Kinetics of the Interaction of Indium(III) with 8-Quinolinol-5-sulfonic Acid and with Sulfate

Alessio Ricciu,[a] Fernando Secco,*[a] Marcella Venturini,[a] Begoña García,[b] and José María Leal[b]

Abstract: The kinetics and equilibria of indium(III) binding to 8-quinolinol-5-sulfonic acid (HQSA) have been investigated in acidic aqueous solution at 0.2 M ionic strength and 25 °C by stopped-flow, absorption and fluorescence spectrometric methods. Absorption and fluorescence spectrometry revealed that a monoprotonated MHL^{3+} complex is formed in addition to the ML^{2+} chelate. The stability constants of the chelate ($\log K_{ML} = 6.53$), of the monoprotonated complex ($\log K_{MHL} = 3.51$) and its acid dissociation constant ($pK_{C2} = 1.4$) have been determined. Stopped-flow measurements indicate three reaction paths that involve the interaction of M^{3+} with H_2L^+ ($k_1 = (3.21 \pm 0.04) \times 10^2\,M^{-1}s^{-1}$), M^{3+} with HL ($k_2 = (6.52 \pm 0.04) \times 10^4\,M^{-1}s^{-1}$) and MOH^{2+} with HL ($k_3 = (1.60 \pm 0.08) \times 10^6\,M^{-1}s^{-1}$), respectively. The reactivity of In^{3+} toward the uncharged form of HQSA has been found to be approximately two orders of magnitude less than expected based upon water exchange experiments. This behaviour has been explained with the assumption that the ligand is distributed between two forms (neutral and zwitterion) of which only the neutral form is reactive. The rate of complex formation between In^{3+} and SO_4^{2-} ion has been measured by the temperature-jump method with Tropaeolin 00 as the indicator. The second-order rate constant of the binding process is $5.1 \times 10^4\,M^{-1}s^{-1}$. This quantity yields a value for the first-order rate constant of 570 s^{-1} for ligand penetration into the In^{3+} coordination shell, approximately two orders of magnitude less than normal. This finding is interpreted by the hypothesis that SO_4^{2-} forms a chelate with In^{3+} for which ring closure is the rate-determining step.

Keywords: indium · kinetics · reaction mechanisms · thermodynamics

Introduction

Indium(III) and gallium(III) have useful and increasing applications as tumour-localising agents in nuclear medicine. Actually, in order to localise non-osseous tumours, ^{111}In and ^{67}Ga are administered in the form of complexes, mostly with citrate or bleomicine.[1] These ligands exchange the metal with transferrin, which is believed to play the role of biodistributor for the radionuclides. Hence, elucidation of the interactions of these ions with certain ligands is important so that the processes involved in the metal uptake by malignant and inflammatory lesions may be learned, and can thus aid in the identification and design of better radiopharmaceuticals.

However, forty years after the proposal of Eigen and coworkers[2–5] about the general mechanism that accounts for the kinetic features of complex formation of most metal ions, the position of tervalent cations of Group 13 presents several aspects that still have not been elucidated. This fact can be ascribed to the extensive hydrolysis and polymerisation of these cations,[6] which leads to the formation of several reactive species. Moreover, "proton ambiguity"[7] makes it impossible to unequivocally associate a given experimental rate parameter to a particular reaction path when the metal and the ligand are distributed among several reactive forms that differ in their degree of protonation.

In the case of indium(III), an additional difficulty arises due to the high reactivity of this metal ion, which often makes flow methods not applicable. Thus, it is often necessary to resort to relaxation techniques, which are available only in relatively few laboratories. Moreover, it is difficult to determine the kinetic parameters for the water exchange process at indium(III), the knowledge of which would be very enlightening for the understanding of the complex formation mechanism. Actually, the literature values of the rate constants for the water exchange process differ by several orders of magni-

---

[a] Prof. F. Secco, Dr. A. Ricciu, Prof. M. Venturini
Dipartimento di Chimica e Chimica Industriale
Università di Pisa, Via Risorgimento 35
56126 Pisa (Italy)
Fax: (+39) 050-918260
E-mail: ferdi@dcci.unipi.it

[b] Prof. B. García, Prof. J. M. Leal
Departamento de Química, Universidad de Burgos
09001 Burgos (Spain)

Supporting information (fractions of the free and bound forms of the ligand for different hydrogen ion concentrations in the indium(III)–HQSA system) for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author.

tude,[8, 9] whereas data on activation volumes are lacking. Kinetic studies on ligand substitution at indium(III) are relatively scarce and have provided results that should be carefully analysed before mechanistic conclusions about the complex formation of this metal ion are drawn. The systems investigated to date can be divided into two classes, the first group includes ligands with first-order substitution rate constants that are higher than $10^4\,s^{-1}$, the second group includes ligands with substitution rates that range from 10^2–$10^3\,s^{-1}$. The reason for this rate reduction should probably not be ascribed to a lower nucleophilic power, but rather to other characteristics of the ligand.

We report herein on the equilibria and kinetics of the process of indium(III) binding to 8-quinolinol-5-sulfonic acid and to sulfate, two ligands that, for independent and different reasons, bind to indium(III) at rates lower than normal.

Results

The indium(III)–HQSA system (HQSA = 8-quinolinol-5-sulfonic acid)

Equilibria: The equilibria of the indium(III)–HQSA system have been investigated in the presence of excess metal in order to avoid the formation of 1:2 complexes. The spectra recorded during titrations at constant acidity show a single, well-defined isosbestic point (inset of Figure 1A) which indicates that the system can be represented by the reaction given in Equation (1):

$$M_f + L_f \rightleftharpoons ML_T \quad (1)$$

for which $[M_f] = [M^{3+}] + [MOH^{2+}] + [M(OH)_2^{+}] + 2[M_2(OH)_2^{4+}] + 3[M_3(OH)_4^{5+}]$, $L_f = [H_2L] + [HL^-] + [L^{2-}]$ and $[ML_T]$ is the sum of the formed mononuclear complexes.

