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An LC method for measuring complex formation equilibria by competitive chelation

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Abstract: A method, entailing the use of a competitor ligand, is described for measuring complex formation constants by HPLC. The log of the formation constant of Gd(III) 2,6-bis(aminomethyl)pyridinetetraacetate was determined to be 18.6, a previously unreported value.

Keywords: *HPLC; MRI contrast agent; formation constant; gadolinium.*

Introduction

Paramagnetic complexes represent a new class of contrast agents for magnetic resonance imaging (MRI) [1–4]. The toxicity of paramagnetic gadolinium chelates has been shown to correlate with their metal complex formation constants [3]. Knowledge of these constants is therefore important for the evaluation of new MRI agents and for their formulation.

Potentiometric (pH) titration is commonly used to determine metal complex formation constants [5]. The titration measures the competition between hydrogen ion and metal ion for the chelate. The titration method is simple experimentally and widely applicable. Recently, computer programs have become available, which greatly simplify the calculation of formation constants from titration curves [6]. However, the potentiometric titration method requires that significant dissociation of the complex, with concomitant consumption of protons, occurs within the pH range of the titration. For the best, most tightly bound complexes, including many gadolinium chelates, this requirement cannot be met. In favourable cases, the potentiometric method can be extended by introducing a competitive gauge ligand. In order to be potentiometrically detectable, the transfer of metal between the ligand of interest and the gauge ligand must produce a net change in the free hydrogen ion concentration, either by replacing weak acidic groups with stronger, or the reverse. This approach has been used recently for measuring the binding constant of gadolinium diethylenetriaminepentaacetic acid bismethamide [3]. Other competitive methods used for strong complexes involve spectrophotometric assays [6]. Competitive chelation has long been used in the quantitative analysis of metals [7].

The method for evaluating tight binding described here uses a gauge ligand, but, like the spectrophotometric methods, entails no restrictions on its acidity. The calculations are simplified because they can be divided into two independent steps; the determination of the pK_a values, and the calculation of the complex formation constant. The latter does not require a curve fitting procedure. In order to demonstrate the method, the complex formation constant, previously unreported, of gadolinium with 2,6-bis(aminomethyl)pyridinetetraacetate (PBMNTA) (Fig. 1) was determined. Ethylenediaminetetraacetic acid (EDTA) was allowed to compete for gadolinium ions with 2,6-bis(aminomethyl)pyridinetetraacetic acid (PBMNTA) [8, 9] in a buffer of fixed hydrogen ion concentration. An HPLC method, previously described [10], was used to quantify GdPBMNTA and PBMNTA. The method was confirmed by measuring the complex formation of gadolinium with diethylenetriaminepentaacetic acid (GdDTPA), which has been previously reported [3].

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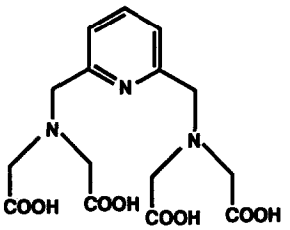

Figure 1
The chemical structure of PBMNTA.

Materials and Methods

Reagents

2,6-Bis(aminomethyl)pyridinetetraacetic acid disodium salt (PBMNTA) and gadolinium(III) lysine salt of 2,6-bis(aminomethyl)-pyridinetetraacetic acid (GdPBMNTA) were provided by the Medicinal Chemistry Department, Sterling Winthrop Pharmaceuticals Research Division, Rensselaer, New York. Ethylenediaminetetraacetic acid disodiuim salt, volumetric standard (49.9 mM); ethylenediaminetetraacetic acid tetrasodium salt dihydrate; gadolinium atomic absorption standard solution (1005 $\mu g\ ml^{-1}$); diethylenetriaminepentaacetic acid (98%); tris(hydroxymethyl)aminomethane (TRIS), ACS reagent grade; potassium hydrogen phthalate, A.C.S. primary standard; and potassium chloride were obtained from Aldrich (Milwaukee, WI). Potassium hydroxide, Dilut-It analytical concentrate (0.1 N), and hydrogen chloride, Dilut-It analytical concentrate (0.1 N), were obtained from J.T. Baker (Phillipsburg, NJ). Hydrochloric acid 1.0 N was obtained from Anachemia (Rouses Point, NY).

