Mechanistic Information on Ligand-substitution Reactions of Gadolinium(III) in Aqueous Solution from High-pressure Stopped-flow Experiments

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Substitution reactions of arsenazo III [3,6-bis(*o*-arsonophenylazo)-4,5-dihydroxynaphthalene-2,7-disulfonic acid] complexes of Gd^{III} with the polyaminocarboxylates ethylenediaminetetraacetate and diethylenetriaminepentaacetate were studied as a function of ligand concentration, pH, temperature and pressure. Under all experimental conditions two consecutive reaction steps were observed, for which the observed first-order rate constants are independent of aminocarboxylate concentration and show significant acid catalysis. The observed kinetic behaviour and the activation parameters determined under limiting conditions, *i.e.* low and high $[H^+]$, can be accounted for in terms of dechelation of the arsenazo III ligand being the rate-determining step. The existence of 1:1 and 1:2 Gd^{III}:arsenazo III complexes is suggested to account for the fast and slow substitution reactions, respectively. The observed volumes of activation can mainly be ascribed to large solvational changes associated with the acid-catalysed dechelation process.

Complex-formation and aquation reactions of 3+ charged lanthanide (Ln^{3+}) metal ions have received considerable attention from various groups over the last few years.[1–10] The thermodynamics and kinetics of such reactions are of importance in the separation of lanthanides, and in their use as contrast-enhancing agents in magnetic resonance imaging and as radiopharmaceuticals. The substitution reactivity of lanthanide complexes varies strongly within the series and reaches a maximum between Sm^{3+} and Gd^{3+}.[11,12] This is believed to be related to a changeover in co-ordination number from nine for the earlier, lighter members to eight for the later, heavier members of the series in the case of water as solvent.[11,12] Water exchange on $[Ln(H_2O)_8]^{3+}$ takes place *via* an associative interchange (I_a) mechanism, that on $[Ln(H_2O)_9]^{3+}$ follows a dissociative interchange (I_d) mechanism.[11,12]

The application of high-pressure kinetic techniques has, in general, been particularly successful in the elucidation of solvent-exchange and ligand-substitution mechanisms.[13–15] This is also true in the case of water exchange on aquated Ln^{3+} and their complexes.[11,16] In the case of non-symmetrical ligand-substitution reactions, data on the volume of activation have in many cases been shown to parallel those for the corresponding solvent-exchange processes[13–15] and in some cases indirectly revealed mechanistic details on the mechanisms of the latter.[17,18]

In the present study we have applied a high-pressure stopped-flow technique to investigate ligand-substitution reactions of Gd^{III} in an effort to resolve the intimate details of the underlying mechanism. As mentioned above, Gd^{III} is unique in its substitution behaviour, and plays an important role in magnetic resonance imaging. No volumes of activation are presently available for any of its substitution reactions, which makes the present study the first effort to use such data to clarify the nature of the substitution mechanism.

Experimental

A stock solution was made by dissolving 4×10^{-4} mol $GdCl_3$ (Strem) and 1×10^{-3} mol arsenazo III [3,6-bis(*o*-arsonophenylazo)-4,5-dihydroxynaphthalene-2,7-disulfonic acid] (Aldrich) in acetate buffer solution (pH 4.8, 100 cm^3) over a period of 20 h at 50 °C. The concentration of the $GdCl_3$ solution was determined by complexometric titration using xylenol orange as indicator. Ethylenediaminetetraacetate (edta) and diethylenetriaminepentaacetate (dtpa) solutions were also prepared in acetate buffer. The pH adjustments were made with $HClO_4$ and NaOH. Substitution reactions of the Gd^{III}–arsenazo III complex with edta and dtpa were followed spectrophotometrically at $\lambda = 660$ nm, where such reactions exhibit characteristic spectral changes.[3,4]

