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Article

Synthesis and Characterization of a Novel Macrocyclic Chelator with 3-Hydroxy-4-Pyrone Chelating Arms and Its Complexes with Medicinally Important Metals

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A new macrocyclic chelator, 6,6′,6′′-(1,4,7-triazonane-1,4,7-triyl)tris(methylene)tris(5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one) (H_3NOKA), was synthesized from the reaction of 1 equiv of 1,4,7-triazacyclononane (TACN) and 3 equiv of kojic acid (KA) in the presence of excess formaldehyde. The reaction of H_3NOKA with metal salt forms complexes M(NOKA) (M = Ga, In, and Fe) and Cu(HNOKA). H_3NOKA and its complexes, M(NOKA) (M = Ga, In, and Fe) and Cu(HNOKA), have been characterized by IR, UV/vis, ESI-MS, and elemental analysis. Structures of Ga(NOKA), Fe(NOKA), and Cu(HNOKA) were determined by X-ray crystallography. In the solid state, Ga(NOKA) and Fe(NOKA) are isostructural with the distorted octahedral geometry. In contrast, Cu(HNOKA) has the distorted square-pyramidal coordination geometry in which NOKA is pentadentate with three amine-N and two enolate-O atoms bonding to Cu(II) and one of three 3-hydroxy-4-pyrone chelating arms remaining free and protonated. The cyclic voltammogram of Fe(NOKA) exhibits a quasi-reversible redox wave at $E_{1/2} = -0.53$ mV from the Fe(III)(NOKA)/Fe(II)(NOKA)$^-$ couple, whereas Cu(HNOKA) shows an irreversible one-electron reduction of Cu(II)(HNOKA)/Cu(I)(HNOKA)$^-$ at $E_{pc} = -0.87$ V. These low redox potentials indicate that Fe(III) in Fe(NOKA) and Cu(II) in Cu(HNOKA) are preferentially stabilized by NOKA. The variable-temperature ^{1}H NMR spectral data show that Ga(NOKA) is more rigid than that of In(NOKA) in the solution. The results from this study suggest that the C-substituted NOKA derivatives might be useful as bifunctional chelators for ^{68}Ga-labeling of small biomolecules, while the corresponding N-substituted analogues are probably more suitable for preparation of the ^{64}Cu-based target-specific radiotracers.

Introduction

There is a great interest in metallic radionuclides, such as ^{99m}Tc, ^{68}Ga, ^{111}In, and ^{64}Cu, for the development of target-specific diagnostic radiotracers due to their wide range of nuclear properties (type of radiation, half-life, and energy) and diverse coordination chemistry.[1–5] While ^{99m}Tc ($t_{1/2}$ = 6.02 h and E = 140 keV), ^{67}Ga ($t_{1/2}$ = 78.1 h and E = 93.3, 185, and 300 keV), and ^{111}In ($t_{1/2}$ = 67 h and E = 173 and 247 keV) are often used for planar imaging and single photon emission computed tomography (SPECT), ^{68}Ga ($t_{1/2}$ = 67.8 min and E_γ = 511 keV from β^+ annihilation) is particularly useful for positron emission tomography (PET).[6–10] A major advantage of ^{68}Ga is the availability of ^{68}Ge−^{68}Ga generators, which can be used for 1–2 years and allow PET imaging at facilities without the on-site cyclotron. ^{64}Cu ($t_{1/2}$ = 12.7 h, 18% abundance and maximum β^+ energy of 0.66 MeV) is

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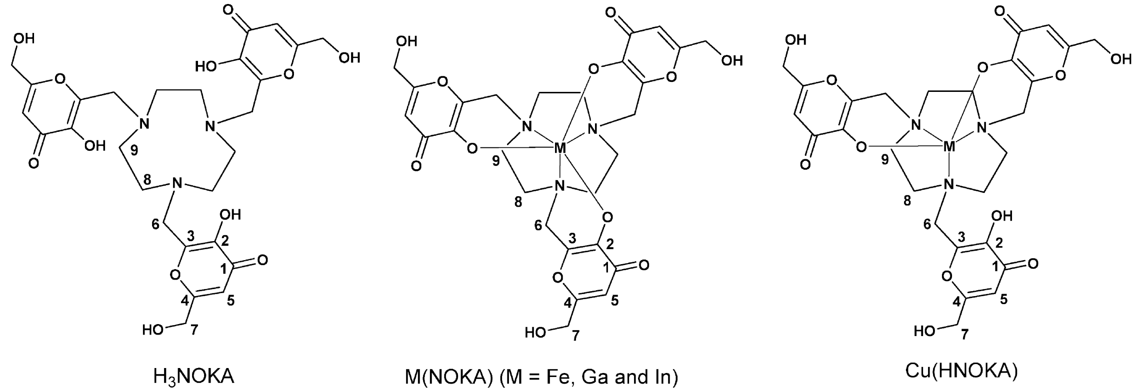

Figure 1. Structures of H_3NOKA and its complexes with Ga(III), In(III), Fe(III), and Cu(II).

another radiometal useful for PET. Recent breakthroughs in the production of ^{64}Cu with high specific activity have made it more available in most research and medical institutions. Both ^{68}Ga and ^{64}Cu are exciting and viable alternatives to ^{18}F ($t_{1/2} = 110$ min, 97% abundance and $E_{\max} = 635$ KeV) for research programs that wish to incorporate the high sensitivity and spatial resolution of PET but do not desire to implement and maintain the expensive radionuclide production infrastructure.

A bifunctional chelator (BFC) is needed for successful labeling of biomolecules with a metallic radionuclide, such as ^{99m}Tc, ^{68}Ga, ^{111}In, and ^{64}Cu.[2–5] The BFC is covalently attached to the targeting biomolecule either directly or through a linker and strongly coordinates to the radiometal. The choice of BFC is determined by the nature and oxidation state of the metallic radionuclide. An ideal BFC is that which is able to form a stable radiometal chelate with high thermodynamic stability and kinetic inertness. For example, 6-hydrazinonicotinic acid (HYNIC) is the best BFC for the ^{99m}Tc-labeling of small biomolecules due to its high ^{99m}Tc-labeling efficiency (rapid radiolabeling and high radiolabeling yield), the high solution stability of its ^{99m}Tc complexes, and the easy use of different coligands for modification of biodistribution characteristic of the ^{99m}Tc-labeled small biomolecules.[11–15] In contrast, DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid) derivatives are particularly useful as the BFCs for ^{64}Cu-, $^{67/68}Ga$-, and ^{111}In-labeling small biomolecules due to the high solution stability of their radiometal chelates.[16–30] Among many macrocyclic BFCs, NOTA is particularly useful for $^{67/68}Ga$ and ^{111}In due to the perfect match between their coordination cavity and the size of Ga(III) and In(III).[28–32] The coordination cavity of DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) is too big for Ga(III), and only six (N_4O_2) out of N_4O_4 donors are used in bonding to Ga(III).[21,25] BFCs for the ^{99m}Tc-, ^{68}Ga-, ^{111}In-, and ^{64}Cu-labeling of biomolecules have been reviewed extensively.[1–5,33–36]