Figure 1A shows the UV spectra of the free ligand (curve a) and of the total complex (curve b). All titrations were performed with excess metal ion, and a typical titration curve is shown in Figure 2A. The reaction parameters were derived according to Equation (2), in which $l = 1$ cm, c_L and c_M are the total concentrations of ligand and metal, respectively, $\Delta A = A - \varepsilon_L c_L$, ($A$ being the absorbance), $\Delta\varepsilon = \varepsilon_{MLT} - \varepsilon_{Lf}$ is the extinction coefficient difference and K_{app} is the equilibrium constant of reaction given in Equation (1).

$$\frac{\Delta A}{c_L} = l\left(\frac{\Delta\varepsilon K_{app} c_M}{1 + K_{app} c_M}\right) \quad (2)$$

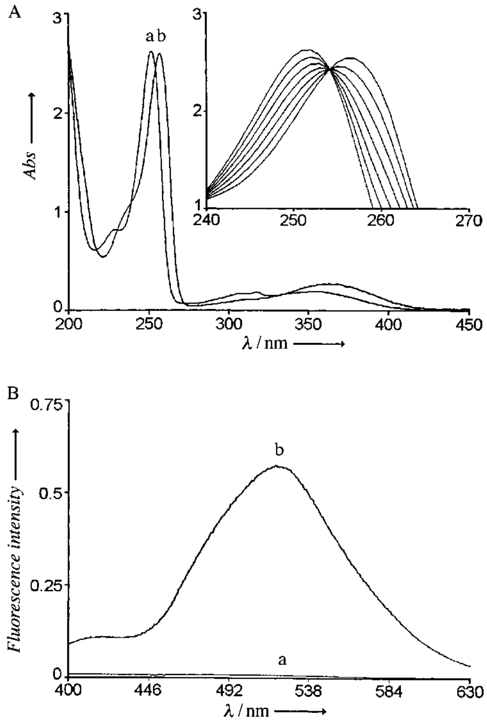


Figure 1. Absorption and fluorescence spectra of the indium(III)–HQSA system at pH = 3, $I = 0.2$ M and $T = 25\,°C$. A) Absorption: a) 7.4×10^{-5} M HQSA; b) 7.4×10^{-5} M HQSA + 1.0×10^{-2} M $In(ClO_4)_3$. The inset shows the spectral changes during a spectrophotometric titration. B) Fluorescence emission at $\lambda_{exc} = 325$ nm: a) 7.4×10^{-5} M HQSA; b) 7.4×10^{-5} M HQSA + 1.0×10^{-2} M $In(ClO_4)_3$.

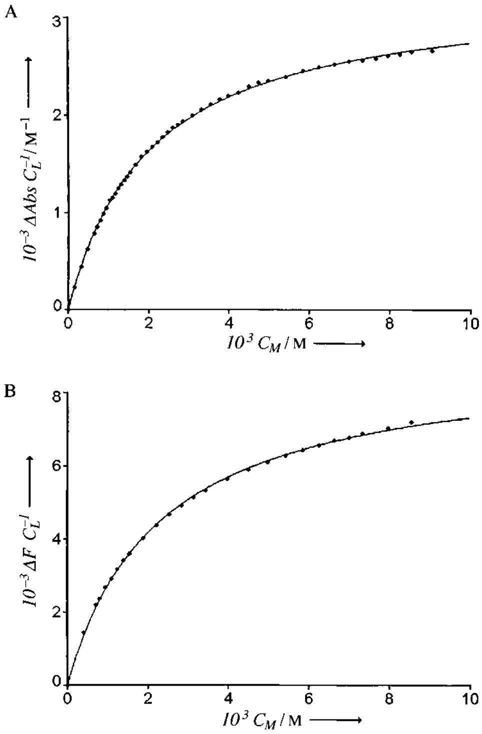


Figure 2. Analysis of the equilibria of the indium(III)–HQSA system: $[H^+] = 7.5\times10^{-3}$ M, $I = 0.2$ M, $T = 25\,°C$. A) Spectrophotometric titration performed at 234 nm; the continuous line is based on Equation (2). B) Spectrofluorimetric titration monitored at 519 nm with $\lambda_{exc} = 325$ nm; the continuous line is based on Equation (3).

It should be noted that $\Delta\varepsilon$ and K_{app} are apparent quantities which, in principle, could be pH dependent.[10] The solid line represents the trend that was calculated on the basis of Equation (2). Values of K_{app} as determined by absorption measurements at different values of hydrogen ion concentration are listed in the second column of Table 1. [Fractions of the free and bound forms of the ligand for different

Table 1. Apparent equilibrium constant (K_{app}) at different hydrogen ion concentrations for the indium(III) – HQSA system at 25 °C.

$10^3[H^+]$ [M]	10^{-2} K_{app} [M^{-1}] [a]	 [b]	 [c]
1.2	–	–	145 ± 70
2.0	–	–	51 ± 5
2.5	27 ± 0.5	26 ± 1	–
3.5	17 ± 0.4	16 ± 0.2	–
3.7	–	15 ± 1	–
4.0	–	–	14.9 ± 0.6
4.3	–	–	14.0 ± 0.7
4.6	–	–	12.2 ± 0.8
5.0	9.1 ± 0.9	8.3 ± 0.1	–
6.0	–	–	6.7 ± 0.4
7.5	4.6 ± 0.4	4.4 ± 0.1	–
8.5	3.5 ± 0.8	3.4 ± 0.1	–
10	2.5 ± 0.8	2.2 ± 0.1	–
12	–	–	1.91 ± 0.03
15	–	–	1.15 ± 0.03
16	–	1.1 ± 0.2	–
25	0.49 ± 0.2	0.35 ± 0.04	–

[a] Spectrophotometry. [b] Spectrofluorimetry. [c] Kinetics ($K_{app} = k_f/k_d$).

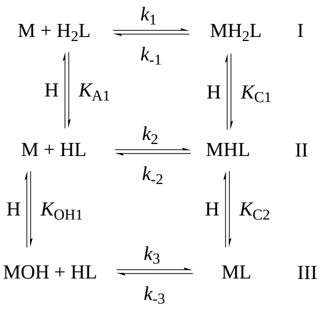
hydrogen ion concentrations in the indium(III) – HQSA system are available in the Supporting Information.]

