Inorg. Chem. **1999,** *38,* 859−868 **859**

O-Alkylated Derivatives of 1,3,5-Triamino-1,3,5-trideoxy-*cis*-inositol: Triamine Ligands with Unexpectedly High Affinity toward Divalent Transition- and d^{10}-Metal Ions

Michael Weber, Dirk Kuppert, and Kaspar Hegetschweiler*

Universität des Saarlandes, Anorganische Chemie, Postfach 15 11 50, D-66041 Saarbrücken, Germany

Volker Gramlich

Institut für Kristallographie, ETH Zentrum, CH-8092 Zürich, Switzerland

Received July 23, 1998

The ligands *all-cis*-2,4,6-trimethoxycyclohexane-1,3,5-triamine (tmca) and *all-cis*-2,4,6-tribenzoxycyclohexane-1,3,5-triamine (tbca) were prepared almost quantitatively by using $[Ni(taci)_2]^{2+}$ (taci = 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol) as precursor, where Ni^{2+} acted as a very efficient protecting group for the nitrogen donors. The structure of tmca in solution was investigated by NMR spectroscopy. A strongly solvent-dependent conformational equilibrium was observed. In CD_3CN, a chair conformation with three axial amino groups formed exclusively, whereas in D_2O, the conformation with three equatorial amino groups predominated. This effect, as well as conformational changes in the course of stepwise protonation, is discussed in terms of hydrogen bonding effects. The crystal structure of H_3tmca^{3+} exhibits a chair conformation with three equatorial ammonium groups and three axial methoxy groups. The trihydrochloride hydrate crystallizes in the monoclinic space group $P2_1/n$, $a = 11.057(5)$ Å, $b = 9.960(6)$ Å, $c = 14.671(6)$ Å, $\beta = 93.79(3)°$, $Z = 4$ for $C_9Cl_3H_{26}N_3O_4$. A variety of bis complexes $[M(tmca)_2]^{2+}$ (M = Ni, Cu, Zn, Cd) and $[M(tbca)_2]^{2+}$ (M = Ni, Cu) were prepared and they were isolated as solid, crystalline trinitrate or trichloride salts. Crystal data: $[Ni(tmca)_2](NO_3)_2{\cdot}4H_2O$, triclinic, space group $P\bar{1}$, $a = 8.919(11)$ Å, $b = 9.293(9)$ Å, $c = 9.942(11)$ Å, $\alpha = 96.73(9)°$, $\beta = 100.66(9)°$, $\gamma = 101.95(9)°$, $Z = 1$ for $C_{18}H_{50}N_8NiO_{16}$; $[Cu(tmca)_2](NO_3)_2$, tetragonal, space group $P\bar{4}2_1c$, $a = 13.017(6)$ Å, $c = 15.985(10)$ Å, $Z = 4$ for $C_{18}CuH_{42}N_8O_{12}$; $[Ni(tbca)_2](NO_3)_2{\cdot}MeCN{\cdot}H_2O$, monoclinic, space group $P2_1/c$, $a = 12.930(8)$ Å, $b = 19.324(10)$ Å, $c = 22.724(14)$ Å, $\beta = 97.21(5)$ °, $Z = 4$ for $C_{56}H_{71}N_9NiO_{13}$. The formation constants of $[M(tmca)]^{2+}$ and $[M(tmca)_2]^{2+}$ were determined by means of a series of potentiometric titration experiments. A comparison of the taci complexes with the corresponding tmca complexes revealed an unexpected increase of stability for the latter. This increase is more than 2 orders of magnitude for the 1:1 complexes and about 5 orders of magnitudes for the 1:2 complexes. Possible reasons for this unexpected increase in stability are discussed.

Introduction

Tailored chelating agents are of interest with respect to a systematic modulation of properties that are related to the electronic characteristics of a metal cation such as the redox potential, the electron-transfer rate, magnetic moment (spin state) and the energy of the d−d transitions.[1] In medicine, selective ligands are used for the treatment of metal intoxications such as Wilson's disease, iron overload, or lead poisoning, and for the stabilization of metal cations in diagnostic radiopharmaceuticals and paramagnetic contrast agents.[2] The electronic characteristics of the donor atoms and the steric demands of the ligand backbone are two key properties for the design of a highly selective chelator.[3] The affinity of a specific metal cation for a donor atom may be described in terms of empirically derived correlations such as the HSAB principle.[4] Steric strain within the complex can be analyzed by Molecular Mechanics in terms of simple force field calculations.[5] Other effects, such as the influence of solvation are much more difficult to predict and are seldom considered by most of the empirical or semiempirical methods.

In an extended investigation of the coordinating properties of 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol (taci) we found that peripheral modifications in the ligand structure may result in a rather unexpected but dramatic change in the complex stability. Taci itself is a versatile ligand,[6] whereas the *N*-methylated 1,3,5-trideoxy-1,3,5-tris(dimethylamino)-*cis*-inositol (tdci) proved to

---

* To whom correspondence should be addressed.

(1) (a) Comba, P. *Coord. Chem. Rev.* **1993**, *123*, 1. (b) Geue, R. J.; Hanna, J. V.; Höhn, A.; Quin, C. J.; Ralph, S. F.; Sargeson, A. M.; Willis, A. C. In *Electron-Transfer Reactions*; Isied, S., Ed.; ACS Symposium Series; American Chemical Society: Washington, DC, 1997; Chapter 8. (c) Comba, P.; Hilfenhaus, P.; Nuber, B. *Helv. Chim. Acta* **1997**, *80*, 1831. (d) Comba, P.; Jakob, H. *Helv. Chim. Acta* **1997**, *80*, 1983. (e) Comba, P.; Sickmüller, A. F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2006. (f) Comba, P.; Sickmüller, A. F. *Inorg. Chem.* **1997**, *36*, 4500.

(2) (a) Hider, R. C.; Hall, A. D. *Prog. Med. Chem.* **1991**, *28*, 41. (b) Martell, A. E.; Hancock, R. D. Metal Complexes in Aqueous Solution. In *Modern Inorganic Chemistry*; Fackler, J. P., Ed.; Plenum Press: New York, 1996; Chapter 5. (c) Jurisson, S.; Berning, D.; Jia, W.; Ma, D. *Chem. Rev.* **1993**, *93*, 1137. (d) Lauffer, R. B. *Chem. Rev.* **1987**, *87*, 901. (e) Dilworth, J. R.; Parrott, S. J. *Chem. Soc. Rev.* **1998**, *27*, 43.

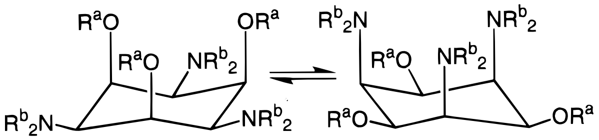
(3) Hancock, R. D.; Martell, A. E. *Chem. Rev.* **1989**, *89*, 1875.

(4) Pearson, R. G. *Chemical Hardness*; Wiley-VCH: Weinheim, Germany, 1997.

(5) (a) Hancock, R. D. *Prog. Inorg. Chem.* **1989**, *37*, 187. (b) Comba, P.; Hambley, T. W. *Molecular Modeling of Inorganic Compounds*; VCH: Weinheim, Germany, 1995. (c) Bygott, A. M. T.; Sargeson, A. M. *Inorg. Chem.* **1998**, *37*, 4795.

10.1021/ic980867m CCC: \$18.00

Scheme 1



taci: $R^a = R^b = H$
tdci: $R^a = H$, $R^b = CH_3$
tmca: $R^a = CH_3$, $R^b = H$
tbca: $R^a = CH_2\text{-}C_6H_5$, $R^b = H$

be selective toward hard and highly charged metal cations (Scheme 1).[7] This is not surprising because a conformation of tdci with the three bulky dimethylamino groups in axial position is expected to be of very high energy. Consequently, tdci binds metal cations mainly using the oxygen atoms whereas taci can bind via both the oxygen and the nitrogen donors. It is, however, surprising that complexes such as $[Al(taci)_2]^{3+}$ and $[Al(tdci)_2]^{3+}$ are of significantly different stability: the formation constant of the tdci complex is 8 orders of magnitude greater than the corresponding taci complex, even though no significant structural differences were encountered within the two coordination spheres.[7]

It would be of interest to know whether similar effects are also observed for an O-methylated derivative such as *all-cis*-2,4,6-trimethoxy-cyclohexane-1,3,5-triamine (tmca). This ligand is expected to show preferential binding through the amino groups. $[Fe(tmca)_2]^{3+}$ exhibited indeed a low-spin FeN_6-hexaamine structure, while $[Fe(taci)_2]^{3+}$ showed a mixed FeO_3N_3 coordination sphere.[8]

The synthesis of such O-alkylated derivatives proved, however, difficult. Direct treatment of taci with alkylating agents resulted in N- rather than O-alkylation. A variety of classical protecting groups such as *tert*-butyloxycarbonyl (BOC) or phthalimide were investigated to get suitable starting materials. Although these groups could readily be attached to the nitrogen atoms, the resulting derivatives showed no significant reactivity toward the alkylating agent.[9] Obviously, the large steric demands of the protecting groups enforce an equatorial orientation of the nitrogen donors and consequently the hydroxy groups are in the axial positions. It is well-known that the axial substituents of a cyclohexane residue exhibit significantly reduced reactivity.[10] Therefore successful O-alkylation would only be possible if the hydroxy groups could be forced into the equatorial positions. In the present investigation, we describe a convenient and effective method for the preparation of O-alkylated ligands such as tmca and *all-cis*-2,4,6-tribenzoxycyclohexane-1,3,5-triamine (tbca) on a large scale as required for the comparative study of the coordinating properties. Binding of a variety of divalent transition and d^{10} metal cations to tmca was investigated by means of single-crystal structure analyses and extended potentiometric measurements, to elucidate whether there is a similar change in stability to that observed in the taci-tdci system.

