Kinetics and Equilibria of the Interactions of Hydroxamic Acids with Gallium(III) and Indium(III)

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The thermodynamics and kinetics of the binding of Ga(III) and In(III) to two hydroxamic acids, $C_6H_5-C(O)N(OH)H$ (BHA) and $C_6H_5-C(O)N(OH)C_6H_5$ (PBHA), have been investigated in acidic media. Spectrophotometric titrations in the UV region reveal that, with excess metal, only the chelate ML forms, whereas the concentration of the protonated species, MHL, is negligible. The thermodynamic parameters indicate that the driving force for formation of ML from MOH^{2+} and HL is mainly enthalpic, with entropic contributions favoring InL^{2+} and disfavoring GaL^{2+} formation. The kinetic (stopped-flow) experiments are interpreted on the basis of two parallel reaction paths both involving reaction of the undissociated ligand (HL): (a) $M + HL \rightleftharpoons MHL \rightleftharpoons ML + H$ where MHL is in a steady state and (b) $MOH + HL \rightleftharpoons ML + H_2O$. Whereas gallium binding to BHA and PBHA proceeds mainly through path b, indium binding to PBHA proceeds through both a and b paths. The rates of both the a and b steps are ligand dependent. Two alternative mechanisms are proposed. The first is based on the electronic characteristics of the ligands and is of the I_a type. The second, of the I_d type, assumes that a considerable fraction of the ligand is unreactive owing to intramolecular hydrogen bonding (possibly including a water molecule) which blocks the reaction site. The reasons for preferring the former mechanism are discussed.

Introduction

Hydroxamic acids (R−CONHOH) are weak acids with a broad variety of applications. They are used as flotation agents in metal extraction, as inhibitors of copper corrosion, and as therapeutic agents for their antibacterial and antimalaria action.[1] They inhibit the activity of urease and have been used in the treatment of epatic coma.[2] All these properties are related to the ability of these acids to complex metal ions, mainly iron(III). Many microorganisms synthesize compounds containing the hydroxamate residue which is able

to bind iron(III),[3] thus providing a way to solubilize the ionic forms of the metal ion under physiological conditions.[4]

Hydroxamic acids act as ligands toward many other metal ions, such as Al(III),[5] Cr(III),[6] Ga(III),[7] Os(III),[8] Eu(II),[9] Be-(II),[10] Co(II),[11] Ni(II),[12] Cu(II),[13] Zn(II),[14] V(V),[15] Pu(IV),[16] Np(IV),[16] U(VI),[16] and Mo(VI).[17]

Despite their interesting applications, hydroxamic acids remain poorly characterized. For instance, recently it has been demonstrated that, under conditions of high acidity, they are able to acquire a second proton, and the protonation constants have been determined in solutions of strong mineral acids for aceto-, benzo-, and salicylhydroxamic acids.[18] However, the assignment of the favored sites of both protons is still puzzling despite the numerous experimental and theoretical investigations performed on this issue. On the other hand, it should also be noted that the structure of hydroxamic acids in solution is not unequivocally determined. A major difficulty in the assignment of the correct structure of the

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(1) Biruš, M.; Kujundžič, N.; Pribanič, M.; Tabor, Z. *Croat. Chem. Acta* **1984**, *57* (3), 313−324.
(2) (a) Brown, D. A.; Googan, R. A.; Fitzpatrick, N. J.; Glass, W. K.; Abukshima, D. E.; Shiiels, L.; Ahlgran, M.; Smolander, K.; Pakkanen, T. T.; Pakkanen, T. A.; Perakyla, M. *J. Chem. Soc., Perkin Trans. 2* **1996**, *12*, 2673−2680. (b) Fishbein, W. N.; Streeter, C. L.; Daly, J. E. *J. Pharmacol. Exp. Ther.* **1973**, *186*, 173−182.

hydroxamic acids comes from their distribution among tautomeric forms.[19,20] Further complications arise from the