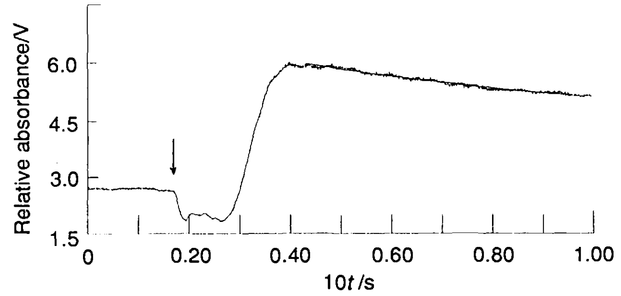
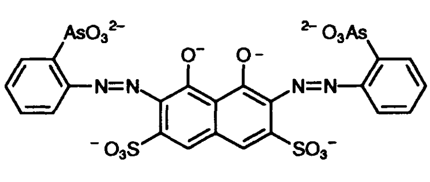
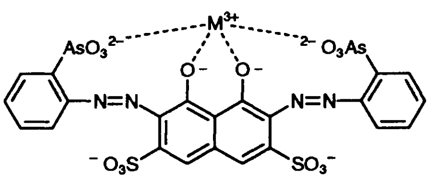


Fig. 1 Typical kinetic trace recorded for the reaction of the Gd^{III}–arsenazo III complex with dtpa to illustrate the dead-time of the stopped-flow instrument. For experimental conditions see Table 1; 10 V on absorbance scale = 1 absorbance unit

Kinetic measurements were made on a laboratory-made high-pressure stopped-flow system for pressures up to 100 MPa (*i.e.* 1 kbar). This instrument was constructed according to details given in the literature,[19] and was coupled to a light source, monochromator and photomultiplier tube detector. Intensity *vs.* time signals were recorded on a storage oscilloscope and transferred to a personal computer, on which the data were fitted with the OLIS KINFIT[20] set of programs. A number of test experiments were performed with this new instrument, in order to check its reproducibility and dead-time. Fig. 1 shows a typical trace recorded to determine the dead-time. The stepping-motor which activates the reactant syringes was



Arsenazo III



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activated at the point indicated by the arrow. The old solution in the optical light path is washed out and a new, fresh reaction mixture introduced. The overall procedure requires 23 ms, of which *ca.* 15 ms represents the time required by the stepping-motor to move the syringes. It follows that the instrument has a dead-time of *ca.* 10 ms. Similar results were obtained at pressures up to 100 MPa.

Results and Discussion

In general, the compound arsenazo III is used to stabilize solutions of lanthanide species in a pH range where spontaneous precipitation due to the formation of hydrolysis products will occur in the absence of this chelating agent. It can co-ordinate *via* four oxygen donor atoms to Ln^{3+}, such that 1 : 1 and 2 : 1 complexes can be formed.[4] Free arsenazo III absorbs only slightly at 660 nm, whereas the 1 : 1 and 1 : 2 Ln^{3+}–arsenazo III complexes have absorption coefficients of 35 000 and 50 000 $dm^3\ mol^{-1}\ cm^{-1}$, respectively, at this wavelength.[4] In earlier studies $[Ln^{3+}]$: [arsenazo III] ratios of 1 : 10 were used in substitution reactions with different polyazapolycarboxylates.[3,5] In the present study we used a $[Gd^{3+}]$: [arsenazo III] ratio of 1 : 2.5 in order to avoid an excess of arsenazo III and to have both 1 : 1 and 1 : 2 complex species in solution as shown in (1). The exact charge on these species is unknown, but in principle the ligand carries an 8− charge (L^{8-}), such that the 1 : 1 and 1 : 2 complexes are highly charged anionic species [equations (1) and (2)].

$$Gd^{3+} + L \rightleftharpoons [GdL] \qquad (1)$$

$$[GdL] + L \rightleftharpoons [GdL_2] \qquad (2)$$

Addition of an excess of a polyaminocarboxylate to [GdL] and $[GdL_2]$ results in the complete substitution of arsenazo III by the polyaminocarboxylate (L′) as indicated in equation (3).

