Acid-catalysed dissociation of the copper(II) and lead(II) complexes of macrocyclic diazapolyoxa-N,N'-diacetic acids

John L. Laing,[a] **Richard W. Taylor**[a] **and C. Allen Chang**[b]

[a] *Department of Chemistry, University of Oklahoma, Norman, Oklahoma 73019, USA*
[b] *Institute of Biological Science and Technology, National Chiao Tung University, Hsinchu, Taiwan 30039, Republic of China*

The dissociation rate constants of the complexes of Cu^{2+} and Pb^{2+} with 1,4,10,13-tetraoxa-7,16-diazacyclo-octadecane-N,N'-diacetic acid (H_2L^2) and the copper(II) complex of 1,4,10-trioxa-7,13-diazacyclopentadecane-N,N'-diacetic acid (H_2L^1) have been determined at 25.0 °C in aqueous media ($I = 0.20$ mol dm^{-3}, LiClO$_4$). In the presence of an excess of strong acid, 1.3–100 mmol dm^{-3} HClO$_4$, the dissociation reactions follow the rate law $-d[ML]_T/dt = (k_d + K_{MHL}k_{H1}[H^+] + K_{MHL}k_{H2}[H^+]^2)/(1 + K_{ML}[H^+])[ML]_T$ where $[ML]_T = [ML] + [MHL]$, k_{H1} and k_{H2} are the respective rate constants for the specified reactions and MHL is the protonated metal–ligand complex. The values of k_{Hi} ($i = 1$ or 2) decrease according to the sequence $[PbL^2] \gg [CuL^2] > [CuL^1]$. The formation rate constants for M^{2+} reacting with $(HL^2)^-$ and H_2L^2 are $(2.3–4.2) \times 10^8$ and $(2.2–17) \times 10^2$ dm^3 mol^{-1}, respectively. The relatively low values for the diprotonated species are attributed to an unfavourable equilibrium concentration of the reactive species $^-O_2CCH_2N(CH_2CH_2OCH_2CH_2OCH_2CH_2)_2N^+HCH_2CO_2H$. The dissociation of $[PbL^2]$, but neither of the copper complexes, is subject to general acid catalysis (HA = MeCO$_2$H and ClCH$_2$CO$_2$H). The exchange reaction of $[PbL^2]$ with Cu^{2+} in buffered (MeCO$_2$H–MeCO$_2^-$) mildly acidic media shows a first-order dependence on $[H^+]$, $[MeCO_2H]$ and $[Cu^{2+}]$.

In recent years many studies have been reported on the complexation equilibria and kinetics of monocyclic polyethers, crown ethers, and macrobicyclic polyethers (cryptands).[1] There has been increasing interest in crown ethers with pendant groups.[2] These compounds represent a class of structure intermediate between the mono- and bi-cyclic donor atom lattices of crowns and cryptands. While some complexation-formation constants have been reported for pendant crowns only a few kinetic studies have been done.[3–6] The compounds H_2L^1 and H_2L^2 are two examples of pendant-arm crown ethers which are also related to some extent to acyclic aminocarboxylates such as ethylene dioxydiethylenedinitrilotetraacetic acid (H_4egta) and ethylenediiminodiacetic acid (H_2edda).

The addition of the carboxymethyl pendant arms results in an increase of $10^4–10^8$ in the stability constants of metal complexes relative to the unsubstituted diaza crown ether.[7–9] These pendant crown compounds are of particular interest due to their complexation selectivity with regard to lanthanide ions.[7,8] The first kinetic study of this type of compound involved the dissociation kinetics of several lanthanide complexes of H_2L^1 and H_2L^2.[4] In that study Cu^{2+} was used as a scavenger ion to drive the dissociation reaction to completion because the copper(II) complexes are the most stable for both macrocycles.[8] Lead(II) also forms very stable complexes with both and may also serve as a scavenger ion in kinetic studies. This paper reports the results of kinetic studies of the dissociation of complexes of Cu^{2+} and Pb^{2+} of H_2L^2 in strongly acidic media (HClO$_4$) and in the presence of weak acids (MeCO$_2$H, ClCH$_2$CO$_2$H) and for the exchange reaction of $[PbL^2]$ with Cu^{2+}. For comparison, the dissociation of $[CuL^1]$ in an excess of strong acid is also reported.

