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Stability Constants for Some Metal Complexes of *cis,cis*-1,3,5-Triaminocyclohexane-*N,N',N''*-triacetic Acid

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The synthesis and equilibrium studies of the new amino acid *cis,cis*-1,3,5-triaminocyclohexane-*N,N',N''*-triacetic acid (*cis,cis*-TACHTA) are described. Reaction stoichiometries for 1:1 metal-*cis,cis*-TACHTA complexes and corresponding equilibrium constants have been determined from potentiometric data. Electronic spectra of several of the complexes are reported. A comparison of the stability constants of the 1:1 complexes of *cis,cis*-TACHTA with those of other sexadentate amino acids is presented and discussed.

Recent work indicates that *cis,cis*-1,3,5-triaminocyclohexane (*cis,cis*-tach) exhibits a tridentate coordination with many transition metal ions.¹ This conclusion is supported by spectroscopic studies.^{2,3} The interesting stereochemistry displayed by *cis,cis*-tach in several metal complexes prompted the synthesis of the potentially sexadentate amino acid derivative *cis,cis*-1,3,5-triaminocyclohexane-*N,N',N''*-triacetic acid (*cis,cis*-TACHTA).⁴ Equilibrium studies of the complexes of *cis,cis*-TACHTA with Co(II), Ni(II), Cu(II), and Zn(II) are now reported.

Experimental Section

***cis,cis*-1,3,5-Triaminocyclohexane-*N,N',N''*-triacetonitrile Hydrochloride.**—To a cold (5°) suspension of 3.38 g (13.2 mmol) of *cis,cis*-tach·3HCl·H₂O in 40 ml of ether was added a solution of 1.94 g (39.6 mmol) of NaCN in 4 ml of water while the temperature was kept below 10°. Formalin (3.5 ml) was then added dropwise and the solution was stirred for 1 hr at 10°. After standing for 15 hr at room temperature 50 ml of methanol was added and the solution was cooled in an ice bath. After 1 hr, the precipitated NaCl was filtered and the filtrate was then saturated with HCl gas while the temperature was kept below 20°. The pale yellow crystals of the amine triacetonitrile hydrochloride were collected and recrystallized from aqueous methanol to give 4.4 g (11.1 mmol, 84%) of white crystals, mp 184–186° dec. *Anal.* Calcd for C₁₂H₁₈N₆·3HCl·H₂O: C, 38.57; H, 6.20; N, 22.49. Found: C, 39.02; H, 6.40; N, 21.92. Nmr: δ_{TMS}^{D₂O} 2.35 (q, H_{axial}), 3.26 (d, H_{equatorial}), 4.27 (t, H_{methine}), 5.00 (s, H_{ethylene}).

***cis,cis*-1,3,5-Triaminocyclohexane-*N,N',N''*-triacetic Acid Hydrochloride.**—Concentrated hydrochloric acid (35 ml) was added dropwise over the period of 1 hr to 4.14 g (11.1 mmol) of the nitrile hydrochloride cooled in an ice bath. The suspension was stirred for 15–20 min and removed from the ice bath. The reaction mixture was refluxed until solution occurred; then HCl gas was passed through the solution until the white hydrochloride salt appeared. After cooling, the salt was collected and washed with concentrated HCl, ethanol, and ether. An additional crop of crystals was obtained by evaporation of the filtrate followed by the addition of ethanol. The combined product was recrystallized from 8 F HCl to yield 4.12 g (10.2 mmol, 92%) of white crystals, mp 186–188° dec. *Anal.* Calcd for C₁₂H₁₈N₆·3HCl·2H₂O: C, 32.11; H, 6.29; N, 9.36; Cl, 23.70. Found: C, 32.77; H, 6.13; N, 9.19; Cl, 23.89. Nmr: δ_{TMS}^{D₂O} 2.33 (q, H_{axial}), 3.24 (d, H_{equatorial}), 4.11 (t, H_{methine}), 4.63 (s, H_{ethylene(glycol)}).

Materials.—Solutions of *cis,cis*-TACHTA·3HCl were prepared from the recrystallized salt and standardized by titration with standard NaOH solution. The number of moles of base

required for the strong acid inflection was assumed to be equal to 3 times the number of moles of *cis,cis*-TACHTA present.

Metal nitrate and chloride solutions prepared from reagent grade chemicals were standardized with EDTA by standard procedures.⁵

The titrant solutions of carbonate-free sodium hydroxide were standardized against potassium acid phthalate.