(3) (a) Obrien, E. C.; Farkas, E.; Gil, M. J.; Fitzgerald, D.; Castiñeiras, A.; Nolan, K. B. *J. Inorg. Biochem.* **2000**, *79*, 47−51. (b) Boukhalfa, H.; Crumbliss, A. L. *Inorg. Chem.* **2000**, *39*, 4318−4325. (c) Boukhalfa, H.; Brickman, T. J.; Armstrong, S. K.; Crumbliss, A. L. *Inorg. Chem.* **2000**, *39*, 5591−5602. (d) Farkas, E.; Enyedy, E. A.; Zekany, I.; Deak, G. *J. Inorg. Biochem.* **2001**, *83*, 107−114. (e) Gallagher, P. A.; Guianen, T. J.; Pike, P. J.; Danielson, N. D. *Mikrochim. Acta* **1998**, *130*, 81−87. (f) Farkas, E.; Kozma, E.; Petho, M.; Herlihy, K. M.; Micera, C. *Polyhedron* **1998**, *17*, 3331−3342. (g) Brown, D. A.; Herlihy, K. M.; Oshea, S. K. *Inorg. Chem.* **1999**, *38*, 5198−5202. (h) Tufano, T. P.; Raymond, N. F. *J. Am. Chem. Soc.* **1981**, *103*, 6617−6624. (i) Biruš, M.; Krznarič, G.; Pribanič, M.; Uršič, S. *J. Chem. Res., Synop.* **1985**, 4−5. (j) Gallagher, P. A.; Guianen, T. J.; Pike, P. J.; Danielson, N. D. *Mikrochim. Acta* **1998**, *130*, 81−87. (k) Biruš, M.; Kujundzič, N.; Pribanič, M. *Prog. React. Kinet.* **1993**, *18*, 171−271. (l) Biruš, M.; Bradič, Z.; Kujundzič, N.; Pribanič, M.; Wilkins, P. C.; Wilkins, R. *Inorg. Chem.* **1981**, *24*, 3980−3983. (m) Biruš, M.; Eldik, R. *Inorg. Chem.* **1991**, *30*, 4559−4563. (n) Caudle, M. Y.; Crumbliss, A. L. *Inorg. Chem.* **1994**, *33*, 4077−4085. (o) Konetschny-Rapp, S.; Jung, G.; Raymond, K. N.; Meiwes, J.; Zahner, H. *J. Am. Chem. Soc.* **1992**, *114*, 2224−2230. (p) Biruš, M.; Gabričevič, M.; Kronja, O.; Klaić, B. *Inorg. Chem.* **1995**, *34*, 3110−3113. (q) Monzyk, B.; Crumbliss, A. L. *J. Org. Chem.* **1980**, *45*, 4670−4675. (r) Roushdy, M. I.; Issa, Y. M.; Elzein, S. M.; Harb, F. M. S. E. *Asian J. Chem.* **1999**, *11*, 359−368. (s) Spasojevic, I.; Armstrong, S. K.; Brickman, T. J.; Crumbliss, A. L. *Inorg. Chem.* **1999**, *38* (3), 449−454. (t) Esteves, M. A.; Vaz, M. C.; Goncalves, M. L.; Farkas, E.; Santos, M. A. *J. Chem. Soc., Dalton Trans.* **1995**, 2565−2573. (u) Monzyk, B.; Crumbliss, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 6203−6213.
(4) Miller, M. J. *Chem. Rev.* **1989**, *89*, 1563−1579.
(5) (a) Gaspar, M.; Grazina, R.; Bodor, A.; Farkas, E.; Santos, M. A. *J. Chem. Soc., Dalton Trans.* **1999**, *5*, 799−806. (b) Garrison, M. J.; Crumbliss, A. L. *Inorg. Chem.* **1987**, *26*, 3660−3664.
(6) Jha, N. N.; Ray, I. P. *Asian J. Chem.* **2000**, *12*, 579−580.
(7) (a) Dietrich, A.; Fidelis, K. A.; Powell, D. R.; van der Helm, D. *J. Chem. Soc., Dalton Trans.* **1991**, 231−239. (b) Chaubet, F.; Duong, K. N.; Courtieu, J.; Gaudemer, A. *Can. J. Chem.* **1994**, *72*, 2361−2368. (c) Fages, F.; Bodenant, B.; Weil, T. *J. Org. Chem.* **1996**, *61*, 3956−3961.
(8) Das, A.; Basuli, F.; Falvello, L. R.; Bhattacharya, S. *Inorg. Chem.* **2001**, *40*, 4085−4088.
(9) Galdecka, E.; Galdecki, Z.; Gawryszewska, P.; Legendziewicz, J. *New J. Chem.* **1998**, *22*, 941−945.
(10) Biruš, M.; Budimir, A.; Gabričevič, M. *J. Inorg. Biochem.* **1999**, *75*, 85−91.
(11) (a) Yilmaz, V. T.; Yilmaz, F. *Thermochim. Acta* **2000**, *348*, 139−146. (b) Jha, N. N.; Ray, I. P. *Asian J. Chem.*, **2000**, *12*, 703−706. (c) Farkas, E.; Csoka, H.; Bell, G.; Brown, D. A.; Cuffe, L. P.; Fitzpatrick, N. J.; Glass, W. K.; Errington, W.; Kem, T. J.; Roushdy, M. I.; Issa, Y. M.; Elzein, S. M.; Harb, F. M. S. E. *Asian J. Chem.* **1999**, *11*, 359−368. (d) Dobosz, A.; Dudarenko, N. M.; Fritsky, I. O.; Glowiak, T.; Karaczyn, A.; Kozlowsky, H. *J. Chem. Soc., Dalton Trans.* **1999**, *5*, 743−749. (e) Yilmaz, V. T.; Yilmaz, F. *Transition Met. Chem.* **1999**, *24* (6), 726−729.
(12) (a) Farkas, E.; Enyedy, E. A.; Micera, G.; Garribba, E. *Polyhedron* **2000**, *19*, 1727−1736. (b) Jha, N. N.; Ray, I. P. *Asian J. Chem.* **2000**, *12*, 703−706. (c) Swiatekkozlowska, J.; Fritsky, I. O.; Dobosz, A.; Karaczyn A.; Dudarenko, N. M.; Sliva, T. Y.; Gumiennakontecka, E.; Jerzykiewicz, L. *J. Chem. Soc., Dalton Trans.* **2000**, *22*, 4064−4068. (d) Arnold, M.; Brown, D. A.; Deeg, O.; Errington, W.; Haase, W.; Herlihy, K.; Kemp, T. J.; Nimir, H.; Werner, R. *Inorg. Chem.* **1998**, *37*, 2920−2925.
(13) (a) Larin, G. M.; Rotov, A. V.; Dzyuba, V. I. *Russ. Chem. Bull.* **1999**, *48* (4), 722−725. (b) Gaspar, M.; Grazina, R.; Bodor, A.; Farkas, E.; Santos, M. *J. Chem. Soc., Dalton Trans.* **1999**, *5*, 799−806. (c) Roushdy, M. I.; Issa, Y. M.; Elzein, S. M.; Harb, F. M. S. E. *Asian J. Chem.* **1999**, *11*, 359−368.
(14) Hockensmith, C. M. *Abstr. Pap. Am. Chem. Soc.* **2000**, *219*, 668-INOR.
(15) (a) Liu, S. X.; Gao, S. *Inorg. Chim. Acta* **1998**, *228*, 149−154. (b) Duarte, H. A.; Paniago, E. B.; Carvalho, S.; Dealmeida, W. B. *J. Inorg. Biochem.* **1998**, *72*, 71−77. (c) Roushdy, M. I.; Issa, Y. M.; Elzein, S. M.; Harb, F. M. S. E. *Asian J. Chem.* **1999**, *11*, 359−368.
(16) Taylor, R. J.; May, I.; Wallwork, A. L.; Denniss, I. S.; Hill, N. J.; Galkin, B. Y.; Zilberman, B. Y.; Fedorov, Y. S. *J. Alloys Compd.* **1998**, *271*, 534−537.

possibilities of geometrical isomerism. The conformational isomeric equilibrium Z (*cis*) $\leftrightharpoons$ E (*trans*) has been observed for monoalkylbenzohydroxamic acids in several solvents, and it has been suggested that, while the E conformation prevails in aprotic solvents, the Z conformation is stabilized in water by solvent-including hydrogen bonding.[21,22]

The study of the complexation of the group IIIA cations is very interesting. Actually, the radioactive forms of Ga-(III) and In(III) have many applications in nuclear medicine.[23] They are able to reveal some particular pathologies such as tumors or inflamations, but they are useful also as markers, to check the functionality of human organs. [67]Ga and ^{111}In are administrated in the form of complexes, and once in the organism, the metal is transferred to transferrin which takes the role of the biodistributor. A detailed knowledge of the modes of complexation of these cations is therefore of great importance for selection of optimal ligands and production of better radiopharmaceuticals.

With the aim of getting some enlightenment on the complexation of these metals and on the chemistry of hydroxamic acids in solution, we have investigated the kinetics and equilibria of the binding of gallium(III) and indium(III) to benzohydroxamic acid (BHA) and *N*-phenyl-benzohydroxamic acid (PBHA) in aqueous solution.

Experimental Section

Chemicals. All chemicals were analytical grade. Indium perchlorate was prepared by dissolution of a known weight of the pure metal in a known excess of perchloric acid. Gallium perchlorate was prepared in the same way, but the dissolution process was very slow due to hydrogen overvoltage. Hence, the metal was put in contact with a platinum wire, and the solution was slightly warmed. This procedure led to a dramatic increase in the speed of dissolution.[24] The concentrations of the stock solutions of gallium-(III) and indium(III) were checked by titrating with EDTA, as previously described,[25] and they were found to coincide with those calculated from the weights of the dissolved metals.

Benzohydroxamic acid was from Aldrich, with a purity of 99%. The stock solutions were prepared by dissolving the solid in water. *N*-Phenylbenzohydroxamic acid was from Aldrich also, with a purity of 98%. The stock solutions were prepared by dissolving the solid in water containing 2% of EtOH. Perchloric acid and perchlorates were used to obtain, respectively, the desired acidity and ionic strength. Conductivity water from a Millipore S.A. 67 120 Mosheim deionizer was used to prepare the solutions and as a reaction medium.

