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Synthesis and Evaluation of Conformationally Restricted N_4-Tetradentate Ligands for Implementation in An(III)/Ln(III) Separations

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Abstract The previous literature demonstrates that donor atoms softer than oxygen are effective for separating trivalent lanthanides (Ln(III)) from trivalent actinides (An(III)) (Nash, K.L., in: Gschneider, K.A. Jr., et al. (eds.) Handbook on the Physics and Chemistry of Rare Earths, vol. 18—Lanthanides/Actinides Chemistry, pp. 197–238. Elsevier Science, Amsterdam, 1994). It has also been shown that ligands that "restrict" their donor groups in a favorable geometry, appropriate to the steric demands of the cation, have an increased binding affinity. A series of tetradentate nitrogen containing ligands have been synthesized with increased steric "limits". The pK_a values for these ligands have been determined using potentiometric titration methods and the formation of the colored copper(II) complex has been used as a method to determine ligand partitioning between the organic and aqueous phases. The results for the 2-methylpyridyl-substituted amine ligands are encouraging, but the results for the 2-methylpyridyl-substituted diimines indicate that these ligands are unsuitable for implementation in a solvent extraction system due to hydrolysis.

Keywords Copper(II) · Stability constants · Acid dissociation constants · Phase distribution · Ligand preorganization · Nitrogen donor complexants

1 Introduction

The separation of lanthanides from transplutonium actinides is critical to the efficient management of spent nuclear fuel. Transplutonium actinides are found predominantly in the

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+3 oxidation state, as are the lanthanides. Therefore, the separation of these elements must exploit the small difference between the solution chemistry of lanthanides and transplutonium actinides in the trivalent oxidation state [1].

Actinides bind the softer bases such as N, S, and Cl^- more strongly than the trivalent lanthanides. The difference in binding affinity can be exploited for successful separations. The 2-methylpyridyl structural analogue of EDTA, N,N,N′,N′-tetrakis(2-pyridylmethyl)-ethylenediamine (TPEN), shows a preference for An^{3+} over Ln^{3+} [2]. The stability constant for the americium (Am) TPEN complex is 100 times greater than for the samarium (Sm) complex, resulting in an overall difference in the ΔG for complexation of 11.6 kJ·mol^{-1} [2].

The effect of donor group preorganization is clearly seen in the difference between the formation constants for a 1:1 complex with Am(III) of N,N′-dimethyl bicyclic diamide (DMBCDA) and tetramethylmalonamide (TMMA) at 0.1 mol·L^{-1} HNO_3 and 0.9 mol·L^{-1} $NaNO_3$ is $\Delta \log_{10} \beta = 1.98$, which represents a difference in the Gibbs energy of formation between TMMA and DMBCDA of -11.3 kJ·mol^{-1} [3].

The preorganizing effect of a cyclohexane backbone can be seen in results of calorimetric studies on the complexation of Am(III) and Cm(III) with polyaminocarboxylate ligands [4]. The amine groups in the hexadentate ligand *trans*-1,2-cyclohexanedinitrilotetraacetic acid (CDTA) are prearranged trans to each other in the 1,2 positions on a cyclohexane ring; the *trans*- arrangement on the cyclohexane ring eliminates free rotation which can occur around the ethylene bridge joining the iminodiacetate groups in ethylendiaminetetraacetic acid (EDTA). In the Cm^{3+} data, the CDTA stability constant is larger than that for EDTA by $\Delta \log_{10} K_{101} = 1.23$, representing ΔG being more favorable by 7.1 kJ·mol^{-1} [4]. The improved ΔG is opposed by an endothermic contribution to ΔH that is overcome by increased ΔS. This difference in $T\Delta S$ results from the CDTA not having to rearrange to any great degree before complexing the Cm^{3+}; changing the hydration sphere around the metal center also contributes to this increased entropic effect [4, 5].

To a first approximation, a significant portion of the entropy difference in the formation of metal complexes must be attributed to molecular rearrangement of the ligand. To rearrange EDTA into an appropriate configuration for binding a metal center, the molecule must, in an acidic solution (both nitrogen atoms are protonated), reconfigure from a conformer in which the nitrogens are as far apart as possible (dihedral angle approx. 180°) to one in which the nitrogens are in close proximity to one another. For CDTA this molecular rearrangement is constrained due to the cyclohexane ring hindering the rotation around the C–C bond of the C's bonded to nitrogen atoms. Cleavage of a ring C–C bond would have to occur to allow free rotation. This high energy process hinders the rotation. The *trans* orientation of the N donor atoms is adopted to minimize steric repulsions between the substituents on the ring (dihedral angle approx. 60°).

The energy difference required for a separation factor of 100 in a solvent extraction system is approximately 11.4 kJ·mol^{-1}, which is comparable to the energy of a single hydrogen bond [1]. Even though "soft" donor-containing ligands in general have an inherent selectivity for An(III) over Ln(III), the binding constants in general are low. To increase the binding constant of the complexant for metal ions, the ligand can be structurally preorganized or preoriented. In this investigation, ligands containing only nitrogen donor atoms have been synthesized. The impact of structural prearrangements of the donor atoms is to be evaluated.

The ligands synthesized for this study and their acronyms are presented in Fig. 1. The sterically restricted 2-methylpyridyl ligands synthesized in this study are N,N′-bis(2-methylpyridyl)-1,2-diaminoethane (BPMDAE), N,N′-bis-[pyridin-2-ylmethylene]-ethane-1,2-diamine (BPMDIE), N,N′-bis(2-pyridylmethyl)piperazine (BPMPIP), N,N′-bis(2-methylpyridyl)-1,3-diaminopropane (BPMDAP), *trans*-N,N′-bis-[pyridin-2-ylmethylene]cyclo-

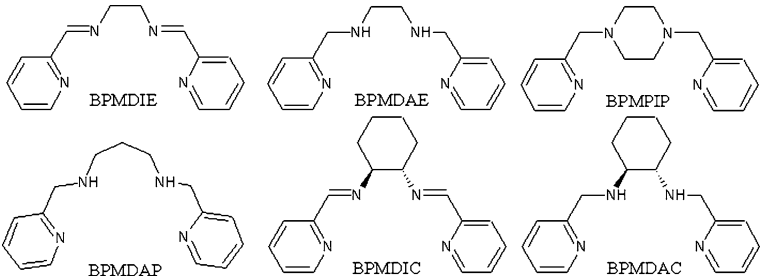

Fig. 1 Conformationally restricted 2-methylpyridyl ligands synthesized in this study: BPMDIE = N,N′-bis-[pyridin-2-ylmethylene]ethane-1,2-diamine; BPMDAE = N,N′-bis(2-methylpyridyl)-1,2-diaminoethane; BPMPIP = N,N′-bis(2-pyridylmethyl)piperazine; BPMDAP = N,N′-bis(2-methylpyridyl)-1,3-diaminopropane; BPMDIC = *trans*-N,N′-bis-[pyridin-2-ylmethylene]-cyclohexane-1,2-diamine; BPMDAC = *trans*-N,N′-bis(2-pyridylmethyl)-1,2-diaminocyclohexane

hexane-1,2-diamine (BPMDIC), and *trans*-N,N′-bis(2-pyridylmethyl)-1,2-diaminocyclohexane (BPMDAC).