Procedures.—Titrations of metal-ligand systems were performed with equimolar quantities of metal and ligand. Several titrations were performed for each system at concentrations ranging from 2 to 6 × 10⁻³ F. Owing to the slow establishment of equilibrium in the Ni(II)-*cis,cis*-TACHTA system, a procedure similar to that previously described was carried out.¹

A Radiometer pHM 26 pH meter was used in combination with Radiometer glass and calomel electrodes. The meter-electrode system was calibrated to provide -log [H⁺] values directly by titration with acetic acid and HCl solutions both 0.1 F in KCl. The values of K_a for acetic acid (2.85 × 10⁻⁵) and K_w (1.63 × 10⁻¹⁴) at 25° in 0.1 M KCl were taken from Harned and Owen.⁶

The test solutions were protected from air by a stream of humidified prepurified nitrogen. All measurements were performed at 25° in 0.1 F KCl.

Electronic spectra were recorded with a Cary Model 14 spectrophotometer. Sample solutions containing equimolar ratios of metal ion and ligand were adjusted to pH 11 by addition of sodium hydroxide solution. Special precautions to exclude oxygen were observed with the cobalt(II) system. This procedure was felt necessary because of the formation of an oxygen-containing complex.

Nmr spectra were recorded with a Varian A-60 spectrometer and chemical shifts are relative to TMS (external capillary).

Calculations.—Equilibrium constants were calculated from the titration data by means of the generalized program SCOGS.⁷ The program was adapted for a time-sharing Control Data Corp. 3600 facility and modified as described below.

The program SCOGS employs an iterative Newton-Raphson procedure in which initial guesses for stability constants are refined until the sum of the squares of the residuals in titer (difference between the experimental titer at any point and the titer calculated using the refined stability constants) passes through a minimum. The concentrations of all chemical species are calculated from the refined constants. A theoretical titration curve was generated by substitution of the concentration for the given species in the mass balance expression for a 1:1 ligand-metal system shown in eq 1. [L]_t is the analytical concentration of

$$a^*[L]_t + [H] - [OH] = \sum_{p=0}^{p=3} (3-p)[H_pL] + \sum_{p=0}^{p=3} p[MH_{3-p}L] + \sum_{q=0}^q (q+3)[ML(OH)_q] + \sum_{q=0}^q q[M(OH)_q] \quad (1)$$

ligand. The symbol *a** corresponds to the number of moles of base added per mole of ligand present and a plot of pH vs. *a** gives the theoretical titration curve.

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TABLE I
 Acidity Constants of *cis,cis*-TACHTA^a

Reaction	-Log K _a
H ₃ L ⇌ H ₂ L ⁻ + H ⁺	6.45 ± 0.01
H ₂ L ⁻ ⇌ HL ²⁻ + H ⁺	8.06 ± 0.01
HL ²⁻ ⇌ L ³⁻ + H ⁺	9.60 ± 0.02

Stability Constants of Metal-*cis,cis*-TACHTA Complexes^a

Reaction	Log K			
	Co(II)	Ni(II)	Cu(II)	Zn(II)
M ²⁺ + L ³⁻ ⇌ ML ⁻	13.81 ± 0.03	16.56 ± 0.05	17.13 ± 0.02	13.41 ± 0.02
M ²⁺ + HL ²⁻ ⇌ MHL	8.34 ± 0.08	10.76 ± 0.08	11.18 ± 0.03	7.87 ± 0.05

^a μ = 0.1 (KCl) and temperature is 25.0°.

Simplifying assumptions made in the region where stability constant calculations were carried out leads to the expression

$$a^*[L] + [H] - [OH] = [H_2L] + 2[HL] + 3[ML] + 2[MHL] \quad (2)$$

The validity of this approximation will be discussed later.

A factor (*F*) included in the computer program to provide for small systematic errors^{8,9} was found to have little effect on the derived stability constants when varied through the range of 0.78–1.00. The standard deviation in titer (SDT) appears to show a minimum in the region of *F* = 1.00, and this was used throughout.

Results

Titration.—The potentiometric titration curve of *cis,cis*-TACHTA·3HCl, H₃L³⁺, features a steep inflection at *a* = 3 (where *a* indicates the moles of base added per mole of ligand present) corresponding to the titration of the three carboxylate protons (strong acid). The three remaining protons dissociate between *a* = 3 and *a* = 6. The acidity constants are listed in Table I.

Titration curves obtained with equimolar mixtures of the trihydrochloride with zinc(II) and similar mixtures with cobalt(II) are superimposable with the titration curve of the free acid alone between *a* = 0 and *a* = 3. This behavior implies that complexes of *cis,cis*-TACHTA with these metal ions are not present in appreciable concentrations until all the carboxylate protons have been neutralized. Between *a* = 3 and *a* = 6 complex formation occurs. This has the effect of depressing both the cobalt(II) and zinc(II) titration curves below that of the free acid. Both the copper(II) and nickel(II) titration curves are depressed below the free-acid curve throughout the *a* = 0–6 range. This indicates that the three weak-acid protons on the ligand are displaced to some degree between *a* = 0 and *a* = 3.

