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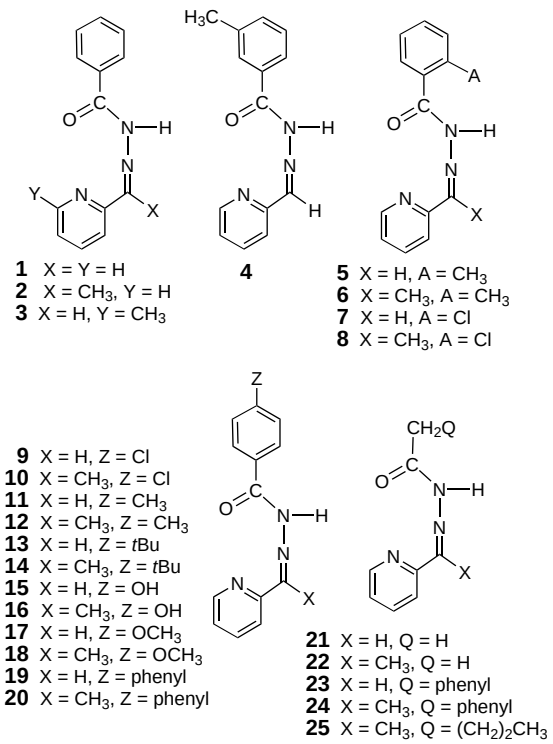
[9] This value is somewhat lower than that obtained by ^{1}H NMR spectroscopy in $CDCl_3/CD_3OH$ (92:8). The discrepancy may be due to a slight difference in experimental conditions; for example, different amounts of adventitious water may have been present in the two solvent systems.

Dynamic Acylhydrazone Metal Ion Complex Libraries: A Mixed–Ligand Approach to Increased Selectivity in Extraction**

Seema Choudhary and Janet R. Morrow*

Metal ion coordination chemistry is well suited to dynamic combinatorial chemistry approaches.[1–3] Diverse metal ion complex libraries can be created simply by mixing a labile metal ion with different ligands.[4] If ligand exchange is rapid, these metal ion complexes form the equilibrating components of a dynamic library. The equilibrium between complexes may be shifted upon addition of molecular targets. For example, small molecule or biopolymer targets perturb the equilibrium between metal ion complexes to increase the concentration of the metal ion complex that best binds the target.[5–7] We previously reported on dynamic combinatorial libraries of metal ion Schiff-base complexes of limited diversity.[8] Our selection protocol utilizes extraction of metal ion complex libraries from aqueous into organic solvent. In this method, the organic solvent is the ultimate target and complexes with the greatest stability and solubility in organic solvent versus aqueous solution are selected.[9] Here we present studies using acylhydrazone ligand libraries and show that these libraries lead to improvements in efficiency and selectivity of metal ion extraction in comparison to single ligand systems.

Acylhydrazone ligands (Scheme 1) were chosen to explore the possibility of forming a double-orthogonal library[4] by exchange at metal–ligand (M–L) and C=N bonds.[10–13] Initial studies were carried out to establish the feasibility of using these exchange processes. Zn^{II} extracts into chloroform from a buffered aqueous solution in the presence of two equivalents of acylhydrazone ligand **1** (Table 1, Scheme 1). The predominant complex that extracts into chloroform is the neutral complex $[Zn(\mathbf{1}^-)_2]$ as determined by comparison of ^{1}H NMR and mass spectral data to that of an authentic sample. After two hours, the extent of extraction of Zn^{II} from a water/chloroform mixture containing 0.0500 mM $[Zn(\mathbf{1}^-)_2]$ is identical within experimental error to a second experiment containing 0.0500 mM $Zn(NO_3)_2$ and 0.100 mM **1,** confirming that our system is at equilibrium. Addition of a different acylhydrazone ligand (**13**) to either of the solutions above followed by stirring for 2 h increases the amount

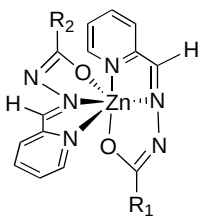


Scheme 1. Acylhydrazone ligands used in this study.

Table 1. Extraction of Zn^{2+} or Cd^{2+} into chloroform by acylhydrazone ligands.