The acid dissociation constants for the ligands are reported for the first time at $I = 0.5$ mol·L^{-1}, along with their copper complex stability constants and partitioning constants for the resulting complexes between aqueous phase ($I = 0.5$ mol·L^{-1}) and 1-octanol as a function of pH. The screening of these compounds using Cu(II) was initially pursued to explore the aqueous stability of these ligands as well as investigating using the Cu(II) chromophore formation as an indicator to explore ligand phase distribution as a function of pH. The stability of the ligands in solution and how they distribute between an organic and aqueous phase will be used to screen these ligands as to how effectively they may be for implementation in an Am(III) and Ln(III) separation.

The variation in the arrangement of nitrogen donor atoms in the ligands addresses two important issues, the effect of prearrangement of ligand donor atoms and the impact of converting imine into amine groups. The backbone of the ligand has been changed, in order to preorganize the amine or imine donor groups into configurations that maximize metal interactions, from the flexible alkyl backbones of BPMDAE, BPMDIE, BPMDAP and BPMDIE, to the *trans*-arrangement using a cyclohexane backbone (BPMDIC and BPMDAC), to the more rigid boat/chair cyclohexane backbone of BPMPIP. The change from diimine to diamine decreases the planarity of the 2-methyl pendant arms and was hypothesized to decrease the possibility of metal–ligand interaction. In the diimine bonds the C and N atoms are sp_2 hybridized and conjugated to the pyridyl ring, giving the pendant arm-pyridine portion of the ligand a planar configuration that does not readily undergo free rotation. The effect of chelate ring size can be investigated in the chemistry of BPMDAP when compared with BPMDAE. The binding of the backbone of BPMDAP will form a 6 membered chelate ring with a metal center, whereas BPMDAE will form a 5 membered chelate ring. In general it is considered that with large metal ions, 5 membered chelate rings are more stable than 6.

2 Experimental

2.1 Ligand Synthesis

The ligands were synthesized following modifications of established synthetic procedures (BPMDAE, BPMDIE, and BPMDAP [6], BPMDIC [7], and BPMDAC [8]). In general, the

diimines were synthesized by condensation of 2-pyridinecarboxaldehyde with the appropriate diamine in methanol over 5 Å molecular sieves. The addition of 5 Å molecular sieves only marginally increased yields above those of previous syntheses. The tetradentate diamines were then prepared by reduction of the diimine with sodium borohydride ($NaBH_4$) in ice cold methanol (MeOH). After purification by solvent extraction, the tetradentate diamines were precipitated as the HCl salts from diethyl ether. Before precipitation, the structure and purity of the final compounds were confirmed by comparison of the NMR spectra with literature data [6–9]. BPMPIP was synthesized by the reaction of piperazine with a slight stoichiometric excess of 2-chloromethylpyridine in the presence of triethylamine in acetonitrile following an established procedure [9].

2.1.1 Synthesis of N,N′*-bis-[Pyridin-2-ylmethylene]ethane-1,2-diamine (BPMDIE)*

2-Pyridinecarboxaldehyde (6.492 g, 60 mmol) was added dropwise to a solution of 1,2-diaminoethane (1.803 g, 30 mmol) in anhydrous methanol (MeOH, 50 mL) with stirring under a nitrogen balloon. Activated 5 Å molecular sieves were added to this reaction mixture and the reaction allowed to stand for 2 h at room temperature. The reaction mixture was then refluxed for 3 h. The solution was filtered and solvent evaporated to yield crude product. The orange product was recrystallized from hot MeOH and subsequently from hot hexanes. The product was isolated as a yellow crystalline material (60.8% yield). ^{1}H NMR ($CDCl_3$): δ 4.07 (s, 4H), 7.31 (m, 2H), 7.73 (m, 2H), 8.42 (s, 2H), 8.62 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 61.56, 121.58, 125.00, 149.63, 154.58, 163.67.

2.1.2 Synthesis of N,N′*-bis(2-Pyridylmethyl)ethane-1,2-diamine (BPMDAE)*

Sodium borohydride ($NaBH_4$) (1.579 g, 41.75 mmol) was added slowly with stirring over 2 h to a solution of BPMDIE (B) (4.003 g, 16.7 mmol) in anhydrous MeOH (100 mL), under a nitrogen atmosphere and held at 0 °C using an ice bath. After the addition was completed, the reaction mixture was refluxed for 15–20 minutes, and then left to stir at room temperature overnight. Sodium hydroxide (1.0 mol·L^{-1}, 150 mL) was added to the reaction mixture and the compound was then extracted into methylene chloride (CH_2Cl_2) (4 × 15 mL). The CH_2Cl_2 solution was dried using anhydrous potassium carbonate (K_2CO_3), filtered, and the solvent evaporated to leave behind a light yellow oil (96.4% yield). The light yellow oil was taken up in 25 mL of diethyl ether and the ligand precipitated with 3 equivalents of HCl (48.6 mL, 1.0 mol·L^{-1} HCl in diethyl ether). The precipitate was washed (diethyl ether) and dried by multiple evaporations of diethyl ether on a rotary evaporator (care must be taken as the compound is very hydroscopic before the excess HCl is removed). ^{1}H NMR ($CDCl_3$): δ 2.71 (s, 4H), 3.80 (s, 4H), 7.02 (m, 2H), 7.20 (m, 2H), 7.50 (m, 2H), 8.42 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 49.13, 55.21, 122.20, 122.58, 136.77, 149.27, 159.66.

2.1.3 Synthesis of N,N′*-bis(2-Pyridylmethyl)piperazine (BPMPIP)*

A solution of piperazine (1.010 g, 11.73 mmol) in CH_3CN (40 mL) was treated with 2-picolyl chloride hydrochloride (3.943 g, 24.04 mmol) and triethylamine (6.5 mL). The resultant mixture was stirred in a loosely sealed flask at room temperature. After 48 h, the mixture was poured into 1 mol·L^{-1} NaOH (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over anhydrous K_2CO_3, filtered, then the solvent was evaporated to yield the crude product as a brown solid. The solid was dissolved in diethyl ether (50 mL) and heated to reflux, resulting in the deposition of an insoluble brown oil. The ether

solution decanted from the oil was evaporated to yield the pure product as a very light yellow crystalline solid (45.7% yield). ^{1}H NMR ($CDCl_3$): δ 2.58 (s, 8H), 3.68 (s, 4H), 7.18 (m, 2H), 7.39 (m, 2H), 7.64 (m, 2H), 8.56 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 39.75, 122.45, 126.45, 137.53, 148.39, 149.90, 165.26.

