

## Zn(II) Complex of Tachquin, *N,N',N''*-Tris(2-quinolinylmethyl)-*cis,cis*-1,3,5-triaminocyclohexane); Synthesis and X-ray Structure of [Zn(tachquin)](ClO<sub>4</sub>)<sub>2</sub>·H<sub>2</sub>O

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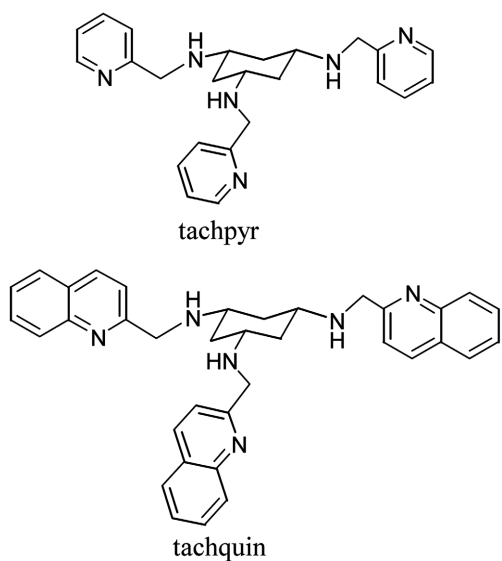
Ligands derived from the *cis*-1,3,5-triaminocyclohexane (tach) framework have shown versatility in binding transition metal ions of varied charges and sizes.<sup>1-3</sup> Derivatizations of the triamine framework in order to prepare hexadentate chelators based on the tach have been succeeded by addition of the 2-methylpyridyl pendant arms (tachpyr in Fig. 1),<sup>4</sup> by preparation of the *N*-alkylated derivatives of tachpyr ((*N*-Me)<sub>3</sub>tachpyr and (*N*-Et)<sub>3</sub>tachpyr),<sup>5</sup> and by preparation of the pyridine-ring alkylated tachpyr derivatives (tach-*n*-Me-pyr, *n* = 3-6).<sup>6,7</sup> The tachpyr ligand forms a nearly octahedral complex with Zn(II) (0.88 Å),<sup>8</sup> while it forms a complex intermediate between octahedral and trigonal-prismatic with Cd(II) (1.09 Å) and a slightly distorted trigonal-prismatic complex with Hg(II) (1.16 Å) exhibiting effects of metal radius on coordination geometry.<sup>9</sup> The tachpyr also have been demonstrated to affect the cellular iron metabolism of tumor cells, and to be quite cytotoxic to a variety of tumor cells as seen by an IC<sub>50</sub> of 4.8 μM toward cultured bladder tumor cells.<sup>5,10,11,12</sup>

The steric effects caused by *N*-alkylated tachpyr on the coordination geometry of the 3d transition metal complexes, ([M((*N*-Me)<sub>3</sub>tachpyr)]<sup>2+</sup>, M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II), were reported by Park *et al.*<sup>12</sup> The studies of effects of pyridyl ring alkylated tachpyr (tach-*n*-Me-pyr, *n* =

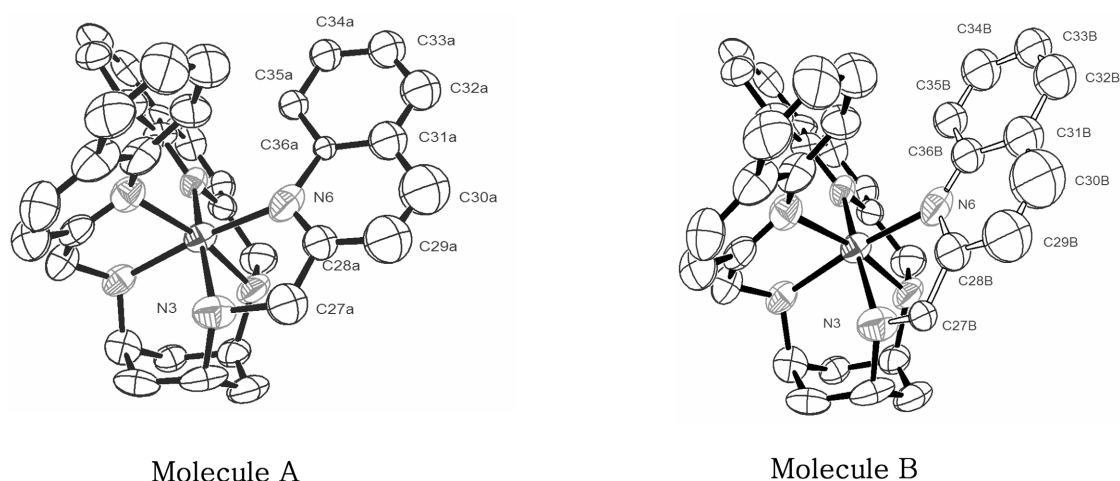
3, 4, 5, and 6) on complexation of Mn(II), Fe(II), Ni(II), Cu(II) and Zn(II) were also investigated. The steric repulsions between the 6-substituents at the threefold axis of the pseudo-octahedral coordination sphere in the 6-alkylated complexes result in a substantially weakened metal-ligand interaction, cause bond angle and length distortions, decrease of the coordination number to five, and shift of d-d electronic transitions to lower energies.<sup>7</sup> To better define the impact of the steric hindrance caused by bulk 2-quinolinyl-methyl pendent arms on metal complexation by tach-family chelators, the Zn(II) complexes of tachquin was synthesized and characterized (Fig. 1). The X-ray structure of [Zn(tachquin)]<sup>2+</sup> is described and compared to those of other tachpyr derivatives herein.