Experimental

Materials

The ligands were synthesized and purified according to the reported methods.[2e,7,8] Aqueous solutions of the macrocycles were prepared by weight and standardized by spectrophotometric titration with standard lead or copper perchlorate solutions.[10] Standard solutions of Pb^{2+} and Cu^{2+} were prepared

H_2L^1 n = 1
H_2L^2 n = 2
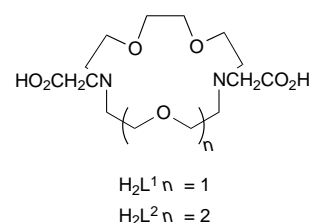
from the reagent-grade nitrates and standardized by compleximetric titrations with ethylenedinitrilotetraacetic acid (H_4edta).[11] Aqueous LiClO$_4$ solutions were prepared by mixing diluted concentrated HClO$_4$ with dried reagent-grade Li$_2$CO$_3$ (Aldrich). The metal–ligand complexes were prepared by mixing either an equivalent amount or a slight excess (5–10%) of the macrocycle with the metal-ion solution and adjusting the pH to 6.0–6.5 with either HClO$_4$ or NEt$_4$OH. Stock solutions of HClO$_4$ were standardized with NaOH (Baker) using phenolphthalein indicator, MeCO$_2$H and ClCH$_2$CO$_2$H by potentiometric titration with NaOH. Acid solutions for kinetic runs were prepared by dilution of the appropriate stock acid solution and addition of sufficient LiClO$_4$ to adjust the ionic strength to 0.2 mol dm^{-3}. All solutions were prepared using doubly distilled water.

Spectral and kinetic measurements

Spectra of the macrocycles and their metal-ion complexes were recorded with a Cary 118 or Hitachi 100-80 double-beam spectrophotometer equipped with a thermostatted cell holder. The reactions were initiated by mixing equal volumes of solutions of the metal-ion complex with the appropriate scavenger. The reaction rates were measured using a Durrum-Dionex D-130 stopped-flow spectrophotometer interfaced to either a Cromemco Z-2D microcomputer or an OLIS data-acquisition system. Reactions were monitored by recording absorbance changes at 270–272 (CuL) and 245 nm (PbL). The temperature of the observation cell was maintained at 25.0 ± 0.1 °C. All reactions were first order and the observed rate constants, k_{obs}, were obtained using standard least-squares procedures to fit the data by expression (1) where A_t, A_0 and A_∞ are the instantaneous,

Table 1 Protonation constants and stability constants of the complexes of Pb^{2+} and Cu^{2+} with H_2L^1 and H_2L^2 [a]

	H_2L^2 [b]	H_2L^1 [c]
log K_{H1}	8.45 (9.09)[d]	9.02 (8.90)[e]
log K_{H2}	7.80 (8.17)[d]	8.79 (8.58)[e]
log K_{H3}	2.40 (2.25)[d]	2.95 (3.23)[e]
log K_{CuL}	14.99 (15.89, 2.56)[d,f]	16.02
log K_{PbL}	13.55 (14.97, 1.83)[d,f]	12.91

[a] $K_{Hi} = [H_iL]/[H^+][H_{i-1}L]$, $K_{ML} = [ML]/[M][L]$; $I = 0.1$ mol dm^{-3}, 25.0 ± 0.1 °C. [b] Ref. 7. [c] Ref. 8. [d] Refs. 9 and 12. [e] Ref. 13. [f] Second value listed is for the equilibrium CuL + H$^+$ $\rightleftharpoons$ CuHL$^+$.

Table 2 Observed rate constants for the dissociation of copper and lead complexes in HClO$_4$ at 25.0 °C[a]

$10^2[H^+]/$ mol dm^{-3}	k_{obs}/s^{-1} [PbL^2][b]	[CuL^2][c]	$10^2[H^+]/$ mol dm^{-3}	$10^2 k_{obs}/s^{-1}$ [CuL^1][d]
0.133	3.14 ± 0.02	—	1.05	0.52 ± 0.02
0.268	8.68 ± 0.08	0.222 ± 0.001	2.48	1.21 ± 0.03
0.518	23.0 ± 0.4	0.256 ± 0.002	3.50	1.68 ± 0.04
0.760	37.4 ± 0.2	—	4.79	2.39 ± 0.07
1.02	56.7 ± 1.0	0.312 ± 0.001	7.02	3.38 ± 0.03
1.26	75.8 ± 1.4	—	9.75	5.01 ± 0.05
1.52	92.6 ± 1.9	0.358 ± 0.003	12.6	6.22 ± 0.08
2.02	137 ± 6	0.408 ± 0.001	15.2	7.68 ± 0.02
2.52	—	0.452 ± 0.002	17.5	8.76 ± 0.06
4.02	—	0.584 ± 0.003	20.0	—
5.03	—	0.658 ± 0.006		
7.53	—	0.872 ± 0.005		
10.04	—	1.077 ± 0.004		

[a] $I = 0.2$ mol dm^{-3} (LiClO$_4$–HClO$_4$); k_{obs} values are the average of three to six replicates. Uncertainty expressed as one standard deviation of the mean. [b] $[Pb^{2+}] = 4.28 \times 10^{-5}$, $[H_2L^2] = 4.51 \times 10^{-5}$ mol dm^{-3}. [c] $[Cu^{2+}] = 4.09 \times 10^{-5}$, $[H_2L^2] = 4.54 \times 10^{-5}$ mol dm^{-3}. [d] $[Cu^{2+}] = [H_2L^2] = 5.0 \times 10^{-5}$ mol dm^{-3}.

$$A_t = A_\infty + (A_0 - A_\infty)\exp(-k_{obs}t) \quad (1)$$

initial and final absorbance values, respectively. Each value of k_{obs} reported represents the average from four to six replicate runs.