(17) Farkas, E.; Megyeri, K.; Somsak, I.; Kovacs, L. *J. Inorg. Biochem.* **1998**, *70*, 41−47.
(18) García, B.; Ibeas, S.; Hoyuelos, F. J.; Leal, J. M.; Secco, F.; Venturini, M. *J. Org. Chem.* **2001**, *66*, 24, 7986−7993.
(19) Buglass, A. J.; Hudson, K.; Tillett, J. G. *J. Chem. Soc. B* **1971**, 123−126.
(20) Agrawal, M. A.; Harjit, J.; Pande, R. *Acta Chem. Scand.* **1999**, *53*, 381−386.
(21) Brown, D. A.; Glass, W. K.; Mageswaran, R.; Girmany, B. *Magn. Reson. Chem.* **1988**, *26*, 970−973.
(22) Senent, M. L.; Niño, A.; MuñozCaro, C.; Ibeas, S.; García, B.; Leal, J. M.; Secco, F.; Venturini, M. *J. Org. Chem.* **2003**, *68*, 6535−6542.
(23) Hayes, R. L.; Hubner, K. F. *Metal ions in biological systems*; Sigel, H., Ed.; Dekker: New York, 1983; Vol. 16, p 279.
(24) Precipitation of gallium(III) and indium(III) perchlorates was avoided in order to prevent possible violent decomposition of the solid salts.
(25) Horrichi, H. *Treatise on Analytical Chemistry, Part II*; Kolthoff, I. M., Helving, P. J., Eds.; Interscience: New York, 1962; Vol. 2, p 87.

Methods. The hydrogen ion concentrations of solutions with $[H^+] \leq 0.01$ M were determined by pH measurements performed with a PHM 84 Radiometer Copenhagen instrument. A combined glass electrode was used after replacing the usual KCl bridge by 3 M NaCl to avoid precipitation of $KClO_4$. The electrode was calibrated against sodium perchlorate−perchloric acid solutions of known concentration and ionic strength to give directly $-\log[H^+]$; solutions with $[H^+] > 0.01$ M were prepared by adding suitable amounts of $HClO_4$. Spectrophotometric titrations were performed on a Perkin-Elmer lambda 17 double-beam spectrophotometer. Increasing amounts of gallium and indium perchlorate were added with a microsyringe to a solution of the ligand that was already thermostated in the spectrophotometric cell. The temperature fluctuations were within ± 0.1 °C throughout. The acidity and ionic strength were kept constant at the desired value during each titration. The data were evaluated by nonlinear least-squares procedures.

The course of the complex formation reactions was monitored using a stopped-flow apparatus constructed in our laboratory. A Hi-Tech SF-61 mixing unit was coupled to a spectrophotometric line through two optical guides. The UV radiation produced by a 75 W mercury xenon Hamamatsu L248102 "quiet" lamp was passed through a Bausch & Lomb 338875 high intensity monochromator and then split into two beams: the reference beam was sent directly to a 1P28 photomultiplier; the measuring beam was sent through an optical quartz guide to the observation chamber and then, through a second optical guide, to the measuring photomultiplier, also 1P28. The outputs of the two photomultipliers were balanced before each shot, and the signal revealing the course of the reaction was sent to a Tektronix TDS 210 digital oscilloscope with a storage capability of 2500 data points. Finally, the acquired signal was transferred to a personal computer, via a GPIB interface, using the WaveStar 2.0 program, and analyzed by a nonlinear least-squares procedure.[26] The time constants used to evaluate the kinetic parameters are the average of at least six repeated experiments and display a maximum spread of 10%.

Results

Equilibria. Gallium. The interaction of BHA and PBHA with Ga(III) is revealed by large spectral changes in the UV region (Figure 1). Under conditions of excess metal ($C_M \gg C_L$), only 1:1 complexes are formed. At constant pH the equilibria could be described by the apparent complex formation reaction

$$M_f + L_f \underset{k_f}{\overset{k_d}{\rightleftharpoons}} ML_T \qquad (1)$$

where k_f and k_d are the rate constants for complex formation and dissociation respectively; $[M_f] = [M^{3+}] + [MOH^{2+}]$; $[L_f] = [HL]$ and $[ML_T] = [MHL^{3+}] + [ML^{2+}]$. The species L^- and $M(OH)_2^+$, and the dimer and trimer of In(III), have not been included, since in the investigated range of pH their contribution to the reaction can be neglected.[3q,27]

The equilibrium constant, K_{app}, of reaction 1 has been evaluated for different pH values by titrations of hydroxamic acid with $Ga(ClO_4)_3$ at 260 nm for Ga(III)/BHA and 280 nm for Ga(III)/PBHA, according to a procedure already described.[28] The values of K_{app} were found to decrease as

(26) Provencher, S. W. *J. Chem. Phys.* **1976**, *64*, 2772−2777.
(27) Baes, C. F.; Mesmer, P. E. *The hydrolysis of cations*; John Wiley: New York, 1976.
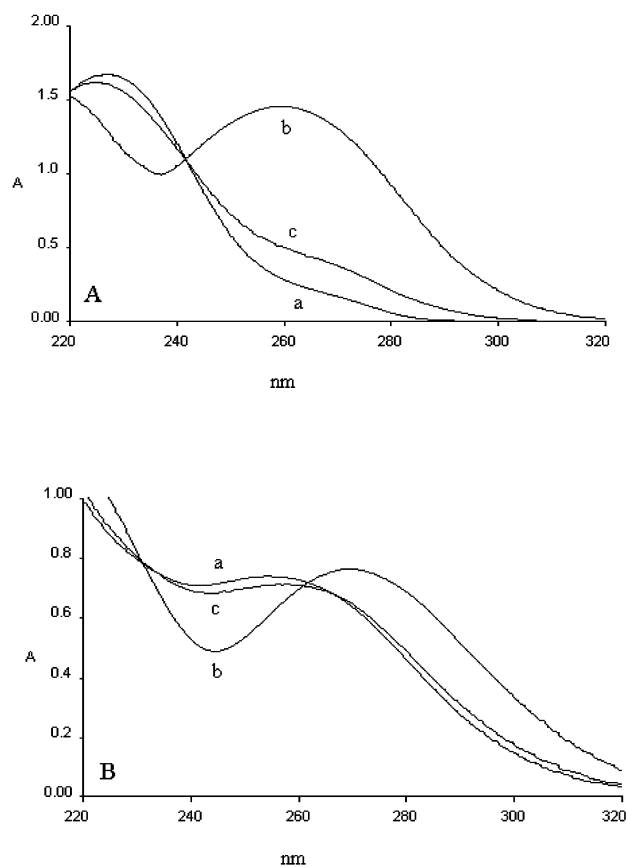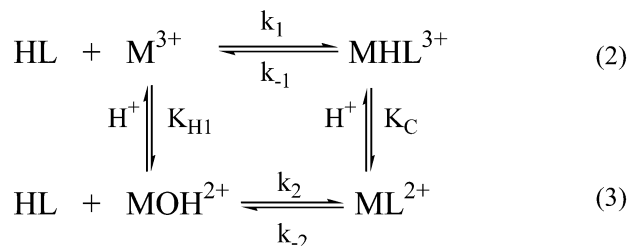
Figure 1. Spectral behavior of the investigated systems at $[H^+] = 0.01$ M ($HClO_4$), $I = 0.2$ M, $T = 25$ °C. (A) (a) BHA 2×10^{-4} M, (b) BHA 2×10^{-4} M + $Ga(ClO_4)_3$ 2×10^{-2} M, (c) BHA 2×10^{-4} M + $In(ClO_4)_3$ 2×10^{-2} M. (B) (a) PBHA 1×10^{-4} M, (b) PBHA 1×10^{-4} M + Ga-$(ClO_4)_3$ 2×10^{-2} M, (c) PBHA 1×10^{-4} M + $In(ClO_4)_3$ 2×10^{-2} M.