By suitable use of the program SCOGS, it is possible to obtain a high degree of discrimination in the selection of chemical species.⁸ This involved the simultaneous treatment of data from several metal–ligand titrations performed at different concentrations. Data obtained between *a* = 3 and *a* = 6 were employed in the calculations. The *a* values were suitably adjusted for use with eq 1 and 2 (*a** = *a* – 3).

Studies have indicated that *cis,cis*-tach coordinates to a single metal ion, the nitrogen atoms occupying axial positions in the cyclohexane ring (chair conformation).^{1–3} On the assumption that *cis,cis*-TACHTA coordinates in a similar manner, the predominant species are likely limited to the 1:1 complex, its protonated and hydrolyzed forms.

The inclusion of hydrolyzed species of the form ML(OH)_q^{(q+1)-} did not improve the SDT and the es-

timated value of the equilibrium constants progressively decreased without convergence. Attempts to evaluate the stability constants for negligible species have resulted in this type of behavior with SCOGS and similar programs.¹⁰ However, it was necessary in all metal–ligand systems studied to introduce a protonated form of the complex, MHL, in order to minimize the SDT. The improvement in the SDT obtained by inclusion of the protonated species in the calculations for the metal–ligand systems studied here is illustrated in Figures 1 and 2.

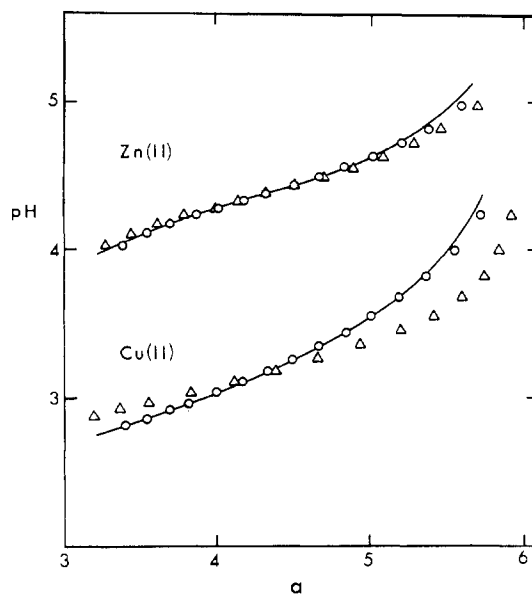


Figure 1.—Titration curves for Zn(II):H₃L = 1:1 and Cu(II):H₃L = 1:1. The titrant was 0.1 *F* NaOH and the titration was conducted in 0.1 *F* KCl at 25° with [M(II)] = 5 × 10⁻³ *M*. The solid lines are experimental titration curves. The points (Δ without protonated species, ○ including protonated species) were computed from the derived stability constants.

In the case of all 1:1 metal-*cis,cis*-TACHTA systems only two complexed species ML⁻ and MHL are required to fit experimental data within the estimated uncertainty in measurement. The stability constants obtained in this study are summarized in Table I.

Electronic Spectra.—The electronic spectra of solutions containing equimolar ratios of metal ion and ligand were recorded at pH 11, where equilibrium studies indicate complex formation is essentially complete. Details of the spectra are given in Table II.

Electronic spectra of the nickel(II) and cobalt(II) complexes seem to indicate octahedral coordination.

(8) C. W. Childs and D. D. Perrin, *J. Chem. Soc. A*, 1039 (1969).

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(10) D. D. Perrin and V. S. Sharma, *J. Chem. Soc. A*, 724 (1967).

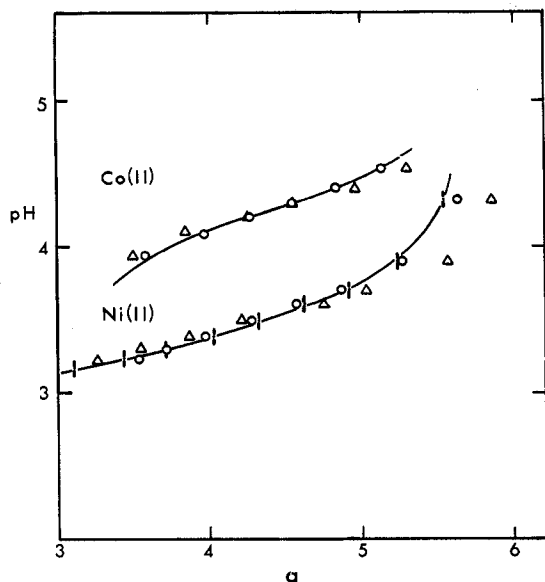


Figure 2.—Titration curves for Co(II):H₆L = 1:1 and Ni(II):H₆L = 1:1. The titrant was 0.1 *F* NaOH and the titration was conducted in 0.1 *F* KCl at 25° with [Co(II)] = 6 × 10⁻³ *M* and [Ni(II)] = 2 × 10⁻³ *M*. The solid lines are experimental titration curves (the experimental points for the Ni(II) titration are indicated (Δ) with the smooth curve drawn through these points). The points (Δ without protonated species, O including protonated species) were computed from the derived stability constants.