The title complex was prepared by the reactions of the metal ion perchlorate salts Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O and the ligand (1 : 1) in methanol. The formation of the complex and the rigidity of coordination spheres of the title compound were investigated by <sup>1</sup>H NMR studies. Upon complexation, the cyclohexyl framework of tachpyr derivatives including the tachquin undergoes a chair-chair flip that brings the coordinating arms into the axial positions from the equatorial positions which causes the distinctive change in the splitting pattern (AMM'XX') of the cyclohexyl protons in <sup>1</sup>H NMR due to relative positions of cyclohexyl ring protons. The formation of metal complexes also causes a diagnostic change in chemical shifts of the cyclohexyl protons in <sup>1</sup>H NMR.

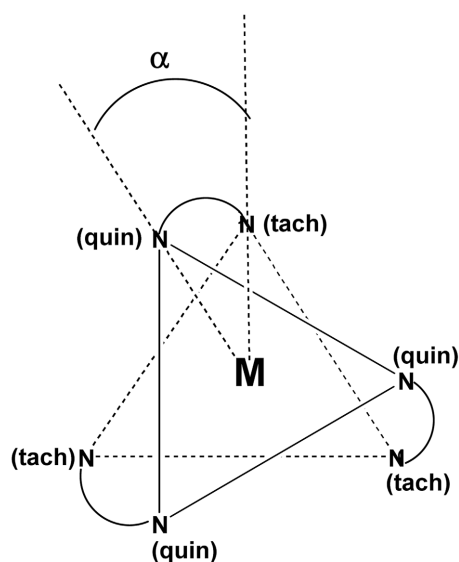
The Zn(II) complex of the tachquin, [Zn(tachquin)]-(ClO<sub>4</sub>)<sub>2</sub>·H<sub>2</sub>O, crystallize in the monoclinic space group *P*2<sub>1</sub>/*c*. Because Zn(II) metal ion does not have an electronic preference for either an octahedral or a trigonal-prismatic configuration, the structures of Zn(II) complex of tachquin should reflect the conformational preference of tachquin and non-bonded repulsions between donor groups. The coordination sphere of ZnN<sub>6</sub> in the title complex is best described as a slightly distorted octahedron with twist angle (α)<sup>15</sup> (Fig. 3), which is the angle through which one face of an octahedron has been rotated with respect to the opposite face, as viewed along with a threefold axis of the octahedron, of 51.8(5)°, 53.5(4)°, and 55.9(4)°, average 53.7(8)°. The twist angles in [Zn(tachquin)](ClO<sub>4</sub>)<sub>2</sub>·H<sub>2</sub>O are well compared to the average twist angle of 43.7(2)° in [Zn(tachpyr)](ClO<sub>4</sub>)<sub>2</sub>·CH<sub>3</sub>OH<sup>10</sup> and of 43.19(8)° in [Zn(N-



**Figure 1.** Tachpyr and tachquin ligands.



**Figure 2.** ORTEP view (50% probability of thermal ellipsoids) of  $[\text{Zn}(\text{tachquin})]^{2+}$  showing two disordered molecules with C27A to C36A at 50% occupancy (molecule A) and with C27B to C36B at 50% occupancy (molecule B), respectively. The two counter anions, two  $\text{ClO}_4^-$  ions, have been omitted for clarity.