Preparation of competition solutions

Stock solutions of TRIS HCl (0.111 M), prepared with HCl and TRIS (0.111 M), containing 0.111 M KCl, were prepared in purified water. From these solutions, buffer solutions of TRIS were prepared at pHs of 6.4, 7.4, 8.4, 9.4 and 10.4. A GdPBMNTA stock solution (16.08 mM) and PBMNTA stock solution (16.10 mM) were prepared in purified water. An EDTA stock solution (3.234 mM) was prepared from a 16.20 ml aliquot of EDTA disodium salt (49.9 mM) solution diluted to 250 ml with 0.1 M KCl. A GdEDTA stock solution (3.227 mM) was prepared from a 12.96 ml aliquot of EDTA disodium salt solution (49.9 mM), 100 ml of gadolinium standard solution (1005 $\mu g\ ml^{-1}$), and 15.5 ml of 1.0 N NaOH, diluted to 200 ml with 0.1 M KCl.

Competition solutions containing GdPBMNTA (0.804 mM) and EDTA (1.617 mM) were prepared from a 0.3 ml aliquot of GdPBMNTA (16.08 mM), 2.7 ml of buffer solution and 3.0 ml of EDTA stock (3.234 mM). A second set of competition solutions containing GdPBMNTA (0.804 mM) and EDTA (0.808 mM) were prepared from a 0.3 ml aliquot of GdPBMNTA (16.08 mM), 2.7 ml of buffer stock, 1.5 ml of EDTA stock (3.234 mM), and 1.5 ml of 0.1 M KCl. Equilibrations were carried out in polypropylene containers to avoid possible contamination from ions leached from glass.

Competition solutions containing PBMNTA (0.805 mM) and GdEDTA (1.614 mM) were prepared from a 0.3 ml aliquot of PBMNTA stock solution (16.10 mM), 2.7 ml of buffer solution, and 3.0 ml of GdEDTA stock solution (3.227 mM). A second set of competition solutions containing PBMNTA (0.805 mM) and GdEDTA (0.807 mM) were prepared from a 0.3 ml aliquot of PBMNTA stock solution (16.10 mM), 2.7 ml of buffer solution, 1.5 ml of GdEDTA stock solution (3.227 mM), and 1.5 ml of 0.1 M KCl. The competition solutions were adjusted so that the concentration of TRIS was 50 mM with a total ionic strength of 0.1, adjusted with KCl or HCl. Competition solutions were prepared in triplicate and equilibrated for at lest 5 days at 25°C.

To determine the GdDTPA complex formation constant, a GdPBMNTA primary stock solution was prepared (14.78 mM) in purified water. From this, a 7.39 mM secondary stock solution was prepared from a 25 ml aliquot added to 25 ml of 0.5 M HCl and 0.934 g of KCl. A DTPA primary stock solution (6.30 mM) was prepared in 0.1 M KOH. Competition solutions were prepared as follows. From GdPBMNTA stock (7.39 mM), a 0.8 ml aliquot was added to 1.0 ml of DTPA stock (6.30 mM). To this were added 0.4 ml of 0.5 M TRIS, 1.8 ml of purified water, and 4.0 ml of 0.1 M KCl. The measured pH was 7.9. The pH was reduced by the addition of 1.0 N HCl (0.1–0.075 ml). Samples were prepared in triplicate at a pH of 2.7 and singularly at pHs of 4.0, 4.35 and 5.0. Samples were assayed after 6 or 7 days to ensure that equilibrium had been achieved. The time course of the approach to equilibrium was not

determined; equilibrium may have actually been achieved in a shorter period of time, although the result with pH 7.9 samples suggests that the time period was not unreasonably generous. The samples at pH 7.9 had not reached equilibrium after 7 days, and the formation constant was not calculated.

Following Martell and Motekaitis [6], acidities were represented by p[H], the negative logarithm of the hydrogen ion concentration, rather than by the measure of activity, pH. Buffers of known activity were used to calibrate the pH meter, which was subsequently used to measure a series of solutions of known hydrogen ion concentration, generated by titration HCl with KOH, in the presence of KCl, at experimental concentrations. The KOH solution was standardized against potassium hydrogen phthalate, and the acid was standardized against the base. The pH reading of the meter was corrected to p[H] by adding the difference between the concentration calculated from the volumes of the titrants added and the pH reading. The correction term was −0.073 (p[H] − pH) in the low pH range and −0.064 in the high pH range. Although pH values were used in the preparation of solutions, the p[H] values listed in the Tables were used for all calculations of the formation constants. This procedure was also followed in the determination of the pK_a values of PBMNTA (see below).