Aqueous solutions of HQSA, when illuminated with ultraviolet light, display a very weak fluorescence that is enhanced strongly upon binding to indium(III) (Figure 1B). Figure 2B shows a fluorescence titration recorded at $\lambda_{exc} = 325$ nm and $\lambda_{em} = 519$ nm. In order to minimise the inner filter effect, the system was excited at 325 nm, a wavelength at which the absorbance is less than 0.1. The results have been analysed according to the relationship in Equation (3),

$$\frac{\Delta F}{c_L} = l\left(\frac{\Delta f\, K_{app} c_M}{1 + K_{app} c_M}\right) \tag{3}$$

for which $l = 1$ cm, ΔF is the difference between the fluorescence measured during the titration and the fluorescence of the free ligand, Δf is a parameter that depends on the intensity of the excitation signal, on the difference of the quantum yield between complex and ligand and on the geometry of the apparatus. The values of K_{app} as determined by fluorescence measurements at different hydrogen ion concentrations are shown in the third column of Table 1.

The dependence of the apparent equilibrium constant on the hydrogen ion concentration and the kinetic behaviour of the system suggest the kinetic pattern shown in Scheme 1.



Scheme 1. Kinetic pattern for the binding process of indium(III) to 8-quinolinol-5-sulfonic acid (HQSA). Charges and water molecules involved in the process are omitted.

Figure 3 shows the analysis of the dependence of K_{app} on the hydrogen ion concentration. The linear plot agrees with Equation (4), in which K_{MHL} and K_{C2} are the stability constant of the MHL complex and its acid dissociation constant, respectively. The variables α and β are defined by Equations (5) and (6), respectively.

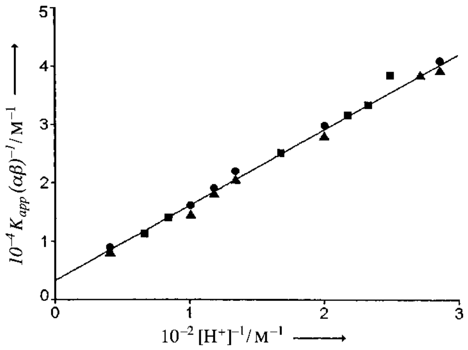


Figure 3. Analysis of the equilibria of the indium(III) – HQSA system: $I = 0.2$ M, $T = 25$ °C. The dependence of the apparent equilibrium constant, K_{app}, on $[H^+]$: ● absorption, ▲ fluorescence, ■ kinetics.

$$\frac{K_{app}}{\alpha\beta} = K_{MHL} + \frac{K_{MHL}K_{C2}}{[H^+]} \tag{4}$$

$$\alpha = \frac{[HL^-]}{[L_f]} = \frac{1}{1 + \frac{[H^+]}{K_{A1}} + \frac{K_{A2}}{[H^+]}} \tag{5}$$

$$\beta = \frac{[M^{3+}]}{[M_f]} = \frac{1}{1 + \frac{K_{OH1}}{[H^+]} + \frac{K_{OH2}}{[H^+]^2} + \frac{2K_D c_M}{[H^+]^2} + \frac{3K_T c_M^2}{[H^+]^4}} \tag{6}$$

The equilibrium constant of step III is evaluated as $K_{ML} = K_{MHL}K_{C2}/K_{OH1}$. The plot shown in Figure 3 is linear over the full range of the investigated acidity, which means that the species MH_2L^{3+} is present in small amounts and the equilibrium constant K_{C1} could not be evaluated. Noticeable amounts of MH_2L^{3+} would be revealed by upward deviations from linearity at low values of $1/[H^+]$. However, this species was included in Scheme 1 since its presence is revealed by the kinetic experiments. The values of the individual equilibrium constants are presented in Table 2.

Table 2. Reaction parameters for the indium(III) – HQSA system at $I = 0.2$ M and $T = 25$ °C.

pK_{A1}	3.79[a]
pK_{A2}	7.96[a]
pK_{OH1}	4.42[b]
pK_{OH2}	8.30[b]
pK_D	5.21[b]
pK_T	9.70[b]
K_{C2}	$(3.9 \pm 0.8) \times 10^{-2}$ M^{-1}
K_{MHL}	$(3.2 \pm 0.7) \times 10^3$ M^{-1}
K_{ML}[c]	$(3.4 \pm 0.2) \times 10^6$ M^{-1}
k_1	$(3.21 \pm 0.04) \times 10^2$ $M^{-1}s^{-1}$
k_2	$(6.52 \pm 0.01) \times 10^4$ $M^{-1}s^{-1}$
k_3	$(1.60 \pm 0.08) \times 10^6$ $M^{-1}s^{-1}$
$k_{-1}K_{C1}^{-1}$	$(6.01 \pm 0.06) \times 10^2$ $M^{-1}s^{-1}$
k_{-2}	$(1.92 \pm 0.05) \times 10^1$ s^{-1}
k_{-3}	$(4.9 \pm 1.7) \times 10^{-1}$ s^{-1}

[a] Ref. [14]. [b] Ref. [31]. [c] $K_{ML} = [ML]/([MOH][HL])$.

Kinetics: The stopped-flow experiments were performed by monitoring the absorbance change both for complex formation (Figure 4A) and complex dissociation (Figure 4B). The amplitude of the kinetic effect drops to zero at $\lambda = 254$ nm, which corresponds to the isosbestic point shown in the inset of Figure 1A. Below that wavelength, the amplitudes are negative, and above they are positive according to the spectra. Moreover, the time constants do not depend on the chosen wavelength. These observations confirm that the reacting system is adequately represented by the reaction in Equation (1). Under the conditions of excess metal ion, the reciprocal relaxation time, $1/\tau$, depends on the total metal concentration, c_M, according to Equation (7) (Figure 5), in which k_f and k_d are the rate constants of the Equation (1) in the forward and reverse direction, respectively.