$$[GdL] + L' \rightleftharpoons [GdL'] + L \qquad (3)$$

The rate of reaction (3) depends on the nature of L′ and can vary over several orders of magnitude.[3] In general, acyclic compounds L′ are significantly more reactive than cyclic ones.[3] In the present study edta and dtpa were used as L′, and the rate of reaction (3) is such that it can be followed conveniently on a spectrophotometer at ambient pressure and on a stopped-flow instrument at elevated pressure. Preliminary kinetic experiments indicated that very similar kinetic traces (and similar rate constants) were obtained with both edta and dtpa. This is rather surprising since in aqueous solution the stability constant of $[Gd(dtpa)]^{2-}$ is five orders of magnitude larger than that of $[Gd(edta)]^{-}$, which indicates that the basicity of L′ (expressed as the sum of the pK_a values)[4] plays a minor role in reaction (3). Furthermore, it also indicates that reaction (3) does not occur according to an associative process. Ligand structure, *viz.* acyclic *versus* cyclic, obviously plays a more important role.[3] In addition, the observed rate constants for reaction (3) in the presence of an excess of L′, are independent of the concentration of L′ in the range (1–10) × 10^{-3} mol dm^{-3} in both cases. It follows that the rate-determining step in reaction (3) does not involve the attack of L′ on the gadolinium(III) complex. All subsequent work was therefore performed for dtpa at a concentration of 0.010 mol dm^{-3}. Variation of the buffer concentration employed had no meaningful effect on the observed kinetic traces.

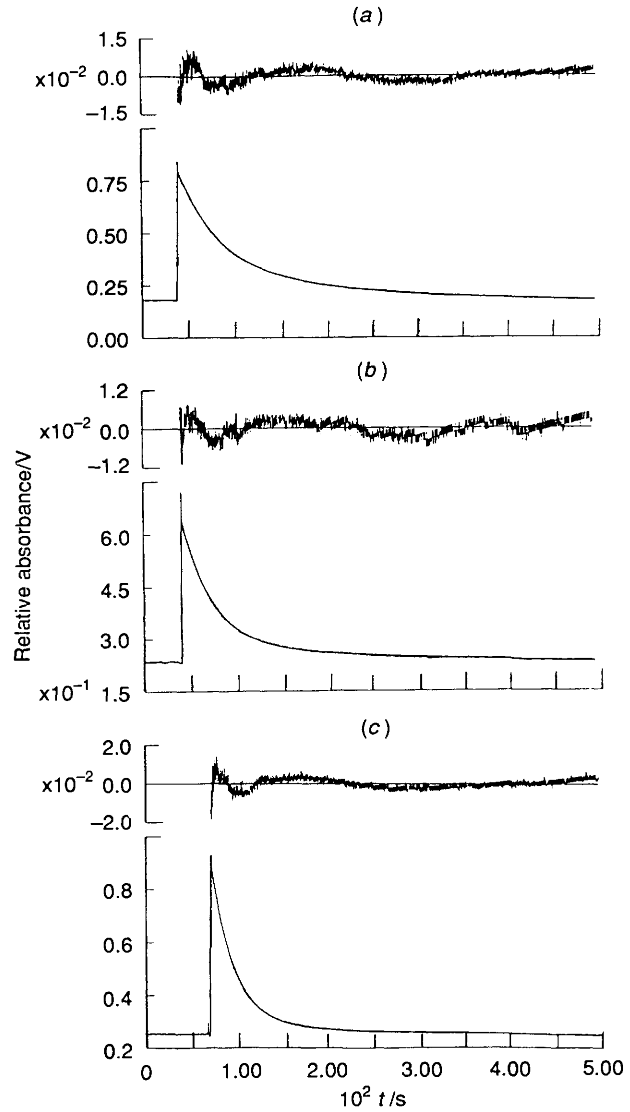


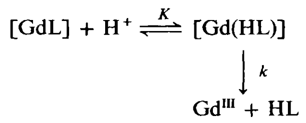
Fig. 2 Typical kinetic traces recorded for the reaction of the Gd^{III}–arsenazo III complex with dtpa as a function of pressure at 25 °C and pH 5.7. For experimental conditions see Table 1. Pressure = 5 (*a*), 50 (*b*) and 100 MPa (*c*). 10 V on absorbance scale = 1 absorbance unit