Experimental Section

Physical Measurements. ^1H and ^{13}C NMR spectra were measured on a Bruker DRX 500 spectrometer (with resonance frequencies of 500.13 and 125.9 MHz for ^1H and ^{13}C, respectively) with δ scale (ppm) and tetramethylsilane or sodium (trimethylsilyl)propionate-d_4 (=0 ppm) as internal standard. Two-dimensional NMR experiments (gradient-selected $^1H,^1H$ COSY and gradient-selected $^{13}C,^1H$ HMQC) were performed according to the literature.[11] Coupling constants are given in Hertz and multiplicity labels are abbreviated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad signal. pD values were calculated from the pH (measured by a glass electrode) according to $pD = pH + 0.4$.[12] UV−vis spectra were recorded in water at 25 °C on a Uvikon 820 spectrophotometer. Maxima are listed in the form λ_{max} [nm] (ϵ [M^{-1} cm^{-1}]). FAB^+ mass spectra were measured on a VG ZAB-VSEQ instrument. The samples were dissolved in water or DMSO and were mixed with a glycerol or a 3-nitrobenzyl alcohol matrix, respectively, prior to introduction into the spectrometer. Data are given as *m*/*z* (%, assignment).

Materials and Analyses. Metal salts used for the synthetic work and the organic solvents were commercially available products of reagent grade quality. For the potentiometric titrations, metal salts of highest available quality (>99.95%) were used. taci and $[Ni(taci)_2]SO_4$ were prepared as described previously.[13] Dowex 50 W-X2 (100−200 mesh, H^+ form) and Dowex 2-X8 (50−100 mesh, Cl^- form) were from Fluka. The OH^- form of Dowex 2-X8 was generated by elution with 0.2 M NaOH and extensive rinsing with CO_2-free water until a neutral eluent was obtained. C, H, N, and H_2O analyses were performed by D. Manser, Laboratorium für Organische Chemie, ETH Zürich.

tmca·3HCl·2H$_2$O and tmca·3HNO$_3$. Solid $[Ni(taci)_2]SO_4$ (5.47 g, 10.7 mmol) was suspended in 550 mL of DMF. Powdered KOH (18.0 g, 321 mmol) was then added and the mixture was stirred at room temperature for 1 h. The pink suspension was cooled in an ice bath and CH_3I (45.5 g, 321 mmol) was added slowly within 1 h. The mixture was stirred for additional 20 h at room-temperature resulting in the formation of a pink solution and a white solid (KI). Excess CH_3I was destroyed by addition of ammonia (25% in water) followed by stirring for 2 h. Aqueous 8 M HCl was then added until a pH of 1 was reached and stirring was continued until the solution turned pale green. The solution was diluted with water to a total volume of 1.5 L and sorbed on Dowex 50 W-X2. The column was washed with water and with 0.5 M HCl (removing Ni^{2+} as a greenish fraction). Elution with 3 M HCl gave a colorless fraction, which was evaporated to dryness. The white solid was dried for 3 days in vacuo over P_2O_5, yielding anhydrous tmca·3HCl (6.68 g, 20.3 mmol, 95%). Anal. Calcd for $C_9Cl_3H_{24}N_3O_3$: C, 32.89; H, 7.36; N, 12.78. Found: C, 32.73; H, 7.35; N, 12.62. Equilibration of the dried product in humid air (60% atmospheric moisture, 23 °C) resulted in the formation of the dihydrate tmca·3HCl·2H$_2$O. Anal. Calcd for $C_9Cl_3H_{28}N_3O_5$: C, 29.64; H, 7.74; N, 11.52; H_2O, 9.87. Found: C, 29.64; H, 7.80; N, 11.38; H_2O, 9.79. The free triamine was obtained by deprotonation of the trihydrochloride on Dowex 2-X8 (OH^- form). Evaporation of the solvent and drying in vacuo over P_2O_5 yielded a white, highly hygroscopic solid. Dissolution of dry tmca in ethanol followed by the addition of concentrated aqueous HNO_3 resulted in nearly quantitative precipitation (>95%) of tmca·3HNO$_3$. This was filtered off and dried in vacuo over P_2O_5. Anal. Calcd for $C_9H_{24}N_6O_{12}$: C, 26.47; H, 5.92; N, 20.58. Found: C, 26.39; H,

---

(6) Ghisletta, M.; Hausherr-Primo, L.; Gajda-Schrantz, K.; Machula, G.; Nagy, L.; Schmalle, H. W.; Rihs, G.; Endres, F.; Hegetschweiler, K. *Inorg. Chem.* **1998**, *37*, 997.

(7) Hegetschweiler, K.; Kradolfer, T.; Gramlich, V.; Hancock, R. D. *Chem. Eur. J.* **1995**, *1*, 74.

(8) (a) Hegetschweiler, K.; Weber, M.; Huch, V.; Veith, M.; Schmalle, H. W.; Linden, A.; Geue, R. J.; Osvath, P.; Sargeson, A. M.; Willis, A. C.; Angst, W. *Inorg. Chem.* **1997**, *36*, 4121. (b) Hegetschweiler, K.; Ghisletta, M.; Hausherr-Primo, L.; Kradolfer, T.; Schmalle, H. W.; Gramlich, V. *Inorg. Chem.* **1995**, *34*, 1950.

(9) Weber, M. Ph.D. Thesis, Dissertation No. 12071, ETH Zürich, Switzerland, 1997.

(10) Eliel, E. L.; Haubenstock, H.; Acharya, R. V. *J. Am. Chem. Soc.* **1961**, *83*, 2351.

(11) (a) Hurd, R. E. *J. Magn. Reson.* **1990**, *87*, 422. (b) von Kienlin, M.; Moonen, C. T. W.; van der Toorn, A.; van Zijl, P. C. M. *J. Magn. Reson.* **1991**, *93*, 423. (c) Hurd, R. E.; John, B. K. *J. Magn. Reson.* **1991**, *91*, 648. (d) Ruiz-Cabello, J.; Vuister, G. W.; Moonen, C. T. W.; van Gelderen, P.; Cohen, J. S.; van Zijl, P. C. M. *J. Magn. Reson.* **1992**, *100*, 282. (e) Wilker, W.; Leibfritz, D.; Kerssebaum, R.; Bermel, W. *Magn. Reson. Chem.* **1993**, *31*, 287.

(12) Delgado, R.; Fraústo Da Silva, J. J. R.; Amorim, M. T. S.; Cabral, M. F.; Chaves, S.; Costa, J. *Anal. Chim. Acta* **1991**, *245*, 271.

(13) Ghisletta, M.; Jalett, H.-P.; Gerfin, T.; Gramlich, V.; Hegetschweiler, K. *Helv. Chim. Acta* **1992**, *75*, 2233.

Table 1. Crystallographic Data for tmca$\cdot$3HCl$\cdot$$H_2O$, $[Ni(tmca)_2](NO_3)_2\cdot 4H_2O$, $[Cu(tmca)_2](NO_3)_2$, and $[Ni(tbca)_2](NO_3)_2\cdot MeCN\cdot H_2O$

	H_3tmca^{3+}	$[Ni(tmca)_2]^{2+}$	$[Cu(tmca)_2]^{2+}$	$[Ni(tbca)_2]^{2+}$
empirical formula	$C_9Cl_3H_{26}N_3O_4$	$C_{18}H_{50}N_8NiO_{16}$	$C_{18}CuH_{42}N_8O_{12}$	$C_{56}H_{71}N_9NiO_{13}$
fw	346.7	693.4	626.1	1136.9
space group	$P2_1/n$ (No. 14)	$P\bar{1}$ (No. 2)	$P\bar{4}2_1c$ (No. 114)	$P2_1/c$ (No. 14)
a, Å	11.057(5)	8.919(11)	13.017(6)	12.930(8)
b, Å	9.960(6)	9.293(9)	13.017(6)	19.324(10)
c, Å	14.671(6)	9.942(11)	15.985(10)	22.724(14)
α, deg	90.00	96.73(9)	90.00	90.00
β, deg	93.79(3)	100.66(9)	90.00	97.21(5)
γ, deg	90.00	101.95(9)	90.00	90.00
V, Å^3	1612.2(14)	781.8(15)	2709(2)	5633(6)
Z	4	1	4	4
T, °C	20(2)	20(2)	20(2)	20(2)
λ (Mo Kα), Å	0.710 73	0.710 73	0.710 73	0.710 73
ρ_{calcd}, g cm^{-3}	1.428	1.473	1.535	1.341
μ, cm^{-1}	5.81	7.02	8.80	4.61
R [$I > 2\sigma(I)$][a]	0.0335	0.0463	0.0491	0.0366
wR_2 (all data)[b]	0.0962	0.1201	0.1283	0.0793

[a] $R = \sum|F_o - F_c|/\sum|F_o|$. [b] $wR_2 = [\sum w(F_o^2 - F_c^2)^2/\sum wF_o^4]^{1/2}$.