Recently, we prepared a novel macrocyclic chelator, 6,6′,6″-(1,4,7-triazonane-1,4,7-triyl)tris(methylene)tris(5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one) (Figure 1: H_3NOKA), and its complexes with Ga(III), In(III), Fe(III), and Cu(II). We are interested in its coordination chemistry with Ga(III), In(III), and Cu(II) because of the potential of its C- and/or N-substituted derivatives as BFCs for $^{67/68}Ga$-, ^{111}In-, and ^{64}Cu-labeling of small biomolecules. The coordination chemistry

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Table 1. Selected Crystallographic Data and Structure Refinements Details for Ga(NOKA)·$3H_2O$, Fe(NOKA)·$3H_2O$, and Cu(HNOKA)·$3H_2O$

formula	$C_{27}H_{36}GaN_3O_{15}$	$C_{27}H_{36}FeN_3O_{15}$	$C_{27}H_{37}CuN_3O_{15}$
fw	712.32	698.45	707.15
space group	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)
λ, Å	Mo Kα (0.71073)	Mo K_a (0.71073)	Mo K_a (0.71073)
a, Å	7.8250(3)	7.8566(4)	16.3115(9)
b, Å	20.1632(11)	20.3057(7)	11.8257(8)
c, Å	17.9449(9)	17.9823(9)	20.0319(9)
β, deg	97.257(16)	97.32(2)	126.10(3)
V, Å^3	2808.6(2)	2845.4(2)	3122.0(3)
Z	4	4	4
d_{calc}, g/cm^3	1.68	1.630	1.504
temp, K	150	150	150
μ, mm^{-1}	1.055	0.608	0.773
transmission coeff	0.900, 0.844	0.872, 0.752	0.872, 0.752
$R(F_o)$	0.054^a	0.047^a	0.040^a
$R_w(F_o^2)$	0.133^b	0.126^b	0.099^b

^{a} $R = \Sigma|F_o| - |F_c|/\Sigma|F_o|$ for $F_o^2 > 2\sigma(F_o^2)$. ^{b} $R_w = [\Sigma w(|F_o^2| - |F_c^2|)^2/\Sigma w|F_o^2|^2]^{1/2}$.

of H_3NOKA with Fe(III) is of our interest for its potential application as a chelating agent for iron detoxification in thalassemia patients.[37,38] In this report, we present the synthesis and characterization of H_3NOKA and its metal complexes (Figure 1: M(NOKA) (M = Ga, In, and Fe) and Cu(HNOKA)). The main objective of this study is to understand some aspects of the coordination chemistry of this new chelating system with $^{67/68}$Ga, ^{111}In, and ^{64}Cu by determining structures of Ga(III), In(III), Fe(III), and Cu(II) complexes in the solid state and in solution.

Experimental Section

Materials and Instruments. Chemicals were purchased from Sigma/Aldrich (St. Louis, MO). Solvents were reagent grade from Mallinckrodt. The NMR (^{1}H, ^{13}C, NOESY, and HMQC) data were obtained using a Bruker DRX 500 MHz FT NMR spectrometer. Chemical shifts are reported in parts per million relative to TMS. Infrared (IR) spectra (4000−400 cm^{-1}) were recorded on a Perkin-Elmer FT-IR spectrophotometer. Mass spectral data were collected using positive mode on a Finnigan LCQ classic mass spectrometer, School of Pharmacy, Purdue University. Elemental analysis was performed by Dr. H. Daniel Lee using a Perkin-Elmer Series III analyzer, Department of Chemistry, Purdue University. The UV/visible spectra were recorded on a Beckman DU-640 UV/vis spectrophotometer.

H_3NOKA. To a solution of kojic acid (0.42 g, 3.0 mmol) in ethanol (18 mL) was added excess of formaldehyde (30% aqueous solution, 2 mL). After stirring at room temperature for 0.5 h, a solution of 1,4,7-triazacyclononane (0.13 g, 1.0 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 20 h. The white precipitate was filtered, washed with diethyl ether, and dried under vacuum. The yield was 0.31 g (54%). IR (cm^{-1}, KBr pellet): 1583, 1627, 1657 (s, $\upsilon_{C=C}$, $\upsilon_{C=O}$), 3432 (br s, υ_{O-H}). ESI-MS: m/z = 614.56 for $[M + Na]^+$ (614 calcd for $[C_{27}H_{33}N_3O_{12}Na]^+$). ^{1}H NMR ($D_2O$, 25 °C, 500 MHz): δ 2.90 (m, 12H, J_{HH} = 9.8 Hz), 3.98 (s, 2H, CH_2), 4.38 (d, 2H, CH_2OH, J_{HH} = 9.8 Hz), 6.42 (s, 1H, aromatic). ^{13}C NMR (DMSO-d_6, 25 °C, 500 MHz, chemical shift δ in ppm relative to TMS): 53.4 (s, 3C, C-6), 54.5 (s, 6C, C-8, C-9), 59.8 (s, 3C, C-7), 109.1 (s, 3C, C-5), 143.3 (s, 3C, C-3), 148.4 (s, 3C, C-2), 167.8 (s, 3C, C-4), 173.9 (s, 3C, C-1). Anal. Calcd for $C_{27}H_{33}N_3O_{12}$·C_2H_5OH: C, 54.63; H, 5.96; N, 6.59. Found: C, 54.84; H, 5.92; N, 6.53.

Ga(NOKA). To a suspension of H_3NOKA (90.0 mg, 0.15 mmol) in water (10 mL) was added $Ga(NO_3)_3$ (31.0 mg, 0.15 mmol) in methanol (10 mL), followed by 1.5 mL of NH_4OAc buffer (0.5 M, pH = 6.0). The mixture was stirred at room temperature for 60 min. The pale yellow solution was concentrated on a rotary evaporator. To the sticky residue was added 10 mL of the 50:50 (v/v) mixture of methanol and acetonitrile to afford a white solid. The solid was filtered, washed with diethyl ether, and dried under vacuum. The yield was 25.9 mg (35%). The sample was dried in vacuum overnight before being submitted to elemental analysis. Colorless crystals of Ga(NOKA)·$3H_2O$ suitable for X-ray crystallography were grown by slow evaporation of Ga(NOKA) in a mixture of MeOH and H_2O (50:50 = v/v). IR (cm^{-1}, KBr pellet): 1572, 1607, 1631 (s, $\upsilon_{C=C}$, $\upsilon_{C=O}$), 3435 (br s, υ_{O-H}). ESI-MS: m/z = 680.02 for $[M + H]^+$ (680 calcd for $[C_{27}H_{30}GaN_3O_{12}]^+$). ^{1}H NMR ($D_2O$, 25 °C, 500 MHz): δ 2.73 and 2.89 (m, 6H, H-8, J_{HH} = 9.8 Hz), 3.14 and 3.33 (m, 6H, H-9, J_{HH} = 9.8 Hz), 3.93 and 4.55 (AB quartet, 2H, H-6, C H_2), 4.47 (d, 2H, H-7, C H_2OH, J_{HH} = 9.8 Hz), 6.45 (s, 1H, H-5, aromatic). ^{13}C NMR (DMSO-d_6, 25 °C, 500 MHz, chemical shift δ in ppm relative to TMS): 49.2 (s, 3C, C-8), 55.6 (s, 3C, C-9), 59.1 (s, 3C, C-6), 59.8 (s, 3C, C-7), 110.3 (s, 3C, C-5), 145.8 (s, 3C, C-3), 149.7 (s, 3C, C-2), 166.5 (s, 3C, C-4), 179.2 (s, 3C, C-1). Anal. Calcd for $C_{27}H_{30}GaN_3O_{12}$·CH_3OH: C, 48.77; H, 4.93; N, 6.10. Found: C, 49.04; H, 4.90; N, 6.27.