2.1.4 Synthesis of N,N′*-bis(2-Methylpyridyl)-*1,3*-diaminopropane (BPMDAP)*

2-Pyridinecarboxaldehyde (6.492 g, 60 mmol) was added dropwise to a solution of 1,3-diaminopropane (2.224 g, 30 mmol) in anhydrous MeOH (50 mL) with stirring under a nitrogen atmosphere. To this reaction mixture, activated 5 Å molecular sieves were added and the reaction allowed to stand for 2 h at room temperature after which time the solution was refluxed for 3 h. The reaction was filtered and the solvent evaporated to yield the product as a yellow oil (84.6% yield). The oil product (6.406 g, 16.7 mmol) was redissolved in anhydrous MeOH (100 mL), held at 0 °C using an ice bath under a nitrogen atmosphere, and $NaBH_4$ (2.401 g, 63.47 mmol) was added slowly with stirring over 2 h. The reaction mixture was refluxed for 20 minutes and left to stir at room temperature overnight. To this solution 1.0 mol·L^{-1} NaOH (150 mL) was added and the product was then extracted with CH_2Cl_2 (4 × 15 mL). The CH_2Cl_2 solution was dried using anhydrous K_2CO_3, filtered, and the solvent evaporated leaving a light yellow oil (96.5% yield). The light yellow oil was taken up in 25 mL of diethyl ether and the tetradentate diamine precipitated with 3 equivalents of HCl (72.3 mL of 1.0 mol·L^{-1} HCl in diethyl ether). The precipitate was washed with diethyl ether and dried by multiple evaporations of diethyl ether on a rotary evaporator (care must be taken as the compound is very hydroscopic before excess HCl is removed). ^{1}H NMR (D_2O): δ 2.15 (m, 2H), 3.20 (t, 4H), 4.55 (s, 4H), 7.84 (m, 2H), 7.95 (m, 2H), 8.28 (m, 2H), 8.65 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 22.83, 45.26, 48.35, 127.67, 127.95, 144.42, 145.77, 146.37.

*2.1.5 Synthesis of trans-*N,N′*-bis-[Pyridin-2-ylmethylene]-cyclohexane-*1,2*-diamine (BPMDIC)*

2-Pyridinecarboxaldehyde (6.492 g, 60 mmol) was added drop wise to a solution of *trans*-1,2-diaminocyclohexane (3.426 g, 30 mmol) following the same method used for making BPMDIE. The crude yellow product was recrystallized from hot methanol. The product was isolated as a yellow crystalline material (80.9% yield). ^{1}H NMR ($CDCl_3$): δ 1.50 (m, 4H), 1.85 (m, 4H), 3.52 (m, 2H), 7.20 (m, 2H), 7.62 (m, 2H), 7.86 (m, 2H), 8.30 (s, 2H), 8.53 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 24.56, 32.93, 73.77, 121.57, 124.70, 136.67, 149.47, 154.80, 161.66.

*2.1.6 Synthesis of trans-*N,N′*-bis(2-Pyridylmethyl)-*1,2*-diaminocyclohexane (BPMDAC)*

A solution of BPMDIC (4.065 g, 13.9 mmol) in anhydrous MeOH (100 mL) was cooled to 0 °C using an ice bath, $NaBH_4$ (1.461 g, 34.76 mmol) was added slowly with stirring over 2 h. The solution was then worked up following the previous method for the synthesis of BPMDAE resulting in a light yellow crystalline material (98.4% yield). The crystals were taken up in 25 mL of diethyl ether and the diamine precipitated with 3 equivalents of HCl (42.0 mL of 1.0 mol·L^{-1} HCl in diethyl ether). ^{1}H NMR (D_2O): δ 1.50 (m, 4H), 1.17 (m, 4H), 1.67 (m, 2H), 2.17 (m, 2H), 2.85 (m, 2H), 4.20 (d, 2H), 4.40 (d, 2H) 7.62 (m, 2H), 7.64 (d, 2H), 8.16 (m, 2H), 8.43 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 25.43, 32.54, 53.40, 63.27, 123.95, 124.70, 137.84, 149.58, 161.68.

2.2 Potentiometric Measurements of Acid Dissociation Constants

All measurements were made using a Mettler Toledo DL50 Autotitrator fitted with an Orion Ross ultra semi-micro glass electrode with 3 mol·L^{-1} NaCl as the filling solution. The experimental and titration solutions were made up to 0.5 mol·L^{-1} ionic strength ($NaClO_4$), temperature was maintained at 25 °C and a slow stream of nitrogen was passed through the titration vessel to reduce the interference from CO_2. All titration were corrected (p_CH) back to theoretical pH after the titration of standardized strong acid (0.01 mol·L^{-1} $HClO_4$) and strong base (0.01 mol·L^{-1} NaOH).

All the ligand solutions were titrated with standardized 0.01 mol·L^{-1} NaOH. Solutions of BPMDIE, BPMPIP, and BPMDIC (1×10^{-3} mol·L^{-1}) were prepared by dissolving the crystalline material in 18 MΩ water with an excess of acid (8 equivalents 0.01 mol·L^{-1} $HClO_4$) resulting in a solution of approximately pH = 2. Solutions of BPMDAE, BPMDAP, and BPMDAC (1×10^{-3} mol·L^{-1}) were prepared from the neutralized HCl salt. The HCl salt was weighed out and the combined with 1.0 mol·L^{-1} NaOH (20 mL). The free amine was then solvent extracted into CH_2Cl_2 (5 × 5 mL) and transferred to a weighed round bottom flask. The solvent was evaporated and the mass of the free amine determined. The stock solution of the free amine for potentiometric titration was made up following a similar procedure to that described for the imines. All potentiometric titrations were performed in triplicate, in both static and dynamic modes. The potentiometric curves were fit using PSEQUAD [10] and the most acidic pK_a fit by minimization of the standard error in the data.

2.3 Spectrophotometric Measurements and Determination of Stability Constants

Ligand–metal complex solutions were made using $Cu(ClO_4)_2{\cdot}6H_2O$, 99.99% purity (0.001 mol·L^{-1}) and an excess of the neutralized ligand (0.01 mol·L^{-1}). The solution was acidified using 0.01 mol·L^{-1} $HClO_4$ (approximately pH = 2) and $NaClO_4$ was added to maintain the ionic strength at 0.5 mol·L^{-1}. The ligand–metal complex solution was then titrated with standardized 0.1 mol·L^{-1} NaOH. The absorption spectra of the copper complexes with the ligands (structures shown in Fig. 1) were recorded as a function of pH at 23 (±2) °C in the range of 350–950 nm using a Varian Cary 50 Bio UV–vis or Cary 13 UV–vis spectrophotometer. For the ligands that underwent hydrolysis, SQUAD fitting was only carried out on the spectra of the hydrolyzed Cu(II) species.