6.03; N, 20.33. ^{1}H NMR (D_2O, pD 2): 3.55 (s, 9H), 3.77 (t, 3H, J = 3.6 Hz), 4.05 (t, 3H, J = 3.6 Hz). ^{13}C NMR (D_2O, pD 2): 53.5, 65.5, 77.6. ^{13}C NMR (D_2O, pD 12): 55.2, 66.1, 86.9. MS (FAB$^+$): 220.1 (100, Htmca$^+$).

tbca$\cdot$3HCl$\cdot$2H$_2$O. The procedure described above for the preparation of tmca was applied to $[Ni(taci)_2]SO_4$ (1.00 g, 1.96 mmol), 80 mL of DMF, powdered KOH (3.30 g, 59 mmol) and benzyl bromide (10.1 g, 59 mmol). After destruction of surplus benzyl bromide by addition of ammonia (25% in water) to the reaction mixture, the solvent was evaporated under reduced pressure at 80 °C and the pink residue was suspended in 100 mL of EtOH. Concentrated aqueous HCl was added, and the color of the solution changed from pink to blue and finally to pale green. The white solid which precipitated was filtered off, washed twice with ethanol, and dried in vacuo (50 °C, 24 h). Yield: 2.07 g (3.49 mmol, 89%) of tbca$\cdot$3HCl$\cdot$2H$_2$O. Anal. Calcd for $C_{27}Cl_3H_{40}N_3O_5$: C, 54.69; H, 6.80; N, 7.09. Found: C, 54.69; H, 6.74; N, 7.07. The free triamine was obtained by adding 3 equiv of KOH to an aqueous solution of the product. The resulting suspension was extracted 3 times with dichloromethane. The organic fraction was then separated, dried over Na_2SO_4, and evaporated to dryness, yielding pure tbca as a white hygroscopic solid. Anal. Calcd for $C_{27}H_{33}N_3O_3$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.63; H, 7.49; N, 9.32. tbca$\cdot$3HNO$_3$ was obtained quantitatively by adding 3 equiv of concentrated HNO_3 to an ethanolic solution of tbca. The white precipitate was separated by filtration, and the monohydrate tbca$\cdot$3HNO$_3$$\cdot$H$_2$O formed upon exposure to humid air (60% atmospheric moisture, 23 °C). Anal. Calcd for $C_{27}H_{38}N_6O_{13}$: C, 49.54; H, 5.85; N, 12.84. Found: C, 49.78; H, 5.76; N, 13.04. ^{1}H NMR (D_2O, pD 2): 4.00 (t, 3H, J = 3.5 Hz), 4.50 (t, 3H, J = 3.5 Hz), 4.81 (s, 6H), 7.32 (m, 15H). ^{1}H NMR of the free triamine ($CDCl_3$): 2.16 (s, br, 6H), 3.12 (t, 3H, J = 3.8 Hz), 3.70 (t, 3H, J = 3.8 Hz), 4.66 (s, 6H), 7.35 (m, 15H). ^{13}C NMR (D_2O, pD 2): 53.7 (CH), 75.6 (CH), 78.5 (CH_2), 129.8 (CH), 130.8 (CH), 131.4 (CH), 139.6 (C_{tert}). ^{13}C NMR of the free triamine ($CDCl_3$): 52.2, 70.1, 76.1, 127.7, 127.8, 128.5, 138.3. MS (FAB$^+$): 448.1 (100, Htbca$^+$).

Preparation of Metal Complexes. Complexes of the composition $[M(tmca)_2](NO_3)_2$ (M = Cu, Cd, Zn) and $[Ni(tmca)_2](NO_3)_2\cdot 2H_2O$ were prepared by adding aqueous solutions of the metal nitrates (1 equiv) to an aqueous solution of tmca (2 equiv). The resulting clear solutions were stirred for an additional 10 min and were then evaporated to dryness. The solid residues were recrystallized from hot ethanol (Cu, Ni) or hot 2-propanol (Zn, Cd) and dried in vacuo. Yields were almost quantitative (>90%). $[Ni(tbca)_2](NO_3)_2\cdot 2H_2O$ and $[Cu(tbca)_2]Cl_2$ precipitated quantitatively when 6 equiv of aqueous KOH was added to a mixture of 2 equiv of the protonated ligand (tbca$\cdot$3HNO$_3$$\cdot$H$_2$O or tbca$\cdot$3HCl, respectively) and 1 equiv of the corresponding metal salt, dissolved in water. The solids were filtered off and dried in vacuo.

$[Cu(tmca)_2](NO_3)_2$. Anal. Calcd for $C_{18}CuH_{42}N_8O_{12}$: C, 34.53; H, 6.76; N, 17.90. Found: C, 34.60; H, 6.82; N, 17.94. UV−vis: 640 (33). MS (FAB$^+$): 282.0 (100, $[Cu(tmca)]^+$), 344.0 (17, $[Cu(tmca)(NO_3)]^+$), 500.2−504.2 (overlap of: 7, $[H_{-1}Cu(tmca)_2]^+$ and 17, $[Cu(tmca)_2]^+$), 563.2 (4, $[Cu(tmca)_2(NO_3)]^+$).

$[Ni(tmca)_2](NO_3)_2\cdot 2H_2O$. Anal. Calcd for $C_{18}H_{46}N_8NiO_{14}$: C, 32.89; H, 7.05; N, 17.05. Found: C, 32.95; H, 7.02; N, 17.16. UV−vis: 302 (19.1), 522 (5.4), 842 (4.9). MS (FAB$^+$): 339.1 (100, $[Ni(tmca)(NO_3)]^+$), 495.4 (62, $[H_{-1}Ni(tmca)_2]^+$), 558.4 (46, $[Ni(tmca)_2(NO_3)]^+$).

$[Zn(tmca)_2](NO_3)_2$. Anal. Calcd for $C_{18}H_{42}N_8O_{12}Zn$: C, 34.43; H, 6.74; N, 17.84. Found: C, 34.34; H, 6.53; N, 17.89. ^{1}H NMR (D_2O): 3.38 (t, 6H, J = 4.0 Hz), 3.47 (s, 18H), 3.94 (t, 6H, J = 4.0 Hz). ^{13}C NMR (D_2O): 51.9, 59.7, 78.9. MS (FAB$^+$): 345.1 (100, $[Zn(tmca)(NO_3)]^+$), 501.4, (34, $[H_{-1}Zn(tmca)_2]^+$), 564.4 (21, $[Zn(tmca)_2(NO_3)]^+$).

$[Cd(tmca)_2](NO_3)_2$. Anal. Calcd for $C_{18}CdH_{42}N_8O_{12}$: C, 32.03; H, 6.27; N, 16.60. Found: C, 31.84; H, 6.03; N, 16.54. ^{1}H NMR (D_2O): 3.39 (t, 6H, J_{HH} = 4.4 Hz), 3.48 (s, 18H), 4.01 (t + d × t, 6H, J_{HH} = 4.4 Hz, J_{HCd} = 23.2 Hz). ^{13}C NMR (D_2O): 52.3 (s + d, J_{CCd} = 6.9 Hz), 59.6, 79.0. MS (FAB$^+$): 395.1 (100, $[Cd(tmca)(NO_3)]^+$), 551.3 (30, $[H_{-1}Cd(tmca)_2]^+$), 614.3 (33, $[Cd(tmca)_2(NO_3)]^+$).

$[Ni(tbca)_2](NO_3)_2\cdot 2H_2O$. Anal. Calcd for $C_{54}H_{70}N_8NiO_{14}$: C, 58.23; H, 6.33; N, 10.06. Found: C, 58.33; H, 6.21; N, 10.14. MS (FAB$^+$): 567.0 (100, $[Ni(tbca)(NO_3)]^+$), 951.3 (11, $[H_{-1}Ni(tbca)_2]^+$), 1014.3 (16, $[Ni(tbca)_2(NO_3)]^+$). Single crystals of the composition $[Ni(tbca)_2](NO_3)_2\cdot MeCN\cdot H_2O$ suitable for X-ray analysis where grown by slow evaporation of a CH_3CN/benzene solution of the dihydrate at 4 °C.

$[Cu(tbca)_2]Cl_2$. Anal. Calcd for $C_{54}Cl_2CuH_{66}N_6O_6$: C, 62.99; H, 6.46; N, 8.16. Found: C, 62.90; H, 6.69; N, 8.10. MS (FAB$^+$): 510.1 (100, $[Cu(tbca)]^+$), 957.4 (8, $[Cu(tbca)_2]^+$), 992.3 (18, $[Cu(tbca)_2Cl]^+$).

Crystal Structure Determination. Diffraction Data were collected on a Syntex P21 (tmca$\cdot$3HCl$\cdot$H$_2$O and $[Ni(tbca)_2](NO_3)_2\cdot MeCN\cdot H_2O$) or a Picker-Stoe ($[Cu(tmca)_2](NO_3)_2$ and $[Ni(tmca)_2](NO_3)_2\cdot 4H_2O$) four-circle diffractometer at 20 °C using graphite-monochromated Mo Kα radiation. The crystallographic data are summarized in Table 1. Checking of standard reflections during data collection gave no indication of crystal decay. The data were corrected for Lorentz and polarization effects. A face-indexed, numerical absorption correction was applied to the data of the two tmca complexes. The structures were solved by direct methods (tmca$\cdot$3HCl$\cdot$H$_2$O) or the Patterson method (metal complexes) of SHELXS-86.[14] All non-hydrogen atomic positions were refined in the anisotropic mode by full-matrix least-squares calculations (SHELXL-93)[15] on F^2. The phenyl rings of $[Ni(tbca)_2](NO_3)_2\cdot MeCN\cdot H_2O$ were treated as rigid groups with constrained C−C bond distances of 1.39 Å and C−C−C angles of 120°. One of the nitrate counterions of this compound proved to be disordered and could be described by a superposition of two different orientations with an occupancy of 50% for each of the two sites. Additional disorder was assumed for the methoxy carbon atoms of $[Cu(tmca)_2]^{2+}$, particularly for C(14). The disorder is indicated by the large displacement factors

---

(14) Sheldrick, G. M. SHELXS-86. *Acta Crystallogr.* **1990**, *A46*, 467.
(15) Sheldrick, G. M. *SHELXL-93*: *A Program for the Refinement of X-ray Structures*; University of Göttingen: Germany, 1993.