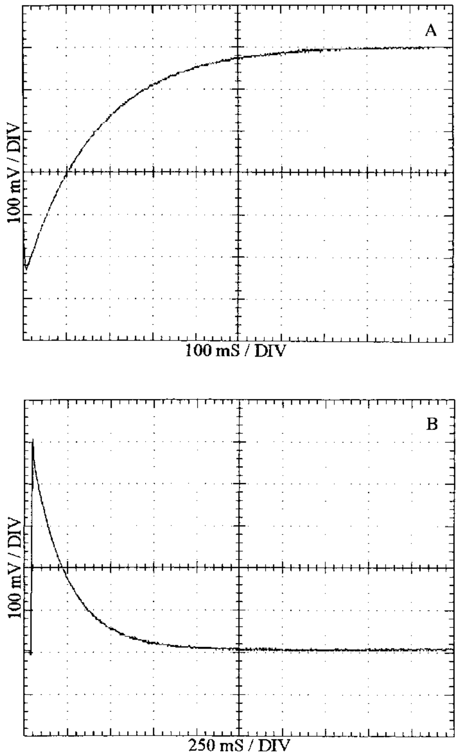


Figure 4. Stopped-flow experiments on the indium(III) – HQSA system: $I = 0.2$ M, $T = 25\,^{\circ}$C. A) Complex formation curve; $c_L = 4 \times 10^{-5}$ M, $c_M = 2 \times 10^{-3}$ M, $[H^+] = 4 \times 10^{-3}$ M. B) Complex dissociation curve; $c_{ML} = 4 \times 10^{-5}$ M, $[H^+] = 1.7 \times 10^{-3}$ M.

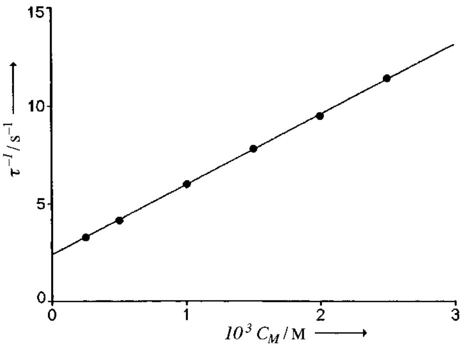


Figure 5. Dependence of the time constant, $1/\tau$, on the metal ion concentration for the indium(III) – HQSA system: $[H^+] = 4 \times 10^{-3}$ M, $I = 0.2$ M, $T = 25\,^{\circ}$C.

$$1/\tau = k_f c_M + k_d \quad (7)$$

Note that, at the highest hydrogen ion concentrations investigated, the $1/\tau$ versus c_M plots derived from the complex formation experiments provide slope values that are too small to be reliable. Therefore, for $[H^+] > 0.015$ M, the k_f values were obtained by evaluating k_d from the complex dissociation experiments and by using the relationship $k_f = K_{app}k_d$.

The complex-containing solutions to be used in the dissociation experiments were prepared before each experiment by mixing small amounts of metal and ligand in equimolar concentration (4×10^{-5} M) and then increasing the pH value to 6. The complex dissociation experiments were accomplished by mixing the preformed complex with calibrated amounts of perchloric acid in the stopped-flow apparatus. Under these circumstances, the concentration of free metal is negligible and Equation (7) is reduced to $1/\tau = k_d$.

Figure 6 shows the dependence of the forward and reverse rate constants on the hydrogen ion concentration. The change of k_f with $[H^+]$ (Figure 6A) is best represented by the three-term equation,[11] Equation (8), whereas the change of k_d with $[H^+]$ (Figure 6B) is best represented by Equation (9)[11], for which the value of γ is given by Equation (10).

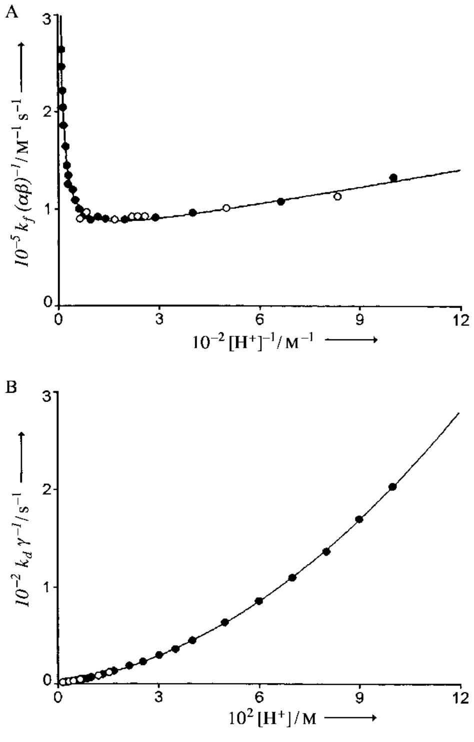


Figure 6. Dependence of the apparent rate parameters on the hydrogen ion concentration for the indium(III) – HQSA system: $I = 0.2$ M, $T = 25\,^{\circ}$C: ● complex formation, ○ complex dissociation. A) The continuous line is based on Equation (8); B) The continuous line is based on Equation (9).

$$k_f = \left(\frac{k_3 K_{OH1}}{[H^+]} + k_2 + \frac{k_1[H^+]}{K_{A1}}\right)\alpha\beta \quad (8)$$

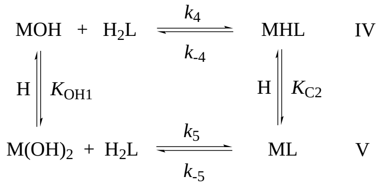
$$k_d = \left(k_{-3} + \frac{k_{-2}[H^+]}{K_{C2}} + \frac{k_{-1}[H^+]^2}{K_{C1}K_{C2}}\right)\gamma \qquad (9)$$

$$\gamma = \frac{[ML]}{[ML_T]} = \frac{1}{1 + \frac{[H^+]}{K_{C2}} + \frac{[H^+]^2}{K_{C1}K_{C2}}} \qquad (10)$$

Since $K_{C1} \gg [H^+]$, Equation (10) reduces to $\gamma = K_{C2}/([H^+] + K_{C2})$.