A different methodology was developed to determine the stability constants of ligands that have copper complexes forming at pH = 1 (BPMDAE, BPMDAP, and BPMDAC). At a constant acid concentration (0.25 mol·L^{-1}), ionic strength (I = 0.5 mol·L^{-1} using $NaClO_4$), and constant copper (0.001 mol·L^{-1}), the metal:ligand ratio was changed (0.0004–0.004 mol·L^{-1} ligand concentration). The resulting spectra for the spectrophotometric titrations were fit using SQUAD [11] and the $\log_{10} K_{101}$ value determined.

2.4 Phase Distribution Study

Partitioning constants for ligand distribution between *n*-octanol and water were determined as follows: 1 cm^3 of octanol was spiked with 50 µL of a methanolic solution containing 4×10^{-2} mol·L^{-1} of ligand creating a 5% MeOH/octanol (v/v) phase. This organic solution was equilibrated with 1 cm^3 of aqueous solution containing 0.49 mol·L^{-1} of $NaClO_4$ and 1×10^{-2} mol·L^{-1} of a buffer (dichloroacetic acid, chloroacetic acid, acetic acid, metanilic acid, 2-(*N*-morpholino)ethanesulfonic acid (MES) or N-(2-hydroxyethyl)piperazine-N′-2-ethanesulfonic acid (HEPES)) by shaking for 12 h. After centrifugation the aqueous phase

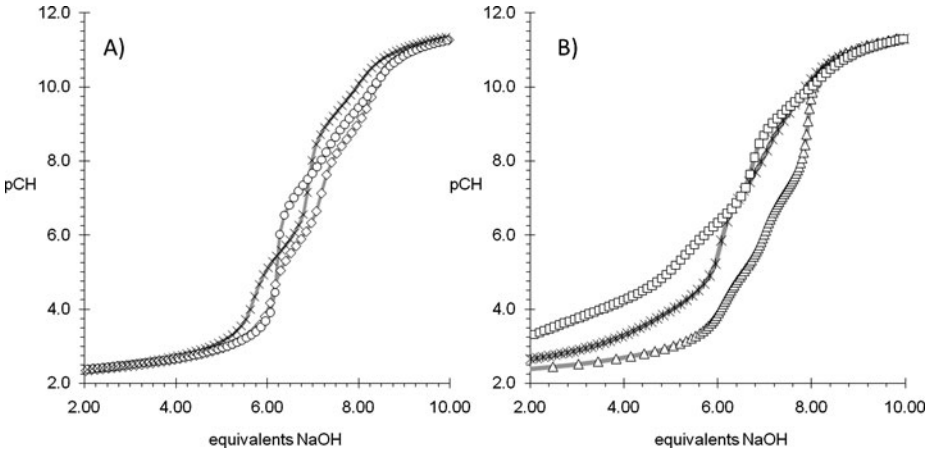

Fig. 2 Potentiometric titrations of fully protonated N_4-tetradentate ligands with NaOH at 0.5 mol·L^{-1} $NaClO_4$. PSEQUAD fit shown by solid grey line: (**A**) ◇, BPMDAE; ○, BPMDAP; ×, BPMDAC; (**B**) △, BPMPIP; ∗, BPMDIE; □, BPMDIC

was separated and a 400 µL sample taken and 400 µL of indicator solution added. The indicator solution consisted of excess copper (0.006 mol·L^{-1}) at an ionic strength of 0.5 mol·L^{-1} using $NaClO_4$, at pH = 5.5 set by sodium acetate buffer (approximately 0.4 mol·L^{-1}) made up in a 50% (v/v) methanol/water solution. Using the experimentally measured extinction coefficients, the aqueous concentration of ligand was determined and the concentration of ligand in the organic phase was determined assuming mass balance. All phase distribution samples were performed in triplicate and the pH measured before and after contact. Ligand concentration of the stock solution was determined spectrophotometrically using the formation of the copper complex chromophore by addition of a copper containing solution, as an indicator, buffered at pH = 5.5 using (0.2 mol·L^{-1}) sodium acetate containing 50/50 (v/v) H_2O/MeOH and (0.008 mol·L^{-1}) $Cu(ClO_4)_2$ at 0.5 mol·L^{-1} ionic strength ($NaClO_4$).

3 Results and Discussion

3.1 Determination of Acid Dissociation Constants

The results of potentiometric titrations of the fully protonated forms of the ligands with NaOH are shown in Fig. 2. The protonation constants for BPMDAE and BPMDAP have been determined previously at 0.1 mol·L^{-1} ionic strength [12], but acid dissociation constants for all these ligands have not been determined previously at $I = 0.5$ mol·L^{-1}. The resolved acid dissociation constants determined by PSEQUAD using non-negative least-square analysis (NNLS) are given in Table 1. The PSEQUAD fit for each potentiometric ligand titration is shown by the solid dark grey line in each of the titration runs (Fig. 2). Modeling of the aqueous speciation of BPMDAE, BPMDAP, BPMDAC and BPMPIP were carried out using the hyperquad simulation program Hyss2009 and the resulting diagrams are shown in Fig. 3.

The error in pK_1 for BPMDAE, BPMDAP, BPMPIP and BPMDAC are considerably large. This error is due to the fact the pK_a is not directly measurable under these experimental conditions and the values were thus determined by minimization of the standard

Table 1 Acid dissociation constants for 2-methylpyridyl based ligands at 25 °C

Compound	BPMDAE	BPMDAP	BPMDAC	BPMPIP	BPMDIE	BPMDIC
pK_4	8.65 (±0.02)	9.29 (±0.02)	9.25 (±0.02)	7.26 (±0.01)	9.09 (±0.01)	9.39 (±0.01)
pK_3	5.79 (±0.01)	7.31 (±0.01)	5.55 (±0.01)	5.12 (±0.01)	7.38 (±0.02)	6.33 (±0.01)
pK_2	2.14 (±0.03)	2.29 (±0.02)	1.55 (±0.08)	2.57 (±0.03)	4.80 (±0.02)	4.35 (±0.01)
pK_1	1.6 (±0.7)	1.2 (±0.7)	1.0 (±0.7)	1.8 (±0.7)	3.84 (±0.02)	3.78 (±0.01)