A detailed analysis of the kinetic traces using OLIS software indicated that all absorbance *vs.* time plots exhibit two exponential decays which could be analysed in terms of a fast (k_1) and a slow (k_2) reaction step. Some typical traces recorded under different experimental conditions are shown in Fig. 2. The residuals between the experimental and calculated traces are acceptable if the relative long reaction time is taken into consideration. In general the fit of the traces is good, and k_1 and k_2 can be resolved within 10–15% error limits. The pH dependence of k_1 and k_2 is summarized in Table 1, from which it follows that both reaction steps exhibit significant acid catalysis, and k_1 and k_2 reach limiting values at high $[H^+]$. In principle, the kinetic data can be fitted with a general scheme shown in Scheme 1, in which displacement of arsenazo III involves a protonation step. The rate equation (4) predicts a linear

$$k_{obs} = kK[H^+]/(1 + K[H^+]) \qquad (4)$$

dependence of k_{obs} on $[H^+]$ at low $[H^+]$, $k_{obs} = kK[H^+]$, and a limiting value at high $[H^+]$, $k_{obs} = k$. Furthermore, according to equation (4), plots of k_{obs}^{-1} *versus* $[H^+]^{-1}$ should be linear, which is indeed the case as shown in Fig. 3 for the data in Table 1. A non-linear least-squares fit (NESSIE[21]) of the data on the basis of equation (4) resulted in $k = 0.28 \pm 0.03$ and 0.041 ± 0.002 s^{-1} and $K = (3.2 \pm 0.8) \times 10^4$ and $(7.1 \pm 1.1) \times 10^4$ dm^3 mol^{-1} for the k_1 and k_2 data, respectively. These values of K correspond to pK_a values of 4.5 and 4.8 for the protonated [Gd(HL)] species, respectively. The very similar pH dependence of both reaction steps indicates that they must involve very similar protonation equilibria which probably facilitate the dissociation of arsenazo III before the binding of L′.

The temperature and pressure dependence of k_1 and k_2 were studied under limiting conditions, *i.e.* at low and high $[H^+]$, where rate equation (4) reduces to $k_{obs} = kK[H^+]$ and $k_{obs} = k$, respectively. The experimental data are reported in Table 2 and the corresponding activation parameters in Table 3. These parameters are composite quantities at low $[H^+]$ and tend to represent the values for k at high $[H^+]$. A detailed mechanistic discussion is required in order to interpret these in terms of the kinetic observations reported above.



$$[GdL] + H^+ \underset{}{\overset{K}{\rightleftharpoons}} [Gd(HL)] \xrightarrow{k} Gd^{III} + HL$$

Scheme 1

Table 1 Rate constants as a function of pH for the substitution of arsenazo III by dtpa on Gd^{III} [a]

pH	10^2k_1 [b]/s^{-1}	10^2k_2 [b]/s^{-1}
3.55	33.2 ± 4.9	4.3 ± 0.5
3.78	23.2 ± 1.1	4.0 ± 0.3
3.91	22.9 ± 2.6	3.8 ± 0.5
4.14	17.2 ± 2.3	2.9 ± 0.3
4.14	17.5 ± 2.3	3.0 ± 0.3
4.77	8.5 ± 0.5	2.4 ± 0.1
5.70	2.0 ± 0.1	0.50 ± 0.06

[a] Experimental conditions: $[Gd^{III}] = 5 \times 10^{-5}$, $[dtpa] = 1 \times 10^{-2}$, $[MeCO_2H, Na(O_2CMe)]_T = 0.1$ mol dm^{-3}, $I = 0.3$ mol dm^{-3}; 25.0 °C; λ = 660 nm. [b] Mean value of between eight and ten kinetic runs.

Table 2 Rate constants as a function of temperature and pressure for the substitution of arsenazo III by dtpa on Gd^{III} [a]

pH	T/°C	P/MPa	10^2k_1 [b]/s^{-1}	10^2k_2 [b]/s^{-1}
3.78	12.0	5	6.4 ± 0.8	1.3 ± 0.2
	20.0		15.1 ± 2.9	2.4 ± 0.3
	25.0		23.2 ± 1.1	4.0 ± 0.3
	32.0		36.0 ± 4.3	4.9 ± 0.6
	39.0		47.7 ± 6.2	6.7 ± 0.6
	25.0	5	22.5 ± 3.0	4.2 ± 0.4
		50	37.0 ± 3.5	4.5 ± 0.3
		100	56.6 ± 4.3	4.0 ± 0.4
5.70	12.0	5	1.44 ± 0.18	0.22 ± 0.05
	20.0		2.19 ± 0.26	0.39 ± 0.11
	25.0		2.61 ± 0.09	0.56 ± 0.05
	32.0		4.08 ± 0.44	0.99 ± 0.14
	39.0		5.99 ± 0.41	1.66 ± 0.25
	25.0	5	2.45 ± 0.18	0.52 ± 0.08
		50	3.07 ± 0.21	0.13 ± 0.01
		100	4.17 ± 0.28	0.036 ± 0.003