Metal	Ligand	Extracted [%][a]	Metal	Ligand	Extracted [%][a]
Zn^{2+}	**1**	25	Zn^{2+}	**2**	62
Zn^{2+}	**3**	12	Zn^{2+}	**4**	26
Zn^{2+}	**5**	3.0	Zn^{2+}	**6**	28
Zn^{2+}	**7**	9.0	Zn^{2+}	**8**	43
Zn^{2+}	**9**	54	Zn^{2+}	**10**	62
Zn^{2+}	**11**	23	Zn^{2+}	**12**	56
Zn^{2+}	**13**	20	Zn^{2+}	**14**	54
Zn^{2+}	**15**	0	Zn^{2+}	**16**	0
Zn^{2+}	**17**	21	Zn^{2+}	**18**	54
Zn^{2+}	**19**	44	Zn^{2+}	**20**	64
Zn^{2+}	**21**	0	Zn^{2+}	**22**	1.2
Zn^{2+}	**23**	1.8	Zn^{2+}	**24**	2.0
Zn^{2+}	**25**	0	Cd^{2+}	**1**	15
Cd^{2+}	**2**	48	Cd^{2+}	**5**	2.1
Cd^{2+}	**6**	3.7	Cd^{2+}	**7**	4.0
Cd^{2+}	**8**	14	Cd^{2+}	**13**	13
Cd^{2+}	**14**	32			

[a] Extractions were carried out in 5.0 mM Mes buffer (10 mL), 0.100 M NaCl, and $CHCl_3$ (1 mL) at 23 °C at pH 5.50 for Zn^{II} (0.0500 mM) or pH 6.50 for Cd^{II} (0.0500 mM) with 0.100 mM ligand.



$[Zn(\mathbf{1}^-)_2, R = C_6H_5]$

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of extraction from 25 to 53%, consistent with ligand exchange to form mixed–acylhydrazone complexes. Analysis of these mixtures by ^{1}H NMR spectroscopy and by electrospray ion mass spectrometry confirms the presence of mixed–acylhydrazone complexes. In contrast, exchange and formation of the C=N bond is slow. Incubation of **1** with one equivalent of *o*-toluic acid hydrazide at pD 5.9, 23°C, for 14 h leads to the formation of **5** (50%) as determined by ^{1}H NMR spectroscopy. Incubation of **1**, *o*-toluic acid hydrazide, and $Zn(NO_3)_2$ in a 2:2:1 ratio fails to produce free or bound acylhydrazone (**5**) after several days. In addition, if 2-pyridinecarboxaldehyde and benzoic hydrazide are used in lieu of **1** for extraction of Zn^{II}, equilibrium is attained only after 80 h. All further extractions used acylhydrazone ligands under conditions where M–L exchange is dynamic but no C=N exchange is anticipated.

A library of 25 different acylhydrazone ligands was studied for extraction of Zn^{II} and Cd^{II}. These d^{10} ions were chosen based on their flexible coordination geometries that can be readily distorted by ligand substituents.[8] Such distortions in coordination geometry affect the stability and solubility of the complex. A variety of ligand substitutents were chosen with the goal of varying the steric and electronic nature of the ligand (Table 1). A few important trends are discussed here. For both Zn^{II} and Cd^{II}, acylhydrazones derived from the ketone (compare **1** and **2**) extract metal ions better than do ligands derived from aldehydes, consistent with the extra methyl group forming a more hydrophobic metal ion complex with a higher molar volume. Ligands with benzyl substituents (**23**, **24**) extract little at pH 5.5, but efficiently at pH 8.5. This suggests that an aryl group is necessary to lower the pK_a of the acylhydrazone ligand for extraction at acidic pH. Acylhydrazones with substituents in the 2-position of the aryl ring (**5**–**8**) are less effective than analogous ligands substituted in the 4-position (**9**–**12**), likely due to steric interference of the substituent with binding. Ligands with methyl or *tert*-butyl groups on the aryl or pyridine rings (**3**, **4**, **11**–**14**) do not increase extraction over the unsubstituted derivatives (**1**, **2**), despite their higher molar volume.

Metal ion complex libraries are created by using two different ligands. In these experiments, ligand exchange leads to the formation of at least three different complexes in each experiment ($[M(L1)_2]$, $[M(L1)(L2)]$, $[M(L2)_2]$); the most stable and soluble combinations extract into chloroform. An increase in metal ion extraction by two different ligands compared to that by a single type of ligand is referred to as a ligand synergistic effect.[14,15] Synergistic effects are detected here as deviations from calculated values for the extent of extraction (see Supporting Information). Positive deviations arise from the formation of mixed–acylhydrazone complexes with improved extraction properties. Mixed–ligand studies are carried out in three groups; the first contains ligands derived from ketones, the second contains ligands derived from aldehydes, and the third is a mixture of the two types of ligands.