In(NOKA). It was prepared according to the procedure similar to that for Ga(NOKA) using $In(NO_3)_3$·$5H_2O$ (38.0 mg, 0.10 mmol), H_3NOKA (60.0 mg, 0.10 mmol), and 0.8 mL of NH_4OAc (0.5 M, pH = 6) buffer. The pale-yellow solid was filtered, washed with diethyl ether, and dried under vacuum overnight. The yield was 29.3 mg (40%). IR (cm^{-1}, KBr pellet): 1573, 1602, 1632 (s, $\upsilon_{C=C}$, $\upsilon_{C=O}$), 3435 (br s, υ_{O-H}). ESI-MS: m/z = 703.76 for $[M + H]^+$ (704 calcd for $[C_{27}H_{30}InN_3O_{12}]^+$). ^{1}H NMR ($D_2O$, 25 °C, 500 MHz): δ 2.53 and 2.86 (m, 6H, H-8, J_{HH} = 9.8 Hz), 3.07 and 3.26 (m, 6H, H-9, J_{HH} = 9.8 Hz), 3.93 and 4.40 (AB quartet, 2H, H-6, CH_2), 4.46 (d, 2H, H-7, C H_2OH, J_{HH} = 9.8 Hz), 6.52 (s, 1H, H-5, aromatic). ^{13}C NMR (DMSO-d_6, 25 °C, 500 MHz, chemical shift δ in ppm relative to TMS): 47.7 (s, 3C, C-8), 55.4 (s, 3C, C-9), 58.7 (s, 3C, C-6), 60.1 (s, 3C, C-7), 110.1 (s, 3C, C-5), 142.5 (s, 3C, C-3), 152.0 (s, 3C, C-2), 166.1 (s, 3C, C-4), 177.1 (s, 3C, C-1). Anal. Calcd for $C_{27}H_{30}InN_3O_{12}$·$2H_2O$: C, 43.85; H, 4.60; N, 5.68. Found: C, 43.74; H, 4.51; N, 5.79.

Fe(NOKA). To a solution of H_3NOKA (150.0 mg, 0.25 mmol) dissolved in a mixture of NH_4OAc (2.0 mL, 0.5 M, pH = 6) and methanol (15 mL) was added $FeCl_3$ (67.5 mg, 0.25 mmol) in water (15 mL). The reaction mixture was stirred at room temperature for 4 h. The reddish brown solid was separated by filtration, washed with diethyl ether, and dried under vacuum overnight before being submitted for elemental analysis. The yield was 96.3 mg (58%). The product was dissolved in a mixture of MeOH and H_2O (70:30 = v/v). Slow evaporation of solvents afforded crystals suitable for X-ray crystallographic analysis. IR (cm^{-1}, KBr pellet): 1560, 1596, 1626 (s, $\upsilon_{C=C}$, $\upsilon_{C=O}$), 3438 (br s, υ_{O-H}). UV/vis (H_2O, λ_{max}, nm (ϵ, L·mol^{-1}·cm^{-1})): 467 (499), 320 (245), 280 (sh). ESI-MS: m/z = 644.93 for $[M + H]^+$ (644 calcd for $[C_{27}H_{30}FeN_3O_{12}]^+$); m/z = 666.93 for $[M + Na]^+$ (666 calcd for $[C_{27}H_{30}FeNaN_3O_{12}]^+$). Anal. Calcd for $C_{27}H_{30}FeN_3O_{12}$·H_2O: C, 48.95; H, 4.83; N, 6.35. Found: C, 48.84; H, 4.65; N, 6.29.

Cu(HNOKA). Cu(HNOKA) was prepared by following the procedure similar to that for Ga(NOKA) using $CuCl_2$·$2H_2O$ (42.6

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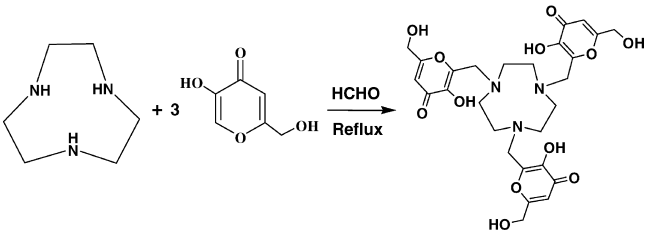
mg, 0.25 mmol), H_3NOKA (150.0 mg, 0.25 mmol), and 2.0 mL of NH_4OAc (0.5 M, pH = 6). The resulting green solid was filtered, washed with diethyl ether, and dried under vacuum overnight before being submitted for elemental analysis. The yield was 103.2 mg (61.5%). The product was dissolved in a mixture of MeOH and H_2O (50:50 = v/v). Slow evaporation of solvents afforded crystals suitable for X-ray crystallographic analysis. IR (cm^{-1}, KBr pellet): 1584, 1597, 1629 (s, $\upsilon_{C=C}$, $\upsilon_{C=O}$), 3429 (br s, υ_{O-H}). UV/vis (MeCN; λ_{max}, nm (ϵ, $L\cdot mol^{-1}\cdot cm^{-1}$)): 540 (438), 315 (326), 279 (sh). ESI-MS: m/z = 652.96 for $[M + H]^+$ (653 calcd for $[C_{27}H_{31}CuN_3O_{12}]^+$); m/z = 674.97 for $[M + Na]^+$ (675 calcd for $[C_{27}H_{31}CuNaN_3O_{12}]^+$). Anal. Calcd for $C_{27}H_{30}CuN_3O_{12}\cdot H_2O$: C, 48.32; H, 4.77; N, 6.26. Found: C, 48.13; H, 4.58; N, 6.31.

