *110*, 4379.

Table 5. Geometrical Data

residue	radius (Å) ^a	distance (Å) ^b	angle (deg) ^c	tilt angle (deg) ^d	planarity (Å) ^e
G1	5.21	4.37	126.2	8.07	-0.345
G2	5.14	4.45	131.6	4.70	-0.032
G3	5.26	4.32	126.9	21.12	0.292
G4	5.17	4.39	125.7	24.61	-0.040
G5	4.78	4.46	130.6	12.74	-0.324
G6	4.79	4.30	127.8	7.36	0.200
G7	4.99	4.37	127.8	24.48	0.245

^a The radius is measured from the center of gravity of the seven O(4) atoms to each O(4) atom. ^b The distance is defined as the O(4)_n–O(4)_{n+1} distance. ^c The angle is defined as the O(4)_{n-1}–O(4)_n–O(4)_{n+1} angle. ^d The tilt angle is defined as the angle made by the plane of the O(4) atoms and the plane formed by O(4)_{n+1}, C(1)_n, C(4)_n, O(4)_n of each glucose residue. ^e Planarity is the defined as the O(4)_n distance from the plane of the O(4) atoms.

“away” from the center of the cavity to form hydrogen bonds with water molecules and neighboring βCD molecules, whereas the C(6)–O(6) bond of G4 points “inward” toward the center of the cavity.

Metal Surrounding and Chelation Sites. The molecular structure of the ternary complex shows the coordinating features of the histamine moiety, L-tryptophanate, and the Cu²⁺ ion located outside the βCD cavity, whereas the primary hydroxyl groups of βCD are not involved in any direct coordination to the metal ion. Both L-tryptophanate and CDhm act as bidentate ligands, giving rise to five- and six-membered chelate rings formed by means of the terminal nitrogen and carboxylate oxygen atoms of the L-amino acidate and the two nitrogen atoms of the histamino moiety, respectively. These atoms form the base for the square-pyramidal surrounding of the Cu²⁺ ion as represented in Figure 3, where the structural details for the mode of coordination of the Cu²⁺ ion with the histamino moiety and L-TrpO⁻ are indicated. In Table 7 are reported the geometrical details of the copper(II) coordination mode in the ternary complex. The central copper(II) ion assumes a distorted square-pyramidal geometry, a water molecule occupying the apical position to complete the square pyramid. The basal coordination plane is planar to within 0.02 Å, and the Cu–Ow2 bond is almost orthogonal to this plane. The Cu²⁺ ion is displaced 0.17 Å out of the main square plane through the four basal atoms toward the apical water molecule. The copper(II)–ligand Cu–O and Cu–N bond lengths and the angles at the bonded ligand atom in this complex are in agreement with those generally found in square-planar Cu²⁺ complexes, while the axial Cu–Ow2 bond length of 2.35 Å compares well with those reported for similar five-coordinated pyramidal Cu²⁺ complexes.³²

A significant feature of this complex is represented by the relative orientation of side chain rings of L-tryptophanate with respect to the imidazole ring of the histamino moiety and the Cu²⁺ coordination plane. The aromatic rings face each other in approximately parallel fashion, the angle between these planes being 25°, whereas the angles between the Cu²⁺ coordination square plane and the planes of the imidazole ring and side chain rings of tryptophanate are 18 and 16°, respectively. The result is the presence of a close contact between the Cu²⁺ ion and the carbon atoms C^γT and C^{δ2}T of the side chain of tryptophanate, the distances Cu–C^γT and Cu–C^{δ2}T being 3.19 and 3.30 Å, respectively. Similar intermolecular contacts (3.04–3.34 Å) between Cu²⁺ and aromatic rings have been found in Cu(L-

Tyr)₂,³² in copper(II)–peptide complexes,^{34,35} and also in a copper(II) ternary complex.³⁶ As expected, this finding indicates that the presence of concomitant effects due to Cu–aromatic ring interaction and intramolecular aromatic ring stacking can contribute to increasing the complex stability in aqueous solution.