**Figure 3.** Twist angle ( $\alpha$ ).

$\text{Me}_3\text{tachpyr}](\text{ClO}_4)_2$ .<sup>12</sup> The tachquin ligand seems to have a ligand conformation preference for an octahedral geometry without a major perturbation caused by the metal ion as like tachpyr and  $(\text{N-Me})_3\text{tachpyr}$  do. However, the ligand conformation preference for the octahedron geometry of the tachquin ligand seems to be stronger than that of the tachpyr ligand and the  $(\text{N-Me})_3\text{tachpyr}$  because of the steric effects of the quinolinyl groups, generating a distorted octahedron and allowing the quinolinyl groups to avoid each other by substantial twisting of the pendent arms. In a stereochemistry point of view, according to X-ray crystallography, the counter-clockwise twist of the pendant arms forms only delta ( $\Delta$ ) isomers.

The selected bond lengths and angles are given in Table 2. The Zn-N(tach) bond lengths in the title compound are of 2.124(9) Å, 2.135(9) Å and 2.171(9) Å. The bond lengths

**Table 1.** Crystal Data and Structure Refinement for  $[\text{Zn}(\text{tachquin})](\text{ClO}_4)_2 \cdot \text{H}_2\text{O}$

Compound	$[\text{Zn}(\text{tachquin})](\text{ClO}_4)_2 \cdot \text{H}_2\text{O}$
Color / Shape	colorless / fragment
Empirical formula	$\text{C}_{36}\text{H}_{38}\text{Cl}_2\text{N}_6\text{O}_9\text{Zn}$
Formula weight	834.99
Temperature	173(2) K
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	$a = 19.4136(13) \text{ \AA}$ $\alpha = 90^\circ$ $b = 16.2968(11) \text{ \AA}$ $\beta = 98.662(2)^\circ$ $c = 11.8519(8) \text{ \AA}$ $\gamma = 90^\circ$
Volume	$3706.9(4) \text{ \AA}^3$
Z	4
Density (calculated)	$1.496 \text{ Mg/m}^3$
Absorption coefficient	$0.870 \text{ mm}^{-1}$
Diffractometer / scan	Siemens SMART / CCD area detector
Radiation / wavelength	Mo $k\alpha$ (graphite monochrom.) / $0.71073 \text{ \AA}$
F(000)	1728
Crystal size	$0.20 \times 0.32 \times 0.40 \text{ mm}$
$\theta$ Range for data collection	$1.06$ to $20.41^\circ$
Index ranges	$-19 \leq h \leq 18$ , $-15 \leq k \leq 15$ , $-11 \leq l \leq 10$
Reflections collected	12064
Independent refls.	3651 ( $R_{\text{int}} = 0.00965$ )
Observed refls.	2190 ( $[I > 2\sigma(I)]$ )
Data / restraints / parameters	3305 / 0 / 525
Goodness-of-fit on $F^2$	1.076
SHELX-93 weight parameters	0.1420, 0.0000
Final R indices $[I > 2\sigma(I)]$	$R_1 = 0.0827$ , $wR_2 = 0.2042$
R indices (all data)	$R_1 = 0.1463$ , $wR_2 = 0.2614$
Largest diff. peak and hole	$1.060$ and $-0.430 \text{ e \AA}^{-3}$

of Zn-N(quin) in the title compound are of 2.296(9) Å, 2.255(9) Å and 2.198(10) Å. Typical Zn-N distances in zinc hexamine complexes are 2.143(5) Å (Zn-N(amine)) and 2.215(5) Å (Zn-N(pyridyl)) in  $[\text{Zn}(\text{ampy})_3]^{2+}$  (ampy = 2 pyridylmethylamine)<sup>16</sup> and an average Zn-N distance of 2.23 Å in  $[\text{LZn}]^{2+}$  (L = 1,4,7-tris(*o*-aminobenzyl)-1,4,7-triazacyclononane).<sup>17</sup> The tachquin ligand relieves the steric strain caused by the 2-quinolinylmethyl group through lengthening of Zn(II)-N(quin) bond and shortening of Zn(II)-N(tach) bond in its Zn(II) complex relative to the Zn(II) complex of tachpyr. The average bond lengths of Zn-N(tach nitrogen) and Zn-N(pyridyl nitrogen) in  $[\text{Zn}(\text{tachpyr})(\text{ClO}_4)_2 \cdot \text{CH}_3\text{OH}]$  are 2.160(3) and 2.165(4) Å, respectively.<sup>9</sup>