Scheme 1

$$HL + M^{3+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} MHL^{3+} \qquad (2)$$

$$H^+ \Updownarrow K_{H1} \qquad\qquad H^+ \Updownarrow K_C$$

$$HL + MOH^{2+} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ML^{2+} \qquad (3)$$

$[H^+]$ increases. The dependence of K_{app} on $[H^+]$ and the kinetic results described below would suggest the reaction described in Scheme 1 (coordinated water omitted).

According to Scheme 1, the acidity dependence of K_{app} is given by the equation[28]

$$\frac{K_{app}}{\alpha\beta} = K_{MHL} + \frac{K_{MOH \cdot HL} K_{H1}}{[H^+]} \qquad (4)$$

where $\alpha = [H^+]/([H^+] + K_A)$ and $\beta = [H^+]/([H^+] + K_{H1})$, and $K_{MHL} = k_1/k_{-1}$ and $K_{MOH \cdot HL} = k_2/k_{-2}$ are the equilibrium constants of steps 2 and 3, respectively. Plots of $K_{app}/\alpha\beta$ versus $[H^+]^{-1}$ are shown in Figure 2A. The intercepts of the straight lines are indistinguishable from zero, meaning that

(28) Ricciu, A.; Secco, F.; Venturini, M.; Garcia, B.; Leal, J. M. *Chem. Eur. J.* **2001**, *7* (21), 4613−4620.

Table 1. Rate and Equilibrium Constants for the Interaction of BHA and PBHA with Ga(III) and In(III)

system	k_1, M^{-1} s^{-1}	k_{-1}/K_C, M^{-1} s^{-1}	$10^{-3}k_2$, M^{-1} s^{-1}	$10^1 k_{-2}$, s^{-1}	$10^{-3}K_{MOH\cdot HL}$,[a] M^{-1}	$10^{-8}K_{ML}$,[b] M^{-1}	pK_{H1}	pK_A[e]
Ga/BHA	5.7 ± 5.8	0.93 ± 0.13	4.0 ± 0.1	4.6 ± 0.1	7.7 ± 0.2	83	2.91[c]	8.94
In/BHA					8.4 ± 0.3	2.8	4.42[d]	8.94
Ga/PBHA	1.9 ± 3.9	0.15 ± 0.02	0.94 ± 0.08	0.98 ± 0.01	10.3 ± 4.7	40	2.91[c]	8.50
In/PBHA	$(1.9 \pm 0.3) \times 10^4$	$(1.4 \pm 0.1) \times 10^5$	550 ± 140	789 ± 340	5.2 ± 0.5	0.63	4.42[d]	8.50

$I = 0.2$ M (NaClO$_4$), $T = 25$ °C. [a] $K_{MOH\cdot HL} = [ML]/[MOH]\,[HL]$ [b] $K_{ML} = [ML]/[M]\,[L]$ [c] Reference 32. [d] Reference 44. [e] Derived by transforming the values of ref 3q ($I = 1.1$ M) to $I = 0.2$ M with the Davies equation.

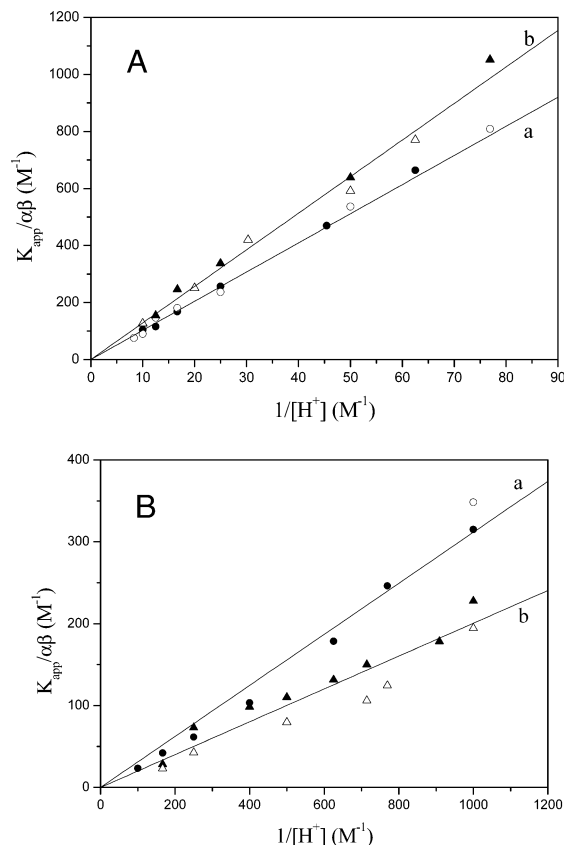**Figure 2.** Dependence of K_{app} on the acid concentration at $I = 0.2$ M, $T = 25$ °C; (●, ▲) static measurements, (○, △) kinetic measurements. (A) (a, ●, ○) Ga(III)/BHA, (b, ▲, △) Ga(III)/PBHA. (B) (a, ●, ○) In(III)/BHA, (b, ▲, △) In(III)/PBHA.

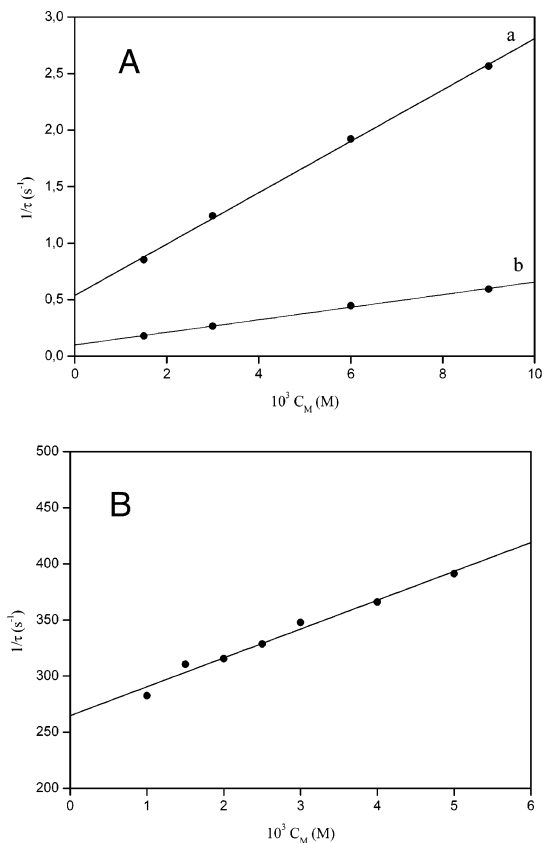**Figure 3.** Kinetic behavior of the investigated systems at $I = 0.2$ M and $T = 25$ °C. (A) Dependence of the time constant $1/\tau$ on the Ga(ClO$_4$)$_3$ concentration for (a) Ga(III)/BHA and (b) Ga(III)/PBHA at [H$^+$] = 0.022 M. (B) Dependence of the time constant $1/\tau$ on the In(ClO$_4$)$_3$ concentration for In(III)/PBHA at [H$^+$] = 0.001 M.

the values of K_{MHL} are too small to be evaluated. On the other hand, the slopes divided by K_{H1}, the first hydrolysis constant of Ga^{3+} ion, give values of $K_{MOH\cdot HL}$ (Table 1).