Packing and Water Molecules. In the crystalline state, as shown in Figure 4, the CDhm molecules are stacked along the 2-fold screw axis, forming a herringbone-like pattern in the *bc* plane as monomer units. Along the screw axis, the molecules give rise to a polymeric column structure in which a single CDhm molecule can be considered as a guest and as a host. Both the histamino moiety and the side chain rings of tryptophan are directed into the cavity of an adjacent CDhm from the secondary hydroxyl side. The N2H atom of the imidazole ring is partially enclosed at a distance of 0.8 Å by the least-squares plane of the O(4) atoms, while the shorter distance of the side chain carbon atoms of tryptophan C^{δ1}T, C^{HT} is approximately 2.50 Å. A similar interaction has been observed for 6-deoxy-6-(phenylthio)-βCD,³⁷ heptakis 2,6-(OMe)-βCD³⁵ and 6-O-D-glucosyl-αCD.³⁶ The nitrate ion is located on the top of the cavity from the primary side at a distance of 3.5 Å of the plane of O(4).

Alternate layers of Cu²⁺-coordination moieties and βCD macrocycles parallel to the *ac* plane are present in the complex structure. The macrocycle layers are stabilized by a complicated intermolecular hydrogen-bond network, involving hydroxyl groups themselves or water molecules and hydroxyl groups (Table 6), but no direct intermolecular hydrogen bonds between macrocycles are present in the crystal. Hydrogen-bond interactions between the amino group of L-TrpO⁻ and water molecules also occur. In addition, the nitrate ion is involved in several hydrogen bonds with primary and secondary hydroxyl groups, as well as with one water molecule (Ow12). In contrast to other structures of this type, no disorder was found for primary hydroxyl group positions and water molecules.

With the mean least-squares plane of O(4) inclined to the screw fold axis, the stacking of macrocycles produces channels running along the *c* axis that are available to contain water molecules (Figure 5). Fifteen solvent water molecules distributed in this channel are involved within the crystal in several different hydrogen-bonded interactions. Of these, Owl, Ow3, Ow4, Ow6, and Ow7 participate in several H-bonds with themselves and with primary hydroxyl groups, bridging symmetry-related macrocycles. The other remaining water molecules fill the lattice space between the macrocycles, giving rise to a long chain in which are also involved oxygen atoms of symmetry-related nitrate groups.

ESR Spectroscopic Data. The magnetic parameters from frozen solution spectra, reported in Table 3, are mean values taken over four independent measurements on increasing the methanol percentage up to 10%. These parameters ($g_{||} > g_{\perp} \geq 2.04$) are characteristic of copper(II) complexes in their typical elongated octahedral geometry with a $d_{x^2-y^2}$ ground state. Unfortunately, the ESR spectra of these complexes did not show resolved superhyperfine structure, so direct evidence of the nitrogen atoms bound to copper was lacking. But, $g_{||}$ and $A_{||}$

(32) Pajunen, A.; Pajunen, S. *Acta Crystallogr.* **1982**, B38, 3093.

(33) van der Helm, D.; Tatsch, C. E. *Acta Crystallogr.* **1972**, B28, 2307.

(34) Franks, W. A.; van der Helm, D. *Acta Crystallogr.* **1970**, B27, 1299.

(35) Hursthouse, M. B.; Jayaweera, S. A. A.; Milburn, H.; Quick, A. J. *Chem. Soc., Dalton Trans.* **1975**, 2569.

(36) Yamauchi, O.; Kohzuma T.; Masuda, H.; Toriumi, K.; Saito, K. *Inorg. Chem.* **1989**, 28, 4066.

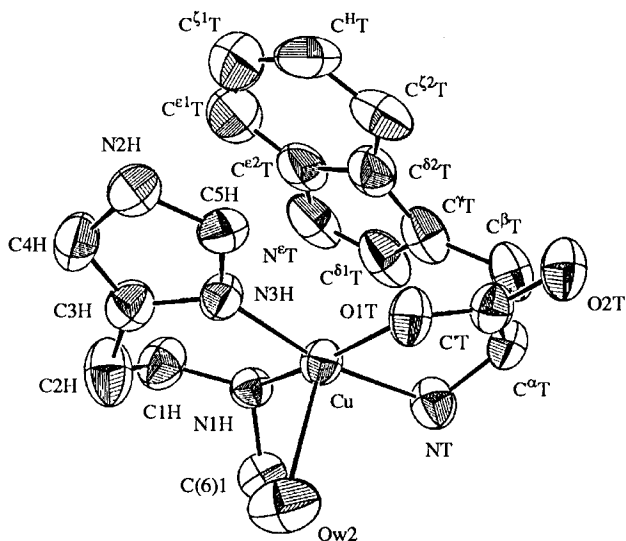
(37) Kamitori, S.; Hirotsu, K.; Higuchi, T. *J. Chem. Soc., Perkin Trans. 2* **1987**, 7.