Table 2. Summarized Bond Lengths (Å) and Angles (deg) of tmca·3HCl·H_2O

	range	mean
C−C	1.524(4)−1.531(4)	1.526
C−N	1.481(4)−1.490(3)	1.487
C_{ring}−O	1.418(4)−1.421(4)	1.420
O−CH_3	1.433(4)−1.445(4)	1.438
C−C−C	109.0(2)−116.3(2)	112.3
N−C−C	108.7(2)−109.9(2)	109.4
C−C−O	110.9(2)−111.9(2)	111.5
C−O−C	113.1(2)−115.2(2)	113.9

Table 3. Selected Bond Lengths (Å) of $[Cu(tmca)_2]^{2+}$, $[Ni(tmca)_2]^{2+}$, and $[Ni(tbca)_2]^{2+}$ with Esd's in Parentheses

distance	$[Cu(tmca)_2]^{2+}$	$[Ni(tmca)_2]^{2+}$	$[Ni(tbca)_2]^{2+}$
M−N(1)	2.041(6)	2.123(4)	
M−N(3)	2.053(6)	2.117(3)	
M−N(5)	2.446(5)	2.134(3)	
Ni−N(11)			2.133(3)
Ni−N(13)			2.130(3)
Ni−N(15)			2.116(3)
Ni−N(21)			2.122(3)
Ni−N(23)			2.141(3)
Ni−N(25)			2.129(3)

Table 4. Experimental Potentiometric Data (25 °C, 0.1 M KNO_3 or 0.1 M KCl) and Evaluated Acidity Constants (pK_a) for tmca and tbca

	ligand		
	tmca[a]	tmca[b,c]	tbca[b]
solvent	H_2O	MeOH/H_2O 4:1 (v/v)	H_2O
$[L]_t$, mM	1.94	0.99	1.00
evaluated range[d]	0.0−3.0	0.0−3.5	0.0−3.0
no. of data points	61	36	30
pK_a values[e]			
pK_1[e]	5.19	4.40	3.55
pK_2[e]	6.88	6.14	6.40
pK_3[e]	9.30	9.67	9.4(1)
σ_{pH}[f]	0.0027	0.0081	0.0045

[a] 0.1 M KNO_3. [b] 0.1 M KCl. [c] A value of 14.066 was used for pK_w. [d] No. of equivalents of titrant per equivalent of ligand. [e] $K_i = [H_{3-i}tmca][H][H_{4-i}tmca]^{-1}$, $pK_i = -\log K_i$, estimated standard deviations <0.01 unless otherwise noted. [f] $\sigma_{pH} = (\sum w(pH_{obs} - pH_{calcd})^2/\sum w)^{1/2}$, $w = [pH_{i+1} - pH_{i-1}]^{-2}$.

and some of the C−O bond distances which are obviously too short. The C−H hydrogen position of the cyclohexane ring of tmca·3HCl·H_2O, the NH_2-hydrogen positions of $[Ni(tmca)_2]^{2+}$ and $[Cu(tmca)_2]^{2+}$, and the H-positions of all H_2O molecules were obtained from the difference Fourier map. All other hydrogen positions were calculated using a riding-model. Atomic coordinates, bond distances and bond angles are available as Supporting Information. Summarized bond lengths and bond angles of tmca·3HCl·H_2O and selected bond distances of the metal complexes are listed in Tables 2 and 3, respectively.

Potentiometric Measurements. All potentiometric titrations were carried out as described previously[16] at 25 °C in 0.1 M KNO_3 or 0.1 M KCl under argon using 50 mL sample solutions with concentrations as indicated in Tables 4 and 5. The stability of the electrode was checked by a calibration titration prior to and after each measurement. A total of 6 independent titrations were used to establish the acidity constants (pK_a values) of the ligands. Representative data is given in Table 4. Formation constants of the metal complexes were determined by a series of alkalimetric and acidimetric titrations (Table 5). The crystalline, analytically pure solids $[M(tmca)_2](NO_3)_2$ were used to prepare sample solutions of the Cu, Ni, Zn, and Cd complexes with a total M/total tmca molar ratio of 1:2. They were titrated with 0.1 M HNO_3. All other sample solutions were made up by using standardized stock solutions of tmca·$3HNO_3$ and of the corresponding metal nitrates. At least two independent measurements were performed for each titration.

Calculations of Equilibrium Constants. All equilibrium constants were calculated as concentration constants and pH is defined as −log[H^+]. The protonation constants of the ligands (pK_a's) were evaluated using fixed values for pK_w (=13.79,[17] obtained from several calibration titrations) and for the total concentrations of the ligand (total L) and acid (total H). The determination of the formation constants of metal complexes was performed with a fixed pK_w, fixed pK_a's and fixed total concentrations of M, L, and H. Consistent models were evaluated using the computer program SUPERQUAD[18] and double checked using the computer program BEST.[19] The data were fitted by least squares calculations, minimizing $\sigma_{pH} = [\sum w(pH_{obs} - pH_{calc})^2/\sum w]^{1/2}$, $w = (pH_{i+1} - pH_{i-1})^{-2}$. The results are listed in Tables 4 and 5.

Results and Discussion

Selective O-Alkylation of taci. The failure of the alkylation of taci derivatives having organic protecting groups on the nitrogen atoms was mainly attributed to the enforced axial orientation of the hydroxy groups. Greater reactivity was expected for a compound having the hydroxy groups in the more reactive equatorial position.[10] Such a structure, together with an effective protection of the amino groups can be achieved by converting taci to an N-bonded metal complex. Moreover, the presence of a metal center is expected to result in further activation, since the positive charge of the cation should facilitate deprotonation of the hydroxy groups, as required for O-alkylation. A variety of metal cations was tested, with Ni^{2+} proving to be the most suitable for this purpose.[20]

$[Ni(taci)_2]^{2+}$ was alkylated in DMF in the presence of KOH and an alkyl halide. Under these conditions, ligand dissociation was not observed. However, the alkylated ligand could be liberated readily by adding aqueous acid to the reaction mixture. The product could conveniently be purified by ion exchange chromatography, since the triprotonated ligand was retained on the resin while Ni^{2+} and other byproducts were removed by elution with diluted hydrochloric acid. Further elution with acid of higher concentration yielded an analytically pure trihydrochloride in excellent yield.

Structure of tmca in Solution and in the Solid State. The solution structure of taci and of the O-alkylated derivatives are influenced by a variety of parameters such as the degree of protonation, the steric bulk of the alkyl substituents and the corresponding 1−3-diaxial repulsions, intra- and intermolecular hydrogen bonding, and solvation effects. The energies of a variety of different structures, including several chair, boat, twisted boat, and envelope conformations, have been analyzed

---

(16) Kradolfer, T.; Hegetschweiler, K. *Helv. Chim. Acta* **1992**, *75*, 2243.

(17) Smith, R. M.; Martell, A. E.; Motekaitis, R. J. Critically Selected Stability Constants of Metal Complexes. *NIST Standard Reference Database 46*, Version 5.0; NIST Standard Reference Data: Gaithersburg, MD 20899, 1998.

(18) Gans, P.; Sabatini, A.; Vacca, A. *J. Chem. Soc., Dalton Trans.* **1985**, 1195.

(19) Motekaitis, R. J.; Martell, A. E. *Can. J. Chem.* **1982**, *60*, 2403.

(20) With regard to the very high inertness and the +3 charge of $[Co(taci)_2]^{3+}$ (see ref 13), we expected even better reactivity for this Co^{III} complex. A titration experiment (25 °C, 1 M KNO_3) established that the hydroxy groups can be deprotonated even in aqueous media. After addition of more than 2 equiv of base, an orange solid precipitated which dissolved again upon addition of excess base, indicating the formation of anionic species of the tentative composition $[H_{-x}Co(taci)_2]^{3-x}$, $x \geq 4$. The visible spectrum of such a solution (pH = 14) showed the expected ${}^1A_{1g}-{}^1T_{1g}$ transition at 471 nm (ϵ = 53), indicating that the hexaamine-Co^{III} chromophore is preserved. The first pK_a value was found to be 11.75 ± 3. Although such deprotonation products seem to form readily, corresponding alkylation experiments, using a suitable base, excess CH_3I and a variety of different solvents, were not successful. We either observed no reaction at all, or a complete degradation of the complex.

Table 5. Potentiometric Data (25 °C, 0.1 M KNO_3) and Evaluated Equilibrium Constants[a] for tmca Complexes

	Mn^{2+}		Fe^{2+}		Co^{2+}		Ni^{2+}		Cu^{2+}		Zn^{2+}		Cd^{2+}	
							Experimental Data							
$[M]_t/[tmca]_t/[H]_t$	1:2:6	1:1:3	1:2:6	1:1:3	1:2:6	1:1:3	1:2:0	1:1:3	1:2:0	1:1:3	1:2:0	1:1:3	1:2:0	1:1:3
$[tmca]_t$, mM	1.84	1.08	1.84	1.11	1.93	0.97	2.04	1.94	2.00	1.02	2.00	0.96	2.00	0.98
method[b]	cont	cont	cont	cont	cont	cont	batch	batch	cont	cont	cont	cont	cont	cont
titrant (0.1 M)	KOH	KOH	KOH	KOH	KOH	KOH	HNO_3	KOH	HNO_3	KOH	HNO_3	KOH	HNO_3	KOH
evaluated range[c]	0.1−2.9	0.0−2.6	0.0−2.5	0.0−2.9	0.0−2.4	0.0−2.5	0.1−2.9	0.2−2.8	0.2−3.5	0.0−3.9	0.1−2.6	0.0−2.7	0.1−2.5	0.0−2.8
time per point, min	10	10	10	10	10	10	>5000	>5000	3.3	3.3	5.3	5.3	5	5
no. of data points	67	15	59	17	24	13	20	16	48	41	34	17	41	18
							Equilibrium Constants[a]							
$\log \beta_1$[d]	6.16(1)	6.18(1)	9.03(1)	9.00(4)	11.50(2)	11.44(3)	14.64(3)	14.61(3)	14.44(1)	14.43(2)	10.80(1)	10.81(1)	8.87(1)	8.84(1)
$\log \beta_2$[d]	10.84(2)		16.14(2)		20.59(4)		25.91(5)		23.63(2)		18.54(1)		15.77(1)	
$\log \beta_{121}$[e]									28.1(1)					
$\log \beta_{22\text{-}2}$[f]										16.24(7)				
σ_{pH}[g]	0.0074	0.0050	0.0055	0.0162	0.0086	0.0090	0.0087	0.0090	0.0044	0.0058	0.0030	0.0009	0.0036	0.0015

[a] The uncertainties given in parentheses correspond to the standard deviations estimated by SUPERQUAD (ref 18), multiplied with a factor of 3. [b] Type of titration (continuous or batchwise, see refs 16 and 26). [c] Moles of titrant added per moles of tmca. [d] $\beta_i = [M(tmca)_i][M]^{-1}[tmca]^{-i}$. [e] $\beta_{121} = [M(tmca)(Htmca)][M]^{-1}[tmca]^{-2}[H]^{-1}$. [f] $\beta_{22\text{-}2} = [M_2(tmca)_2(OH)_2][H]^2[M]^{-2}[tmca]^{-2}$. [g] $\sigma_{pH} = [\Sigma w(pH_{obs} - pH_{calcd})^2/\Sigma w]^{1/2}$, $w = (pH_{i+1} - pH_{i-1})^{-2}$.