Indium. The interaction of In(III) with BHA and PBHA is revealed by spectral changes in the UV region (Figure 1). The equilibria have been measured at 275 nm for In(III)/BHA and at 290 nm for In(III)/PBHA.

The analysis of the dependence of K_{app} on the hydrogen ion concentration, according to eq 4, is shown in Figure 2B. The values of $K_{MOH\cdot HL}$ ($K_{MHL} \cong 0$ for both complexes) and K_{H1} are quoted in Table 1.

Kinetics. Gallium. The kinetic curves for complex formation are single exponential, meaning that reaction 1 represents adequately the apparent kinetic behavior of both Ga(III)/BHA and Ga(III)/PBHA. For $C_M \gg C_L$, the time constant $1/\tau$ depends on the metal concentration according to relationship 5, as shown in Figure 3A.

$$\frac{1}{\tau} = k_d + k_f C_M \tag{5}$$

Both k_f and k_d have been found to change with the medium acidity. According to Scheme 1, the dependencies of the apparent rate constants on [H$^+$] are given by the relationships

$$k_f = \left(k_1 + \frac{k_2 K_{H1}}{[H^+]} \right) \cdot \alpha\beta \tag{6}$$

and

$$k_d = \left(k_{-2} + \frac{k_{-1}[H^+]}{K_C} \right) \cdot \gamma \tag{7}$$

where $\gamma = [ML^{2+}]/[ML_T] \cong 1$. Plots of $k_f/\alpha\beta$ versus [H$^+$]$^{-1}$ (Figure 4A) allow the forward rate constants k_1 and k_2 of the individual complex formation steps to be obtained, whereas plots of k_d/γ versus [H$^+$] (Figure 4B) yield k_{-1}/K_C and k_{-2}. The values of the individual rate constants are collected in Table 1.

Table 2. Activation and Equilibrium Parameters for the Interaction of BHA and PBHA with Ga(III) and In(III)[a]

system	$\Delta H_f^{\ddagger}$	$\Delta S_f^{\ddagger}$	$\Delta H_2^{\ddagger b}$	$\Delta S_2^{\ddagger}$	$\Delta H_d^{\ddagger}$	$\Delta S_d^{\ddagger}$	$\Delta H^{\ominus}_{app}$	$\Delta S^{\ominus}_{app}{}^d$	$\Delta H^{\ominus}_{H1}$	$\Delta H^{\ominus}_{A}$	$\Delta H^{\ominus\prime h}$	$\Delta S^{\ominus\prime h}$	$\Delta H^{\ominus}_2$	$\Delta S^{\ominus}_2$
Ga/BHA	91 ± 3	100	52	-14	79 ± 7	5.4	10 ± 2^d 12 ± 3^c	79	39^e	23^g	10 12	52	-29	-22
In/BHA							5.0 ± 2.1^d	54	20^f		5	4.2	-15	24
Ga/PBHA	94 ± 1	88	56	-15	80 ± 1	-2.1	14 ± 1^d 14 ± 3^c	92	39^e	32^g	14 14	65	-25	-7.7
In/PBHA	34 ± 7	-50			23 ± 7	-130	12 ± 3^d 11 ± 2^c	84	20^f		12 12	27	-8.0	46

[a] $I = 0.2$ M (NaClO$_4$). ΔH values are in kJ mol^{-1}, and ΔS values are in J mol^{-1} K^{-1}. [b] $\Delta H_2^{\ddagger} = \Delta H_f^{\ddagger} - \Delta H^{\circ}_{H1}$. [c] From activation parameters. [d] From Van't Hoff analysis. The superscript $\ominus$ indicates that the values of ΔH and ΔS are not corrected to the standard state. [e] Reference 45. [f] Reference 46. [g] Reference 3q. [h] $\Delta H^{\ominus\prime} = \Delta H^{\ominus}_{app}$; $\Delta S^{\ominus\prime} = \Delta S^{\ominus}_{app} + R \ln[H^+]$.
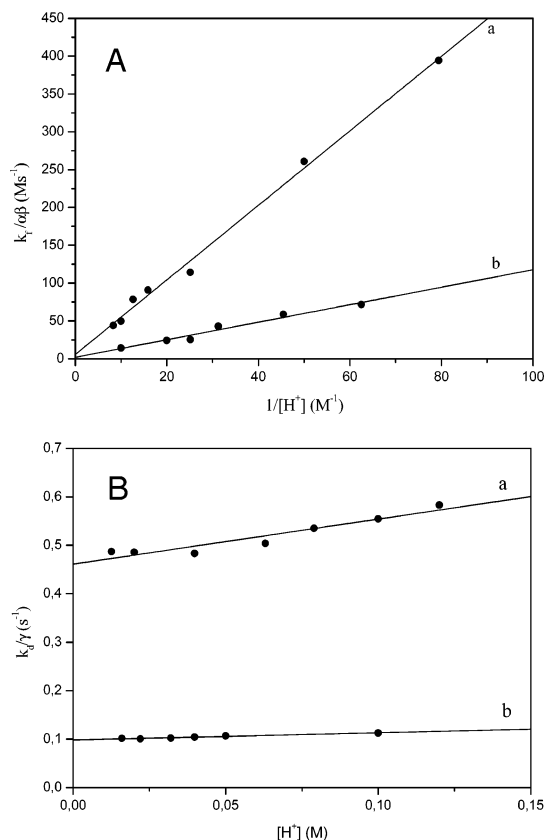

Figure 4. Dependence of the complex formation (A) and complex dissociation (B) rate constants on the hydrogen ion concentration for Ga-(III)/BHA (a) and Ga(III)/PBHA (b). $I = 0.2$ M, $T = 25$ °C.

Temperature Effect. The temperature dependence of K_{app} and the kinetic constants k_f and k_d of both systems have been investigated at 20, 25, 30, and 35 °C and $[H^+] = 0.04$ M. The reaction parameters are collected in Table 2. Since K_{MHL} is negligible, and since for $[H^+] = 0.04$ M α and β are about unity at all investigated temperatures, eq 4 is reduced to $K_{app} = K_{MOH \cdot HL} K_{H1} [H^+]^{-1}$. In excess acid, we can assume that $[H^+]$ does not change with temperature. The same assumption holds for α and β. Hence, it follows that the reaction enthalpy of step 3, $\Delta H^{\ominus}_2$, can be obtained as the difference between $\Delta H^{\ominus}_{app}$, the reaction enthalpy of the apparent reaction 1, and $\Delta H^{\ominus}_{H1}$, the reaction enthalpy of the first acid dissociation of Ga^{3+}.