(38) Harata, K. *Bull. Chem. Soc. Jpn.* **1988**, 61, 1939.

(39) Fujiwara, T.; Tanaka, N.; Hamada, K.; Kobayashi, S. *Chem. Lett.* **1989**, 1131.

Table 6. Inter- and Intramolecular H-Bonds

A. O(2) <i>n</i> –O(3) <i>n</i> –1 Distances (Å)							
O(2)1–O(3)7	2.69		O(2)5–O(3)4	2.99			
O(2)2–O(3)1	2.90		O(2)6–O(3)5	2.99			
O(2)3–O(3)2	2.85		O(2)7–O(3)6	2.82			
O(2)4–O(3)3	2.91						
B. Intramolecular βCD and L-Tryptophan Interaction (Å)							
NεT–O(6)7				2.74			
C. βCD and Solvent Molecule Interactions							
dist (Å)		symmetry		dist (Å)		symmetry	
N1H–Ow2	3.19	<i>x, y, z</i>		O(3)4–Ow13	2.76	$-x, y + 1/2, -z + 1$	
N2H–O1S	3.39	$-x - 1, y - 1/2, -z$		O(6)4–Ow4	2.80	<i>x, y, z</i>	
N2H–O3S	2.89	$-x - 1, y - 1/2, -z$		O(6)4–Ow5	3.16	<i>x, y, z</i>	
NT–Ow8	2.98	<i>x, y, z</i>		O(6)4–O2S	3.04	<i>x + 1, y, z</i>	
NT–Ow9	2.98	$-x, y + 1/2, -z$		O(2)5–Ow15	2.62	$-x, y + 1/2, -z + 1$	
O(2)1–O2S	2.81	$-x - 1, y + 1/2, -z$		O(3)5–Ow4	2.72	$-x + 1, y + 1/2, -z + 1$	
O(3)1–Ow12	2.78	<i>x, y + 1, z</i>		O(6)5–Ow3	2.78	<i>x + 1, y, z</i>	
O(2)2–Ow7	2.85	$-x, y + 1/2, -z$		O(2)6–Ow10	2.67	$-x + 1, 1/2 + y, -z$	
O(3)2–Ow6	2.85	$-x, y + 1/2, -z$		O(3)6–Ow2	2.79	$-x, y + 1/2, -z$	
O(6)2–Ow3	2.75	<i>x, y, z</i>		O(3)6–Ow7	2.79	$-x + 1, 1/2 + y, -z$	
O(2)3–Ow4	2.72	$-x, y + 1/2, -z + 1$		O(6)6–Ow7	2.89	<i>x, y, z</i>	
O(3)3–Ow5	2.70	$-x, y + 1/2, -z + 1$		O(6)6–Ow14	2.76	$-x, y + 1/2, -z$	
O(6)3–Ow1	2.72	<i>x, y, z</i>		O(2)7–Ow11	2.89	$-x + 1, 1/2 + y, -z$	
O(6)3–Ow5	2.74	<i>x, y, z</i>		O(3)7–Ow1	2.77	$-x, y + 1/2, -z$	
O(3)4–Ow1	2.70	$-x, y + 1/2, -z + 1$		O(6)7–Ow6	2.66	<i>x, y, z</i>	
D. Water–Water Interactions							
dist (Å)		symmetry		dist (Å)		symmetry	
Ow1–Ow3	2.78	<i>x, y, z</i>		Ow8–Ow14	2.76	$-x - 1, y + 1/2, -z$	
Ow2–Ow14	2.83	$-x - 1, y + 1/2, -z$		Ow8–Ow15	2.97	$-x - 1, y + 1/2, -z$	
Ow3–Ow11	3.10	<i>x + 1, y, z</i>		Ow10–Ow13	2.81	$-x, y + 1/2, -z$	
Ow4–Ow9	2.81	<i>x, y, z</i>		Ow11–Ow15	2.44	<i>x, y, z</i>	
Ow6–Ow7	2.85	<i>x, y, z</i>		Ow12–Ow15	2.60	$-x - 1, y - 1/2, -z$	
Ow6–Ow10	2.86	<i>x, y, z</i>		Ow12–O2S	3.09	$-x - 1, y - 1/2, -z$	
Ow8–Ow13	2.94	$-x - 1, y + 1/2, -z$		Ow13–Ow14	2.39	<i>x, y, z</i>	