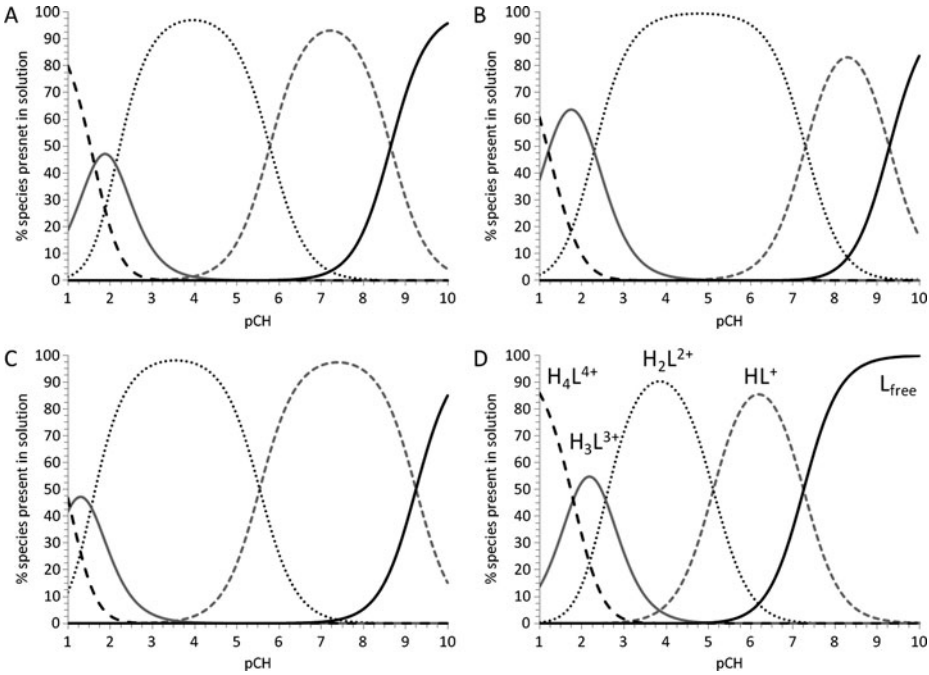

Fig. 3 Speciation diagrams for (**A**) BPMDAE; (**B**) BPMDAP; (**C**) BPMDAC; (**D**) BPMPIP at 0.001 mol·L^{-1} ligand concentration, 25 °C and 0.5 mol·L^{-1} ionic strength ($NaClO_4$). In all speciation diagrams: H_4L^{4+}, *black dashed line*; H_3L^{3+}, *grey solid line*; H_2L^{2+}, *grey dotted line*; HL^+, *grey dashed line*, L_{free}, *black solid line*

deviation in the pK_1 value. The lowest two pK_a values for BPMDAE, BPMDAP, BPMPIP, and BPMDAC (shown in Table 1) indicate the more acidic nature of the pyridinium moieties when compared with the completely aliphatic analogue triethylenetetramine (trien) [13].

The higher pK_a values for BPMDIE and BPMDIC appear counterintuitive based on the effect of conjugation on the overall acidity of a ligand. The pK_1 values for both BPMDIE and BPMDIC match that of 2-pyridine carboxaldehyde at 3.8 [14] and indicate that both of these ligands undergo hydrolysis in aqueous solution to produce a complex mixture of both the synthetic precursors pyridine carboxaldehyde and the bridging amine, as well as the mono-substituted and bis-substituted pyridylmethylene amine. Based on this data BPMDIE and BPMDIC are not suitable for use in a solvent extraction system.

The values for BPMDAE are in good agreement with the earlier literature, in which the pK_a values are reported at 0.1 mol·L^{-1} ionic strength as 1.62, 1.81, 5.45, and 8.23, respec-

Table 2 Absorption data for the complexes of with Cu^{2+}

Compound	λ_{max} (nm)	Molar absorptivity ε ($L \cdot mol^{-1} \cdot cm^{-1}$)	Lowest observable conc. of ligand ($mol \cdot L^{-1}$)
BPMDAE	606	149 (±6)	1.34×10^{-5}
BPMDAP	598	158 (±3)	1.18×10^{-5}
BPMDAC	589	188 (±4)	0.80×10^{-5}
BPMPIP	650	288 (±8)	0.69×10^{-5}
BPMDIC	606	71 (±3)	2.61×10^{-5}
BPMDIE	606	156 (±6)	1.28×10^{-5}

tively [12]. The increase in pK_a values for BPMDAE is due to the increase in ionic strength (0.5 versus 0.1 $mol \cdot L^{-1}$) [13]. In previous studies it has been asserted that the relative affinity of the ligand BPMDAE for protons does not correlate with its affinity for selected divalent metal ions [12]. The pK_a values of these ligands may not reflect their distribution between an organic and aqueous phase as this is also a function of the lipophilicity of the amine backbone.

The pK_a values for BPMDAP are similar to the values reported in the NIST database at 1.0 $mol \cdot L^{-1}$ ionic strength [13], which are reported as 8.99, 7.28, 2.34 and 1.3, respectively. We do see that pK_3 and pK_4 are more acidic at lower ionic strength, as would be expected, at 2.29 and 1.2. The pK_3 of BPMDAP at 7.31 is within the literature error of 7.28; the values for pK_3 and pK_4 at 7.31 and 9.29 do not follow the expected trend of increased acidity with increasing ionic strength and pK_4 is more basic than expected. The effect could be due to a degree of impurity in the prepared BPMDAP compound (residual presence of unreacted 1,3-diaminopropane) as this was the only ligand made via a one-pot synthesis methodology. Overall the trend in the total basicity ($\sum pK_a$) for these ligands is a follows:

$$\text{BPMPIP} < \text{BPMDAC} < \text{BPMDAE} < \text{BPMDAP} < \text{BPMDIC} < \text{BPMDIE}$$

3.2 Determination of Copper–Ligand Stability Constants

The spectral details for the ligands screened with copper are given in Table 2. The lowest observable amount of ligand (as the Cu^{2+} complex) is calculated from the observed spectra of the 1:1 complex greater than 5σ (limit of quantification) of the baseline at the λ_{max}. It is noteworthy that the Cu-BPMPIP complex has a molar absorptivity nearly double the values of the other complexes. This is probably due to the distortion of the metal center from ideal symmetry when complexed to BPMPIP ligand [9].

In all of the UV–vis spectrophotometric pH titrations, the growth of a single peak is observed with pH increase or increased ligand concentration. In Fig. 4 the spectrophotometric titrations under high acidic conditions are shown (BPMDAE, BPMDAP, and BPMDAC). These experiments were carried out as metal–ligand titrations at high acidity so that protons could effectively compete with the strength of the metal ligand complex. In Fig. 5 the spectrophotometric titrations of the diimine based ligands and BPMPIP are presented. These experiments were carried out as complex pH titrations from pH = 2.00 to neutral conditions to prevent precipitation of hydrolyzed species. The stoichiometry of the copper species was determined for all ligands as 1:1 by using Job plot analysis.