The bond length of Zn-N(tach), Zn-N(3) from the disordered 2-quinolinylmethyl arms, 2.171(9) Å, is slightly longer than those of Zn-N(tach) from non-disordered 2-quinolinylmethyl arms, 2.124(9) and 2.135(9) Å, respectively. The bond length of Zn-N(quin), Zn-N(6) from the disordered 2-quinolinylmethyl arms, 2.198(10) Å, is slightly shorter than those of Zn-N(quin) nitrogen from non-disordered 2-quinolinylmethyl arms, 2.296(9) and 2.255(9) Å, respectively. Because of substantial twisting of the 2-quinolinylmethyl pendent arms to avoid each others, one of the cyclohexyl nitrogen is expanded away from the axial position and coordinates at a greater distance from Zn(II) ion resulting in a longer Zn(II)-N(tach) bond. Consequently, the identical pendent arm is pushed toward the metal ion, leading the quinolinyl nitrogen closer to the metal ions, resulting in a shorter Zn(II)-N(quin) bond.

The bond angles of N(tach)-Zn(II)-N(quin) in the each pendent arms are 79.5(4)°, 79.5(4)°, and 79.3(4)°, respec-

tively, and the bond angles of N(tach)-Zn(II)-N(tach), from one N(tach) to Zn(II) and then to the other two N(tach), are 92.3(3)° and 90.0(4)°, respectively. There is no difference in the average bond angles of cyclohexyl(C)-N(tach)-methyl(C)quinolinyl from non-disordered pendent arms and from the disordered pendent arm, 113(1) and 113(2), respectively. The average bond angle of quinolinyl(C)-N(quin)-Zn from the non-disordered pendent arms, 129(1)°, is smaller to that from the disordered pendent arm, 132(2)°. However, the average bond angle of quinolinyl(C)-N(quin)-methyl(C)-quinolinyl from the non-disordered pendent arms, 118(1)°, is bigger than that from the disordered pendent arm, 113(2)°.

In conclusion, the tripodal quinolinyl chelator tachquin demonstrates a strong preference for octahedral coordination geometry with the average twist angle ( $\alpha$ ) of 53.7(8). The steric effect of the bulk quinolinyl is pronounced and resulted that one of the pendent arms of the title compound is disordered with two different positions of the 2-methylquinilnyl arm with C27A to C36A at 50% occupancy and with C27B to C36B at 50% occupancy, respectively.

## Experimental Section

**Materials and methods.** All the materials were of a research grade or a spectro-quality grade in the highest purity available and were generally used without further purification except Et<sub>2</sub>O. Et<sub>2</sub>O was distilled from Na/K and used immediately. Anhydrous grade MeOH and CH<sub>3</sub>CN, and the salts Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O were obtained from Aldrich. DMSO-*d*<sub>6</sub> was obtained from Cambridge Isotope Laboratories. <sup>1</sup>H spectra were obtained using a Bruker AM360 instrument. Elemental analysis was performed by Atlantic Microlabs (Atlanta, Georgia). Tachquin was prepared as previously reported with small modification.<sup>4</sup> Tach was reacted with quinoline-2-carbaldehyde to form the respective tris(imine), which was then reduced by borohydride to provide the hexadentate tachquin ligand.

**Synthesis of  $[\text{Zn}(\text{tachquin})(\text{ClO}_4)_2 \cdot \text{H}_2\text{O}]$ .** To a colorless solution of Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (0.0340 g, 9.11 × 10<sup>-5</sup> mol) in anhydrous MeOH (2 mL) was added a brown solution of tachquin (0.0986 g, 9.11 × 10<sup>-5</sup> mol) in anhydrous MeOH (2 mL) affording a pale yellow precipitate. Et<sub>2</sub>O (12 mL) was added to form more precipitates, which were isolated by decanting supernatant and dried under reduced pressure giving a pale yellow solid. This was dissolved in CH<sub>3</sub>CN, and Et<sub>2</sub>O was diffused into it giving a yellow precipitate and colorless prisms. The crystals were isolated, washed with Et<sub>2</sub>O, and dried under reduced pressure affording a white solid in 39.0% yield (0.0290 g, 3.55 × 10<sup>-5</sup> mol). Single crystals suitable for X-ray crystallography were obtained by Et<sub>2</sub>O diffusion into a CH<sub>3</sub>CN solution of the complex. Anal. Calcd for C<sub>36</sub>H<sub>36</sub>Cl<sub>2</sub>N<sub>6</sub>O<sub>8</sub>Zn·2H<sub>2</sub>O: C, 50.69; H, 4.73; N, 9.85. Found: C, 50.87; H, 4.82; N, 9.69. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 25 °C): δ 8.59, 7.99, 7.65, 7.54, 7.42, 7.15 (d, d, d, d, t, t, 6H, <sup>3</sup>J = 8.2 and 7.2 Hz, C<sub>9</sub>H<sub>6</sub>N); 4.63 (br s, AXY, 1H, NH-CH<sub>2</sub>); 4.38 (br s, AXY, 2H, NH-CH<sub>2</sub>-py); 3.20 (br s,