**Figure 3.** Details of the copper(II) coordination mode, showing 50% probability thermal ellipsoids and the atom-labeling scheme.

values, reflecting the presence of the type of ligands coordinated to copper, gave an indirect indication of the number of nitrogen or oxygen atoms bound to copper. By comparison with magnetic parameters of similar systems previously reported,^{40–43} it was possible to state that full coordination to copper by both ligands occurred. The slight differences shown by the copper(II)–

Table 7. Selected Bond Lengths (Å) and Angles (deg) of the Coordination Mode of Copper(II) in the Ternary Complex

Distances			
Cu–N1H	2.066(6)	Cu–O1T	1.974(5)
Cu–N3H	1.943(7)	Cu–Ow2	2.353(8)
Cu–NT	2.010(7)		
Angles			
N1H–Cu–N3H	93.8(3)	N3H–Cu–NT	168.6(3)
N3H–Cu–O1T	89.8(2)	N1H–Cu–Ow2	92.4(3)
O1T–Cu–NT	81.6(3)	N3H–Cu–Ow2	94.3(3)
NT–Cu–N1H	93.1(3)	O1T–Cu–Ow2	98.1(2)
N1H–Cu–O1T	168.3(3)	NT–Cu–Ow2	94.8(3)

CDhm–TrpO[−] system in water or in aqueous solution with low content of methanol disappeared when the methanol percentage reached 50%, showing that these subtle differences are solvent dependent. Figure 6 shows parallel regions of ESR experimental spectra of frozen solutions with low and the highest content of methanol containing the two copper(II) mixed complexes with L- and D-TrpO[−]. In the solid state as well (see Figure 1 and Table 4), no substantial differences were seen. Some slight variation in these magnetic parameters can be ascribed to the influence of packing on the coordination site.

It is important to give reasons for the subtle differences found among the magnetic parameters obtained from the aqueous frozen solutions of the two ternary complexes with L-TrpO[−] and D-TrpO[−]. As one can see from inspection of Table 3, no difference was present between the magnetic parameters associated with the mixed complexes containing L- or D-AlaO[−] in frozen solution either with low content of methanol or with the highest. On the contrary, in the case of the analogous

(40) Bonomo, R. P.; Riggi, F.; Di Bilio, A. *J. Inorg. Chem.* **1988**, *27*, 2510.(41) Amico, P.; Bonomo, R. P.; Cali, R.; Cucinotta, V.; Daniele, P. G.; Ostacoli, G.; Rizzarelli, E. *Inorg. Chem.* **1989**, *28*, 3555.(42) Arena, G.; Bonomo, R. P.; Casella, L.; Gullotti, M.; Impellizzeri, G.; Maccarrone, G.; Rizzarelli, E. *J. Chem. Soc., Dalton Trans.* **1991**, 3203.(43) Bonomo, R. P.; Bonsignore, F.; Conte, E.; Impellizzeri, G.; Pappalardo, G.; Purrello, R.; Rizzarelli, E. *J. Chem. Soc., Dalton Trans.* **1993**, 1295.

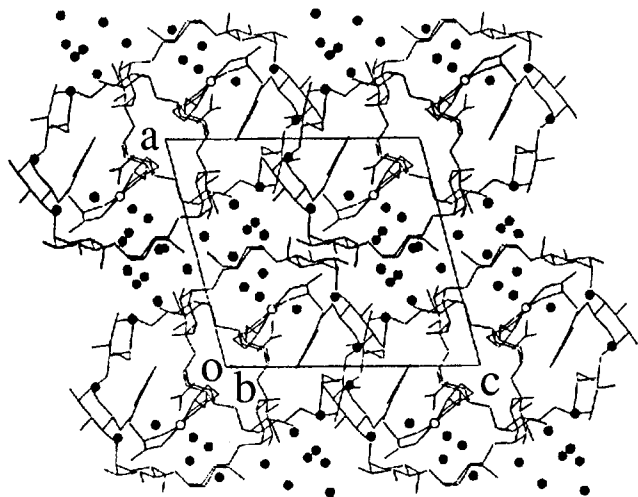


Figure 4. Crystal packing of the CDhm-copper(II)-L-tryptophan complex as viewed down the crystallographic *b* axis. Water molecules are indicated as filled circles.