[a] For experimental conditions see Table 1. [b] Mean value of between eight and ten kinetic runs.

As mentioned in the introduction, Gd^{3+} is a borderline case which can either have a co-ordination number of eight or nine, which will result in associative or dissociative substitution reactions, respectively.[11,12] In the absence of a chelating agent, the aquated gadolinium(III) species is $[Gd(H_2O)_8]^{3+}$ and undergoes associative ligand substitution for which a $\Delta V^‡$ value close to −6 cm^3 mol^{-1} is expected.[11,16] Co-ordination of dtpa and 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetate (tadota) to aquated Gd^{III} results in the formation of nine-co-ordinated species, *viz.* $[Gd(dtpa)(H_2O)]^{2-}$ and $[Gd(tadota)(H_2O)]^-$, respectively. The latter species undergo solvent exchange at a rate that is two orders of magnitude slower than that for $[Gd(H_2O)_8]^{3+}$, which is accompanied by $\Delta V^‡$ values of +12.5 and +10.5 cm^3 mol^{-1}, respectively.[16] These $\Delta V^‡$ values clearly indicate that the nine-co-cordinate species are sterically hindered, cannot bind an additional solvent molecule to produce a ten-co-ordinate species, and must react in a dissociative way.[16]

The exact co-ordination modes of [GdL] and $[GdL_2]$ are presently unknown, but it is safe to assume that both species will include co-ordinated water molecules, *viz.* four or five for the 1:1 and at least one for the 1:2 complex. These solvent molecules will be extremely substitution labile and are expected to exchange with free solvent molecules at rates between 5×10^6 and 1×10^9 s^{-1}.[16] This is significantly faster than anything measured in the present study, from which we conclude that dtpa (and edta) could rapidly co-ordinate to [GdL] and $[GdL_2]$ within the mixing time of the stopped-flow

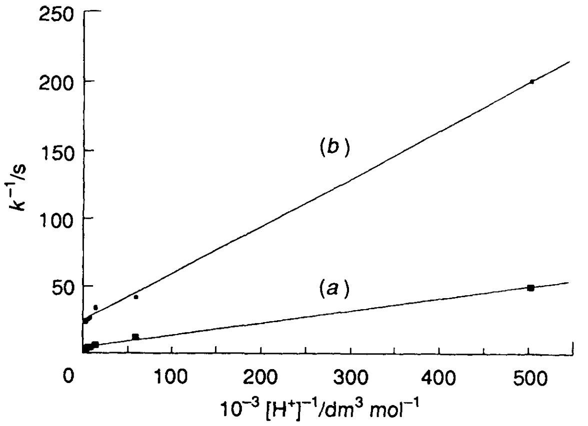


Fig. 3 Plots of k_1^{-1} (*a*) and k_2^{-1} (*b*) *versus* $[H^+]^{-1}$ for the data in Table 1

Table 3 Summary of rate and activation parameters for the substitution of arsenazo III by dtpa on Gd^{III} at 25 °C *

Parameter	pH 3.78	pH 5.70
10^2k_1/s^{-1}	23.2 ± 1.1	2.61 ± 0.09
$\Delta H_1^‡$/kJ mol^{-1}	53 ± 5	36 ± 2
$\Delta S_1^‡$/J K^{-1} mol^{-1}	−82 ± 18	−152 ± 7
$\Delta V_1^‡$/cm^3 mol^{-1}	−24.0 ± 1.8	−13.9 ± 0.8
10^2k_2/s^{-1}	4.0 ± 0.3	0.56 ± 0.05
$\Delta H_2^‡$/kJ mol^{-1}	42 ± 5	53 ± 2
$\Delta S_2^‡$/J K^{-1} mol^{-1}	−130 ± 17	−109 ± 5
$\Delta V_2^‡$/cm^3 mol^{-1}	+1.4 ± 2.8	+69.6 ± 3.7