Results and Discussion

Dissociation kinetics in strong acid

The two macrocycles form very stable complexes with Cu^{2+} and Pb^{2+} ions.[7-9] Calculations using the values of the protonation constants and stability constants listed in Table 1 indicate that ≥99% of either metal ion exists in the complexed form at pH ≥ 6.0 under the conditions employed in this study. The minimum concentrations of strong acid (HClO$_4$) required to induce ≥95% dissociation of [CuL^1], [CuL^2] and [PbL^2] are 0.0036, 0.0021 and 0.009 mol dm^{-3}, respectively. Therefore, H$^+$ can act as a scavenger ion in the overall dissociation reaction (2) of a metal–ligand complex, ML.

$$ML + nH^+ \xrightarrow{k_{obs}} M^{2+} + H_nL^{(n-2)+} \quad (2)$$
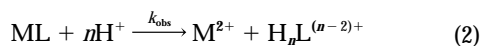
As found with a number of other metal-ion complexes of acyclic and macrocyclic polyamine ligands, the observed rate constants, k_{obs}, display a dependence on [H$^+$].[14-19] The values of k_{obs} for the [CuL^1] system have a first-order [H$^+$] dependence in the concentration range studied as shown in Fig. 1 and Table 2. The behaviour of [CuL^2] is more complicated. For [H$^+$] < 10 mmol dm^{-3} the values of k_{obs} fall below the extrapolated line as shown in Fig. 1. The plot of k_{obs} vs. [H$^+$] for [PbL^2] shown in Fig. 2 indicates that the [H$^+$] dependence is greater than first order. The data for these systems are listed in Table 2. In all
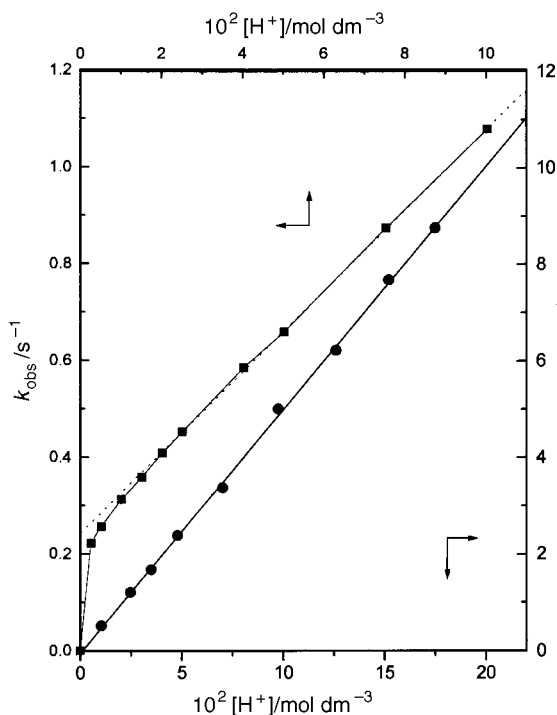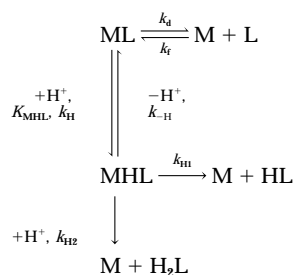
Fig. 1 Plots of k_{obs} vs. [H$^+$] for the dissociation of [CuL^2] (■) and [CuL^1] (●) in acidic media, $I = 0.2$ mol dm^{-3} (LiClO$_4$–HClO$_4$) at 25.0 °C. Concentrations given in Table 2

Scheme 1

cases only a single reaction was observed and no appreciable initial absorbance jumps were noted. Scheme 1 is consistent with the observed behaviour for the three complexes (charges omitted), where $K_{MHL} = [M(HL)]/[ML][H^+]$.

The protonated metal–ligand complex, MHL, is assumed to be in rapid equilibrium with ML. The rate law based on Scheme 1 is given by equation (3) where $[ML]_T = [ML] + [MHL]$ and

$$-d[ML]_T/dt = (k_d + K_{MHL}k_{H1}[H^+] + K_{MHL}k_{H2}[H^+]^2)/$$
$$(1 + K_{ML}[H^+])[ML]_T \quad (3)$$

k_{H1} and k_{H2} are the respective rate constants for the specified reactions. Under the conditions employed in this study, k_d may be neglected since its maximum value should be 10^{-4}–10^{-5} s^{-1} [$k_d = k_f/K_{ML}$; $k_f < 10^7$–10^8 dm^3 mol^{-1} s^{-1} (ref. 19)]. Therefore, the hydrogen-ion concentration dependence of k_{obs} is given by equation (4). For the case where $K_{MHL}[H^+] \gg 1$, this expression

$$k_{obs} = (K_{MHL}k_{H1}[H^+] + K_{MHL}k_{H2}[H^+]^2)/(1 + K_{MHL}[H^+]) \quad (4)$$

reduces to $k_{obs} = k_{H1} + k_{H2}[H^+]$. Based on the minimum [H$^+$] values employed (see Table 2) this condition is satisfied by log K_{MHL} values of 3.0 and 3.6 for [CuL^1] and [CuL^2], respectively. A value of log $K_{MHL} = 2.56$ has been determined for [CuL^2].[9] Since the points for [H$^+$] < 1.0 mmol dm^{-3} fall below the values expected from a simple linear relationship, the data for [CuL^1] were fitted by equation (4) and a value of log $K_{MHL} = 3.2 \pm 0.1$ was obtained by non-linear least-squares analysis. The data for