Chromatographic conditions

Samples were assayed by LC without dilution. The HPLC system consisted of a Waters 510 solvent delivery system (Waters, Milford, MA), a Waters 486 Tunable Absorbance Detector, a Waters Maxima 820 data module, and a Waters 700 Satellite WISP. Samples were separated on a PRP-X100 stainless steel column (Hamilton, Reno, NV), 150 × 4.1 mm. The mobile phase consisted of 0.1 M TRIS, 0.025 M KCl, and 1 mM EDTA tetrasodium salt adjusted to pH 8.0 with concentrated hydrochloric acid. The injection volume was 15 μl. Detection was at 272 nm. The flow rate was variable, increasing linearly from 1 to 4.0 ml min^{-1} at 7.0 min. Under these conditions, the retention times of GdPBMNTA and PBMNTA were 2.7 and 8.0 min, respectively. Linear calibration plots were prepared from peak responses of at least four standards each of GdPBMNTA and PBMNTA. Standards were prepared in 0.05 M TRIS.

Determination of the pK_a values for PBMNTA

A solution, 0.1 N KOH, was prepared from distilled water, which had been boiled for 30 min to remove carbon dioxide and allowed to cool protected by a soda lime trap. J.T. Baker Dilut-It concentrate was the source of KOH. A Gran regression established that the solution contained a negligible concentration of carbonate [6]. The solution was standardized against potassium hydrogen phthalate. The end point was established by means of the appropriate Gran regression (weak acid, strong base) [11]. The average of three replicate titrations was 0.1004 N with a RSD of 0.4%. The base titrant was protected with a continuous blanket of argon (Union Carbide Corp., Linde prepurified grade). Dilut-It 0.1 N HCl was standardized with the base, and was found to be 0.1006 N.

All titrations were carried out by means of a Radiometer ABU93 automatic burette controlled by a Radiometer VIT90 titrator (Radiometer Analytical Instruments; Copenhagen, Denmark). The titration vessel was thermostated at 25 ± 0.2°C, and was continuously purged with argon. The titration data were transferred to a PC computer for processing. All titrations were carried out in triplicate; agreement between the replicates was excellent and the average values were used. A Radiometer pH electrode and a single junction silver–silver chloride reference electrode (Fisher Scientific, Pittsburgh, PA) were used. The pH electrode was calibrated with buffers at pH 4 and 10 for the endpoint determinations. The response was 99.0% of the theoretical. To calibrate the electrode for the pK_a determinations, a range of hydrogen ion concentrations was generated by adding 2 ml of the HCl titrant to 20 ml of 0.1 M KCl and titrating with the KOH solution. This procedure gave a concentration calibration, expressed as p[H] [6], and a value for the dissociation of water, pK_w, of 13.86 under the experimental conditions.

A sample of PBMNTA disodium salt was dried over calcium sulphate in an Abderhalden apparatus at 4 mbar over boiling methanol for 3 h. Moisture content was determined by thermogravimetric analysis, using a Perkin–Elmer, TGA 7 Thermogravimetric Analyzer (Perkin–Elmer, Norwalk, CT), which gave a

value of 2.4% residual water content. A solution of PBMNTA disodium salt (3.45 M) was prepared in 0.1 M KCl. To 20 ml of this solution, which contained 0.0691 mM of PBMNTA disodium salt (nominally 0.138 meq of acid), was added 2 ml (0.201 meq) of the HCl titrant, and the resulting solution titrated with the KOH titrant. The end point was located by a Gran regression; it occurred at 0.345 meq, indicating that the PBMNTA disodium salt sample contained 0.345 − 0.201 − 0.138 = 0.006 meq excess acid. This brought the total excess acid in the system to 0.069 meq (0.201 meq acid added originally; less the base associated with the PBMNTA disodium salt, 0.138 meq; plus the excess acid associated with the PBMNTA disodium salt, 0.006 meq). The titration data were analysed with the computer programme, PKAS [6]. The experimental and the calculated titration curves were superposable; the pK_a values are listed in Table 1.