The calculated stability constants for the Cu(II) complexes at 0.5 $mol \cdot L^{-1}$ ionic strength and 21 °C are given in Table 3. The stability constants were calculated using SQUAD from

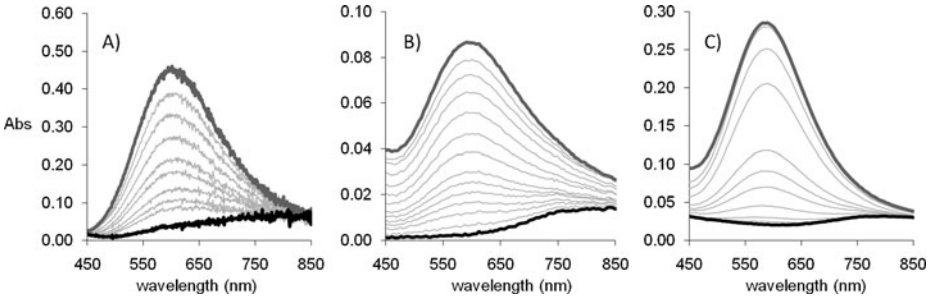

Fig. 4 Spectrophotometric titrations of 0.001 mol·L^{-1} $Cu(ClO_4)_2$, 0.15–0.25 mol·L^{-1} $HClO_4$, I = 0.5 mol·L^{-1} ($NaClO_4$) and 21 °C, by incremental addition of ligand, *black line*—M:L ratio 1:0, *grey line*—M:L ratio 1:4; (**A**) BPMDAE, (**B**) BPMDAP, and (**C**) BPMDAC with Cu(II)

Table 3 Stability constants for the complexation of Cu^{2+} by N_4-tetradentate ligands determined at 21 °C and I = 0.5 mol·L^{-1} ($NaClO_4$)

Compound	$\log_{10} K_{101}$	ΔG (kJ·mol^{-1})
BPMDAE	17.7 ± 0.9	−99 ± 5
BPMDAP	18.9 ± 0.2 (18.7 ± 0.2[a])	−106 ± 1 (−105 ± 1[a])
BPMDAC	19.5 ± 0.6	−109 ± 3
BPMPIP	7.41 ± 0.06	−41.7 ± 0.3
BPMDIE	11.73 ± 0.02	−66.1 ± 0.1
BPMDIC	14.13 ± 0.03	−79.6 ± 0.1

[a]Data fitted using selected pK_a values for BPMDAP at 1.0 mol·L^{-1} ionic strength from the NIST database [13]

the changes in the absorption spectra as a function of changing ligand concentration or changing pH. The high errors associated with fitting the amine based ligands (BPMDAE, BPMDAP, and BPMDAC) is predominantly due to the uncertainty in pK_1 when operating at high acidic conditions. The stability constant values determined for BPMDIE and BPMDIC are of questionable value due to the fact that these ligands undergo rapid hydrolysis in solution and the nature of these mixtures is highly uncertain.

The complex formed between BPMDAE and Cu^{2+} is strong, with $\log_{10} K_{101} = 16.3$ [12] at 0.1 mol·L^{-1} ionic strength. The Cu^{2+} complex with BPMDAP is approximately 100 times stronger ($\log_{10} K_{101} = 18.9$). This difference in the strength of these complexes is consistent with previous reports, as the steric demands imposed by smaller Cu^{2+} cation lead to a preference for six-membered chelate rings (over five-membered rings) due to the reduced steric strain on the ligand backbone with the longer propyl spacer of BPMDAP [18].

At 0.5 mol·L^{-1} ionic strength we see an increase in the Cu(II) $\log_{10} K_{101}$ for BPMDAE and BPMDAP (17.7 and 18.9 respectively) when compared to those obtained at 0.1 mol·L^{-1} as is seen for triethylenetetramine (trien) [13]. Using the pK_a values determined for BPMDAP (Table 1) in fitting the Cu(II) $\log_{10} K_{101}$, we get an increased value more typically expected for an increase in ionic strength. Using values for pK_1 and pK_2 between the values available in the NIST database for 0.1 and 1.0 mol·L^{-1} ionic strength and the pK_3 and pK_4 for 1.0 mol·L^{-1} ionic strength in the SQUAD fitting gives a predicted $\log_{10} K_{101}$ value approximately equal to the literature value of 18.35 at 0.1 mol·L^{-1} ionic strength for cop-

Table 4 Cu(II) stability constants at 0.1 mol·L^{-1} ionic strength with selected ligands [13]

Ligand[a]	Cu(II) $\log_{10} K_{101}$
PipDA	7.37
EDDA	16.2
Ethylenediamine	10.49
trans-Cyclohexane-1,2-diamine	11.09
BPMDAE	16.3

[a]PipDA = piperazine-1,4-diacetic acid; EDDA = ethylenedinitrilodiacetic acid

per complexation ($\log_{10} K_{101} = 18.4 \pm 0.2$). Fitting the data using the 1.0 mol·L^{-1} ionic strength pK_a values gives a result of $\log_{10} K_{101} = 18.7 \pm 0.2$, which is nearer to the expected value. The highest Cu(II) $\log_{10} K_{101}$ value (19.5 ± 0.6) for all the ligands tested is seen for the Cu^{2+} complex with BPMDAC and is evidence of the effect of constraining the N-donor groups using a cyclohexane backbone when compared with BPMDAE. A parallel comparison can be made for the complexes of Cu^{2+} with ethylene diamine (en) and *trans*-cyclohexane-1,2-diamine (*trans*-cn) [13] (Table 4).

Results from the potentiometric titration clearly indicate that BPMDIE and BPMDIC undergo rapid hydrolysis and since the nature of these hydrolysis mixtures is highly uncertain, the numerical value for any equilibrium constant obtained from them is of questionable value. One clear result from the spectrophotometric titration of BPMDIC with Cu^{2+} is the indication that the ligand is more stable to hydrolysis than the BPMDIE. At the start of the titration, at acidic pHs, we see a λ_{max} at 634 nm which may be indicative of the Cu(BPMDIC)$^{2+}$ complex and, as the titration continues, hydrolysis of the ligand occurs and λ_{max} shifts down to 606 nm, similar to the λ_{max} observed in the BPMDIE and BPMDAE complexes.