No synergistic effects are observed for extraction of Zn^{II} by mixtures of two ligands derived from ketones. In addition, no ligand synergistic effects are observed for extraction of Cd^{II} by any ligand combination. However, ligands derived from aldehydes show synergy in Zn^{II} extraction in a few cases including a 1.4-fold increase in extraction for **1** and **13** over that expected (53% observed, 39% calculated) and **1** and **7** (43% observed, 31% calculated). Larger effects are observed when the two classes of ligands are mixed. The percent extraction is nearly doubled for a mixture of **6** and **7** (61% observed, 34% calculated). Other combinations that show significant synergistic effects include a 1.6-fold increase for **7** and **8** (64% observed, 47% calculated), a 1.4-fold increase for **5** and **6** (47% observed, 30% calculated), and a 1.3-fold increase for **5** and **8** (58% observed, 44% calculated).

The largest synergistic effects are observed for Zn^{II} with ligands containing substituent variations in two positions (X and A in Scheme 1). The fact that there are no Cd^{II} ligand synergistic effects suggests that the size of the metal ion and thus steric considerations are important. It is also noteworthy that the substituent positions giving rise to synergistic effects are those that are most likely to influence the conformation and binding of the ligand through ligand steric effects. Methyl groups attached to the imine carbon atom influence the overall conformation of Schiff-base complexes[16] by reducing the flexibility of the ligand. However, not just any combination is synergistic; acylhydrazones must have 2-aryl substituents for optimal results. Given that substituents at the 2-position decrease the ability of the ligand to bind to the metal ion, it is puzzling that these substituents increase the extent of synergy in extraction. Further studies are underway to determine the effect of these multiple ligand substituents on Zn^{II} complex structure.

An important goal in metal ion separations is to increase the selectivity of the ligand for a metal ion. Zn^{II} is normally more easily extracted than Cd^{II} due to its higher Lewis acidity; this is attested to by the negligible amount of Cd^{II} compared to Zn^{II} extracted at pH 5.5 . In fact, selectivity for Zn^{II} versus Cd^{II} would be higher if the two metal ions were extracted at the same pH. Nonetheless, it is interesting that selectivity for Zn^{II} over Cd^{II} is enhanced for certain ligands and ligand mixtures. For example, a combination of **5** and **6** gives a selectivity of 12-fold for Zn^{II} versus Cd^{II}. Additional favorable combinations exhibiting higher selectivity include **6** and **7**, **7** and **8**, **5** and **8**, and **6** and **8** as shown in Figure 1. Four of the five involve combinations of ligands that are synergistic in the

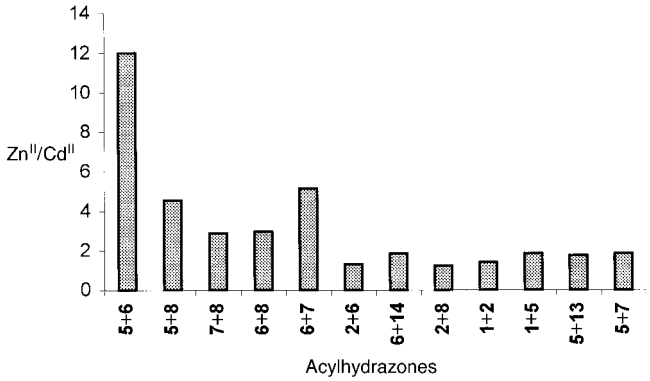

Figure 1. Comparison of percent extraction of Zn^{II} versus Cd^{II} by mixtures of acylhydrazone ligands. Extractions had 5.0 mM Mes buffer (10.00 mL), 0.100 M NaCl, $CHCl_3$ (1.00 mL) at 23°C, at pH 5.50 for Zn^{II} (0.500 mM) or pH 6.50 for Cd^{II} (0.0500 mM) with 1.00 mM of each ligand.

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extraction of Zn^{II} but not Cd^{II}. The highest selectivity with single ligands (Table 1) are 7.6-fold (**6**) and 3.1-fold (**8**). Interestingly both **6** and **8** are ketone-derived ligands with 2-aryl substituents, suggesting that this combination of substituents enhances extraction of Zn^{II}.