for taci and tmca by molecular mechanics and density functional calculations.[21] These calculations suggested that the difference in energy between some of the conformers is rather small. It is therefore difficult to predict the structure of lowest energy. However, the available crystal data of taci,[22] $Htaci^+$,[23] H_3taci^{3+},[13] its alkylated derivatives,[24,25] and the corresponding metal complexes[6−8,26−31] showed the clear predominance of the two distinct chair conformations, having either the oxygen or the nitrogen atoms in axial positions. Only one structure has been reported for a taci derivative with a twisted boat conformation of the cyclohexane ring.[32]

In the present investigation, extended NMR experiments have been performed to examine the structure of the conformers of taci and tmca in both aqueous and non aqueous solution. The ^1H NMR characteristics of taci, exhibiting a AA′A″XX′X″ spin system with a significant long-range contribution ($J_{AX} = 3.6$ Hz, $J_{AA} = 0$ Hz, $J_{XX} = 1.2$ Hz), has previously been reported.[24] The pH dependence of the two signals of A and X can be rationalized in terms of a fast protonation equilibrium of the four species taci, $Htaci^+$, H_2taci^{2+}, and H_3taci^{3+} (Figure 1). In agreement with the previous assignment, the low-frequency (=A) signal which corresponds to the H(−C−N) hydrogen atoms showed a significantly stronger pH dependent shift. Both signals remain sharp over the entire pH range. Line broadening or splitting of the signals, as expected for a sufficiently slow equilibrium between different conformers, was not observed. These findings are consistent with the formation of only one dominant conformer having the same structure, with the oxygen atoms in axial and the nitrogen atoms in equatorial positions, regardless of the degree of protonation.

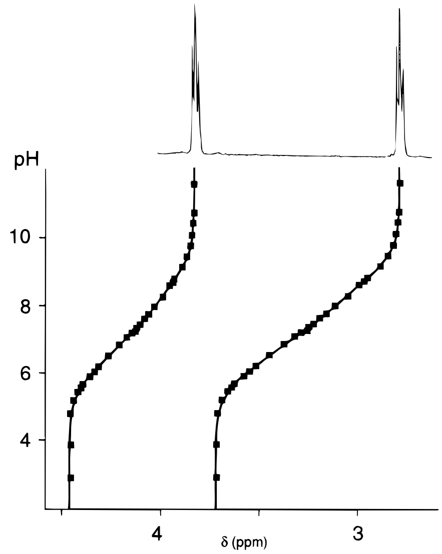


Figure 1. pD dependence of the ^1H NMR resonances of taci (D_2O, 25 °C, TSP = 0 ppm). Squares correspond to the experimental values, the lines are calculated (minimization of $[\delta_{obs} - \delta_{calcd}]^2$), assuming a rapid equilibrium between the species $H_x taci^{x+}$ ($0 \le x \le 3$) with pK_a values (refined) of 6.07, 7.32, 8.84 (the values in H_2O, 0.1 M KCl, 25 °C, are 5.96, 7.42, 8.91).

In contrast, tmca exhibited much more complex behavior (Figure 2). The ^1H NMR spectrum of the free base in CD_3CN showed a total of four sharp signals. The two triplets at 3.56 and 2.95 ppm could be assigned to the H−(C−N) and H−(C−O) ring protons, respectively. In addition, a singlet at 3.33 ppm and a signal at 1.75 ppm arose from the methoxy groups and the NH_2 protons. It is noteworthy that the chemical shifts of

---

(21) MM calculations: see ref 7. DFT functional calculations were performed by Eggenschwiler, A. (unpublished work, ETH Zürich, 1995). The computer programs SPARTAN and GAUSSIAN 94 were used. The PM3 method with the Becke3 functional, the 3-21G(d) basis set, and nonlocal PW91 corrections was used for geometry optimization.

(22) Hegetschweiler, K.; Hancock, R. D.; Ghisletta, M.; Kradolfer, T.; Gramlich, V.; Schmalle, H. W. *Inorg. Chem.* **1993**, *32*, 5273.

(23) Reiss, G. J.; Hegetschweiler, K.; Sander, J. *Acta Crystallogr. Sect. C* **1999**, *C55*, 126.

(24) Hegetschweiler, K.; Erni, I.; Schneider, W.; Schmalle, H. *Helv. Chim. Acta* **1990**, *73*, 97.

(25) Schmalle, H. W.; Hegetschweiler, K. *Acta Crystallogr. Sect. C* **1996**, *C52*, 1288.

(26) Hegetschweiler, K.; Gramlich, V.; Ghisletta, M.; Samaras, H. *Inorg. Chem.* **1992**, *31*, 2341.

(27) Hegetschweiler, K.; Ghisletta, M.; Fässler, T. F.; Nesper, R.; Schmalle, H. W.; Rihs, G. *Inorg. Chem.* **1993**, *32*, 2032.

(28) (a) Schmalle, H. W.; Hegetschweiler, K.; Ghisletta, M. *Acta Crystallogr., Sect. C* **1991**, *C47*, 2047. (b) Hegetschweiler, K.; Ghisletta, M.; Gramlich, V. *Inorg. Chem.* **1993**, *32*, 2699. (c) Hegetschweiler, K.; Ghisletta, M.; Fässler, T. F.; Nesper, R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1426. (d) Hegetschweiler, K.; Raber, T.; Reiss, G. J.; Frank, W.; Wörle, M.; Currao, A.; Nesper, R.; Kradolfer, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1964.

(29) Hegetschweiler, K.; Wörle, M.; Meienberger, M. D.; Nesper, R.; Schmalle, H. W.; Hancock, R. D. *Inorg. Chim. Acta* **1996**, *250*, 35.

(30) Reiss, G. J.; Frank, W.; Hegetschweiler, K.; Kuppert, D. *Acta Crystallogr., Sect. C* **1998**, *C54*, 614.

(31) Hedinger, R.; Ghisletta, M.; Hegetschweiler, K.; Toth, E.; Merbach, A. E.; Sessoli, R.; Gatteschi, D.; Gramlich, V. *Inorg. Chem.* **1998**, *37*, 6698−6705.

(32) Kramer, A.; Alberto, R.; Egli, A.; Novak-Hofer, I.; Hegetschweiler, K.; Abram, U.; Bernhardt P. V.; Schubiger, P. A. *Bioconj. Chem.* **1998**, *9*, 691.

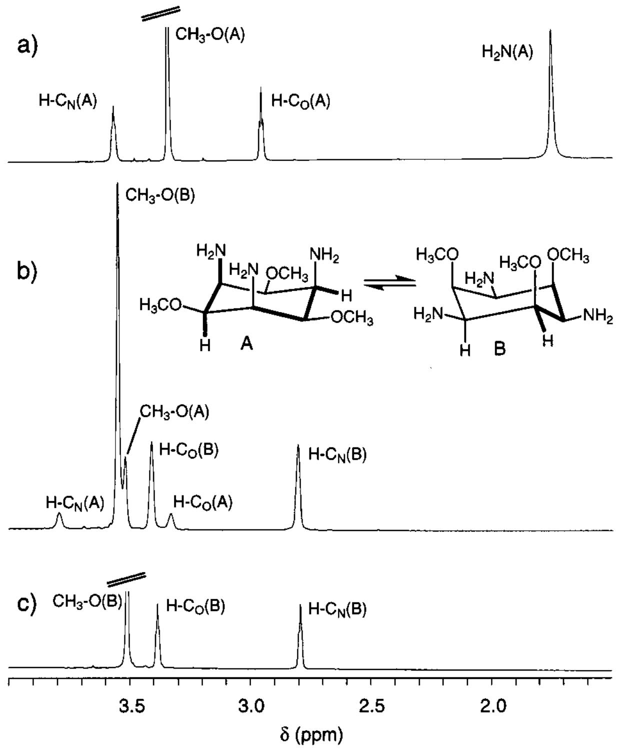


Figure 2. ^{1}H NMR spectra of tmca (ambient temperature) (a) in CD_3CN, (b) in D_2O, and (c) in 0.1 M NaCl (D_2O). The signals of the two conformers, shown in Figure 3b, are assigned by a series of $^1H-^1H$ COSY, $^{13}C-^1H$ HMQC, and $^{15}N-^1H$ HMQC experiments (ref 11). The assignment of the two conformations is based on characteristic differences of the three-bond coupling constants shown in the scheme of Figure 2b, where large coupling is observed only for a dihedral angle of 180° (bold bonds).

the H−(C−N) ring protons are more deshielded than the H−(C−O) protons, despite the fact that they are attached to the carbon atom with the less electronegative substituent. This is different from taci, where the H(−C−O) ring protons appeared at higher frequency. Obviously, taci and tmca differ in their solution structure. Close inspection of $^1H-^{13}C$, and $^1H-^{15}N$ long-range coupling[33] indicated unambiguously that tmca adopts a chair conformation with three axial amino groups and three equatorial methoxy groups. In D_2O two separate species were found in the ^{1}H and ^{13}C NMR spectra. A 2D EXSY experiment showed that these two species interconvert slowly on the NMR time scale. At 25 °C the analysis of $^1H-^{13}C$ and $^1H-^{15}N$ long-range coupling exhibited that the two species correspond to the two chair conformers having either the amino groups (15%) or the methoxy groups (85%) in axial position. Addition of small amounts of acid significantly increased the proportion of the species with three axial amino groups (Figure 3). However, acidification of the solution also led to significant line broadening and in the range $4 < pD < 10$, the signals of the two species could not be resolved. The range where the two individual species were observable could be extended to pD 7.1 by lowering the temperature to 5 °C. Separate signals could be observed over the entire pD range at −40 °C using a CD_3OD/D_2O mixture (4:1 v/v) as solvent. It must be emphasized that the equilibrium of the two conformers is strongly dependent on the temperature and the nature of the solvent. The results of the low temperature experiment thus cannot be directly correlated with the findings observed at room temperature in water. Nevertheless, the results summarized in Figure 3 clearly demonstrate that the conformer with the three axial amino groups has a maximal abundance for the monoprotonated $Htmca^+$. In water at room temperature, the estimated maximum exceeds 50%. At high acid concentration, however, ($pD < 4$) where the fully protonated H_3tmca^{3+} is exclusively present, the conformer with three equatorial ammonium groups is observed as the only species. It is further noteworthy that the presence of Na^+ strongly affects this equilibrium (Figure 2c). After addition of three equivalents of NaOD to a solution of H_3tmca^{3+} in D_2O, the conformer with three axial amino groups could not be detected. Corresponding effects with K^+ are much less pronounced. A change in the equilibrium composition was only observed at very high K^+ concentration (>1 M).