Electrochemistry. Cyclic voltammograms of Fe(NOKA) and Cu(HNOKA) were recorded on a Bioanalytical System BAS-100A electrochemical analyzer. A standard three-electrode cell was used with a polished glassy carbon as the working electrode, a Pt wire as the auxiliary electrode, and a Ag/AgCl in 3 M NaCl solution as the reference electrode. The measurements were performed in aqueous solution for Fe(NOKA) and in acetonitrile for Cu(HNOKA) containing 0.1 M tetrabutylammonium hexafluorophosphate ($TBAPF_6$) at a scan rate of 50 $mV\cdot s^{-1}$. Before measurements, the sample solution was purged with extra pure N_2 gas to remove the dissolved oxygen and a continuous nitrogen stream was blanketed over the solution during each measurement.

X-ray Crystallographic Analysis. Crystallographic data for Ga(NOKA)•$3H_2O$, Fe(NOKA)•$3H_2O$, and Cu(HNOKA)•$3H_2O$ were collected on a Nonius Kappa CCD diffractometer and are listed in Table 1. Crystals were mounted on a glass fiber in a random orientation. Unit cell parameters and the intensity data collection were performed using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles in the range of $2° < \theta < 26°$ for both Ga(NOKA)•$3H_2O$ and Fe(NOKA)•$3H_2O$. For Ga(NOKA)•$3H_2O$, a total of 18 283 reflections were collected and 5675 reflections were unique. Lorentz and polarization corrections were applied to the data. The linear absorption coefficient was 10.6 cm^{-1} for Mo Kα radiation in Ga(NOKA)•$3H_2O$. An empirical correction was applied using the program SCALEPACK.[39] The structure of Ga(NOKA)•$3H_2O$ was solved using SIR 2004.[40] Refinement was performed on a LINUX PC using SHELX-97.[41] Crystallographic drawings were done using the programs ORTEP[42] and PLATON.[43] For Fe(NOKA)•$3H_2O$, a total of 21 458 reflections were collected and 6664 reflections were unique. Lorentz and polarization corrections were applied to the data. The linear absorption coefficient was 6.1 cm^{-1} for Mo Kα radiation in Fe(NOKA)•$3H_2O$. An empirical correction was applied using the program SCALEPACK.[39] The structure of Fe(NOKA)•$3H_2O$ was solved using the structure solution program PATTY in DIRDIF99.[44] The SHELX-97 program was used for structure refinement.[41] The ORTEP[42] and PLATON[43] packages were used for crystallographic drawing. For Cu(HNOKA)•$3H_2O$, cell constants for data collection were obtained from least-squares refinement, using the setting angles of 31 357 reflection in the range of $2° < \theta < 27°$. A total of 31 357 reflections were collected, of which 7102 were unique. Frames were integrated with DENZO-SMN.[39] Lorentz and polarization corrections were applied to the data. The linear absorption coefficient was 7.7 cm^{-1} for Mo Kα radiation. An empirical correction was applied using the program SCALEPACK.[39] The structure was solved by direct methods using Charge Flipping[45] in PLATON.[43] Refinement was performed on a LINUX PC using SHELX-97.[41] Crystallographic drawings were done using the programs ORTEP[42] and PLATON.[43]

Chart 1. Synthesis of H_3NOKA



Results

H_3NOKA. H_3NOKA was prepared according to Chart 1 in relatively high yield by reacting 1 equiv of 1,4,7-triazacyclononane (TACN) and 3 equiv of kojic acid in the presence of excess formaldehyde. Kojic acid underwent Mannich aminomethylation at the *ortho* position to the enolic hydroxyl group.[46–48] It has been characterized by ESI-MS and NMR (^{1}H and ^{13}C). The ESI-MS spectrum of H_3NOKA shows a molecular ion at m/z = 614.56 for $[M + Na]^+$ for $[C_{27}H_{33}N_3O_{12}Na]^+$. The sodium cation was probably from glassware or water. The elemental analysis data are completely consistent with the proposed formula of H_3NOKA.

Metal Complexes. M(NOKA) (M = Ga, In, Fe) and Cu(HNOKA) were prepared by reacting H_3NOKA with the respective metal salts. These complexes are soluble in a mixture of methanol and water. Slow evaporation of solvents (methanol and water) afforded crystals suitable for X-ray crystallographic analysis. M(NOKA) (M = Ga, In, and Fe) and Cu(HNOKA) have been characterized by IR, UV/vis, ESI-MS, and elemental analysis. Structures of Ga(NOKA), Fe(NOKA), and Cu(HNOKA) were determined by X-ray crystallography. The NMR methods (^{1}H, ^{13}C, NOESY, and HMQC) were used to determine the solution structures of In(NOKA) and Ga(NOKA).

IR, UV/Vis, and ESI-MS. The IR spectra of these complexes show a strong and broad band at ~3450 cm^{-1} due to υ_{O-H} of crystallization water or methanol molecules. Four strong bands at 1600–1400 cm^{-1} are characteristic of the $\upsilon_{C=O}$ and $\upsilon_{C=C}$ of the coordinated NOKA chelator. There is no significant shift for the pyrone stretching bands upon chelation. It suggests that only the hydroxy-O atom is bonded

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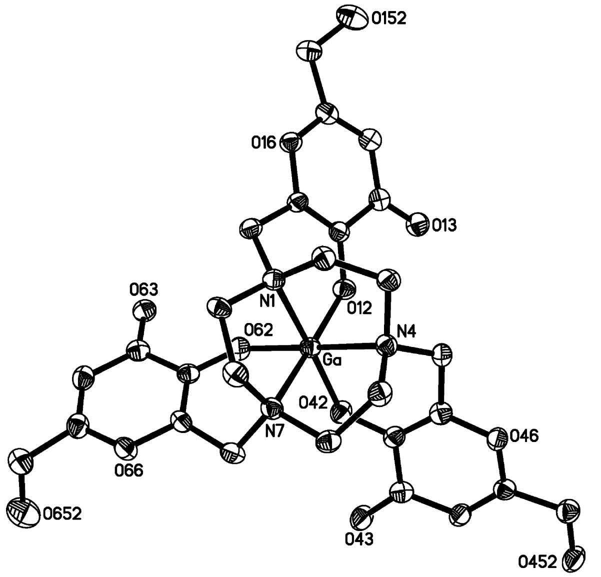

Figure 2. ORTEP drawing of Ga(NOKA) (ellipoids are at 50% probability). Crystallization water molecules and hydrogen atoms are omitted for the sake of clarity.