Table 1
Protonation constants (pK_a) used in calculation (25°C, μ = 0.10 M)

Equilibrium	EDTA*	PBMNTA†	DTPA‡
$[HL]/[L][H]$	10.17	8.68	10.49
$[H_2L]/[HL][H]$	6.11	8.15	8.60
$[H_3L]/[H_2L][H]$	2.68	2.62	4.28
$[H_4L]/[H_3L][H]$	1.95	2.10	2.64
$[H_5L]/[H_4L][H]$	1.56		2.0
$[H_6L]/[H_5L][H]$			1.6

*Reference 12.
†This work.
‡Reference 13.

Results and Discussion

The complex formation constant of GdPBMNTA was determined by competition using EDTA as a gauge ligand. The calculations are described below. The equilibrium expression for the binding of GdPBMNTA is equation (1), and for the binding of GdEDTA, equation (2). The equilibrium exchange of Gd(III) from GdPBMNTA to EDTA is represented by equation (3) with the corresponding equilibrium expression, equation (4).

$$K_1 = \frac{[\text{GdPBMNTA}]}{[\text{PBMNTA}]\,[\text{Gd}]}, \quad (1)$$

$$K_2 = \frac{[\text{GdEDTA}]}{[\text{EDTA}]\,[\text{Gd}]}, \quad (2)$$

$$\text{GdPBMNTA} + \text{EDTA} \rightleftharpoons \text{GdEDTA} + \text{PBMNTA}, \quad (3)$$

$$K_3 = \frac{[\text{GdEDTA}]\,[\text{PBMNTA}]}{[\text{GdPBMNTA}]\,[\text{EDTA}]}. \quad (4)$$

If K_3 can be determined experimentally, the constant for GdPBMNTA can be calculated from equation (5), using the literature value for GdEDTA (log K of 17.35 [12])

$$K_1 = \frac{K_2}{K_3}. \quad (5)$$

The LC method measures the concentration of the GdPBMNTA complex and the *total* concentration of uncomplexed ligand, which includes all of its protonated forms. The concentration of GdEDTA and the total concentration of uncomplexed EDTA, which includes all of its protonated forms, can be calculated by difference, if it is assumed that the concentration of free Gd(III) is negligible, since the initial concentrations of GdPBMNTA and EDTA are known. If the acidity constants are known, [PBMNTA] and [EDTA] can be calculated from the total concentrations, $[\text{PBMNTA}]_T$ and $[\text{EDTA}]_T$, and the p[H]. This calculation is illustrated in general for a ligand, L; it follows the development of Rocklage [3]. Let the acidity constants be defined as; $K_{H1} = [HL]/[H][L]$, $K_{H2} = [H_2L]/[H][HL] = [H_2L]/K_{H1}[H]^2[L]$, etc. The ligand concentration determined from LC, L_T, is then given by equation (6) and the concentration of the deprotonated ligand by equation (7), [H] being fixed by the buffer

$$L_T = [L] + [HL] + [H_2L] + \ldots \quad (6)$$

$$L_T = [L](1 + K_{H1}[H] + K_{H1}K_{H2}[H]^2 + \ldots)$$

$$[L] = L_T/(1 + K_{H1}[H] + K_{H1}K_{H2}[H]^2 + \ldots). \quad (7)$$

The acidity constants used in the calculations are listed in Table 1, and the equilibrium complex formation constants in Table 2. To show that the complex formation constants of Table 2 result from a true equilibrium, the experiment was repeated starting with GdEDTA instead of GdPBMNTA; the data are presented in Table 3. Figure 2 shows the time-course of the transmetalation of PBMNTA to GdPBMNTA when equimolar

Table 2
Determination of the complex formation constant of GdPBMNTA beginning with GdPBMNTA