Table 3
Dissociation rate constants for complexes of H_2L^2 in the presence of acetic and chloroacetic acids at 25.0 °C*

10^2[HA]/mol dm^{-3} (HA = MeCO$_2$H)	10^2[H$^+$]/ mol dm^{-3}	k_{obs}/s^{-1} [CuL^2]	k_{obs}/s^{-1} [PbL^2]
0.0	7.5	0.902 ± 0.007	—
2.5	7.5	0.929 ± 0.008	—
5.0	7.5	0.911 ± 0.004	—
7.5	7.5	0.916 ± 0.008	—
15.0	7.5	0.914 ± 0.006	—
4.88	0.126	0.228 ± 0.003	4.06 ± 0.08
7.36	0.155	0.224 ± 0.001	5.16 ± 0.07
9.83	0.180	0.226 ± 0.001	6.22 ± 0.02
12.3	0.203	0.226 ± 0.001	7.10 ± 0.02
(HA = ClCH$_2$CO$_2$H)			
2.23	0.288	0.234 ± 0.001	12.06 ± 0.08
3.46	0.300	0.237 ± 0.002	13.79 ± 0.11
4.70	0.306	0.236 ± 0.002	15.24 ± 0.15
5.94	0.309	0.231 ± 0.002	16.69 ± 0.19

* I = 0.2 mol dm^{-3} (LiClO$_4$), [H$_2$L^2] = 4.51 × 10^{-5}, [Pb^{2+}] = 4.30 × 10^{-5}, [Cu^{2+}] = 4.28 × 10^{-5} mol dm^{-3}. Uncertainty expressed as one standard deviation of the mean.

Table 4
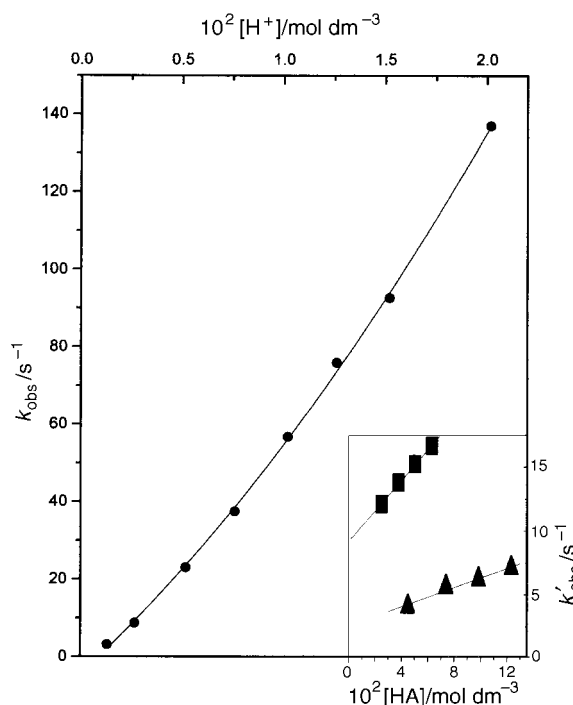Observed rate constants for the [PbL^2]–Cu^{2+} exchange reaction at 25.0 °C^a

10^5[H$^+$]/ mol dm^{-3}	10^3[Cu^{2+}]/ mol dm^{-3}	10^3[HA]^b/ mol dm^{-3}	$10^2 k_{obs}$/ s^{-1}	k_{calc}^c/ s^{-1}
1.22	1.0	5.0	2.56 ± 0.05	2.43
1.93	1.0	5.0	3.00 ± 0.06	2.97
3.06	1.0	5.0	3.92 ± 0.08	3.82
4.84	1.0	5.0	5.18 ± 0.06	5.16
7.68	1.0	5.0	7.57 ± 0.16	7.30
2.98	0.50	5.0	2.82 ± 0.06	3.18
2.98	1.0	5.0	3.86 ± 0.10	3.76
2.98	2.0	5.0	4.64 ± 0.20	4.93
2.98	3.0	5.0	5.99 ± 0.22	6.10
2.98	4.0	5.0	7.26 ± 0.16	7.27
2.98	5.0	5.0	8.62 ± 0.13	8.44
2.98	1.0	1.0	3.28 ± 0.09	3.48
2.98	1.0	2.5	3.44 ± 0.08	3.59
2.98	1.0	2.5	3.38 ± 0.07	3.59
2.98	1.0	5.0	3.91 ± 0.06	3.76