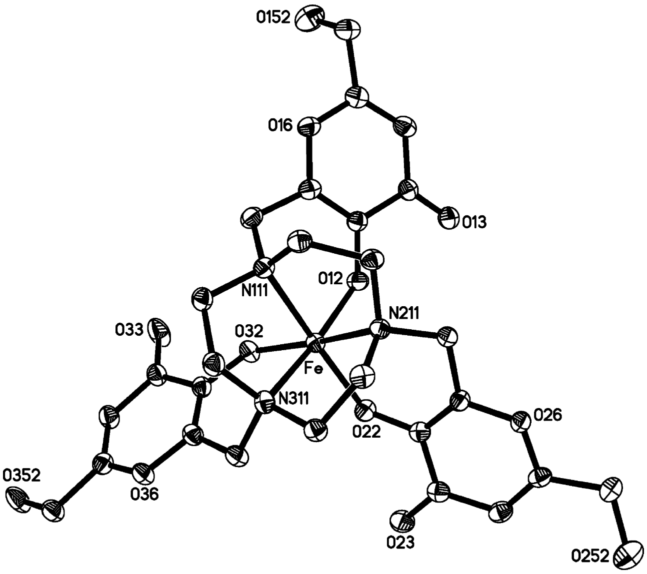

Figure 3. ORTEP drawing of Fe(NOKA) (ellipoids are at 50% probability). Crystallization water molecules and hydrogen atoms are omitted for the sake of clarity.

to the metal.[49,50] The electronic spectra of Fe(NOKA) in water and Cu(HNOKA) in acetonitrile show three absorptions in the range of 550–240 nm. The absorption bands at 467 nm for Fe(NOKA) and 540 nm for Cu(HNOKA) are assigned to ligand-to-metal transition. The absorption bands at 320 and 280 nm for Fe(NOKA) and at 315 and 279 nm for Cu(HNOKA) are assigned to the $\pi \rightarrow \pi^*$ transitions of the coordinated pyrone enolates. This absorption band has been observed in a number of Fe(III) complexes with the N-substituted 1,4,7-triazacyclononane (TACN) chelators.[51–53] ESI-MS data are completely consistent with the proposed formula for M(NOKA) (M = Ga, In, Fe) and Cu(HNOKA).

Structures of Ga(NOKA)$\cdot$3H_2O and Fe(NOKA)$\cdot$3H_2O. Figures 2 and 3 illustrate ORTEP drawings of Ga(NOKA)$\cdot$3H_2O and Fe(NOKA)$\cdot$3H_2O, respectively. Figures SI and SII show the hydrogen bonding networks in Ga(NOKA)$\cdot$3H_2O and Fe(NOKA)$\cdot$3H_2O, respectively. There are four M(NOKA)$\cdot$3H_2O (M = Ga and Fe) molecules (two pairs of Λ and Δ enantiomers) in each unit cell along with the three water molecules. NOKA acts as a hexadentate ligand with all six donors (3 amine-N atoms and 3 enolate-O atoms) bonding to the metal center. The coordination geometry is best described as distorted octahedron for both Ga(NOKA) and Fe(NOKA) with three amine-N atoms occupying one face and the opposite face being occupied by three enolate-O atoms. The degree of distortion from regular octahedron was measured in terms of twist angle φ, where $\varphi = 0°$ for a purely octahedron and $\varphi = 60°$ for a purely trigonal prism.[54] The φ twist angles are 0.60° for Ga(NOKA)$\cdot$3H_2O (Figure 2) and 1.76° for Fe(NOKA)$\cdot$3H_2O (Figure 3). The distortion of the coordination sphere is evident in the compression of N−M−N angles (average N−Ga−*N* = 82.08(11)° for Ga(NOKA)$\cdot$3H_2O and N−Fe−*N* = 79.40(7)° for Fe(NOKA)$\cdot$3H_2O) and expansion of O−M−O angles (average O−Ga−O = 94.28(12)° for Ga(NOKA)$\cdot$3H_2O and O−Fe−O = 98.73(7)° for Fe(NOKA)$\cdot$3H_2O) from 90°. As a result, the three *trans* N−Ga−O angles are 170.42(11), 170.83(11), and 172.75° for O(12)−Ga−N(7), O(42)−Ga−N(1), and O(22)−Ga−N(4) in Ga(NOKA)$\cdot$3H_2O, respectively; the three *trans* N−Fe−O angles are 167.79(7), 164.51(7), and 166.28(7)° for O(12)−Fe−N(311), O(22)−Fe−N(111), and O(32)−Fe−N(211) in Fe(NOKA)$\cdot$3H_2O, respectively. The metal ion is fitted perfectly inside the N_3O_3 coordination cavity of the coordinated NOKA, which has a C_3-symmetry with a 3-fold axis passing through the metal center. The pendant arms emanating from the tertiary N atoms form three six-member chelate rings, and the macrocycle forms three five-member chelate rings. The structure of Ga(NOKA)$\cdot$3H_2O is very similar to those of Ga(L1) (H_3L1 = 1,4,7-tris(3,5-dimethyl-2-hydroxybenzyl)-1,4,7-triazacyclononane)[54,55] and [GaL2]$\cdot$5H_2O (H_3L2 = 1,4,7-triazacyclononane-1,4,7-triyltrimethylenetris(phenylphosphinic acid).[56] The structure of Fe(NOKA)$\cdot$3H_2O is very close to those of [Fe(NOTA)],[51] [FeL3] (H_3L3 = 1,4,7-tris(5-*tert*-butyl-2-hydroxybenzyl)-1,4,7-triazacyclononane),[52] and [FeL4] (H_3L4 = 1,4,7-tris(3-*tert*-butyl-2-hydroxybenzyl)-1,4,7-triazacyclononane).[53] All crystallization water molecules are involved in intramolecular and intermolecular H-bonding in Ga(NOKA)$\cdot$3H_2O and

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Table 2. Selected Bond Distances (Å) and Bond Angles (deg) in Fe(NOKA)•$3H_2O$ and Ga(NOKA)•$3H_2O$

[Ga(NOKA)]·$3H_2O$			[Fe(NOKA)]·$3H_2O$		
atom 1	atom 2	distance (Å)	atom 1	atom 2	distance (Å)
Ga	N1	2.152(3)	Fe	N111	2.2308(19)
Ga	N4	2.121(3)	Fe	N211	2.2214(19)
Ga	N7	2.157(3)	Fe	N311	2.187(2)
Ga	O12	1.898(3)	Fe	O12	1.9370(16)
Ga	O42	1.901(3)	Fe	O22	1.9132(17)
Ga	O62	1.912(2)	Fe	O32	1.9170(17)

atom 1	atom 2	atom 3	angle (deg)	atom 1	atom 2	atom 3	angle (deg)
O12	Ga	O42	96.60(11)	O22	Fe	O32	101.05(7)
O12	Ga	O62	93.70(11)	O22	Fe	O12	98.05(7)
O42	Ga	O62	92.53(11)	O32	Fe	O12	97.09(7)
O12	Ga	N4	91.01(11)	O22	Fe	N311	90.57(7)
O42	Ga	N4	92.40(11)	O32	Fe	N311	89.67(7)
O62	Ga	N4	172.75(11)	O12	Fe	N311	167.79(7)
O12	Ga	N1	91.28(11)	O22	Fe	N111	164.51(7)
O42	Ga	N1	170.83(11)	O32	Fe	N111	91.26(7)
O62	Ga	N1	91.63(11)	O12	Fe	N111	89.62(7)
N4	Ga	N1	82.75(11)	N311	Fe	N111	80.05(7)
O12	Ga	N7	170.42(11)	O22	Fe	N211	88.19(7)
O42	Ga	N7	90.91(12)	O32	Fe	N211	166.28(7)
O62	Ga	N7	91.89(11)	O12	Fe	N211	91.56(7)
N4	Ga	N7	82.72(12)	N311	Fe	N211	80.03(7)
N1	Ga	N7	80.78(12)	N111	Fe	N211	78.12(7)

Fe(NOKA)•$3H_2O$. However, there is no recognizable pattern in the solid state.