The adoption of a structure with three equatorial ammonium groups is understandable for H_3tmca^{3+} considering the very high energy resulting from the steric and electrostatic repulsion between the three positive ammonium groups. For the free tmca, on the other hand, the structure with three axial amino groups is stabilized by intramolecular N−H···N hydrogen bonds. This hydrogen bonding is, however, weak (a primary amine is a rather poor hydrogen donor),[34] and consequently, this conformer is only observed to a significant extent in a non protic solvent such as acetonitrile. In water, intermolecular hydrogen bonding between the amino groups and water molecules becomes the dominant factor, and the equatorial position is again favored for the amino groups.[35] The observed equilibrium composition of about 1:6 indicates that the difference in energy of the two conformers of tmca is only small. For the monoprotonated $Htmca^+$, a slight preference for the conformer with three axial amino groups is observed, even in water. This must be attributed to the intramolecular hydrogen bonding between the positive ammonium group (a strong proton donor) and the amino groups. This type of hydrogen bonding is expected to be of significantly higher energy than the weak interactions between amino groups in the free tmca.[34] The effect observed upon addition of Na^+ can readily be explained by complex formation. Obviously, Na^+ (a hard Lewis acid) binds preferentially to the oxygen atoms and stabilizes the conformation with three axial methoxy groups. The comparably low affinity for K^+ is in excellent agreement with some previously performed molecular mechanics calculations, showing that the binding of large metal cations to the three axial substituents of a taci type ligand is significantly less favored.[29,36]

The crystal structure of the triply protonated H_3tmca^{3+} is shown in Figure 4. All bond angles and bond lengths fall in expected ranges (Table 2). The structural analysis confirmed the expected equatorial orientation for the three positive ammonium groups. A similar conformation has already been observed for related cations such as H_3taci^{3+},[13] and the triply protonated *all-cis*-2,4,6-trimethylcyclohexane-1,3,5-triamine reported by Parker and co-workers.[37] As discussed above, the conformation of these fully protonated species, having the ammonium groups in axial position would be strongly destabilized. For H_3taci^{3+}, the structure with three axial hydroxy groups is further stabilized by intramolecular 1−3 diaxial O−H···O hydrogen bonding. This is of course not possible for

---

(33) (a) Kalinowski, H. O.; Berger, S. Braun, S. *^{13}C NMR-Spektroskopie*; Georg Thieme Verlag: Stuttgart, 1984 (in German). (b) von Philipsborn W.; Müller R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 383.

(34) Jorgensen, W. L. *CHEMTRACTS: Org. Chem.* **1991**, *4*, 91.

(35) Perrin, C. L.; Fabian, M. A.; Rivero, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 1044.

(36) Hancock, R. D.; Hegetschweiler, K. *J. Chem. Soc., Dalton Trans.* **1993**, 2137.

(37) de Angelis, S.; Batsanov, A.; Norman, T. J.; Parker, D.; Senanayake, K.; Vepsalainen, J. *J. Chem. Soc., Chem. Commun.* **1995**, 2361.

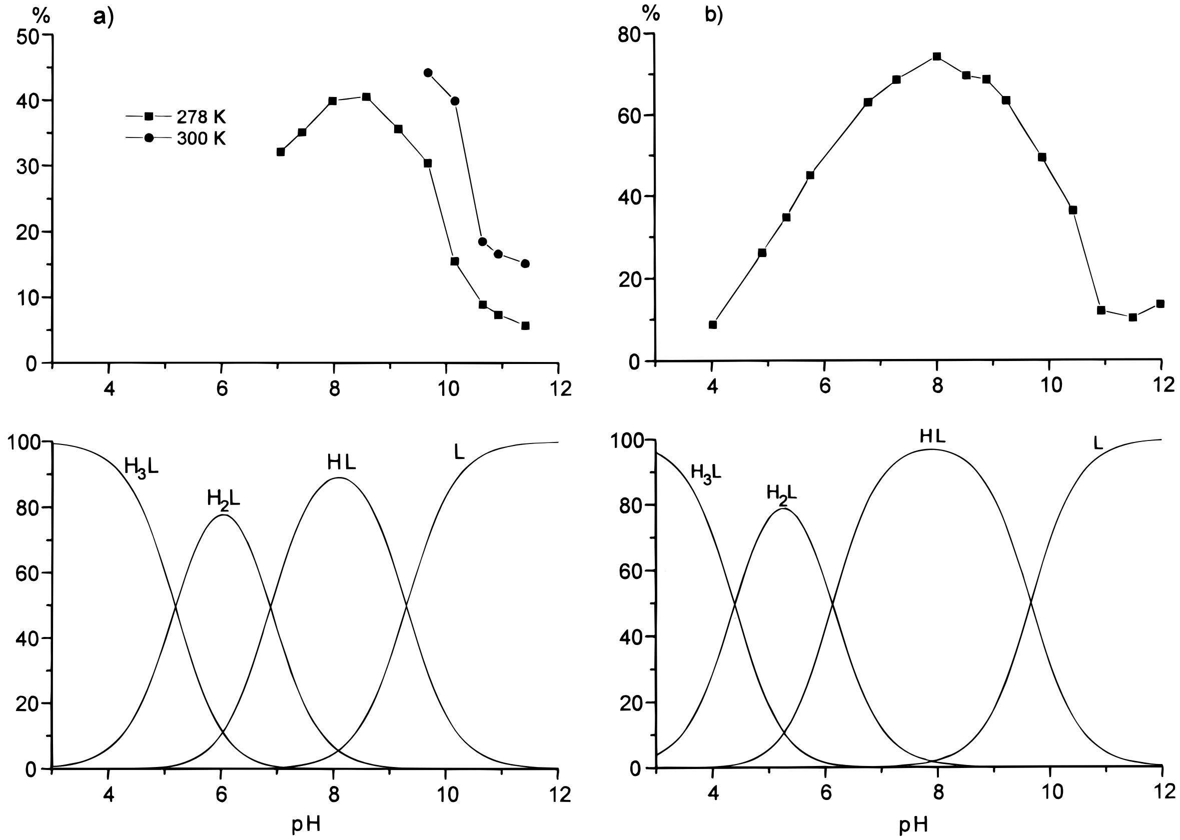


Figure 3. pH dependence of the conformational equilibrium of tmca (a) in D_2O at temperatures as indicated and (b) in a 1:4 (v/v) mixture of D_2O and CD_3OD at −40 °C. The amount of the conformer with three axial amino groups is shown and is correlated with the species distribution calculated from the acidity constants listed in Table 4.

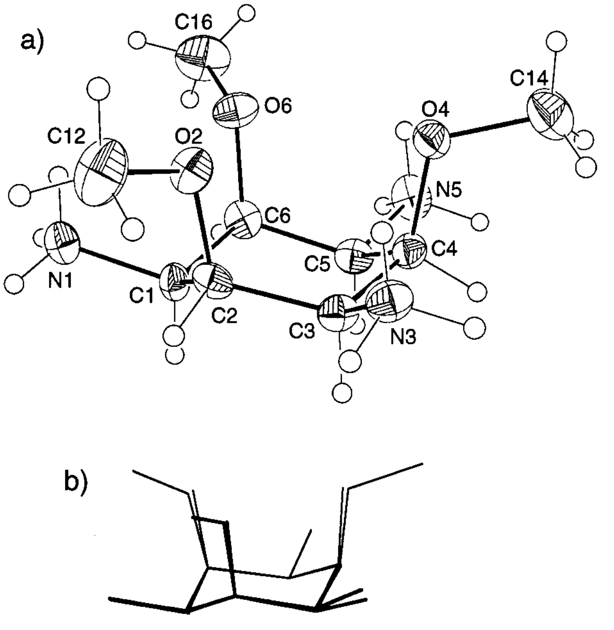


Figure 4. Crystal structure of H_3tmca^{3+}. (a) ORTEP drawing with numbering scheme and vibrational ellipsoids at the 50% probability level. The hydrogen atoms are shown as spheres of arbitrary size. (b) Superposition of the structures of H_3tmca^{3+} and taci (data from ref 22), showing the characteristic increase in the O···O distances in H_3tmca^{3+}.

H_3tmca^{3+} and consequently this molecule is expected to be of some higher energy. The increased repulsion between the three axial methoxy groups of tmca can be visualized by comparing the mean distances between the axial oxygen positions (Figure 4b) for taci (2.84 Å) and H_3tmca^{3+} (3.01 Å). For a strain free cyclohexane derivative the distance between the axial positions would fall in the range of 2.56−2.60 Å.

The present study clearly shows that taci and tmca have distinctly different behavior in aqueous media. In their triply protonated forms, both ligands adopt a chair conformation with equatorial ammonium groups. However, taci retains this structure in its partially protonated and deprotonated form, while for tmca, a strongly solvent- and temperature-dependent equilibrium is observed between the two different chair conformations for the partially protonated and the free triamine.