^{a} I = 0.20 mol dm^{-3} (LiClO$_4$). The k_{obs} values are the average of six to eight replicates. Uncertainty expressed as one standard deviation of the mean. ^{b} [HA] = [MeCO$_2$H]. ^{c} Values obtained using equation (10) and parameters listed in Table 5; i.e. k_{calc} = 750[H$^+$] + 11.7[Cu^{2+}] + 0.69[HA].

$$ML + HA \xrightarrow{k_{HA}} M + H_nL + A \qquad (5)$$
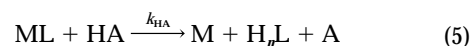
This gives expression (6) for k_{obs}. The contribution from the

$$k_{obs} = (k_{H1}K_{MHL}[H^+] + k_{H2}K_{MHL}[H^+]^2 + k_{HA}[HA])/ $$
$$(1 + k_{MHL}[H^+]) \quad (6)$$

hydrogen-ion-assisted dissociation pathways is given by the first two terms and equation (6) may be rearranged to give (7) where

$$k'_{obs} = (k_{obs} - k'_H)(1 + K_{MHL}[H^+]) = k_{HA}[HA] \qquad (7)$$

$k'_H = k_{obs}$ calculated using equation (4). The [H$^+$] values were calculated from the measured pH of the solution using the relationship [H$^+$] = 10^{-pH}/f_H, where the activity coefficient, f_H, was calculated using the Davies equation.[20] The values of [HA] were calculated using literature values for pK_a(HA) along with the pH and mass-balance conditions.[21a] Plots of k'_{obs} vs. [HA] are shown in the inset of Fig. 2.

[PbL^2]–Cu^{2+} Exchange reaction

Examination of the K_{ML} values in Table 1 suggest that Cu^{2+} should be an effective scavenger for the dissociation of [PbL^2] in mildly acidic media (pH 4–6), as illustrated in equations (8) and (9) where the primed quantities, k'_d, k'_f and k$'_s$, represent

$$[PbL^2] \underset{k'_f}{\overset{k'_d}{\rightleftharpoons}} Pb^{2+} + (L^2)^{2-} \qquad (8)$$

$$Cu^{2+} + (L^2)^{2-} \xrightarrow{k'_s} [CuL^2] \qquad (9)$$

the conditional rate constants which take into account the effects of H$^+$ and HA (acetic acid). The kinetics of the [PbL^2]–Cu^{2+} exchange reaction was studied as a function of [H$^+$], [HA] and [Cu^{2+}]. All reactions were pseudo-first order and the values of k_{obs} obtained are listed in Table 4. The observed rate constants displayed a first-order dependence on [H$^+$], [HA] and [Cu^{2+}] (Fig. 3). Assuming that H$_2$L^2 is subject to steady-state conditions in equations (8) and (9) and, because of the first-order dependence on [Cu^{2+}], a pathway involving direct attack of [PbL^2] by Cu^{2+} is possible. Including this pathway in the rate law, and considering the fact that at pH > 4, $k_{H1} \gg k_{H2}$[H$^+$] and $1 \gg K_{PbHL}$[H$^+$], equation (6) is modified to give (10).

Fig. 2 Plot of k_{obs} vs. [H$^+$] for the dissociation of [PbL^2] in strongly acidic media (LiClO$_4$–HClO$_4$). Inset: dissociation in mixtures of HClO$_4$ and weak acids, HA; acetic acid (▲), monochloroacetic acid (■); I = 0.2 mol dm^{-3} (LiClO$_4$), T = 25.0 °C. Concentrations in Tables 2 and 3

[PbL^2] are also fitted by this model; however, in this case protonation of the complex is less complete, varying from 10 to 65% of [PbL^2].

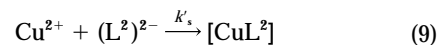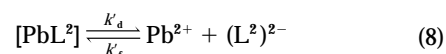### Effects of weak acids

The dissociation kinetics of Cu^{2+}– and Pb^{2+}–H$_2$L^2 complexes were also studied in mixtures of HClO$_4$–HA, where HA was acetic acid or chloroacetic acid. With [CuL^2] neither weak acid has any effect on the observed rate constants, as shown in Table 3. On the other hand, both weak acids increase the rate of dissociation of [PbL^2]. Although it is possible for HA to react with either ML or MHL, the data are best fit by a model in which HA reacts only with the unprotonated form of the complex, ML. Thus, Scheme 1 is modified by inclusion of expression (5) to account for the reaction of the complex with weak acids.