The selected bond distances and bond angles for Ga(NOKA)•$3H_2O$ and Fe(NOKA)•$3H_2O$ are listed in Table 2, respectively. The average Ga−N bond length is 2.143 Å (Ga−N(1) 2.152(3) Å, Ga−N(4) 2.121(3) Å, Ga−N(7) 2.157(3) Å), which is slightly longer than that (average Ga−*N* = 2.090 Å) in Ga(NOTA)[54,55] and close to that (average Ga−*N* = 2.135 Å) in [GaL2]•$5H_2O$.[51] The average Ga−O bond length is 1.904 Å (Ga−O(12) 1.898(3) Å, Ga−O(42) 1.901(3) Å, and Ga−O(62) 1.912(2) Å), which is comparable to that of [GaL2]•$5H_2O$ (average Ga−O distance = 1.912 Å);[51] however, it is shorter than that of Ga(NOTA) (average Ga−O distance = 1.930 Å).[54,55] The average Fe−N bond length is 2.213 Å (Fe−N(111) 2.2308(19) Å, Fe−N(211) 2.214(19) Å, Fe−N(311) 2.187(2) Å), which is in agreement with those previously reported.[52–54] The average Fe−O bond length is 1.9224 Å (Fe−O(12) 1.9370(16) Å, Fe−O(22) 1.9132(17) Å, Fe−O(32) 1.9170(17) Å), which is slightly shorter than that of [FeL4][53] and is slightly longer than that of [Fe(NOTA)].[56] The Ga−O bond distances are very close to Fe−O bond lengths due to the almost identical ionic radii of Ga(III) and Fe(III). The average Ga−N bond lengths are significantly shorter than Fe−N bond distances since Ga(III) has a greater affinity for N atoms. Similar observation was reported previously.[54] Ga(III) has a closed electronic shell ion, whereas Fe(III) has the partially filled 3d orbitals (d^5). As a result, the deviation of Ga(III) (−0.0167 Å) from the N_2O_2 plane in Ga(NOKA)•$3H_2O$ was shorter than that of its Fe(III) analogue (−0.0238 Å).

Structure of Cu(HNOKA)•$3H_2O$. An ORTEP view of Cu(HNOKA)·$3H_2O$ is shown in Figure 4. The hydrogen bonding network in Cu(HNOKA)·$3H_2O$ is illustrated in Figure SIII. There are four Cu(HNOKA) molecules in each unit cell, along with three crystallization water molecules. The coordination geometry in Cu(HNOKA) is best viewed as a distorted square pyramid in which NOKA acts as a pentadentate ligand in bonding to Cu(II) with all three tertiary amine-N, two enolate-O atoms. One of the three 3-hydroxy-4-pyrone chelating arms remains free and protonated. The free 3-hydroxy-4-pyrone in Cu(HNOKA) may become deprotonated under physiological conditions (pH = 7.4). Cu(HNOKA) has the coordination geometry that is very similar to that of Cu(HL5) (L5 = 1,4,7-tris(2-hydroxybenzyl)-1,4,7-triazacyclononane),[53] but it is different from that of Na[Cu(NOTA)]·2NaBr·$8H_2O$, in which all three acetate-O atoms are coordinated to Cu(II) in a distorted pseudoprismatic geometry.[51]

The selected bond lengths and bond angles for Cu(HNOKA)·$3H_2O$ are listed in Table 3. The axial Cu−N bond distance (Cu−N(3) 2.2976(18) Å) is significantly longer than the two equatorial bond distances (Cu−N(1) 2.0639(18) Å, Cu−N(2) 2.0422(19) Å). The equatorial Cu−O distances (Cu−O(1) 1.9282(16) Å, Cu−O(8) 1.9297(15) Å) agree well

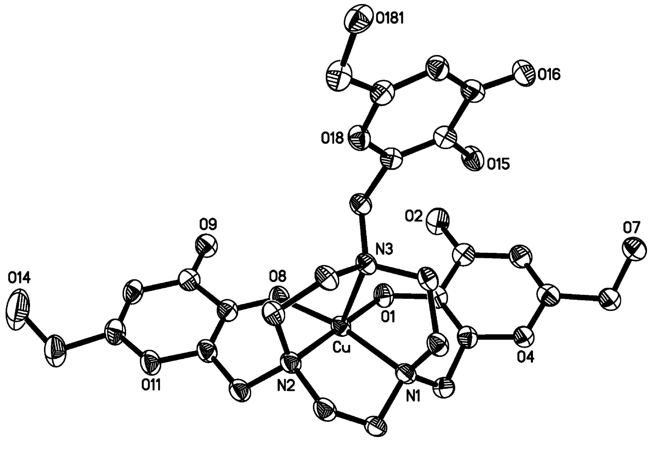

Figure 4. ORTEP drawing of Cu(HNOKA) (ellipoids are at 50% probability). Crystallization water molecules and hydrogen atoms are omitted for the sake of clarity.

Table 3. Selected Bond Distances (Å) and Bond Angles (deg) in Cu(HNOKA)·$3H_2O$

atom 1	atom 2	distance
Cu	O(1)	1.9282(16)
Cu	O(8)	1.9297(15)
Cu	N(1)	2.0639(18)
Cu	N(2)	2.0422(19)
Cu	N(3)	2.2976(18)

atom 1	atom 2	atom 3	angle
O(1)	Cu	O(8)	85.70(7)
O(1)	Cu	N(2)	178.09(7)
O(8)	Cu	N(2)	93.33(7)
O(1)	Cu	N(1)	95.42(7)
O(8)	Cu	N(1)	167.31(7)
N(2)	Cu	N(1)	85.16(7)
O(1)	Cu	N(3)	98.66(6)
O(8)	Cu	N(3)	110.44(7)
N(2)	Cu	N(3)	83.22(7)
N(1)	Cu	N(3)	81.93(7)

with those reported Cu(II) complexes with the square-pyramidal coordination geometry.[53,57]

Electrochemistry. Cyclic voltammograms were recorded in aqueous solution for Fe(NOKA) and acetonitrile for Cu(HNOKA) with 0.1 M $TBAPF_6$ as the supporting electrolyte in the range from 0 to -1.5 V for Fe(NOKA) and from $+0.4$ to -1.0 V for Cu(HNOKA). Figure 5 shows typical cyclic voltammograms of Fe(NOKA) (left) and Cu(HNOKA) (right). Fe(NOKA) exhibits a quasi-reversible redox wave at $E_{1/2} = -0.53$ V ($\Delta E = 75$ mV) versus NHE, which is assigned to the Fe(III)(NOKA)/Fe(II)(NOKA)$^-$ couple. Cu(HNOKA) has a cathodic response at $E_{pc} = -0.87$ V, which is assigned to the one-electron reduction of Cu(HNOKA)/Cu(HNOKA)$^-$.