Preparation and Characterization of Metal Complexes. Crystalline compounds of the composition $[M(tmca)_2](NO_3)_2\cdot xH_2O$ (M = Cu, Ni, Zn, Cd; $x = 0$ or 2) were readily obtained in aqueous media by addition of a metal salt to the deprotonated ligand in a 1:2 molar ratio, followed by evaporation and recrystallization from hot ethanol or 2-propanol. Compounds of the composition $[Ni(tbca)_2](NO_3)_2\cdot 2H_2O$ and $[Cu(tbca)_2]Cl_2$, which are formed upon addition of base to an aqueous solution of a metal salt and $tbca\cdot 3HNO_3$ or $tbca\cdot 3HCl$, are not soluble in water and precipitate from aqueous solution. All complexes were fully characterized by elemental analysis and MS−FAB$^+$ measurements. The visible spectra of the pink $[Ni(tmca)_2]^{2+}$ and blue $[Cu(tmca)_2]^{2+}$ complexes are almost identical with those of the corresponding taci complexes.[26] For both $[Zn(tmca)_2]^{2+}$ and $[Cd(tmca)_2]^{2+}$, the ^1H and ^{13}C NMR spectra each contained three signals, indicating D_{3d} symmetry. The signals could be assigned unambiguously by C−H-correlated NMR experiments and the differences in the $^{111/113}Cd-^1H$ and $^{111/113}Cd-^{13}C$ coupling. By analogy with the ^1H NMR characteristics of the free tmca, where a significant shift to higher frequency of the H−(C−N) protons is observed for the conformer with axial amino groups in D_2O (Figure 2b), the H−(C−N) signals in both

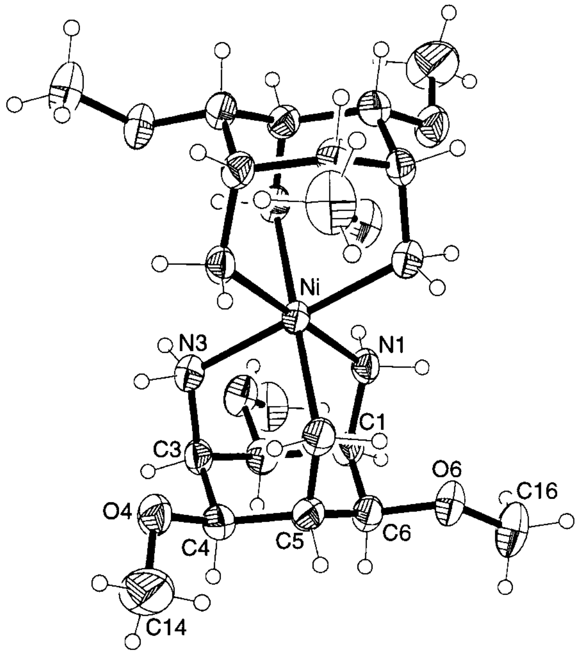


Figure 5. ORTEP drawing of $[Ni(tmca)_2]^{2+}$ with numbering scheme and vibrational ellipsoids at the 50% probability level. The hydrogen atoms are shown as spheres of arbitrary size. An ORTEP drawing of the Cu complex, which adopts virtually the same structure, is provided as Supporting Information.

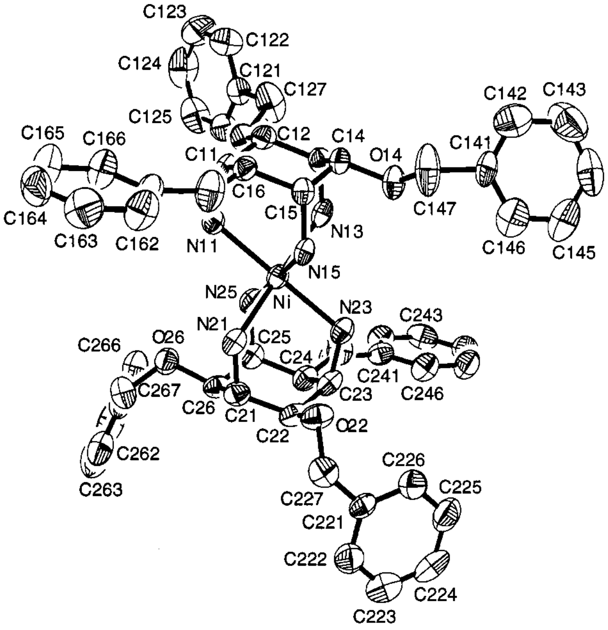


Figure 6. ORTEP drawing of $[Ni(tbca)_2]^{2+}$ with numbering scheme and vibrational ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity.

complexes appeared at higher frequencies than the corresponding H−(C−O) signals.

The two Ni^{II} complexes $[Ni(tmca)_2]^{2+}$ and $[Ni(tbca)_2]^{2+}$ showed a near-octahedral coordination geometry with some trigonal distortion (Figures 5 and 6), and the NiN_6 structure has almost ideal D_{3d} point group symmetry. With respect to the difference in stability, which is discussed below, the structural differences in the coordination spheres of $[Ni(tmca)_2]^{2+}$, $[Ni(tbca)_2]^{2+}$, and the previously reported $[Ni(taci)_2]^{2+}$ are not considered to be significant.[26] $[Cu(tmca)_2]^{2+}$ exhibited considerable Jahn−Teller distortion with four short and two long Cu−N distances of 2.05 and 2.45 Å, respectively, similar to that reported for $[Cu(taci)_2]^{2+}$,[30,26] The structure of $[Ni(tbca)_2](NO_3)_2 \cdot MeCN \cdot H_2O$ also reveals some stacking interactions of the aromatic rings, caused by hydrophobic interactions (a representation of the unit cell is available as Supporting Information).

Protonation Equilibria. The pK_a values of tmca (5.19, 6.88, 9.30) were determined by a series of pH-metric titration experiments (25 °C, 0.1 M KNO_3). Measurements in a CH_3OH/H_2O mixture (4:1 v/v) have also been performed (Table 4). The free tbca, which is more lipophilic than tmca, is not sufficiently soluble in water and precipitated out after more than 2 equiv of base was added to an aqueous solution of H_3tbca^{3+}. Evaluation of the acidic region of the titration curve revealed pK_1 = 3.55 and pK_2 = 6.40 for this triamine. For pK_3, however, only a rough estimate of 9.4 ± 0.1 could be obtained.

For the first protonation step, tmca is a slightly stronger base (pK_3 = 9.30) than the unsubstituted taci (pK_3 = 8.90).[26] The reverse order is found for pK_2 and pK_1: $Htmca^+$ and H_2tmca^{2+} have lower affinity for H^+ than the corresponding protonation products of taci. This result differs from the observations of Parker and co-workers who reported that *all-cis*-2,4,6-trimethylcyclohexane-1,3,5-triamine has a remarkably low pK_3 (7.83), whereas pK_1 and pK_2 fell in the usual range.[38] This unusually low pK_3 value was explained in terms of the conformational changes in going from L and HL^+ (which adopt an axial orientation of the nitrogen atoms) to H_2L^{2+} and H_3L^{3+}, where the nitrogen atoms are in equatorial position. As reported above, NMR spectroscopic measurements provided evidence that tmca undergoes related changes in conformation during protonation. It should, however, be noted that the pattern of pK_a values observed for tmca is in better agreement with such a change in conformation: The adoption of a structure with axial nitrogen atoms for the monoprotonated form HL^+ must be interpreted in terms of a stabilization of this form by hydrogen bonding. Consequently, this stabilization (better hydrogen bonds) should result in an increase of basicity of the ligand. This is indeed found when tmca is compared to taci. In forming H_2L^{2+} and H_3L^{3+} increasing electrostatic and steric repulsion, which finally enforces the equatorial orientation of the ammonium groups, should lower the basicity of the partially protonated species. This is clearly illustrated by comparing ΔpK_a values. For *all-cis*-cyclohexane-1,3,5-triamine (tach), ΔpK_a is 1.50 and 1.49;[39] for taci, 1.49 and 1.46.[26] The close agreement of these values is consistent with an exclusive equatorial orientation of all forms of these two ligands. For tmca, the ΔpK_a values are significantly enlarged (2.42 and 1.69), showing that the uptake of the second proton is particularly unfavorable. Again, this is consistent with the increased repulsion that accompanies addition of more than one proton to the molecule with a triaxial orientation of the amino groups. For *all-cis*-2,4,6-trimethyl-cyclohexane-1,3,5-triamine, the ΔpK_a values are only 1.10 and 1.58. The surprisingly low value of 1.10 actually indicates that the uptake of the *second* proton must be regarded as a particularly favorable process, a phenomenon which seems to be incompatible with a conformational change, enforced by increasing steric and electrostatic repulsion after uptake of a first proton. It is clear that other effects such as solvation will also influence the basicity of these compounds. However, the compilation of pK_a values for a variety of different taci derivatives, where different

---

(38) Parker, D.; Senanayake, K.; Vepsailainen, J.; Williams, S.; Batsanov, A. S.; Howard, J. A. K. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1445.

(39) Childers, R. F.; Wentworth, R. A. D.; Zompa, L. J. *Inorg. Chem.* **1971**, *10*, 302.