**Table 2.** Selected Bond Lengths (Å) and Bond Angles (°)

Bond lengths			
Zn-N(1)	2.124(9)	Zn-N(4)	2.296(9)
Zn-N(2)	2.135(9)	Zn-N(5)	2.255(9)
Zn-N(3)	2.171(9)	Zn-N(6)	2.198(10)
N(1)-C(7)	1.497(13)	N(1)-C(1)	1.496(14)
N(3)-C(5)	1.502(13)	N(3)-C(27A)	1.59(2)
N(3)-C(27B)	1.31(2)	N(6)-C(28A)	1.21(3)
N(6)-C(28B)	1.54(3)	N(6)-C(36A)	1.55(2)
N(6)-C(36B)	1.26(3)		
Bond angles			
N(1)-Zn-N(4)	79.5(4)	N(2)-Zn-N(5)	79.5(4)
N(3)-Zn-N(6)	79.3(4)	N(1)-Zn-N(2)	92.3(3)
N(1)-Zn-N(3)	90.0(4)	N(4)-Zn-N(5)	104.5(4)
N(4)-Zn-N(6)	96.7(4)	N(1)-Zn-N(4)	79.5(4)
C(7)-N(1)-C(1)	112.6(9)	C(7)-N(1)-Zn	112.3(6)
C(1)-N(1)-Zn	115.3(7)	N(1)-C(1)-C(2)	109.2(9)
C(20)-C(19)-C(18)	119.3(12)	N(3)-C(27A)-C(28A)	115.8(20)
N(3)-C(27B)-C(28B)	128.6(27)	N(6)-C(28B)-C(29B)	118.6(27)
N(6)-C(28A)-C(27A)	117.1(23)	N(6)-C(28A)-C(29A)	128.6(27)
C(28A)-N(6)-C(36A)	112.7(16)	C(28B)-N(6)-C(36B)	112.7(16)
N(6)-C(36A)-C(35A)	118.4(17)	N(6)-C(36B)-C(35B)	110.9(24)

*AMM'XX'*, 1H, cyclohexyl methine H's); 2.29 (br d, *AMM'XX'*, 1H, equatorial cyclohexyl methylene H's, diastereotopic), 1.87 (br d, *AMM'XX'*, 1H, axial cyclohexyl methylene H's, diastereotopic).

**X-ray crystallography.** Transparent single crystals of [Zn(tachquin)](ClO<sub>4</sub>)<sub>2</sub>·H<sub>2</sub>O were mounted on fibers and transferred to the goniometer. The crystals were cooled to -100 °C during data collection by using a stream of cold nitrogen gas. Data collection was made on a Siemens SMART diffractometer with a CCD area detector diffractometer ( $-19 \leq h \leq 18$ ,  $-15 \leq k \leq 15$ ,  $-11 \leq l \leq 20$ ;  $1.06 \leq \theta \leq 20.41^\circ$ ), using graphite monochromatic Mo K $\alpha$  radiation at 0.71073 Å. A total of 12064 reflections were measured; 3651 reflections were unique ( $R_{\text{int}} = 0.00965$ ), and 2190 reflections with  $I > 2\sigma(I)$  were considered to be observed for purposes of  $R$  value computation. SHELXTL, version 5, software was used for solutions and refinement.<sup>13</sup> Absorption correction was carried out using the program SADABS.<sup>14</sup> The model was refined by full-matrix least squares on  $F^2$ . A summary of data collection parameters is given in Table 1. The structures were solved by direct methods. One of the 2-quinilinylmethyl arms of the ligand is disordered upon complexation generating two different positions of the 2-methylquinilinylyl arm with C27A to C36A at 50% occupancy and with C27B to C36B at 50% occupancy, respectively, coordinated to Zn(II) through identical nitrogen donor atoms, N(3) and N(6) (Fig. 2). The geometrically constrained hydrogen atoms were placed in calculated positions and allowed to ride on the bonded atom with  $B = 1.2 \text{ Ueq}(\text{C})$ . The twist angles  $\alpha$  were calculated by first determining the centroid in each of the triangles of the three cyclohexyl nitrogens (N(tach); designated as X1) and of the three quinolinylyl nitrogens (N(quin); designated as X2).

Further details of the crystal structure investigation may be obtained in writing from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen, Germany, on quoting the depository number CSD415533.

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