NMR Data for Ga(NOKA) and In(NOKA). The solution structures of Ga(NOKA) and In(NOKA) were elucidated using NMR methods (^{1}H, ^{13}C, NOESY, and HMQC), while the rigidity of the metal chelate was monitored by variable-temperature ^{1}H NMR. Assignments of resonance signals were based on NOESY and HMQC experiments at 25 °C (Figures SIV−SVIII). The assignment of proton resonance signals from the macrocyclic backbone was tentative due to the fact that some of them are superimposed. Similar assignments were also made for the proton resonance signals in the ^{1}H NMR spectrum of In(NOKA) in D_2O at 25 °C. The ^{1}H NMR spectrum of Ga(NOKA) in D_2O at 25 °C shows that the singlet at 6.45 ppm is assigned to the olefinic protons in the pyrone rings. The doublet at 4.47 ppm is assigned to two methylene protons of the hydroxymethyl (C7) group. The AB quartet at 3.93 and 4.55 ppm is observed and assigned to protons in the three methylene (C6) moieties. The two multiplets at 3.33 and 3.14 ppm are assigned to H9a and H9b on the macrocyclic backbone, whereas the two multiplets at 2.89 and 2.73 ppm are assigned to H8a and H8b of the macrocyclic backbone.

Figure 6 illustrates the aliphatic region of variable-temperature (VT) ^{1}H NMR spectra of Ga(NOKA) in D_2O. There is no significant change in all resonance signals at 5–85 °C. It clearly indicates that Ga(NOKA) is rigid in solution, and there is no dissociation of the enolate-O atoms from three 3-hydroxy-4-pyrone chelating arms. Figure 7 shows the aliphatic region of the VT ^{1}H NMR spectra of In(NOKA) in D_2O. There are some minor shifts of proton resonance signals, along with a significant broadening of all signals at 25 °C. Most proton resonance signals in the aliphatic region became broad singlets at 45 °C. The AB quartet at 3.9–4.5 ppm disappears at temperatures above 65 °C. However, there is no coalescence point observed in the VT ^{1}H NMR spectra of Ga(NOKA) and In(NOKA) in D_2O.

Discussion

In this report, we describe the synthesis and characterization of a novel macrocyclic chelator H_3NOKA, with three 3-hydroxy-4-pyrone chelating arms, and its metal complexes, M(NOKA) (M = Ga, In, Fe) and Cu(HNOKA). Unlike the hexadentate chelators derived from the *N*,*N*,*N*-tris(aminoethyl)amine framework, which form the Fe(III) and Ga(III) complexes using three carbonyl-O and three enolate-O donor atoms,[58–60] NOKA bonds to Ga(III) and Fe(III) with three amine-N and three enolate-O atoms (Figures 2 and 3), probably due to the constraints imposed by the macrocyclic chelator backbone. As expected, the solid-state structures of Ga(NOKA)and Fe(NOKA) are almost identical with the N_3O_3 donor atoms bonding to the metal center in a slightly distorted octahedron coordination geometry. In Cu(HNOKA), however, NOKA is pentadentate using all three amine-N, two enolate-O donor atoms with one pendant enolate-O being free and protonated. Cu(HNOKA) has a distorted square pyramidal coordination geometry (Figure 4) due to its d^9 electron configuration.

The solution structures of Ga(NOKA) and In(NOKA) are very similar as indicated by the similarity in their ^{1}H NMR spectra (Figures 6 and 7). The fact that NOKA forms stable complexes with Ga(III) and In(III) suggests that its coordination cavity can accommodate the trivalent metals with a different ionic radius from 0.62 to 0.92 Å.[61] The coordinated NOKA in Ga(NOKA) and In(NOKA) remains rigid, and all enolate-O atoms are firmly bonded to the metal center in aqueous solution at the room temperature. This conclusion is supported by the presence of the AB quartet at 3.93–4.55 ppm for Ga(NOKA) (Figure 6) and 3.93–4.40 ppm for In(NOKA) (Figure 7) in their room temperature ^{1}H NMR spectra. If these three enolate-O donors were dissociated, the resonance signals for the two protons on C6 would have become a singlet.

It is very interesting to note that the rigidity of Ga(NOKA) and In(NOKA) in solution is very different. For example, there is no significant change in all proton resonance signals of Ga(NOKA) from 5 to 85 °C. For In(NOKA), all proton resonance signals in the aliphatic region start to collapse at temperatures >45 °C, indicating that the rotation of 3-hy-

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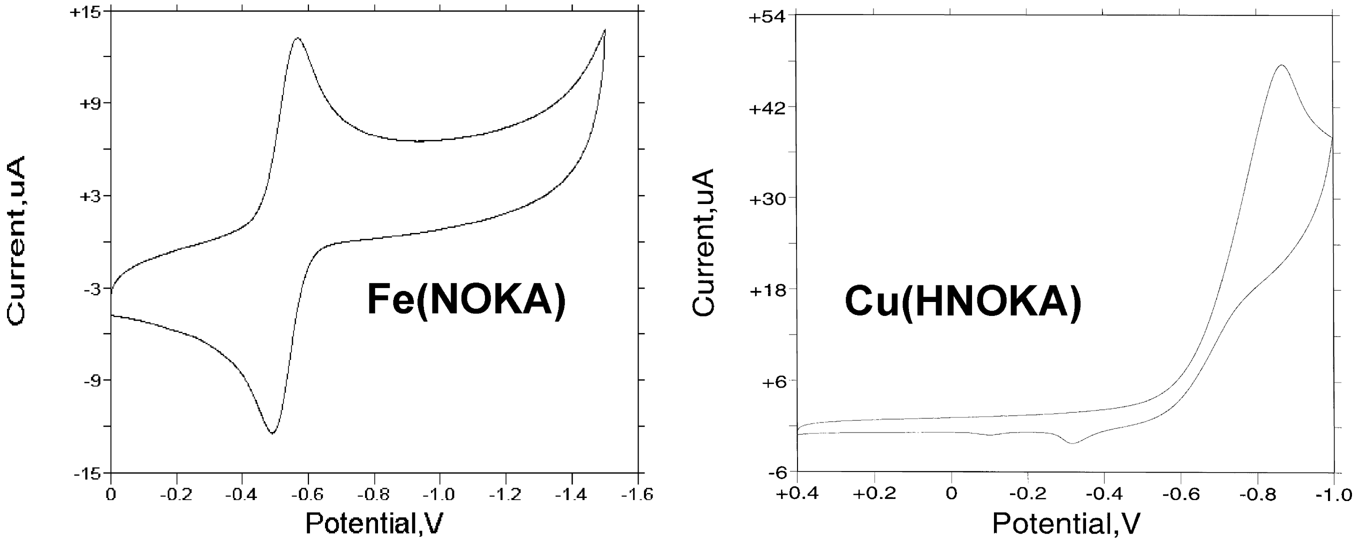

Figure 5. Cyclic voltammograms of Fe(NOKA) in H_2O (left) and Cu(HNOKA) in MeCN (right) at 298 K. Potentials are given as those as vs NHE since the Ag/AgCl electrode has a potential of +0.2 V vs NHE. The scan rate was 50 mV·s^{-1}.