Salt Effects. The values of k_f and k_d have been measured for values of the ionic strength between 0.15 and 0.4 M, at 25 °C and $[H^+] = 0.04$ M. Figure 4 shows that at this acid concentration the kinetic contribution of step 2 could be

neglected. Therefore, eqs 6 and 7 reduce to

$$k_f = \frac{k_2 K_{H1}}{[H^+]} \cdot \alpha\beta \qquad (8)$$

and

$$k_d = k_{-2}\gamma \qquad (9)$$

At $[H^+] = 0.04$ M, the terms α, β, and γ are practically independent of I. Since step 3 in the forward direction involves a neutral molecule, k_2 does not depend noticeably on the ionic strength. Hence, the observed salt effect should be ascribed only to the ionic strength dependence of K_{H1}.

According to Guggenheim,[29] the salt effect on k_f could be described by the equation

$$\log k_f + \frac{4 \times 0.51 \times I^{1/2}}{(1 + I^{1/2})} = \log K'_{H1} k_2 + BI \qquad (10)$$

where $K'_{H1} = K^{\circ}_{H1} \alpha\beta[H^+]^{-1}$.

A plot of the left-hand side of eq 10 versus I should be linear. This prediction has been verified experimentally (Figure 5A) and confirms that the reactive form of the metal is GaOH^{2+}. The rate constant of step 2 in the reverse direction, $k_{-2} = k_d$ (since $\gamma = 1$), is expected not to change with ionic strength (since the complex break up involves a neutral water molecule) as experimentally found and shown in Figure 5B.

Indium. The system In(III)/BHA has been investigated only at pH 3; at higher pH values, an opalescence indicating hydroxide precipitation was observed whereas at lower pH values the reaction becomes too fast to be studied with the stopped-flow technique.

In contrast, the system In(III)/PBHA is less reactive and could be investigated by the stopped-flow method. A plot of $1/\tau$ versus C_M is shown in Figure 3B. A plot of $k_f/\alpha\beta$ versus $[H^+]^{-1}$ and k_d/γ versus $[H^+]$, according to eqs 6 and 7, respectively, is shown in Figure 6. The values of individual rate constants k_1, k_2, k_{-1}/K_C, and k_{-2} are collected in Table 1.

Temperature Effect. The temperature dependences of K_{app}, k_f, and k_d have been investigated at $[H^+] = 0.01$ M for In(III)/PBHA, whereas the temperature dependence of K_{app} for the In(III)/BHA system has been investigated at $[H^+] = 0.0025$ M. The temperature range was between 15 and 35

(29) Guggenheim, E. A.; Prue, J. E. *Physicochemical calculations*; North-Holland: Amsterdam, 1956; p 466.
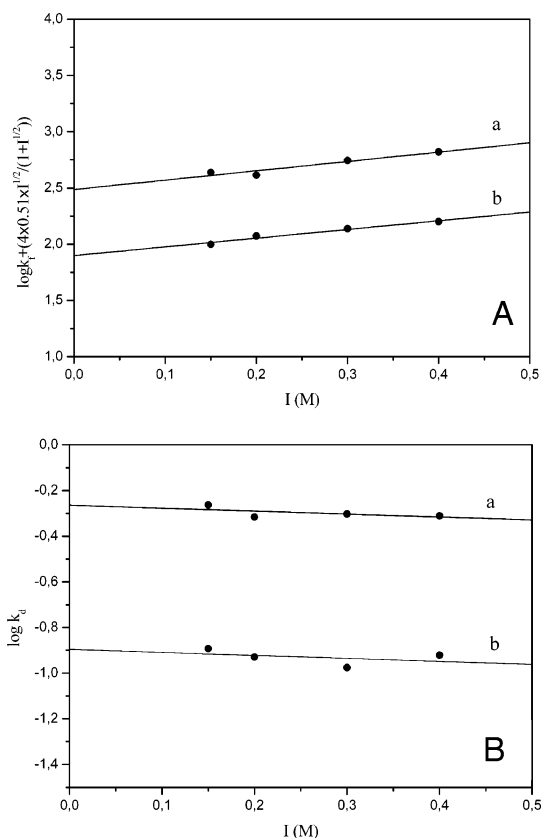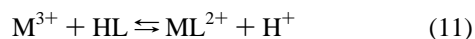
Figure 5. Salt effect on Ga(III)/BHA (a) and Ga(III)/PBHA (b). $[H^+] = 0.04$ M, $T = 25$ °C; (A) complex formation, (B) complex dissociation.
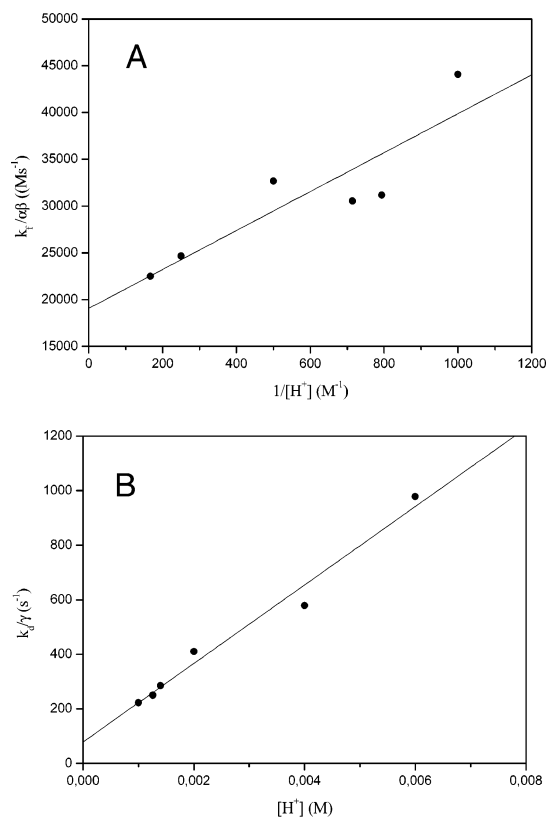

Figure 6. Dependence of the complex formation (A) and complex dissociation (B) rate constants on the hydrogen ion concentration for In-(III)/PBHA. $I = 0.2$ M, $T = 25$ °C.

°C whereas the ionic strength was 0.2 M. The activation parameters, $\Delta H_f^{\ddagger}$, $\Delta S_f^{\ddagger}$, $\Delta H_d^{\ddagger}$, $\Delta S_d^{\ddagger}$, and the reaction enthalpy, $\Delta H^{\ominus}_{app}$, of process 1 are collected in Table 2.

Discussion

Equilibria. It is, at first sight, quite surprising that the protonated species MHL is practically absent ($K_{MHL} \approx 0$ M^{-1}) in the presently investigated systems. A comparison with Ni-(II)/PBHA ($K_{MHL} = 150$ M^{-1})[30] reveals the important role played by the positive charge density on the metal in destabilizing the O−H bond. Ga^{3+}, owing to the reduced volume and higher charge, with respect to Ni^{2+}, is able to induce proton expulsion during chelation more efficiently than Ni^{2+}.