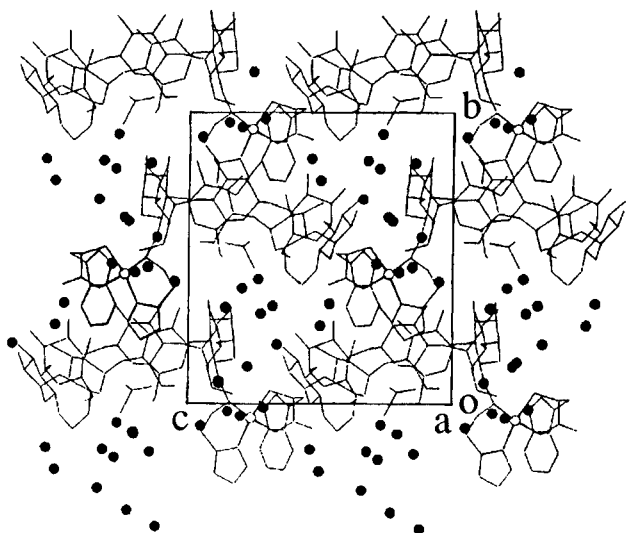


Figure 5. Crystal packing of the CDhm-copper(II)-L-tryptophan complex as viewed down the [100] direction. Water molecules are indicated as filled circle.

complexes with L-TrpO⁻ as the second ligand, the ESR spectra showed a greater g_{\parallel} value and a smaller parallel hyperfine coupling constant than the relative values of the mixed copper(II) complex with D-TrpO⁻. This shift, which, in complexes having the same ligands, is appreciably high in the g_{\parallel} value and a little lower in A_{\parallel} , could arise as a consequence of weak forces such as hydrophobic interactions of amino acidate side chain residues with the cyclodextrin cavity or $d-\pi$ interactions between the π cloud of the TrpO⁻ indole group and the pertinent *d* orbitals of copper. In fact, the magnetic parameters associated with the ternary copper(II) complexes containing L- or D-AlaO⁻, which have methyl groups as side chain residues, no weak interaction thus able to be foreseen, showed no difference when frozen solution ESR spectra were run both in water with added methanol up to 10% and in a water-methanol mixture (50–50%). It is necessary to point out that weak forces could have an influence on the complex geometry, either causing deviation from regular geometry or favoring a particular stereochemical arrangement. Actually, within a series of related copper(II) complexes,⁴⁰ the shifts in the magnetic parameters shown by [Cu(CDhm)(L-TrpO)]⁺ with respect to [Cu(CDhm)(D-TrpO)]⁺ could be caused either by a tetrahedral distortion or by the formation of a square-pyramidal arrangement. Unfortunately,

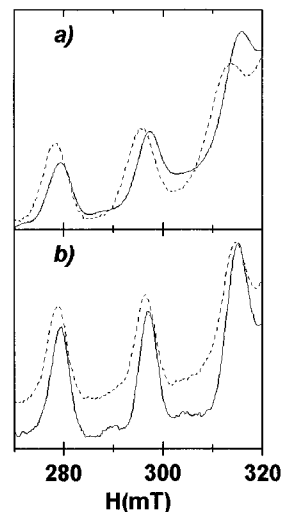


Figure 6. Frozen solution ESR spectra of copper(II) ternary complexes containing CDhm and L-TrpO⁻ (---) or D-TrpO⁻ (—): (a) parallel regions from aqueous solutions with 8% methanol; (b) parallel regions from 50%–50% water-methanol mixtures. Instrumental settings: microwave frequency = 9.548 GHz, modulation frequency = 100 kHz, modulation amplitude = 0.4–0.6 mT, time constant = 0.327 s, microwave power = 20 mW.