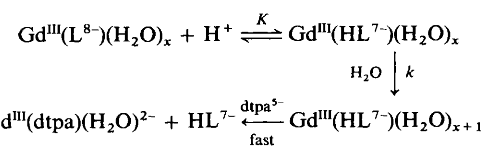
* For experimental conditions see Table 1.

instrument. This partial co-ordination of the entering polyaminocarboxylate will cause no meaningful absorbance change at 660 nm unless it involves dechelation of arsenazo III, which is accompanied by a strong decrease in absorbance. In this case the observed kinetic traces must be due to the dechelation of arsenazo III which will be accompanied by chelation of the partially co-ordinated dtpa. On the basis of this idea it is understandable that the observed kinetic traces do not exhibit a dependence on the concentration of dtpa (or edta) since the rate-determining step is an intramolecular process which is most probably controlled by the dechelation of arsenazo III. The latter follows from the acid dependence of the observed rate constants which is consistent with an acid-catalysed dechelation process. The pK_a values of between 4.5 and 4.8 are very realistic for the protonation of co-ordinated arsenazo III which facilitates the dechelation process.

There are a number of arguments against the rapid pre-co-ordination of dtpa (and edta). The formation of a ternary complex with dtpa^{5-} and edta^{4-} is not favoured by the high negative charge on the $\mathrm{Gd^{III}(L^{8-})(H_2O)_x}$ and $\mathrm{Gd^{III}(L^{8-})_2(H_2O)}$ species. Furthermore, steric and electronic hindrance on especially $\mathrm{Gd^{III}(L^{8-})_2(H_2O)}$ is expected further to prevent the formation of the ternary complex. Recent studies[22] have shown that in the $\mathrm{Gd^{III}(dtpa^{5-})}$ system relatively weak ternary complexes are formed with small anions, but not with larger ones such as citrate. In a related study of the terbium(III) system it was concluded that the acid-catalysed ligand-exchange reaction proceeds *via* a dissociative mechanism, involving rate-determining dissociation of the ligand, followed by rapid co-ordination of the entering group.[23]

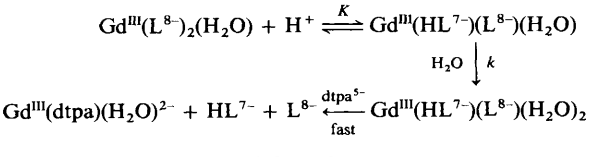
On the basis of these arguments it is probably more appropriate to suggest that dechelation of the arsenazo III is the rate-determining step and occurs without the assistance of dtpa (or edta). This means that the entering nucleophile is only necessary to shift the overall equilibrium in Scheme 1 to the right. Such a mechanism is consistent with the observation that the rate is independent of the concentration of dtpa, and accounts for the similarity between the reactions with dtpa and edta.

It is also possible to account for the two exponential decays observed. We have good reasons to believe that the fast reaction corresponds to dechelation of the 1 : 1 complex and the slow reaction to that of the 1 : 2 complex. This is based on the difference in the pK_a values observed for both reaction steps and the significantly different $\Delta V^\ddagger$ values (see further discussion). Both reaction steps will involve protonation of the arsenazo III chelate, followed by rate-determining dechelation and rapid chelation by dtpa (or edta). The suggested mechanism for the fast (k_1) and slow (k_2) steps can be summarized as shown in Schemes 2 and 3, respectively. In both mechanisms the exact co-ordination geometry of the protonated and ring-opened complexes is unknown. The slow reaction must involve rate-determining ring opening to produce a reactive species which can chelate rapidly with dtpa.