The rate constants k_1, k_2, k_3, $k_{-1}K_{C1}^{-1}$, k_{-2}, and k_{-3}, which refer to the individual steps shown in Scheme 1, have been evaluated by a non-linear least-square fit of the data to Equations (9) and (10), respectively. The solid lines of Figure 6A and B represent the calculated trends. The values of the kinetic parameters are reported in Table 2.

It should be noted that, owing to the proton ambiguity, each of the three steps in Scheme 1 can be replaced by one or even two other possible steps. Three of these steps, two that involve H_3L^+ and one that involves L^{2-}, have been excluded because of the extremely low concentration of such species. The remaining possible steps are represented in Scheme 2, in which steps IV and V are equivalent to steps II and III of Scheme 1, respectively. Reaction steps that involve the metal dimer and trimer have been excluded, since the reaction was found to be strictly first-order with respect to metal ion.



Scheme 2. Alternative reaction paths for the binding of indium(III) to 8-quinolinol-5-sulfonic acid (HQSA).

By using the relationships $k_2\alpha_{HL}\beta_M = k_4\alpha_{H2L}\beta_{MOH}$ and $k_3\alpha_{HL}\beta_{MOH} = k_5\alpha_{H2L}\beta_{M(OH)2}$, one obtains $k_4 = 2.8 \times 10^5\,M^{-1}s^{-1}$ and $k_5 = 2.0 \times 10^6\,M^{-1}s^{-1}$. These values are similar to k_2 and k_3, respectively, which means that step IV could compete with step II, and step V with step III.

The indium(III) – sulfate system

Figure 7 shows a temperature-jump relaxation curve of the indium(III)-sulfate system obtained at $[H^+] = 1.0 \times 10^{-2}\,M$, $c_M = c_L = 5 \times 10^{-2}\,M$, and $I = 0.2\,M$ (I = ionic strength). The course of the reaction was observed by monitoring the color change of the reacting mixtures that contained the indicator Tropeolin 00 ($5 \times 10^{-5}\,M$) and were illuminated with a 0.5 mW He-Ne laser that emitted at 543 nm. The relaxation curves are strictly single exponential and the concentration dependence of the reciprocal relaxation time is described by the relationship in Equation (11),[12]

$$\frac{1}{\tau} = k_1\left([M^{3+}]\frac{\delta L}{\delta M} + [L^{2-}] + K^{-1}\right) \qquad (11)$$

for which $K = 220\,M^{-1}$ is the equilibrium constant[13] of the binding of In^{3+} to SO_4^{2-}. The factor $\delta L/\delta M$ is a concentration variable that accounts for the contribution of the indicator to the relaxation time and is given by the relationship in Equation (12):

$$\frac{\delta L}{\delta M} = \frac{K_A}{[H^+] + K_A}\left\{1 + \frac{[HL^{-1}]/([H^+] + K_A)}{1 + [L^{2-}]/([H^+] + K_A) - [In^-]/([H^+] + K_I)}\right\} \qquad (12)$$

in which $K_A = 3.2 \times 10^{-2}\,M$ and $K_I = 2.0 \times 10^{-2}\,M$ are the acid dissociation constants of HL^- (sulfate monoanion) and HIn (Tropeolin 00), respectively. Under these experimental conditions, the term that contains the indicator concentration is negligible and the second term in braces in Equation (12) is reduced to $[HL^-]/([H^+] + K_A + [L^{2-}])$. The evaluation of the data yields $k_1 = (5.1 \pm 0.1) \times 10^4\,M^{-1}s^{-1}$.

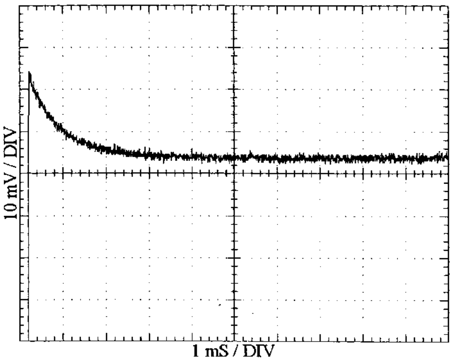


Figure 7. Temperature-jump experiment on the indium(III) – sulfate system. The signal was detected by laser monitoring at 543 nm, with the use of Tropeolin 00 as an acid-base indicator. $c_M = c_L = 5 \times 10^{-2}\,M$, $[H^+] = 0.01\,M$, $I = 0.3\,M$, $T = 25\,°C$.

Discussion and Conclusion

The equilibrium parameters listed in Table 2 for MHL^{2+} are compared with the values $K_{MHL} = 6.9 \times 10^2\,M^{-1}$ and $K_{C2} = 3.4 \times 10^{-1}\,M$ that were obtained for the indium(III) – Ferron system.[11] The structure of the reaction site is the same for both ligands, since Ferron differs from HQSA only by the iodine atom at the α-position with respect to the OH moiety. This comparison indicates that MHL^{2+} becomes more stable in the HQSA case. This result is ascribed to the higher basicity of the phenol oxygen in HQSA ($pK_{A2} = 7.96$)[14] relative to that of Ferron ($pK_{A2} = 7.08$).[11]

Table 3 shows the results of all available kinetic data on complex formation at indium(III); k_1^* and k_2^* are first-order rate constants. According to the Eigen and Tamm argument,[3] the k_i^* values refer to the conversion step of the outer-sphere complex into the corresponding inner-sphere complex. These could be evaluated by the relationship $k_i^* = k_i/K_{OS}$, in which k_i is the second-order rate constant of the binding process, whereas K_{os} is the stability constant of the outer-sphere complex (an electrostatic ion pair).[15] This operation provides a suitable tool to normalise the reaction rates for the charge and ionic strength effects, regardless of the mechanism of complex formation. However, some uncertainty in the evaluation of K_{OS} arises from the arbitrary choice of the charge distance in the ion pair.[15]

The k_1^* and k_2^* values are higher than those found for similar reactions that involve gallium(III) and aluminium(III) and are in agreement with the reactivity sequence $In^{III} > Ga^{III} > Al^{III}$. Table 3 shows that the values of k_1^* for PCV^0,[13] Ferron$^-$,[11] Murexide$^-$,[16] SOX$^-$[17] and PCV$^-$[13] are quite similar and, in

Table 3. Rate parameters for ligand substitution at In^{3+} (k_1^*) and $InOH^{2+}$ (k_2^*). $T = 25\,°C$, $I = 0.2\,M$.