Initial [GdPBMNTA] (mM l^{-1})	Initial [EDTA] (mM l^{-1})	Exper. [GdPBMNTA] (mM l^{-1})	Exper. $[PBMNTA]_T$ (mM l^{-1})	p[H]	Calc. [PBMNTA] (mM l^{-1})	Calc. [EDTA] (mM l^{-1})	Log K_3	Log K_1	Log K_{1cond}
0.804	0.808	0.717	0.077	9.62	6.842E − 02	1.575E − 01	−1.280	18.63	18.58
0.804	1.617	0.687	0.103	9.48	8.854E − 02	2.522E − 01	−1.223	18.57	18.51
0.804	0.808	0.746	0.058	9.17	4.303E − 02	6.757E − 02	−1.303	18.65	18.52
0.804	1.617	0.715	0.083	9.09	5.753E − 02	1.162E − 01	−1.213	18.56	18.41
0.804	0.808	0.759	0.044	8.30	8.447E − 03	1.001E − 02	−1.303	18.65	17.94
0.804	1.617	0.738	0.065	8.30	1.259E − 02	2.032E − 02	−1.258	18.61	17.90
0.804	0.808	0.727	0.079	7.31	4.157E − 04	9.398E − 04	−1.332	18.68	16.40
0.804	1.617	0.675	0.124	7.19	3.877E − 04	1.423E − 03	−1.285	18.64	16.13
0.804	0.808	0.614	0.190	6.07	3.791E − 06	2.318E − 05	−1.296	18.65	13.95
0.804	1.617	0.521	0.283	5.84	1.969E − 06	2.153E − 05	−1.303	18.65	13.49

Table 3
Determination of the complex formation constant of GdPBMNTA beginning with PBMNTA

Initial [GdEDTA] (mM l^{-1})	Initial [PBMNTA] (mM l^{-1})	Exper. [GdPBMNTA] (mM l^{-1})	Exper. $[PBMNTA]_T$ (mM l^{-1})	p[H]	Calc. [PBMNTA] (mM l^{-1})	Calc. [EDTA] (mM l^{-1})	Log K_3	Log K_1	Log K_{1cond}
0.807	0.805	0.742	0.066	9.30	5.229E − 02	8.741E − 02	−1.28	18.63	18.53
0.807	0.805	0.745	0.050	9.04	3.344E − 02	5.095E − 02	−1.27	18.62	18.45
0.807	0.805	0.753	0.047	8.83	2.516E − 02	3.255E − 02	−1.26	18.61	18.34
0.807	0.805	0.759	0.045	8.14	5.522E − 03	6.891E − 03	−1.30	18.65	17.74
0.807	0.805	0.641	0.171	6.28	8.942E − 06	4.876E − 05	−1.32	18.67	14.40
1.614	0.805	0.710	0.101	2.43	3.243E − 14	7.667E − 13	−1.27	18.62	6.13
0.807	0.805	0.557	0.248	2.35	4.602E − 14	3.471E − 13	−1.23	18.58	5.85
1.614	0.805	0.682	0.110	2.00	1.519E − 15	3.003E − 14	−1.16	18.51	4.66

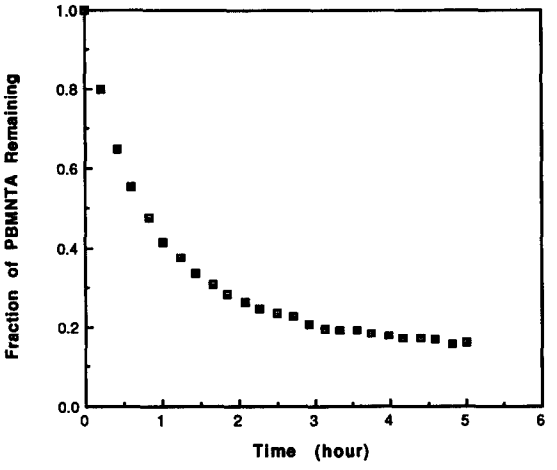

Figure 2
Transmetallation of PBMNTA to GdPBMNTA in the presence of GdEDTA at equimolar concentrations in pH 8.8 TRIS buffer.

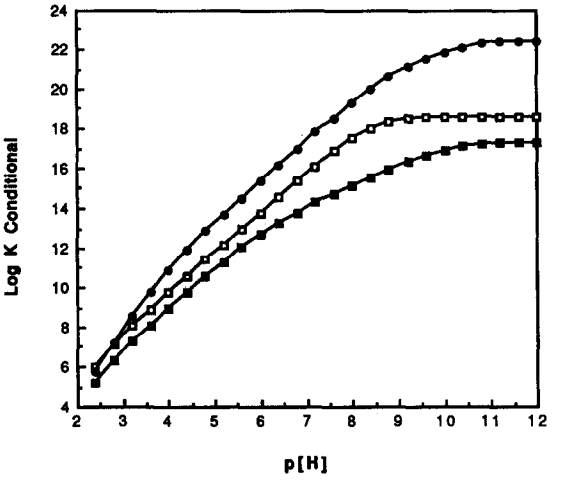

Figure 3
p[H] dependence of conditional stability constant calculated for GdDTPA (●), GdPBMNTA (□) and EDTA (■).