At the hydrogen ion concentrations employed to study the temperature dependence of the equilibria, $\Delta H^{\ominus}_{app}$ coincides with $\Delta H^{\ominus}\prime$, the enthalpy of reaction 11

$$M^{3+} + HL \rightleftharpoons ML^{2+} + H^+ \tag{11}$$

whereas the corresponding reaction entropy could be evaluated as $\Delta S^{\ominus}\prime = \Delta S^{\ominus}_{app} + R\ln[H^+]$.[31] Table 2 shows that the above reaction path is favored by the entropy contribution while it is contrasted by the enthalpy contribution. The

(30) García, B.; Ibeas, S.; Muñoz, A.; Leal, J. M.; Ghinami, C.; Secco, F.; Venturini, M. *Inorg. Chem.* **2003**, *42*, 5434−5441.
(31) The equilibrium constants of reactions 1 (K_{app}) and 11 ($K^{\circ}\prime$) are linked by the relationship $K^{\circ}\prime = K_{app}[H^+]$, since species other than M, HL, ML, and H$^+$ could be neglected. With [H$^+$] independent of temperature, it turns out that $\Delta H^{\circ}\prime \approx \Delta H^{\circ}_{app}$.

positive enthalpy values are certainly correlated with oxygen deprotonation occurring in the chelation step. Actually, the $\Delta H^{\ominus}_3$ values for the experimentally inaccessible path

$$M^{3+} + L^- \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} ML^{2+} \tag{12}$$
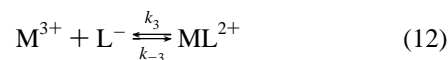
evaluated as $\Delta H^{\ominus}_3 = \Delta H^{\ominus}\prime - \Delta H^{\ominus}_A$ are negative, thus confirming that considerable energy is required to break the O−H bond in HL and form ML^{2+} according to reaction 11. Table 2 shows as well that on going from BHA to PBHA the values of $\Delta H^{\ominus}\prime$ increase. This finding shows that proton expulsion from MHL requires more energy in Ga(III)/PBHA than in Ga(III)/BHA.

Kinetics. The reaction shown in Scheme 1 shows two parallel reaction paths leading to metal−ligand complexes. A third path, kinetically indistinguishable from path 3, namely reaction 12, has been ruled out since the values of its forward rate constant would be $k_3 = k_1/K_A = 4.1 \times 10^9$ M^{-1} s^{-1} for Ga(III)/BHA, 3.8×10^8 M^{-1} s^{-1} for Ga(III)/PBHA, and 6.9×10^9 M^{-1} s^{-1} for In(III)/PBHA. All these values are several orders of magnitude higher than any rate constant so far measured for complex formation reactions of gallium(III) and indium(III). The systems investigated here provide an (uncommon) example where proton ambiguity could be resolved.

As expected, the hydrolyzed forms, M(H$_2$O)$_5$OH^{2+}, are much more reactive than the corresponding hexaquoions. The enhanced reactivity of these species is ascribed to the

Table 3. Comparison of Al(III), Ga(III), and Fe(III) Complex Formation and Dissociation Rate Constants[a]

system	I, M	k_1, $M^{-1} s^{-1}$	$10^{-3}k_2$, $M^{-1} s^{-1}$	$10k_{-1}/K_C$, $M^{-1} s^{-1}$	k_{-2}, s^{-1}
Al/BHA[b]	1	0.17	2.3	9.3	0.14
Ga/BHA	0.2	5.7	4.0	9.3	0.46
Ga/PBHA	0.2	1.9	0.94	1.5	0.098
Fe/BHA[c]	1.1	4.4	4.3	0.34	0.029
Fe/PBHA[c]	1.1	1.0	2.3	0.069	0.011

[a] $T = 25$ °C. [b] Reference 5b. [c] Reference 3u.

Table 4. Comparison of Rate Constants for Complex Formation at Ga(III)[a]

ligand	k_1, $M^{-1} s^{-1}$	$10^{-2}k_2$, $M^{-1} s^{-1}$	k_2/k_1
tropolone[b]	38	78	205
BHA	5.7	40	701
PBHA	1.9	9.4	495
H_2O[c]	400[c]	$600 \div 2000$[c]	$150 \div 500$

[a] $T = 25$ °C. [b] Reference 33. [c] k_1 (s^{-1}), k_2 (s^{-1}), ref 36.

labilization of the water molecules in the coordination shell of the metal ion induced by the presence of the OH group.[32]

Gallium. The kinetic results show that both Ga^{3+} and GaOH^{2+} react slower with PBHA than with BHA. Provided that the ring closure step could not be rate-determining since proton loss from MHL is fast, the causes of the rate reduction should be found in the reaction steps associated with k_1 and k_2. Table 1 shows that $\Delta \log k_2/\Delta \log k_1 \cong 1$ and $\Delta \log k_{-2}/\Delta \log(k_{-1}/K_C) \cong 0.8$. These results indicate that Ga^{3+} and GaOH^{2+} undergo complex formation with the same mechanism. Two mechanisms can be proposed to explain the kinetic features of the Ga(III)/BHA and Ga(III)/PBHA systems.

Mechanism A. Table 3 compares our kinetic data with those related to the complex formation reactions of Fe(III)[3u] with hydroxamic acids. Data on the Al(III)/BHA system are also reported.[5b] Unfortunately, the data for Al(III)/PBHA could not be given, since this system has not been investigated. However, experiments with other substituted hydroxamic acids[5b] show that both k_1 and k_2 are insensitive to the nature of the entering group whereas the contrary is true for k_{-1}/K_C and k_{-2}. On this basis, an interchange dissociative mechanism dominated by water exchange at the metal ion has been proposed for complex formation between aluminum(III) and hydroxamic acids.[5b] Table 3 shows that the behaviors of Ga(III) and Fe(III) are similar. The ratio

$$\Delta \log k_1(\text{Ga}^{3+})/\Delta \log k_1(\text{Fe}^{3+}) = 0.8$$

indicates that Ga^{3+} and Fe^{3+} bind to hydroxamic acids with very similar mechanistic features. The same holds for GaOH^{2+} and FeOH^{2+}, although the higher ratio

$$\Delta \log k_2(\text{GaOH}^{2+})/\Delta \log k_2(\text{FeOH}^{2+}) = 2$$

reveals that GaOH^{2+} is more sensitive than FeOH^{2+} to substituent effects.

Concerning the reverse reaction process, the ratios

$$\Delta \log(k_{-1}/K_C)(\text{Ga}^{3+})/\Delta \log(k_{-1}/K_C)(\text{Fe}^{3+}) = 1.1$$

and

$$\Delta \log k_{-2}(\text{GaOH}^{2+})/\Delta \log k_{-2}(\text{FeOH}^{2+}) = 1.6$$

suggest that the aquation steps for gallium and iron hydroxamates proceed with the same mechanism both for M^{3+} and

MOH^{2+}, although, in this case too, GaOH^{2+} is somewhat more sensitive to the identity of the leaving group than FeOH^{2+}.