The $\log_{10} K_{101}$ value for BPMPIP is approximately 10 orders of magnitude smaller than the value for BPMDAE (Table 3), indicating that protons successfully compete with the metal at much lower concentrations; these complexes become more important at pH values more basic than pH = 2.5. This energy deficit is interpreted as indicating that the free BPMPIP ligand, rather than being preoriented for cation binding, probably maintains the backbone piperazine ring in the chair configuration. For tetradentate bonding of the cation, the piperazine ring would have to "flip" into the boat configuration. The energy penalty associated with this conformational reorganization would be considerable. A parallel quantitation of this effect can be seen when comparing the binding of copper by ethylenediaminediacetic acid (EDDA) and piperazine-1,4-diacetic acid (PipDA) [13] (Table 4). Similarly, the energy required to flip the piperazine from the boat to the chair conformer in the tetradentate nitrogen donor ligand 1,4-bis(2-aminoethyl)-1,4-diazacyclohexane (BAE-P) has been calculated as approximately 29.3 kJ·mol^{-1}, which would equate to a difference in $\log_{10} K_{101}$ of 5.20 at 21 °C [14]. This is approximately half of the $\Delta \log_{10} K_{101}$ value between BPMDAE and BPMPIP ($\Delta \log_{10} K_{101} = 10.3$). It is clear that flipping the piperazine ring accounts for only part of the energy difference in the binding comparison. The rest of the energy difference could be attributed to steric interactions such as those between the methylene hydrogens on the pendant arm (N-CH_2-Pyr) and the hydrogens meta to the pyridyl nitrogen, and interactions of the piperazine backbone with other species in the inner coordination sphere. Taking into account the effect of the polarity and size of the pyridyl ring could also be a factor, but this is probably not the case based on the comparison of the complexation of EDDA and BPMDAE with Cu(II) (Table 4).

The crystal structure of the complex [Cu(BPMPIP)(NO_3)]NO_3 is a 5 coordinate square pyramidal complex with the ligand occupying the equatorial plane with the piperazine in

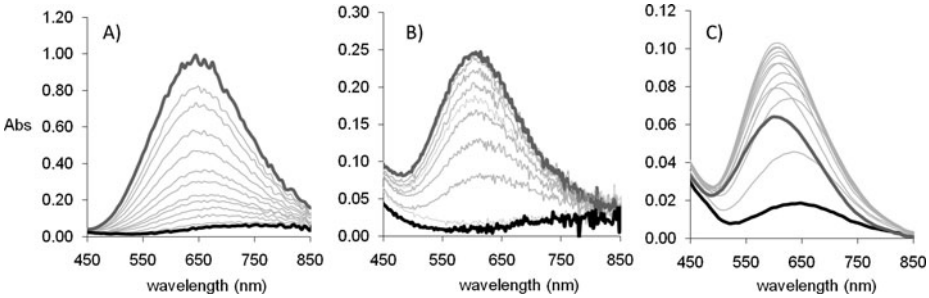

Fig. 5 Spectrophotometric pH titrations of ligands with 0.001 mol·L^{-1} $Cu(ClO_4)_2$, 0.01 mol·L^{-1} ligand, $I = 0.5$ mol·L^{-1} and 21 °C; (**A**) BPMPIP—*black line* starting $p_CH = 2.34$, *dark grey line* is final pH of 7.45; (**B**) BPMDIE—*black line* starting p_CH 2.19, *dark grey line* is final pH of 6.73; (**C**) BPMDIC—*black line* starting $p_CH = 2.26$, *dark grey line* is final pH of 7.23

the boat configuration [15]. A counter ion is held within the inner coordinating sphere in an axial position and the final counter anion is in the second coordination sphere with respect to the nitrate (no distances are given for the second nitrate) [15]. The steric distortion due to the interaction of the piperazine backbone with species coordinated in the axial positions pushes the second anion into the second coordination sphere. A steric interaction of this sort would create a further distortion away from ideal symmetry and thus lead to a much higher molar absorptivity (Table 2).

3.3 Phase Distribution Study

The distribution ratio, D_L, of a ligand between an organic phase and an aqueous phase is given by the partitioning coefficient, K_D:

$$K_D = \frac{[L]_{org}}{[L]_{free}}$$

The expression for D_L, which is the ratio of the concentration of the ligand in the organic phase to the total concentration of all ligand containing species in the aqueous phase, may be rewritten as follows:

$$D_L = \frac{[L]_{org}}{[H_4L^{4+}] + [H_3L^{3+}] + [H_2L^{2+}] + [HL^{+}] + [L]_{free}}$$

This equation can be rearranged to give an expression that shows the dependence of K_D on pH (H^+ concentration):

$$D_L = \frac{K_D}{(\frac{[H^+]^4}{\beta_4} + \frac{[H^+]^3}{\beta_3} + \frac{[H^+]^2}{\beta_2} + \frac{[H^+]}{\beta_1} + 1)}$$

where $[H^+]$ is the hydrogen ion concentration determined by pH measurement, K_D is the distribution equilibrium constant, and β is the overall acid dissociation constant for acid dissociation (e.g. $\beta_4 = K_1 \times K_2 \times K_3 \times K_4$). This expression can be rearranged as

$$D_L \cdot \left(\frac{[H^+]^4}{\beta_4} + \frac{[H^+]^3}{\beta_3} + \frac{[H^+]^2}{\beta_2} + \frac{[H^+]}{\beta_1} + 1 \right) = K_D$$

For the ultimate application of these complexants in solvent extraction, it is important to evaluate the solubility of the reagent in aqueous and acceptable organic solutions. Because

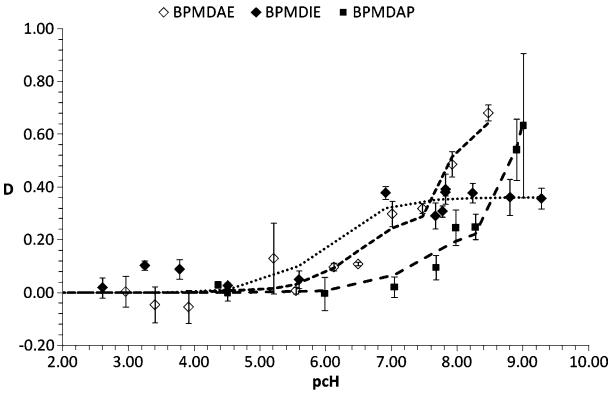

Fig. 6 Distribution[a] of N-donor ligands between an aqueous phase (0.5 mol·L^{-1} $NaClO_4$) and 1-octanol as function of p_CH: ◇, BPMDAE; ◆, BPMDIE; ■, BPMDAP. [a]Distribution fit shown by *dotted lines*

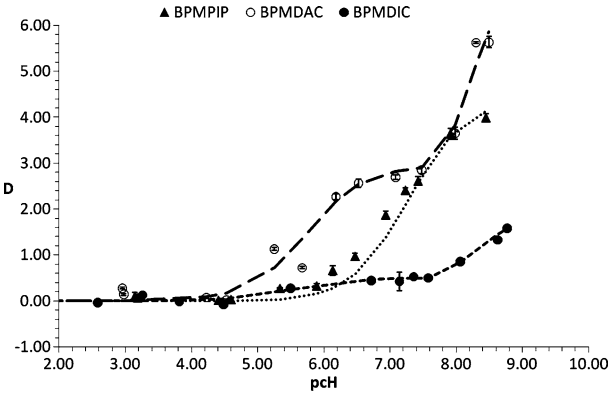

Fig. 7 Distribution[a] of N-donor ligands between an aqueous phase (0.5 mol·L^{-1} $NaClO_4$) and 1-octanol as function of p_CH: ▲, BPMPIP; ○, BPMDAC; ●, BPMDIC. [a]Distribution fit shown by *doted lines*

these tetraaza complexants are moderately polar, it is clear that a polar organic solvent will be needed for any separations application. The distribution of each ligand in 1-octanol as a function of p_CH is shown in Figs. 6 and 7.