TABLE II
ELECTRONIC ABSORPTION SPECTRA (cm⁻¹) OF THE COBALT(II), NICKEL(II), AND COPPER(II) COMPLEXES^a

Co(<i>cis,cis</i> -TACHTA) ⁻	9620 (11), 19700 (45)
Ni(<i>cis,cis</i> -TACHTA) ⁻	10,900 (12), 12,800 sh, 17,900 (5), 28,400 (9), 33,300 sh
Cu(<i>cis,cis</i> -TACHTA) ⁻	10,300 (18), 15,700 (108)

^a Numbers in parentheses are molar extinction coefficients.

The nickel(II) spectrum may be interpreted on the basis of an octahedral field, the bands at 10,900, 17,900, and 28,400 cm⁻¹ being assigned to the ³A_{2g} → ³T_{2g}(F), ³A_{2g} → ³T_{1g}(F), and ³A_{2g} → ³T_{1g}(P) transitions, respectively. The shoulder at 12,800 cm⁻¹ may be due to the ³A_{2g} → ¹E_g transition. The shoulder at 33,300 cm⁻¹ may arise from the splitting of the ³T_{1g}(P) state in the trigonal field imposed by the ligand.¹¹

We interpret the cobalt(II) spectrum by assigning the broad band centered at 19,700 cm⁻¹ to the ⁴T_{1g}(F) → ⁴T_{1g}(P) and ⁴T_{1g}(F) → ⁴A_{2g} transitions, while the band at 9620 cm⁻¹ may be assigned to the ⁴T_{1g}(F) → ⁴T_{2g}(F) transition. The spectrum of the cobalt(II) complex appears to indicate octahedral rather than some other stereochemistry;¹² however we feel this interpretation is conjectural and more evidence must be obtained before any definite conclusion of the cobalt(II) stereochemistry can be obtained.

The spectrum of the copper(II) complex appears con-

sistent with a tetragonally distorted octahedral complex.¹³

Discussion

The stability constants for the 1:1 metal-*cis,cis*-TACHTA complexes follow the Irving-Williams order. Because few sexadentate amino acids, which contain only carboxylate and amino groups, are known, the stability constants obtained here have been compared to those of EDTA and CDTA (Table III).

TABLE III
STABILITY CONSTANTS OF AMINO ACID COMPLEXES

	M ⁿ⁺ + L ^{a-} ⇌ M ⁿ⁻ L		
	<i>cis,cis</i> -TACHTA ^a	EDTA ^b	CDTA ^{b,c}
Co(II)	13.8	16.2	19.6
Ni(II)	16.6	18.6	
Cu(II)	17.1	18.8	22.0
Zn(II)	13.4	16.3	19.3

^a See Table I for experimental conditions. ^b μ = 0.1 (KNO₃) and temperature is 20.0°. L. G. Sillén and A. E. Martell, "Stability Constants of Metal-Ion Complexes," The Chemical Society, London, 1964. ^c *trans*-1,2-Diaminocyclohexane-*N,N,N',N'*-tetraacetic acid.

There are several significant structural differences between *cis,cis*-TACHTA and EDTA and CDTA. The EDTA and CDTA each have two tertiary amino and four carboxylate groups while *cis,cis*-TACHTA features three secondary amino and three carboxylate groups. Despite these structural differences, however, there are some effects which can be compared. The stability constants obtained for the *cis,cis*-TACHTA complexes are several orders of magnitude less than those with EDTA and CDTA. This lower stability may be, in part, due to the different ionic charges of the ligand anions, the EDTA and CDTA being tetraanionic while the *cis,cis*-TACHTA is trianionic. The stereochemical aspects, which depend upon the relative conformation of the donor atoms and are responsible for the differences in stability between EDTA and CDTA complexes, cannot be evaluated for *cis,cis*-TACHTA because closely analogous ligands are not available. However, steric factors may also contribute to the lower stability of the *cis,cis*-TACHTA complexes since this ligand must undergo a conformational change from equatorial to axial chair form in order for the three nitrogen atoms to coordinate to a single metal ion. This conformational rearrangement may be responsible for the relatively slow kinetics observed in the cobalt(II), nickel(II), and zinc(II) titrations (typically titration mixtures required *ca.* 3 hr, 24 hr, and 30 min, respectively, before stable pH readings were obtained). However, equilibrium was rapidly established in the copper(II) titration. This lability is characteristic of copper(II) reactions with amino acid ligands.¹⁴

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(11) Theoretical studies in progress in this laboratory seem to support this statement.

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