Further support for the analogy of behavior comes from the comparison of the activation parameters. The conditions under which the activation parameters of the dissociation paths $\Delta H_d^‡$ and $\Delta S_d^‡$ have been measured are such that step 3 is largely prevailing; hence, the values of $\Delta H_d^‡$ and $\Delta S_d^‡$ given in Table 2 would coincide with the $\Delta H_{-2}^‡$ and $\Delta S_{-2}^‡$, respectively.

From Table 2 one obtains $\Delta H_{-2}^‡(\text{BHA}) - \Delta H_{-2}^‡(\text{PBHA}) = -1$ kJ mol^{-1} and $\Delta S_{-2}^‡(\text{BHA}) - \Delta S_{-2}^‡(\text{PBHA}) = 7.5$ J mol^{-1} K^{-1}. The corresponding differences for Fe(III) are 0.4 kJ mol^{-1} and 12 J mol^{-1} K^{-1}.[3u]

Concerning step 3 in the forward direction, a comparison of $\Delta H_2^‡$ and $\Delta S_2^‡$ values (Table 2) shows that both activation parameters are scarcely sensitive to the entering group identity and the values of $\Delta S_2^‡$ are negative. An analogous behavior is exhibited by Fe(III)/BHA and Fe(III)/PBHA.[3u]

Mechanism B. An alternative explanation of the observed behavior rests on the assumption that, while Ga^{3+} and GaOH^{2+} undergo complex formation according to the I$_d$ mechanism, only a fraction of the ligand can be bound. Table 4 compares our rate constants k_1 and k_2 with those of Ga-(III)/tropolone.[33] This system has been chosen since tropolone, among the various ligands so far investigated, is directly comparable with BHA and PBHA for being a neutral species that does not display proton ambiguity. Moreover, the site for the metal attack is a neutral >C=O oxygen, as in the hydroxamic acids. Finally, the I$_d$ mechanism for tropolone binding to Ga^{3+} and GaOH^{2+} is supported first by the activation volume values ($\Delta V_1^‡ = 4.0$ and $\Delta V_2^‡ = 2 \div 4$ cm^3 mol^{-1}) and second by the values of $k_i^* = K_{\text{OS},i}/k_i$[34,35] which compare well with $k_{\text{H}_2\text{O},i}$.[34,36] On this basis, the comparison of the second-order rate constants provides a good test to evidence deviations from ordinary I$_d$ behavior.

Table 4 shows that the reactivity of the ligands toward Ga^{3+} and GaOH^{2+} changes according to the sequence tropolone > BHA > PBHA. Considering that in water

(32) Burgess, J. *Metal Ions in Solution*; Ellis Horwood Ltd.: Chichester, U.K., 1978.

(33) Yamada, S.; Iwanaga, A.; Funahashi, S.; Tanaka, M. *Inorg. Chem.* **1984**, *23*, 3528−3532.

(34) Eigen, M.; Tamm, K. *Z. Elektrochem.* **1962**, *66* (93), 107−121.

(35) According to the Eigen−Tamm mechanism, the fast formation of an outer-sphere complex (stability constant K_{OS}) precedes the substitution step (rate constant k^*). For excess metal, the second-order rate constant of the process is expressed by the relationship $k = K_{\text{OS}}k^*/(1 + K_{\text{OS}}C_M)$. For the presently investigated systems, $K_{\text{OS}}C_M \ll 1$. Hence, $k^* = k/K_{\text{OS}}$. Note that the value of K_{OS} is small and does not change, since the ligands are neutral. Therefore, the values of k_i can be compared instead of the values of k_i^*.

(36) Hugi-Cleary, D.; Helm, L.; Merbach, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 4444−4450.

hydroxamic acids are largely in the Z form,[22] the rate reduction could be explained with the assumption that this form is partitioned between an "open" and a "closed" configuration in fast equilibrium. The latter is made unreactive by hydrogen bonding, possibly involving a water molecule.[30] Under these circumstances, only the "open" form can react with the metal, and as a consequence, the rate constant would be reduced by a factor $K/(1 + K)$ where K = [open form]/[closed form].

Indium. Concerning the kinetic behavior of In(III)/PBHA, a direct comparison with In(III)/tropolone and water exchange at In^{3+} could not be made for lack of data on these systems. However, it should be noticed that Kowall et al.[37] suggested $\Delta V^{\ddagger} = -5.2$ cm^{3}mol^{-1} for water exchange on In^{3+}, on the basis of bond cleavage and bond formation considerations. This value, hinting at a rejection of the I$_d$ mechanism for complexation of In^{3+}, may find support in the negative value of $\Delta S_f^{\ddagger}$ quoted in Table 2 for the In(III)/PBHA system.

Conclusions

The reactions of gallium(III) and indium(III) with BHA and PBHA lead to formation of the deprotonated complex ML, although kinetic evidence is provided for a reaction path involving the intermediacy of MHL. Deviations from the Eigen−Tamm behavior are observed. Of the two possible mechanisms advanced in this study, we prefer mechanism A for the following reasons: we believe that mechanism B (although recently proposed[30] to explain the kinetic behavior of Ni(II)/PBHA at neutral pH) does not hold for the binding of cations of the IIIA group and iron(III). Support for this idea comes from the comparison of kinetic behavior of M(III)/salicylates with that of M(II)/salicylates. For salicylates, the ratio [open form]/[closed form] shows little change with the substituent nature, being $K \cong 10^{-3}$.[38] A reduction of rate of 3 orders of magnitude is expected if mechanism B is operative, and this has been indeed observed with Ni-(II)/salicylates[39] and Co(II)/salicylates.[40] In contrast, no such rate reduction has been found for Al(III)/salicylates where a rate dependence on ligand basicity was observed.[41] Ligand dependence is displayed by the Ga(III)/salicylates[42] and Fe-(III)/salicylates as well.[43]

(37) Kowall, T.; Caravan, P.; Bourgeois, H.; Helm, L.; Rotzinger, F. P.; Merbach, A. E. *J. Am. Chem. Soc.* **1998**, *120*, 6569−6577.

(38) Diebler, H.; Secco, F.; Venturini, M. *J. Phys. Chem.* **1984**, *88*, 4229−4232.
(39) Diebler, H.; Secco, F.; Venturini, M. *J. Phys. Chem.* **1987**, *91*, 5106−5111.
(40) Diebler, H.; Secco, F.; Venturini, M. *J. Phys. Chem.* **1989**, *93*, 1691−1694.
(41) Perlmutter-Hayman, B.; Tapuhi, E. *Inorg. Chem.* **1977**, *16*, 2742−2745.
(42) Corigli, R.; Secco, F.; Venturini, M. *Inorg. Chem.* **1982**, *21*, 2992−2998.
(43) Mentasti, E.; Secco, F.; Venturini, M. *Inorg. Chem.* **1982**, *21*, 602−606.
(44) Eyring, E. M.; Owen, J. D. *J. Phys. Chem.* **1970**, *74*, 1825−1828.
(45) Uchida, M.; Okuwaki, A. *J. Sol. Chem.* **1998**, *27*, 965−978.
(46) Dodel, P. H.; Taube, H. Z. *Phys. Chem.* (*Muenchen*) **1965**, *44*, 92−100.