These studies demonstrate that dynamic combinatorial chemistry is a useful tool for the discovery of new metal ion complexes. Synergistic interactions of ligands are useful for building in selectivity for metal ions by using simple ligand substituent effects. This method has potential for practical applications given that the ligands are inexpensive and readily synthesized. However, there remains much to learn about the construction of an effective library of metal ion complexes. Future work will focus on exploring strategic positions for substitutents on different types of ligands and on increasing the complexity of the library by using metal complexes that bind three ligands.

Experimental Section

Extraction solutions were stirred in foil-wrapped vials with teflon-lined crimp caps for 2 h and were analyzed for Zn^{II} or Cd^{II} by use of dithizone indicator.[8] Standard deviations in measurements are 10% or less.

Acylhydrazone ligands were prepared by heating a solution of either 2-pyridinecarboxaldehyde (PCA) or 2-acetylpyridine in ethanol, a stoichiometric amount of the corresponding acylhydrazide, and a few drops of hydrochloric acid. Concentration of the solution and cooling followed by recrystallization from ethanol or ethanol/hexane yielded the ligand. In a typical preparation, benzoic hydrazide (0.272 g, 2.00 mmol) was added to a solution of PCA (0.190 mL, 2.00 mmol) in ethanol (20 mL) and a few drops of hydrochloric acid was added. The solution was gently heated and stirred for 0.25 h. Upon cooling, a white precipitate (**1**) formed, which was washed with ethanol, recrystallized, and dried in vacuo. ^{1}H NMR (400 MHz, [D_6]DMSO, 24 °C, TMS): $\delta = 12.0$ (s, 1H; NH), 8.60 (d, $^3J(H,H) = 4$ Hz,1H; H10), 8.46 (s, 1H; H6), 7.92 (m, 4H; H7, H8, H1, H5), 7.60 (t, $^3J(H,H) =$ 4.2 Hz, 1H; H9), 7.53 (t, $^3J(H,H) = 4.7$ Hz, 2H; H2, H4), 7.40 ppm (t, $^3J(H,H) = 5.6$ Hz, 1H; H3) (see Supporting Information for ligand-numbering scheme); ESI-MS: *m/z* (%): 226(52) [PCA-BAH+H^+], 248(100) [PCA-BAH+Na^+].

[$Zn(\mathbf{1}^-)_2$] was prepared by dissolving $Zn(NO_3)_2$ (0.788 g, 2.65 mmol) in hot ethanol (100 mL), followed by the addition of PCA (5.30 mmol), and benzoic hydrazide (0.721 g, 5.30 mol). Triethylamine (5.30 mmol) was added and the solution was heated to boiling for 0.25 h. Upon cooling, a bright yellow precipitate was recovered and recrystallized from ethanol. ^{1}H NMR (400 MHz, [D_1]chloroform, 25 °C, TMS): $\delta = 8.50$ (s, 1H; H6), 8.21 (d, $^3J(H,H) = 7.6$ Hz, 2H; H1, H5), 8.06 (d, $^3J(H,H) = 4.8$ Hz, 1H; H10), 7.72 (t, $^3J(H,H) = 7.6$ Hz,1H; H8), 7.38 (m, 4H; H9, H2, H4, H7), 7.14 ppm (t, $^3J(H,H) = 5.2$ Hz, 1H; H3); ESI MS: *m/z* (%): 513(100), 514(32), 515(63), 516(29), 517(44), [Zn(PCA-BAH)$_2$+H^+].

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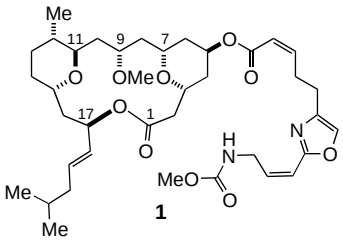
Total Synthesis of Leucascandrolide A**

Alec Fettes and Erick M. Carreira*

Leucascandrolide A (**1**), a polyoxygenated marine macrolide of a new genus, was isolated in 1996 by Pietra and co-



workers from the calcareous sponge *Leucascandra caveolata* along the east coasts of New Caledonia.[1] Despite subsequent intensive efforts, later expeditions failed to provide additional leucascandrolide A.[2] Leucascandrolide A (**1**) displays strong cytotoxic activity in vitro on human KB and P388 cancer cell lines ($IC_{50} = 50$ and 250 ng mL^{-1}, respectively) as well as powerful antifungal activity. An elegant total synthesis has been recently reported by Leighton and co-workers,[3] and a formal synthesis has been documented by Rychnovsky and co-workers[4] along with synthetic studies of the core by Crimmins et al.[5] and Kozmin[6] and a synthesis of the oxazole side chain by Wipf et al.[7] The lack of availability of

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