ESR spectroscopy does not easily discriminate between these two possibilities, so that the solved molecular structure could be taken as a reference point to rationalize these differences. As it is possible to see from Figures 2 and 3, a water molecule is linked apically to the copper(II) ion inserted into an equatorial plane formed by amine and imidazole nitrogen atoms from histamine and amine nitrogen and carboxylate oxygen atoms from L-TrpO⁻. Now, this water molecule is just opposite to the indole group, which probably offers its π cloud to interact with the *d* orbitals of copper. The Cu–O_w bond distance, 2.35 Å, indicates a relatively strong apical bond, so that the real polyhedron for the Cu-CDhm-L-TrpO⁻ system could be regarded as a distorted square pyramid with a longer apical bond distance. This peculiar geometry, which is probably preserved partially in aqueous solution, could account for the greater g_{\parallel} value and the slightly smaller A_{\parallel} constant. In other words, the two apical water molecules, generally present in a complex dissolved in water, could be inequivalently bound to copper, because of the indole-copper interaction. On the contrary, in the case of the mixed complex with D-TrpO⁻, the absence of the indole-copper interaction (assuming the same *cis* configuration as found in the L-isomer complex by the X-ray diffraction study, the indole group pointing outside the copper polyhedron) and a possible indole-cavity interaction, as suggested by the above mentioned thermodynamic parameters pertinent to the mixed copper(II) complex formation,¹⁸ could allow copper to find itself in a more regular arrangement. A tetragonally elongated octahedron with two water molecules equally bound at slightly longer distances could account for the lower g_{\parallel} value and a slightly greater A_{\parallel} constant. These differences disappeared both in the solution with the highest methanol content and in the solid state. The presence of a great amount of organic solvent or the absence of water as in the solid compounds could explain this leveling effect. Actually, hydrophobic interactions need a solution in which the water content predominates, while packing forces certainly exert great control, therefore surpassing weak forces. In other words, in the solid state or in a water-organic solvent mixture, the copper coordination sites in the Cu-CDhm-L-TrpO⁻ and Cu-CDhm-D-TrpO⁻ systems are more regular, since they are not affected by hydrophobic or $d-\pi$ interactions. From the parameters

reported in Table 3, this last interaction seems to impose a larger apical compression on the copper site.

Concluding Remarks

The enantioselective binding of tryptophan to the copper(II) complex of CDhm in aqueous solution has been found to be due to favorable enthalpy factors in the formation of the ternary complex with D-TrpO⁻.¹⁸ The interaction of the indole side chain with the CD cavity in the case of the D-isomer was based on the preferential cis disposition of the amine nitrogen atoms of CDhm and tryptophanate ligands. The X-ray structure reported here supports what has been previously hypothesized on the basis of thermodynamic and c.d. spectroscopic data only, even if structural bonding details found in the solid state should be used with care to explain some results obtained in solution.

Furthermore, the orientation of the indole residue of L-TrpO⁻ with respect to the imidazole ring of the histamine chain and the close contact between the copper(II) ion and the Trp ring suggest that weak forces, such as stacking and d- π interactions, also could occur in the [Cu(CDhm)(L-TrpO)]⁺ complex, favoring its formation. The role of weak forces (or noncovalent interactions) has been widely studied in chiral molecular recognition. Furthermore, the imidazole ring of histidine is one of the most important biological metal-binding sites and, at the same time, is a useful partner in stacking interactions of aromatic rings.^{44,45}

The presence of the above-mentioned noncovalent interactions

(44) Borghesani, G.; Pulidori, F.; Purrello, R.; Remelli, M.; Rizzarelli, E. *J. Chem. Soc., Dalton Trans.* **1990**, 2095.

(45) Pettit, L. D.; Hefford, R. J. W. *Metal Ions in Biological Systems*; Sigel, H., Ed.; Marcel Dekker: New York, 1979; Vol. 9, p 174.

in [Cu(CDhm)(L-TrpO)]⁺ could explain the small differences found in the thermodynamic quantities as well as in the magnetic parameters $g_{||}$ and $A_{||}$ with respect to [Cu(CDhm)(D-TrpO)]⁺. The interaction of the indole ring with the CD cavity favors the formation of the ternary complex with the D-isomer more than the π - π and d- π interactions in the case of the L-isomer.

Not only is this X-ray structure one of the few examples of metal complexes in which intramolecular aromatic ring stacking interactions occur but it also seems to suggest the reason for the cis disposition of amine nitrogen atoms. In fact, in the solid state another kind of interaction favors this disposition: the hydrogen bond between the nitrogen atom of the indole ring (N^cT) and a 6-OH of the CD cavity (O(6)7).

The last point to stress is the peculiarity of the crystal structure of this complex: it is a self-assembled structure in which a single CDhm can be contemporaneously considered guest and host. The histamino moiety and the indole ring are directed into the cavity of an adjacent CDhm molecule from the wider rim, forming a polymeric column structure as found in similar systems without any metal ion.²⁸

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Supporting Information Available: Tables of bond angles, bond distances, torsional angles, and general displacement parameters (15 pages). Ordering information is given on any current masthead page.

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