Table 5 Dissociation rate constants for complexes of Pb^{2+} and Cu^{2+} with H$_2$L^1 and H$_2$L^2 at 25.0 °C^a

	[CuL^1]	[CuL^2]	[PbL^2]
log K_{MHL}^{b}/ dm^3 mol^{-1}	—	3.18 ± 0.06	2.00 ± 0.18
		2.56^c	1.83^c
k_{H1}/s^{-1}	<10^{-4}	(2.5 ± 0.5) × 10^{-1}	(1.8 ± 1.1) × 10^1
			7.5 ± 0.4^d
k_{H2}/dm^3 mol^{-1} s^{-1}	(5.11 ± 0.05) × 10^{-1}	8.3 ± 1.8	(9 ± 4) × 10^3
k_{HA}/dm^3 mol^{-1} s^{-1} (MeCO$_2$H)	—	—	3.5 ± 0.7
			0.7 ± 0.3
(ClCH$_2$CO$_2$H)	—	—	128 ± 2
k_{Cu}/dm^3 mol^{-1} s^{-1}	—	—	11.7 ± 0.4^d

^{a} $I = 0.2$ mol dm^{-3} (LiClO$_4$–HClO$_4$). Uncertainty expressed as one standard deviation of the fitted parameter. ^{b} For the reaction, ML + H$^+$ $\rightleftharpoons$ MHL; L = L^2. ^{c} Ref. 9. ^{d} Obtained from the exchange reaction with Cu^{2+} [equation (10)].
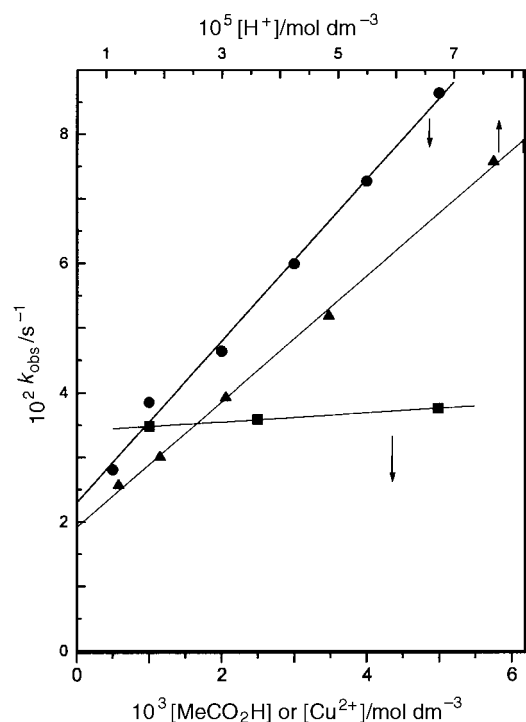
Fig. 3 Plots of k_{obs} for the exchange reaction of [PbL^2] with Cu^{2+} as a function of [H$^+$] (▲), [HA] (acetic acid) (■) and [Cu^{2+}] (●) at $I = 0.2$ mol dm^{-3} (LiClO$_4$), $T = 25.0$ °C. Concentrations in Table 4

$$k_{obs} = k_{H1}K_{MHL}[\text{H}^+] + k_{HA}[\text{HA}] + k_{Cu}[\text{Cu}^{2+}] \qquad (10)$$

Estimates of the parameters were calculated by least-squares analysis of all the data and the values obtained are listed in Table 5. The values of k_{H1} and k_{HA} are in reasonable agreement with the corresponding values obtained from experiments at high [H$^+$] without Cu^{2+} as a scavenger, where competition from other pathways is considerable.

At pH < 4 the Pb^{2+}– and Cu^{2+}–H$_2$L^2 complexes form stable monoprotonated adducts. The initial proton attack may occur either at a carboxylate oxygen atom or at a bridgehead nitrogen atom. The former process requires dissociation of the co-ordinated carboxylate group while the latter involves metal–nitrogen bond cleavage followed by nitrogen inversion to place the lone pair in an *exo* conformation.[14] For the dissociation reactions in strong acid it seems likely that the initial proton attack occurs at a dissociated carboxylate oxygen since the values of K_{MHL} obtained from the kinetic studies are similar to those obtained by potentiometric titration. Furthermore, there is no evidence for stable protonated complexes of the analogous macrobicyclic diamines where only a tertiary nitrogen is available. The protonated intermediate then undergoes rate-determining dissociation either directly or *via* a pathway involving attack by a second proton. In mildly acidic media, *i.e.* pH > log K_{MHL}, a pathway involving initial proton attack at the bridgehead nitrogen may become competitive with protonation of the dissociated carboxylate group. A similar process has been postulated to explain the acid-assisted dissociation of bicyclic diaza polyether cryptates.[14,22,23] The general acid catalysis of the dissociation of [PbL^2] is consistent with a mechanism involving a proton-transfer reaction at the tertiary nitrogen atom. It seems unlikely that proton transfer to the less basic carboxylate group would be rate limiting, and similar general acid-catalysed dissociation has been reported for several cryptate systems.[24,25]