Table 6. Comparison of Formation Constants (log β_i, β_i = $[ML_i][M]^{-1}[L]^{-i}$) for Representative Triamine Ligands[a]

	Ni^{2+}		Cu^{2+}		Zn^{2+}	
	log β_1	log β_2	log β_1	log β_2	log β_1	log β_2
2,2-tri[b,c]	10.6	18.6	15.9	20.9	8.8	14.2
3,3-tri[b,c]	9.2	12.7	14.2		7.9	
tacn[b,c]	13.0		15.5	26.2[d]	11.6	
tame[c,d]	10.1	17.3	11.0	18.7	6.6	10.9
trap[b,e]	9.5	17.4		19.6	6.5	11.4
tach[b,c]	10.3	16.5	10.7	15.5	6.9	
taci[b,c]	12.4	20.9	12.1	18.8	8.4	13.6
tmca[b,f]	14.6	25.9	14.4	23.6	10.8	18.5

[a] 2,2-tri = 1,4,7-triazaheptane; 3,3-tri = 1,5,9-triazanonane; tacn = 1,4,7-triazacyclononane; tame = 1,1,1-tris(aminomethyl)ethane; trap = 1,2,3-triaminopropane; tach = *all-cis*-cyclohexane-1,3,5-triamine; taci = 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol; tmca = *all-cis*-2,4,6-trimethoxycyclohexane-1,3,5-triamine. [b] 25 °C, μ = 0.1 M. [c] From ref 17. [d] 25 °C, μ = 0.5 M. [e] From ref 41. [f] This work (Table 5).

substituents were used to vary the lipophilicity over a wide range, did not reveal any comparably low basicity.[9] In contrast to Parkers's observation, the introduction of more lipophilic substituents resulted in an increase of Δp*K*.[40]

Metal Complex Formation of tmca in Aqueous Media. The formation constants of a variety of tmca complexes with divalent metal centers are listed in Table 5. All constants were determined by pH-metric titrations experiments. The titration curves were evaluated in terms of formation of $[M(tmca)]^{2+}$ and $[M(tmca)_2]^{2+}$. In the alkaline range, additional species of the tentative composition $[M_n(tmca)_n(OH)_n]^{n+}$ are formed as indicated by additional consumption of base after addition of 3 equiv OH^- to 1 equiv of H_3tmca^{3+}. An assignment of the accurate nuclearity proved difficult and the range where such species were formed was omitted from the evaluation. As an example, a dinuclear species was evaluated for the 1:1 titration experiment of the Cu^{II} complex. Some additional systematic deviation in the acidic part of the 1:2 titration curve of the Cu^{II} complex was interpreted by means of formation of the protonated $[HCu(tmca)_2]^{3+}$. An analogous, protonated $[HCuL_2]^{3+}$ complex has been reported previously for taci.[26]

Selected formation constants of tmca, the corresponding taci complexes, and other representative triamine ligands are listed in Table 6. This comparison reveals that the tmca complexes are of significantly higher stability than the corresponding taci complexes. The increase in stability can be described by linear free energy relations as expressed in eqs 1 and 2, and visualized in Figure 7.

$$\log \beta_1(\text{tmca}) = 1.00 \log \beta_1(\text{taci}) + 2.39 \qquad (1)$$

$$\log \beta_2(\text{tmca}) = 1.00 \log \beta_2(\text{taci}) + 4.83 \qquad (2)$$

For free tmca, significant amounts of both chair conformers are found in aqueous media, although the form with equatorial amino groups is more stable. The energy required to convert the ligand to the form with three axial amino groups is +4.3 kJ/mol. For free taci, only the conformation with three axial hydroxy groups is observed in solution (Figure 1) and the difference in energy between the two conformers is not known. The absence of any significant amount of the conformer with three axial amino groups indicates that this difference in energy is even higher (more positive) than for tmca. The amino groups of taci are thus less preorganized for metal complex formation. According to Figure 7, a tmca complex of an N-bonded metal ion is more stable than the corresponding taci complex by 13.8 kJ/mol per coordinated ligand. One could therefore explain the increased stability of the tmca complexes simply by assuming that the energy required to convert the free taci to the conformer with three axial amino groups is +18 kJ/mol. This model would account not only for the observation that the increase in stability is independent of the metal cation (the slopes of eqs 1 and 2 are exactly 1.00) but also for the fact that the effect for the bis complexes is twice as large as for the 1:1 complexes. This explanation is, however, in clear contradiction with our results observed previously for the N-methylated tdci ligand (tdci = 1,3,5-trideoxy-1,3,5-tris(dimethylamino)-*cis*-inositol, Scheme 1).[7] If taci and tdci both adopt the conformation with the hydroxy groups in axial position, these donor groups have an optimal orientation for metal binding in both ligands and comparable stabilities are to be expected in complexes with O-coordination. This is not the case. On the contrary, an even more pronounced increase in stability is observed for tdci in such complexes:[7] log β_2 for $[Al(taci)_2]^{3+}$ is 18.8, but for $[Al(tdci)_2]^{3+}$ it is 26.3! Clearly, this effect cannot be explained in terms of a simple preorganization of the donor groups. For complexes with related structures (i.e. N-coordination for taci−tmca, and O-coordination for taci−tdci) an increase in stability is observed in both cases. Obviously, the substitution of hydrogen atoms by methyl groups on the noncoordinating donors generally results in an increase in stability. It is tempting to explain this observation as a solvation effect.[7] The methyl groups, which are all located on the periphery of the complex, generate a lipophilic surface, whereas the hydrophilic part of the molecule is mostly hidden in the inside, and compared with taci, the tdci and tmca complexes may therefore be stabilized by a more favorable entropy of hydration.

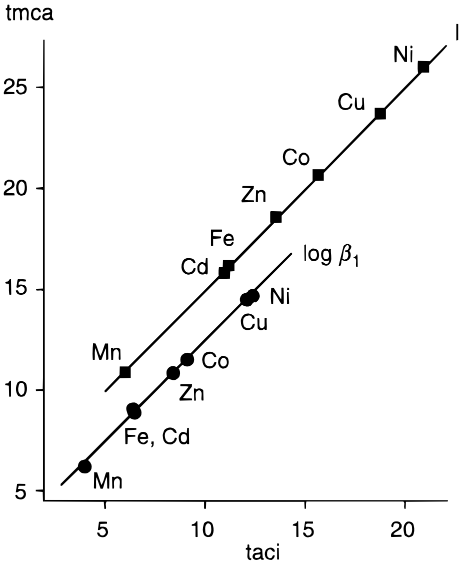


Figure 7. Comparison of formation constants of taci and tmca complexes in terms of a linear free energy (LFE) relation. The values of the tmca complexes are taken from Table 5; the values of the taci complexes are from ref 6.

The crystal structures indicate that methylation of the peripheral donors has no influence on the structural parameters of the coordination sphere. For example, the M−O bond distances are 1.906(2) Å for $[Al(tdci)_2]^{3+}$ [7] and 1.894(2)−1.912(2) Å for $[Al(taci)_2]^{3+}$.[27] Similarly the Ni−N distances of $[Ni(taci)_2]^{2+}$ fall in the range of 2.112(3)−2.136(5) Å,[26] while the corresponding values for $[Ni(tmca)_2]^{2+}$ are 2.117(3)−2.134(3)

---

(40) This effect can be understood in terms of a lower energy of solvation which generally results in destabilization of highly charged species.

(41) Zimmer, A.; Müller, I.; Reiss, G. J.; Caneschi, A.; Gatteschi, D.; Hegetschweiler, K. *Eur. J. Inorg. Chem.* **1998**, 2079.

Å. The differences for X−M−X and C−X−M angles (X = N, O) are generally not significant. In the past few years, molecular mechanics methods have widely been used to interpret the stability of a complex in terms of strain in the coordination sphere or in the ligand backbone.[5] The results presented here provide an illustrative example of some potential problems with this procedure. The parameters used in such calculations were usually obtained from solid state structures, and consequently solvation effects, especially entropic contributions, have not been taken into consideration. Our study suggests that such effects could easily influence the stability of a complex by several orders of magnitude.

The O-methylated tmca has almost ideal properties for binding late divalent transitions metal cations such as Ni^{2+}, and the values of the formations constants (Table 6) show that tmca belongs among the most effective chelating triamines. By contrast, the N-methylated derivative (tdci) has only a weak affinity for such cations.[16] The present investigation provides a further example of the way that the coordinating properties of taci can easily be tuned, simply by adding suitable substituents to the donor groups, disabling some of the coordination modes on the one hand and thereby increasing the affinity of the remaining sites on the other.

Conclusions

With respect to the design and the preparation of selective, tailored chelators, the present work leads to the following conclusions:

(i) Selective O-alkylation of the polyamino-polyalcohol taci was achieved by using the corresponding Ni^{II} complex as starting material. Ni^{2+} acted not only as a very efficient protecting group but also as an activator for the deprotonation of the hydroxy groups. This procedure allowed an almost quantitative and selective alkylation of the oxygen atoms, whereas the use of classical organic protecting groups was not effective.

(ii) It has previously been shown that taci is a very versatile ligand. More selective ligands can readily be obtained by blocking some of the available coordination modes. The previously reported ligand tdci, having an exclusive conformation with three hydroxy group in axial position, represents an example of a selective chelator for oxophilic cations such as Al^{3+}, Fe^{3+}, or Ga^{3+}. tmca, on the other hand, represents a selective chelator for late divalent transition metal cations such as Ni^{2+}. This selectivity is mainly based upon the inability of tmca to adopt a zwitterionic structure with deprotonated oxygen donors rather than an improved preorientation of the amino groups. As shown in this study, the difference in energy of the two chair conformers, having either the oxygen or the nitrogen donors in axial position, is only small as long as water is used as solvent.

(iii) Both taci and tmca are effective ligands for late divalent transition metal cations. However, the stability of bis complexes of tmca exceed those of taci by about 5 orders of magnitude, even though no significant structural differences were observed within the coordination spheres or the ligand backbones of corresponding structures. Again, this result cannot be assigned to an improved preorientation of the amino groups in tmca but must be interpreted in terms of more favorable solvation of the complex. This results underlines the importance of solvation effects and demonstrates that a simple analysis of complex stability in terms of steric considerations may not always be adequate.

Acknowledgment. The evaluation of the pD-dependent NMR spectroscopic measurements of taci has been performed by Andreas Ries (Saarbrücken). We thank Dr. Heinz Rüegger (ETH Zürich) for the measurements of the 2D NMR spectra and Prof. Dr. T. Eicher, Dr. Werner Angst, and Dr. André Egli for helpful advice and discussions. Financial support from Vifor Inc. (St. Gallen), from the ETH Zürich (Kredite für Unterricht und Forschung), and the Studienstiftung des deutschen Volkes is gratefully acknowledged. M.W. is grateful to Prof. W. Koppenol (ETH Zürich) for the kind accommodation in his laboratory and the ETH Zürich (Kredite für Unterricht und Forschung) for financial support.

Supporting Information Available: Listings of crystallographic data, anisotropic displacement parameters, positional parameters of hydrogen atoms, bond distances and bond angles, an ORTEP drawing of $[Cu(tmca)_2]^{2+}$ and a representation of the unit cell of $[Ni(tbca)_2](NO_3)_2 \cdot MeCN \cdot H_2O$. This material is available free of charge via the Internet at http://pubs.acs.org.

IC980867M