Ligand[a]	k_1^* [s^{-1}]	K_{OS} [$mol^{-1}\,dm^3$]	k_2^* [s^{-1}]	K_{OS} [$mol^{-1}\,dm^3$]	Ref.
Ferron^0	3.7×10^3	0.3	–	–	[11]
HQSA^0	1.1×10^3	0.3	–	–	this work
PAN^0	1.8×10^2	0.3	2.7×10^5	0.3	[18]
SO_4^{2-}	5.7×10^2	44	–	–	this work
H_3PAR^+	2.4×10^4	0.02	–	–	[32]
H_2PAR^0	5.0×10^4	0.3	–	–	[32]
PCV^0	5.1×10^5	0.3	–	–	[13]
Ferron$^-$	2.6×10^4	3.7	5.9×10^5	1.6	[11]
Murexide$^-$	1.6×10^5	3.7	4.3×10^6	1.6	[16b]
HQSA$^-$	1.8×10^4	3.7	1.0×10^6	1.6	this work
PCV$^-$	3.2×10^5	3.7	2.7×10^7	1.6	[13]
H_2SOX^{2-}	3.1×10^4	4.1^b	5.7×10^5	1.8[b]	[17]
H_3SOX^-	–	–	3.0×10^6	0.74[b]	[17]
H_2O	2.0×10^4	–	–	–	[8]
	$> 10^7$	–	–	–	[9]

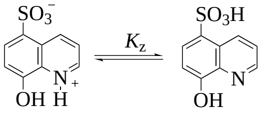
[a] Ferron = 7-iodo-8-hydroxyquinoline-5-sulfonic acid; PAN = 1-(2-pyridylazo)-2-naphtol; HQSA = 8-quinolinol-5-sulfonic acid; PAR = 4-(2-pyridylazo)-resorcinol; PCV = pyrochatecol violet; SOX = semiXylenol orange. [b] $I = 2.0\,M$.

any case, no definite trend emerges that would indicate a ligand dependence of the reactivity of In^{3+} ion. This behaviour would suggest that this species reacts according to the interchange dissociative mechanism (I_d). By contrast, the negative value ($-6.3\,J\,mol^{-1}\,K^{-1}$) of the activation entropy for the In^{3+}–PVC$^-$ system[13] hint at a possible interchange associative (I_a) mode of activation. Note that activation entropy is not a very reliable parameter to use for the assignment of a reaction mechanism owing to the large error limits involved in the extrapolation of the data to infinite temperature. Unfortunately, the k_{H2O} values published to date are too far apart to allow a reliable comparison with k_1^*, which might be helpful for mechanistic purposes. Moreover, as mentioned above, the activation volumes for water exchange and complex formation at indium(III) have not yet been measured. However, it should be mentioned that Kowall et al[9] suggested $\Delta V^{\neq} = -5.2\,cm^3\,mol^{-1}$ for water exchange at In^{3+} based upon bond cleavage and bond formation considerations.

In conclusion, the data available at present do not clearly indicate which of the two mechanisms, I_d or I_a, is operative in the complex formation at In^{3+}, since the rate independence on the ligand nature contrasts with the negative value of the activation parameters. This apparent inconsistency can be overcome by advancing the hypothesis of a concerted mechanism in which the structure of the transition state is such that both the outgoing water and the incoming ligand are loosely bound. This hypothesis does not disagree with the value of $\Delta S^{\neq}$ for the In^{3+}–PVC$^-$ reaction[13], which is much closer to zero than the values found for systems with definite associative or dissociative modes of activation.

In the case of the $InOH^{2+}$ species, the kinetic results show that the hydrolysed species is more reactive than the hexaaquo ion, as already observed with tervalent metal ions (with the exception of lanthanides, V^{III} and Ti^{III}).[7] In order to assess the influence of the ligand basicity on the reactivity of $InOH^{2+}$, the values of k_2^* for HQSA$^-$ and for the less basic Ferron$^-$ should be compared. The difference in $\log k_2^*$ is 0.23, whereas that for pK_{A1} is 1.4. We conclude that the dependence of $\log k_2^*$ on the ligand basicity is too small to indicate an associative mode of activation for complex formation at the $InOH^{2+}$ species.

A discussion of the behaviour of the first four ligands in Table 3 should prove useful. Their values of k_1^* are much lower than those already discussed. Such a large difference can be rationalised if one accounts for the fact that the first three of these ligands, in aqueous solution, are distributed between two isomeric forms with different reactivity. 1-(2-Pyridylazo)-2-naphtol (PAN) is distributed between a nonreactive form, in which the reaction site becomes deactivated by the effect of internal hydrogen bonding, and a reactive form in which the hydrogen bridge is absent.[18] Similarly, HQSA is distributed between two isomers, the zwitterion and the neutral form, as shown in Equation (13):[14]

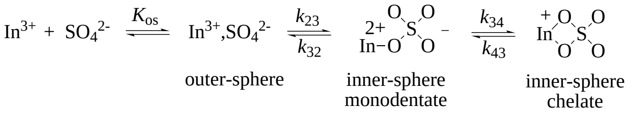


(13)

However, the reaction site in the zwitterion is blocked by a proton, therefore the reactive form should be the neutral one. Since the proton conceivably resides much longer on the nitrogen atom than on the sulfonate group, the zwitterion will be the prevalent form and the value of the equilibrium constant of reaction, K_Z, would be less than one. Under these circumstances, the value of k_1 and, as a consequence, that of k_1^* would be reduced by a factor equal to K_Z.[19] This hypothesis is supported by the value of k_1^* for the In^{3+}–Ferron^0 system, which is somewhat larger than that of the In^{3+}–HQSA^0 system. As the basicity of the nitrogen atom in Ferron is lower than that of the nitrogen atom in HQSA, the K_Z value and that of k_1^* is expected to be larger for the former ligand, as was experimentally observed.