amounts of GdEDTA and PBMNTA were used. Equilibrium was reached relatively slowly. The complex formation constants listed in Table 3 agree well with those of Table 2, however. Also listed in Tables 2 and 3 are conditional complex formation constants, K_{1cond}. K_{1cond} differs from the thermodynamic equilibrium constant in that the total concentration of the ligand, including all of its protonated forms appears in the denominator rather than the concentration of the deprotonated ligand. This ratio, defined in equation (8),

$$K_{1cond} = \frac{[GdPBMNTA]}{[PBMNTA]_T\,[Gd]}, \qquad (8)$$

measures the affinity of the ligand for the metal at a particular p[H], and is important for predicting the metal toxicity of an MRI agent [3]. The dependence of K_{cond} on p[H] is shown in Fig. 3.

The possibility of equilibria involving the protonated species, Gd*H*PBMNTA and Gd*H*EDTA must also be considered. Rocklage has collected the acidity constants for GdHEDTA and GdHDTPA [3]. The log *K*s were 1.53 and 2.39, respectively. If it can be assumed that the corresponding acidity of GdHPBMNTA falls into that range, the protonated species would appear in significant concentrations only at experimental buffer p[H]s near 2. The fact that the log K_1 values reported at low p[H] values (Table 3) agreed with those determined at higher p[H]s indicates, but does not prove, that the protonated forms were not significant.

The experimental error in the complex formation constants of Tables 2 and 3 was estimated to be less than 0.1 log units. This was based on an estimate of the error in the pK_a values and on the replication variability of the HPLC determinations, 1%. The complex formation constants determined at the highest p[H]s are the most reliable, since they do not depend heavily on the pK_a values used and since they are undoubtedly not affected by protonated metal complex. Higher p[H] measurements are limited by the solubility of the metal hydroxide and by the stability of the ligand. No precipitation of hydroxide or decomposition of the ligand was detected in these experiments. The best value for the log of the complex formation constant of GdPBMNTA was 18.6.

In order to generalize and confirm the method, the complex formation constant for GdDTPA was redetermined, using PBMNTA as the gauge ligand. Acidity constants for GdDTPA were taken from the literature [13]. The equilibrium was approached from one direction by reacting GdPBMNTA with DTPA. The results are given in Table 4. The log complex formation constant found ranged from 22.7 to 23.0. These values agree well with the literature values of 22.5 [13] and 23.0 [14]. PBMNTA is an attractive gauge ligand because

Table 4
Determination of the complex formation constant of DTPA

Initial [GdPBMNTA] (mM l^{-1})	Initial [DTPA] (mM l^{-1})	Exper. [GdPBMNTA] (mM l^{-1})	Exper. $[PBMNTA]_T$ (mM l^{-1})	p[H]	Calc. [DTPA] (mM l^{-1})	Calc. [PBMNTA] (mM l^{-1})	Log K_3	Log K_1	Log K_{1cond}
0.732	0.780	0.083	0.702	4.91	5.612E − 11	8.272E − 08	−4.059	22.7	13.2
0.732	0.780	0.095	0.690	4.28	2.041E − 12	4.411E − 09	−4.163	22.8	11.8
0.732	0.780	0.112	0.675	3.89	2.136E − 13	6.972E − 10	−4.257	22.9	10.9
0.730	0.775	0.297	0.480	2.61	4.126E − 17	6.869E − 13	−4.386	23.0	6.9

it can be detected in the HPLC assay at 272 nm. EDTA and DTPA do not have an absorbance in this region of the spectrum.

Conclusions

The method described here for determining complex formation constants appears particularly well-suited for tightly bound metal complexes. It is experimentally rugged. The computations are straightforward. Few restrictions are placed on the gauge ligand. In many cases involving formulation and toxicity assessment, the conditional complex formation constant at physiological p[H] may be all that is required, making acidity constant measurements unnecessary. However, constancy of the thermodynamic, as opposed to the conditional, complex formation constant over a range of p[H] values serves to substantiate both.

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