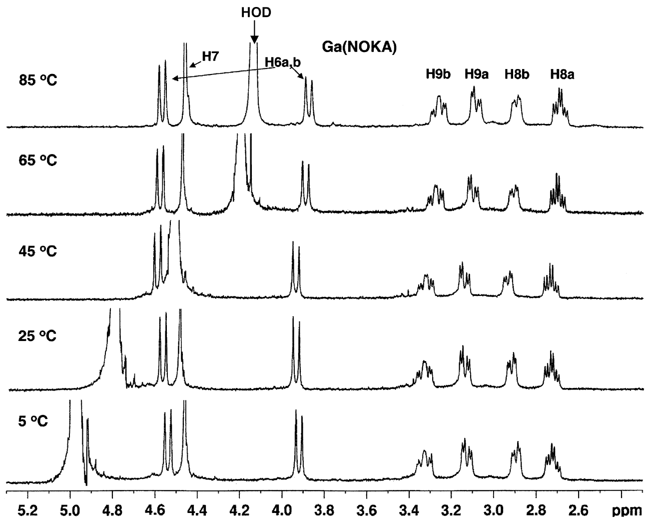

Figure 6. Aliphatic region of the VT ^{1}H NMR spectra of Ga(NOKA) in D_2O.

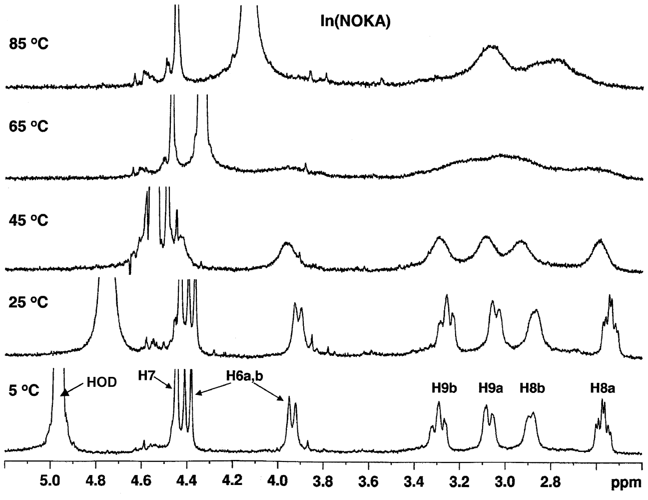

Figure 7. Aliphatic region of the VT ^{1}H NMR spectra of In(NOKA) in D_2O.

droxy-4-pyrone chelating arms is accelerated at higher temperatures. As a result, there is a rapid exchange between the Λ and Δ enantiomers, and In(NOKA) becomes fluxional at temperatures higher 65 °C. The absence of coalescence point in the VT ^{1}H NMR spectra of In(NOKA) suggests that the coordinated NOKA remains firmly bonded to the metal center even at 85 °C. The high rigidity of the coordinated NOKA in Ga(NOKA) strongly suggests that its coordination cavity fits better the smaller Ga(III) (ionic radii = 0.62 Å) than much larger In(III) (ionic radii = 0.92 Å).[61]

In this study, we use cyclic voltammetry to study the solution stability of Fe(NOKA) in water and Cu(HNOKA) in acetonitrile. While the reversibility of cyclic voltammograms is an indication of the energy barrier required for the transition between two oxidation states, the electrochemical potential ($E_{1/2}$) can be used to demonstrate the preferential stabilization of a specific oxidation state. For example, Fe(NOKA) exhibits a redox wave at $E_{1/2} = -0.53$ V from the Fe(III)(NOKA)/Fe(II)(NOKA)$^-$ couple. This negative redox potential is in good agreement with that obtained for [FeL3][52] and [FeL4],[53] suggesting that Fe(III) is preferentially stabilized by coordinated NOKA. The difference (Figure 5; $\Delta E = 75$ mV) between cathodic and anodic waves suggests that the transition between Fe(III)(NOKA) and Fe(II)(NOKA)$^-$ is quasi-reversible. Cu(HNOKA) has the one-electron reduction at $E_{pc} = -0.87$ V (Figure 5) from the Cu(HNOKA)/Cu(HNOKA)$^-$ couple. This potential is very close to those obtained for bis(thiosemicarbazonato) Cu(II) complexes.[62] The high negative potential suggests that Cu(II) is preferentially stabilized by HNOKA.[62–64] The absence of the anodic wave clearly indicates that the transition between Cu(HNOKA) and Cu(HNOKA)$^-$ is irreversible.

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Conclusion

In this report, we present the preparation of a novel macrocyclic chelator H_3NOKA and its complexes with Ga(III), In(III), Fe(III), and Cu(II). There are several important findings from this study. It seems that the coordination cavity of NOKA is quite flexible to accommodate both Ga(III) (ionic radii = 0.62 Å) and In(III) (ionic radii = 0.92 Å), but it fits Ga(III) and Fe(III) better than much larger In(III) as demonstrated by the highly rigidity of Ga(NOKA) at 5–85 °C and the fluxionality of In(NOKA) at temperatures higher than 45 °C. From this point of view, the C-substituted H_3NOKA derivatives might be very useful as BFCs for the ^{68}Ga-labeling of small biomolecules to develop new target-specific PET radiotracers. Because of the similarity between Ga(III) and Fe(III), the coordination cavity of NOKA also fits well the size of Fe(III), suggesting that H_3NOKA might be an efficient chelator for iron detoxification. Since NOKA is pentadentate in Cu(HNOKA) with one of the three 3-hydroxy-4-pyrone chelating arms being free, its N-substituted analogues might be suitable as BFCs for the ^{64}Cu-labeling of small biomolecules.

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Supporting Information Available: X-ray crystallographic files are in CIF format for the reported structures Ga(NOKA)•3H_2O, Fe(NOKA)•3H_2O, and Cu(HNOKA)•3H_2O, 2D NMR spectra for Ga(NOKA) and In(NOKA). This material is available free of charge via the Internet at http://pubs.acs.org.

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