The reactivity of the In^{III} sulfate system appears to be lower than originally expected. Our experiments yield a value of $k_1 = 5.1 \times 10^4\,M^{-1}\,s^{-1}$ for the binding of SO_4^{2-} to In^{3+}. By using a distance of closest approach of $5 \times 10^{-8}\,cm$ to calculate K_{os}, one obtains $k_1^* = 5.7 \times 10^2\,s^{-1}$. This value is somewhat higher than the value of $3 \times 10^2\,s^{-1}$ derived by Miceli and Stuher[20] from relaxation measurements performed at variable ionic strength, but is still two or three orders of magnitude below the values quoted in Table 3 for those ligands that behave normally. The low reactivity of SO_4^{2-} is particularly surprising if one takes into account that SO_4^{2-} is a relatively simple ion with no isomers, which, therefore, supposedly interacts rapidly with indium(III). Actually, we have performed, for comparison purposes, some temperature-jump measurements on the binding of the simple monodentate ligand SCN$^-$ to In^{3+} and found a value of $k_1^* > 10^6\,s^{-1}$. To explain the low substitution rate of SO_4^{2-} with respect to that of murexide[18c] ($k_1^* = 2 \times 10^4\,s^{-1}$), Miceli and Stuher[20] suggested that substitution at In^{3+} proceeds by an associative mechanism. Since the data now available do not reveal a definite dependence of the In^{3+} reactivity on the nucleophilic power of the ligand, we feel that other causes should be responsible for the behaviour of the $In^{3+}-SO_4^{2-}$ system.

It has been demonstrated that, whereas ClO_4^- can cross a liquid membrane only after the loss of its entire hydration shell,[21] SO_4^{2-} is able to cross the same membrane while bearing eight water molecules.[22] The hydration shell of the anion persists even in solid sulfates, such as $NiSO_4 \cdot 7\,H_2O$ for which the seventh water molecule is situated between three water molecules of the $Ni(H_2O)_6^{2+}$ group and one O atom of the SO_4^{2-} ion.[23] Hence, assuming that the metal and the ligand are both solvated in the outer-sphere complex, the distance between the charge centres should be of the order of $7.5- - 10 \times 10^{-8}$ cm (two hydration layers). This would cause k_1^* to increase by a factor of about three, which is insufficient to reach the value expected for ligands that behave normally ($10^4 - 10^5\ s^{-1}$). Therefore, other factors should be at work, such as the ability of the SO_4^{2-} ion to form chelates with suitable metal ions. Infrared spectra of the species $[Co(en)_2SO_4]$ provide evidence for coordination of two oxygen atoms from SO_4^{2-} to the cobalt centre.[24] The Goldsmith radius of Co^{2+} is 0.82 nm, which is almost the same as that of In^{3+} (0.81 nm). On the basis of this similarity, it seems conceivable that the final $InSO_4^+$ species could be a chelate. The sequence of steps of the complex formation process can thus be written as shown in Scheme 3; the water molecules involved in the process are not shown. Step 1 ⇌ 2 is fast (diffusion controlled). Steady – state application to the inner-sphere monodentate complex gives $k_1/K_{os} = k_{23}k_{34}/(k_{32} + k_{34})$. Step 2 ⇌ 3 corresponds to the penetration of the first oxygen into the metal coordination sphere; therefore, the value of k_{23} should be similar to that of k_1^* for "normal" ligands. The prevailing term in the denominator of this equation is k_{32}, since the oxygen atoms of SO_4^{2-} are weak donors and, under these circumstances, k_{32} is always larger than k_{34}.[25] As a consequence, step 3 ⇌ 4 becomes rate-determining and the ratio k_1/K_{OS}, instead of providing a value of k_{23} ($=k_1^*$), yields $k_{23}k_{34}/k_{32}$, in the limiting case. For the Ni^{II}-malonate[26] and Ni^{II}-tartrate[27] systems, where the closure of the six-membered ring is rate – determining, the k_1/K_{OS} values are five and ten times, respectively, lower than normal substitution at Ni^{II}. Since formation of a four-membered ring is less favoured than formation of a six-membered ring, the reduction of k_{34}, and by consequence of k_1/K_{os}, by more than a factor of ten appears to be reasonable.



1 2 3 4

Scheme 3. Kinetic pattern for the reaction of complex formation between indium(III) and sulfate ion.

Experimental Section

Chemicals: All chemicals were analytical grade. Twice distilled water was used to prepare the solutions and as a reaction medium as well. Indium perchlorate was prepared by dissolving a known amount of the pure metal in a known excess of perchloric acid. The indium(III) concentration was verified by titration with EDTA[28] and was found to coincide with that calculated from the weight of the dissolved metal. The ligand, 8-quinolinol-5-sulfonic acid (HQSA), was from Fluka (purity > 95 %). Stock solutions of HQSA were prepared weekly. Perchloric acid and sodium perchlorate were used to attain the desired medium acidity and ionic strength, respectively.

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 the standard KCl bridge was replaced by 3M NaCl in order to avoid precipitation of $KClO_4$. The electrode was calibrated against sodium perchlorate/perchloric acid solutions of known concentration and ionic strength to directly give $-\log[H^+]$. Absorption titrations were performed on a Perkin – Elmer Lambda 17 double-beam spectrophotometer, whereas fluorescence titrations were performed on a Jasco FP 770 spectrofluorimeter. Increasing amounts of indium perchlorate were added by microsyringe to a solution of the ligand already at steady temperature in the measuring cell. Temperature fluctuations were kept within ±0.1 °C throughout. The medium acidity and ionic strength were kept constant at the desired value during each titration. Data were evaluated by non-linear least-square procedures.