Formation reactions

In order to gain further insight into the reaction mechanism it is useful to consider the complex formation reactions of HL$^-$ and H$_2$L as defined by equations (11) and (12) where L = L^2. These

$$\text{M}^{2+} + \text{HL}^- \underset{k^{ML}_{H}}{\overset{k^{HL}_{M}}{\rightleftharpoons}} \text{ML} + \text{H}^+ \qquad K^{ML}_{HL} \qquad (11)$$

$$\text{M}^{2+} + \text{H}_2\text{L} \underset{k^{ML}_{2H}}{\overset{k^{H_2L}_{M}}{\rightleftharpoons}} \text{ML} + 2\text{H}^+ \qquad K^{ML}_{H_2L} \qquad (12)$$
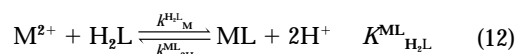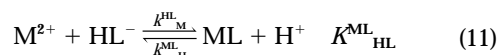
reactions are the reverse of the overall acid-induced reactions shown in Scheme 1. Combining values obtained from the rate and equilibrium constants k^{ML}_{H} and $k_{H1}K_{MHL}$ and $k^{ML}_{2H} = k_{H2}K_{MHL}$ with the appropriate value of $K^{ML}_{H_2L}$ or $K^{H_2L}_{HL}$ yields estimates of k^{HL}_{M} and $k^{H_2L}_{M}$ for Pb^{2+} reacting with H$_2$L^2. For the purpose of comparison, one may also calculate values of k^{HL}_{M} and $k^{H_2L}_{M}$ as predicted by a dissociative model based on stepwise solvent replacement with first bond formation as the rate-determined step, equation (13), where K_{os} and k^{M-H_2O}

$$k^{H_2L}_{M} = K_{os}\,k^{M-H_2O} \qquad (13)$$

are the outer-sphere association constant and water-exchange rate constant, respectively.[26] The values obtained are listed in Table 6.

For reactions involving HL$^-$, the experimental values are ≈6–20 times lower than those predicted by equation (13). The dissociable proton of HL$^-$ resides on one of the tertiary nitrogen atoms and the initial co-ordination of the metal ion is most likely to be a carboxylate oxygen atom. Similar behaviour has been reported for a number of aminocarboxylate ligands.[27a] The values of k^L_{M} reported for simple amino acids are in the range (1.6–4.0) × 10^9 dm^3 mol^{-1} s^{-1} where ring closure and steric effects were judged to be negligible.[29a] In the case of H$_2$L^2, formation of the five-membered chelate ring involving the tertiary nitrogen may become the rate-determining step. This could account for the lower predicted values of k^{HL}_{M}.

The experimental rate constants for the reaction of the diprotonated form H$_2$L^2 are considerably different from those pre-

Table 6 Formation rate constants (dm^3 mol^{-1} s^{-1}) for the reaction of Cu^{2+} and Pb^{2+} with mono- and di-protonated L^2
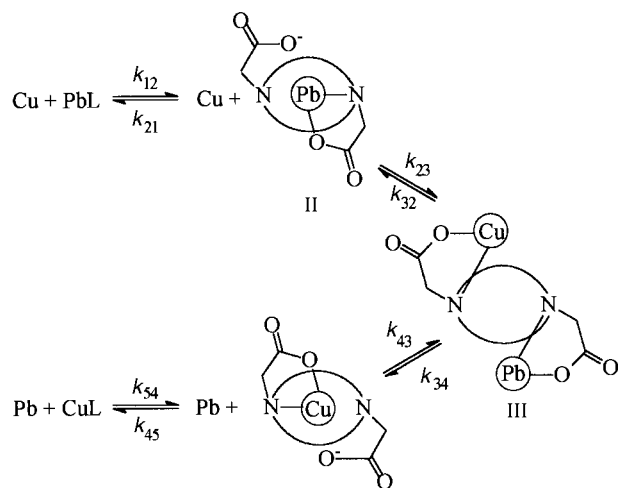
M	Rate constant	Experimental^a	Predicted^b	k_{exptl}/k_{pred}
Cu^{2+}	k^{HL}_{M}	4.2 × 10^8	2.6 × 10^9	0.16
	$k^{H_2L}_{M}$	2.2 × 10^2	2.0 × 10^8	≈1 × 10^{-6}
Pb^{2+}	k^{HL}_{M}	2.3 × 10^8	≈4 × 10^9	≈0.06
	$k^{H_2L}_{M}$	1.7 × 10^3	≈3 × 10^8	≈6 × 10^{-6}

^{a} Calculated from values in Table 5 and equations (11) and (12). ^{b} Calculated from equation (13) using $K_{os} = 0.16$ and = 2.0 dm^3 mol^{-1} for M^{2+} reacting with H$_2$L and HL$^-$, respectively,[27b] $k^{Cu-H_2O} = 1.39 \times 10^9$ s^{-1}[28] and $k^{Pb-H_2O} = 2.00 \times 10^9$ s^{-1}.[27c]