The acid dissociation equilibria in aqueous solution also must be considered in developing the phase partitioning equilibria. The calculated values for K_D for each ligand are shown in Table 5. The K_D of the ligand was determined using the pK_a values from the potentiometric titrations at 0.5 mol·L^{-1} ionic strength. The K_D value for all the complexes were fitted using SOLVER program in Excel. In most instances a distribution of the HL^+ had to be included into the fitting to get a closer representation of the experimentally determined distribution value.

The K_D for BPMDIE, *trans*-BPMDIC, and BPMDIB have been determined previously between nitrobenzene and aqueous phases [16, 17] as 0.98, 0.80, and 1.87, respectively. From these distribution constants and that calculated for TPEN ($K_D = 0.82$) [18] it was determined that the distribution equilibria are primarily governed by the lipophilicity of the 2-pyridyl moiety rather than the aliphatic backbone of the ligand. The caveat to these previous distribution studies of BPMDIE, *trans*-BPMDIC and BPMDIB is that the tendency for the ligands to hydrolyze was never taken into account. For the distribution of the amine complexants into octanol, the opposite effect is seen, in that the lipophilicity of the backbone directly correlates to the phase distribution. BPMDAC has the highest K_D whereas BPMDIC and BPMDIE fall exactly as would be expected considering that the ligand undergoes hydrolysis.

Table 5 Distribution coefficients of N_4-tetradentate ligands from 1-octanol arranged by K_D

Compound	K_D (HL^+)	K_D (L)
BPMDAE	0.32 ± 0.09	0.71 ± 0.06
BPMDAP	0.26 ± 0.09	1.89 ± 0.02
BPMDAC	2.9 ± 0.1	7.7 ± 0.6
BPMPIP	NC[a]	4.4 ± 0.1
BPMDIE	NC[a]	0.36 ± 0.04
BPMDIC	0.50 ± 0.05	2.0 ± 0.1

[a]NC = not calculated

The K_D values for BPMDIE, and BPMDIC must be treated with some caution, since these ligands readily undergo hydrolysis leading to the composition of the organic and aqueous phase changing as a function of time and pH. The chromophores used to identify the phase transfer of these ligands are the hydrolysis products and not the ligand. The clearly observable double step in the distribution of BPMDAC (Fig. 7) is noteworthy. In the distribution curve, an initial partitioning of the ligand into the organic phase around a pH of 5.7 is observed, which coincides with the third pK_a of BPMDAC as shown in Table 1. It appears that both $H(BPMDAC)^+$ and the neutral BPMDAC ligand partition to the 1-octanol phase. More data points at lower pHs are needed to fit the K_D accurately but it appears that the K_D for $HBPMDAC^+$ is calculated as 2.9 ± 0.1 (Table 4); if taken directly from the level part of the distribution curve a value of 2.6 ± 0.2 can be determined.

4 Conclusions

The determination of the individual pK_a values for the ligands with amine backbones (BPMDAE, BPMDAP, BPMDAC and BPMPIP) follows the corresponding trend in the overall basicity of the free amine [13], in that:

BPMDAP > BPMDAE > BPMDAC > BPMPIP

propane-1,3-diamine > ethane-1,2-diamine > *trans*-cyclohexane-1,2-diamine > piperazine

The values of the last two pK_a values for BPMDAE, BPMDAP, BPMPIP, and BPMDAC indicate the more acidic nature of the pyridinium moieties when compared with the aliphatic analogue triethylenetetramine (trien) [13]. The pK_1 for both BPMDIE and BPMDIC match that of 2-pyridine carboxaldehyde at 3.8 [19] and suggests that both of these ligands undergo rapid hydrolysis in aqueous solution and are not compatible with a solvent extraction system.

From these studies it has been ascertained that the relative affinity of the N-based donor ligands for protons does not correlate with its affinity for the divalent copper ion. The stability constants for the tetradentate ligands, containing secondary amines, are exceedingly high. The most preorganized ligand, BPMDAC, has the highest value of $\log_{10} K_{101}$ (19.5) with BPMDAP and BPMDAE running up with values of 18.9 and 17.7, respectively. BPMDAP has a higher Cu(II) $\log_{10} K_{101}$ than BPMDAE which is indicative of the greater stability of Cu(II) for 6-membered chelate rings over 5 [20]. The $\log_{10} K_{101}$ value for BPMPIP is approximately 10 orders of magnitude smaller than the value for BPMDAE. This deficit is at least partially due to the energy penalty associated with the reorganization of the piperazine ring from the chair to the boat configuration. The lowest value for the Cu(II) $\log_{10} K_{101}$ is for the bidentate ligand PBIm (4.4).

The formation of a Cu(II) chromophore allows the direct detection of the ligand and the measurement ligand distribution ratio as a function of pH. The distribution coefficient for the ligand between 1-octanol and an aqueous phase as a function of pH is as follows:

$$\text{BPMDAC} > \text{BPMPIP} > \text{BPMDAP} > \text{BPMDAE}$$

Contrary to previous distribution studies in nitrobenzene [16, 17] the distribution of the ligands in 1-octanol directly correlates to the lipophilicity of the backbone. What is clear from the distribution studies of all the tested ligands is that extraction experiments must be carried out at higher pH to prevent loss of ligand to the aqueous phase. It can be argued that the K_D values for these ligands are too low to be useful in conventional solvent extraction but they may still prove to be effective at separating Am(III) from Ln(III) much like TPEN, under the following conditions, 0.001 mol·L^{-1} TPEN, 0.1 mol·L^{-1} NH_4NO_3, pH = 4.16 and nitrobenzene as the organic phase can still achieve as separation factor of 200 [21] even though the TPEN K_D is 0.82 [18].

The work presented here is part of an on-going project to determine the structural features of complexing ligands that are important in increasing the binding affinity and selectivity for An(III) over Ln(III). With a better understanding of the factors that are required for affinity and selectivity, more effective and efficient ligands can be designed.

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