The kinetic behaviour of the indium(III) – HQSA system was monitored at 260 nm with the use of a stopped-flow apparatus that was constructed in our laboratory. A Hi-Tech SF-61 mixing unit was coupled to a spectrophotometric line through two optical guides. The ultraviolet radiation produced by a Hamamatsu L248102 "quiet" lamp was passed through a Bausch and 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 a quartz optical guide to the observation chamber and then, through a second optical guide, to the measuring photomultiplier, also a 1P28. The outputs of the two photomultipliers were balanced before each shot. The signal that revealed the course of the reaction was sent to a Tektronix TDS 210 oscilloscope equipped with a digital storage unit capable of memorizing 2500 data points at a maximum sampling rate of 60 MHz. Finally, the acquired signal was transferred to a personal computer via a GPIB interface and analysed by a non-linear least-square procedure.[29] The observed time constants used in this work were averaged over at least four repeated experiments, the maximum spread was within 10 %, and usually much less.

The rate measurements of the $In^{III}-SO_4$ system were performed on a Messanlagen temperature-jump instrument in which, to improve the signal-to-noise ratio, the detection system was replaced by a spectrophotometric device that makes use of lasers as light sources.[30] The indicator, Tropeoline 00, was used to monitor the course of the reaction[12] with a laser module that emits at 543 nm. The signals were collected and processed by the same devices and methods used in the stopped-flow experiments. Here too, the agreement among repeated runs was within 10 %.

Acknowledgement

This work has been supported by Ministero dell'Università per la Ricerca Scientifica e Tecnologica (MURST, Roma) within the program CO-FIN 2000.

---

[1] R. L Hayes, K. F. Hubner, *Metal Ions in Biological Systems*, *Vol. 16* (Ed.: H. Sigel), Marcel Dekker, New York, **1983**, pp. 279 – 315.
[2] H. Diebler, M. Eigen, *Z. Phys. Chem.* **1959**, *20*, 299 – 306.
[3] M. Eigen, K. Tamm, *Z. Elektrochem.* **1962**, *66*, 107 – 121.
[4] M. Eigen, *Pure Appl. Chem.* **1963**, *6*, 97 – 115.
[5] "Mechanisms of Inorganic Reactions": M. Eigen, R. G. Wilkins, *Adv. Chem. Ser.* **1963**, *49*, 55 – 67.
[6] C. F Baes, Jr., R. E. Mesmer, *The Hydrolysis of Cations*, Wiley, New York, **1976**.
[7] J. Burgess, *Metal Ions in Solution*, Horwood, Chichester, **1978**.
[8] G. E. Glass, W. B. Schwabacher, R. S. Tobias, *Inorg. Chem.* **1968**, *7*, 2471 – 2478.
[9] T. Kowall, P. Caravan, H. Bourgeois, L. Helm, F. P. Rotzinger, A. E. Merbach, *J. Am. Chem. Soc.* **1998**, *120*, 6569 – 6577.

[10] a) R. Corigli, F. Secco, M. Venturini, *Inorg. Chem.* **1979**, *18*, 3184–3187; b) R. Corigli, F. Secco, M. Venturini, *Inorg. Chem.* **1982**, *21*, 2992–2998.

[11] B. Perlmutter-Hayman, F. Secco, M. Venturini, *J. Chem. Soc. Dalton Trans.* **1982**, 1945–1948.

[12] G. G.Hammes in *Techniques of Chemistry*, *Vol. 16*, *Part 2* (Ed.: G. G. Hammes), Wiley-Interscience, New York, **1974**, pp. 174–185.

[13] A. Ricciu, F. Secco, M. Venturini, B. Garcia, J. L. Leal, *J. Phys. Chem. A* **2000**, *104*, 7036–7043.

[14] R. Nanasen, A. Ekman, *Acta Chem. Scand.* **1952**, *6*, 1384–1390.

[15] R. M. Fuoss, *J. Am. Chem. Soc.* **1958**, *80*, 5059–5061.

[16] a) Y. Kawai, T. Imamura, M. Fujimoto, *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3142–3145; b) Y. Ohtani, S. Yagihashi, M. Fujimoto, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1345–1346; c) G. Z. Geier, *Z. Elektrochem.* **1965**, *69*, 617–625.

[17] Y. Kawai, T. Takahashi, K. Hayashi, T. Imamura, H. Nakayama, M. Fujimoto, *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1417–1423.

[18] B. Perlmutter-Hayman, F. Secco, M. Venturini, *Inorg. Chem.* **1985**, *24*, 3828–3831.

[19] H. Diebler, F. Secco, M. Venturini, *J. Phys. Chem.* **1987**, *91*, 5106–5111.

[20] J. Miceli, J. Stuehr, *J. Am. Chem. Soc.* **1968**, *90*, 6967–6972.

[21] F. Malatesta, L. Carbonaro, N. Fanelli, S. Ferrini, A. Giacomelli, *J. Solution Chem.* **1999**, *28*, 593–619.

[22] F. Malatesta, R. Zamboni, *J. Solution Chem.* **1997**, *26*, 791–815.

[23] A. F. Wells, *Structural Inorganic Chemistry*, 5th ed., Clarendon, Oxford, **1984**.

[24] K. Nakamoto, *Infared Spectra of Inorganic and Coordination Compounds*, 2nd ed., Wiley-Interscience, New York, **1970**.

[25] D. W. Margerum, G. R. Caylay, D. C. Weatherburn, G. K. Pagenkopf, *ACS Monogr.* **1978**, *174*, 1–219.

[26] H. Hoffmann, *Ber. Bunsenges. Phys. Chem.* **1969**, *73*, 432–437.

[27] H. Hoffmann, U. Nickel, *Ber. Bunsenges. Phys. Chem.* **1968**, *72*, 1096–1101.

[28] K. I. Cheng, *Anal. Chem.* **1955**, *27*, 1582–1583.

[29] a) S. W. Provencher, *J. Chem. Phys.* **1976**, *64*, 2772–2777; b) S. W. Provencher, *Biophys. J.* **1976** *16*, 27–41.

[30] M. Citi, C. Festa, F. Secco, M. Venturini, *Instrum. Sci. Technol.* **1995**, *23*, 191–199.

[31] E. M. Eyring, J. D. Owen, *J. Phys. Chem.* **1970**, *74*, 1825–1828.

[32] E. Mentasti, C. Baiocchi, *J. Chem. Soc. Dalton Trans.* **1985**, 2615–2621.

Received: March 30, 2001 [F3164]