$$\begin{array}{rcl} & & \mathrm{Gd^{III}(L^{8-})(H_2O)_x + H^+ \overset{K}{\rightleftharpoons} Gd^{III}(HL^{7-})(H_2O)_x} \\ & & \qquad\qquad\qquad\qquad {}^{\mathrm{H_2O}}\big\downarrow{}^{k} \\ & & \mathrm{Gd^{III}(dtpa)(H_2O)^{2-} + HL^{7-} \xleftarrow[\text{fast}]{\mathrm{dtpa^{5-}}} Gd^{III}(HL^{7-})(H_2O)_{x+1}} \end{array}$$

Scheme 2



$$\begin{array}{c} \mathrm{Gd^{III}(L^{8-})_2(H_2O) + H^+ \overset{K}{\rightleftharpoons} Gd^{III}(HL^{7-})(L^{8-})(H_2O)} \\ \qquad\qquad\qquad\qquad {}^{\mathrm{H_2O}}\big\downarrow{}^{k} \\ \mathrm{Gd^{III}(dtpa)(H_2O)^{2-} + HL^{7-} + L^{8-} \xleftarrow[\text{fast}]{\mathrm{dtpa^{5-}}} Gd^{III}(HL^{7-})(L^{8-})(H_2O)_2} \end{array}$$

Scheme 3

The activation parameters in Table 3 indicate that both reaction steps are characterized by significantly negative $\Delta S^\ddagger$ values, indicating a highly structured transition state for the rate-determining steps. In contrast, the reported $\Delta V^\ddagger$ values differ significantly for the k_1 and k_2 data, which could assist a further clarification of the ligand-exchange process. At high $[\mathrm{H^+}]$, *i.e.* low pH, $\Delta V^\ddagger$ mainly represents $\Delta V^\ddagger(k)$. The very negative value of $\Delta V^\ddagger$ found for k_1 under these conditions can be assigned to a volume collapse associated with dechelation of the arsenazo III ligand, which will be accompanied by significant charge creation. The slow (k_2) reaction exhibits almost no pressure dependence under these conditions, which means that the volume changes associated with dechelation and charge creation must cancel each other. It is obvious that charge creation accompanied by an increase in electrostriction around the ring-opened moiety of the arsenazo III chelate will be less significant for the highly charged 1 : 2 than for the 1 : 1 complex.

The $\Delta V^\ddagger$ values for k_1 and k_2 at low $[\mathrm{H^+}]$, *i.e.* at high pH, are a composite quantity, *viz.* $\Delta V^\ddagger = \Delta\bar{V}(K) + \Delta V^\ddagger(k)$ where $\bar{V}$ = partial molar volume. The difference between $\Delta V^\ddagger$ at low and high pH therefore represents the value of $\Delta\bar{V}(K)$, which is *ca.* 10 cm^3 mol^{-1} for k_1 and *ca.* 70 cm^3 mol^{-1} for k_2. Both protonation equilibria involve charge neutralization which will be accompanied by a decrease in electrostriction and an overall increase in volume. The difference of *ca.* 60 cm^3 mol^{-1} in $\Delta\bar{V}$ for the protonation step in Schemes 2 and 3 can easily be accounted for in terms of the net change in charge on the complexes. According to an earlier reported correlation between $\Delta\bar{V}$ and ΔZ^2 [$= Z^2$(product) $- Z^2$(reactant)],[24] an increase in Z by -8 for the co-ordination of the second arsenazo III molecule in the 1 : 2 complex can cause an increase in $\Delta\bar{V}$ of 40 cm^3 mol^{-1}. It therefore is reasonable to conclude that the values of $\Delta\bar{V}(K)$ are controlled by large changes in electrostriction.

Conclusion

The results of this investigation have shown that ligand-substitution reactions of gadolinium(III) complexes can be studied in quite some detail by using spectrophotometric techniques to monitor the process. Such studies will be restricted to systems which exhibit characteristic spectral changes in the UV/VIS range. Since almost no detailed kinetic data have been published before, the concentration, pH, temperature and pressure effects studied in this investigation have revealed new mechanistic information on the behaviour of such chelated gadolinium(III) species which could help to provide a better understanding of the behaviour of gadolinium(III) complexes in the applications referred to in the Introduction. Future work in our laboratories will focus on a systematic elucidation of the substitution behaviour of gadolinium(III) and closely related lanthanide(III) species in systems for which structural information has recently become available and are therefore better defined than is the present one.

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