Scheme 2 Representation of the exchange reaction of [PbL²] *i.e.* PbL with Cu²⁺. The charges and the macrocycle ether oxygen atoms have been omitted for clarity. In some reactions several steps have been combined, *e.g.* initial carboxylate co-ordination to Cu²⁺ in species II and III

dicted by equation (13). The experimental values are $\approx(1–5) \times 10^{-6}$ times smaller than expected for Cu²⁺ and Pb²⁺, respectively. The ligand most likely exists predominantly in the zwitterionic form with both nitrogen atoms protonated. The zwitterionic form of amino acids has been found to be much less reactive than the anionic or neutral forms.[27a,29] If the initial site of metal-ion co-ordination is the free carboxylate oxygen, a proton must be shifted (or lost) from the amine nitrogen prior to chelate formation. Thus, proton loss and the accompanying macrocycle conformational change could be the rate-determining step. Values of $100–500$ s⁻¹ have been estimated for proton-loss rate constants for amino acids.[27d,29b,30] For the case of rate-determining proton loss, following rapid formation of a carboxylate oxygen–metal ion bond, an estimate of the formation rate constant, $k^{H_2L'}_M$, can be obtained from equation (14) where $k_{M'CO_2}$ is the equilibrium constant for the metal ion–

$$k^{H_2L'}_M = K_{M'CO_2} k_{-H} \qquad (14)$$

carboxylate intermediate and k_{-H} is the rate constant for proton loss. Using values of $K_{M'O_2CMe}$[21a] to approximate $K_{M'CO_2}$, the values of $k^{H_2L'}_M$ fall in the ranges $(6–30) \times 10^3$ and $(14–70) \times 10^3$ s⁻¹ for Cu²⁺ and Pb²⁺, respectively. These values are at least one order of magnitude larger than the experimental values listed in Table 6. On the other hand a small fraction of the diprotonated ligand may exist in a form with the second proton on the carboxylate oxygen of the arm attached to the protonated nitrogen atom. This would be a much more reactive species since one end of the ligand would be unprotonated (similar to the case for HL⁻). The fraction of the diprotonated species in this form can be estimated to be 5×10^{-6} (of [H₂L][21b]). This is approximately the same as the ratio of the experimental to predicted $k^{H_2L}_M$ values in Table 6. Thus, the relatively small values of the formation rate constant, $k^{H_2L}_M$, are due to an unfavourable equilibrium concentration of a reactive form of the diprotonated ligand. Similar arguments have been proposed to explain the low reactivity of monoprotonated nitrilotriacetic acid.[*,27c,29]

In contrast to the behaviour observed for the exchange reactions of lanthanide–H₂L² complexes with Cu²⁺,[5] the rate of the exchange reaction of [PbL²] with Cu²⁺ has a first-order dependence on [Cu²⁺]. Many other metal–metal exchange reactions with aminocarboxylate ligands exhibit a pathway involving a binuclear intermediate or transition state.[27e] A modified version of the mechanism proposed for exchange reactions of M(edta) is shown in Scheme 2. Space-filling Corey–Pauling–Koltun (CPK) models indicate that H₂L² can readily form a binuclear complex (species III). The observed rate constant, k_{Cu}, in the forward direction is given by equation (15). Based on electrostatic, steric

$$k_{Cu} = k_{12}k_{23}k_{34}/(k_{23} + k_{21})(k_{32} + k_{34}) \qquad (15)$$

and proximity effects, it is reasonable to assume that $k_{21} \gg k_{23}$. Therefore, the location of the rate-determining step will depend on the ratio $k_{23}k_{34} : (k_{32} + k_{34})$. Utilizing the relationships (16)

$$k_{32} = k_{23}/K_{Cu(aa)} = K_{os}k^{Cu-H_2O}/K_{Cu(aa)} \qquad (16)$$

and (17) where k^{M-H_2O} is the solvent-exchange rate con-

$$k_{34} = k_{43}/K_{Pb(aa)} = K_{os}k^{Pb-H_2O}/K_{Pb(aa)} \qquad (17)$$

stant[27c,28] and $K_{M(aa)}$ the stability constant of a metal ion–amino acid complex,[21b] the ratio $k_{32} : k_{34}$ is estimated to be 5×10^{-4}. Therefore, the rate constant, k_{Cu}, would be equal to $k_{12}k_{23}/k_{21}$ and the rate-determining step would involve formation of the binuclear species with both cations chelated. The general validity of this proposed mechanism awaits additional studies of complexes of H₂L² with other leaving and entering cations. The failure to observe a direct binuclear pathway for the exchange reactions of lanthanide–H₂L¹ complexes with Cu²⁺ may be due to the less favourable electrostatic parameters and decreased flexibility of the smaller macrocyclic ring.

Acknowledgements

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* The uncomplexed diprotonated pro-ligand can exist in the following forms: ⁻ONNH⁺OH (H₂L)ₐ; HONNH⁺O⁻ (H₂L)_c and ⁻OHN⁺NH⁺O⁻ (H₂L)_d. The fraction *f*, that exists as (H₂L)ₐ can be calculated from the expression $[H_2L]_a/([H_2L]_a + [H_2L]_c + [H_2L]_d) = K_{HA}/(K_{Ha} + K_{Hc} + K_{Hd})$, where $K_{HI} = [H_2L]/[H^+][HL^-]$. The values of K_{HI} were estimated to be $K_{Ha} = 10^{2.5}$,[21b] $K_{Hc} = K_H$ (carboxylic acid) $= 10^{4.9}$, and $K_{Hd} = K_{H2(L²)} = 10^{7.8}$ (Table 1).

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