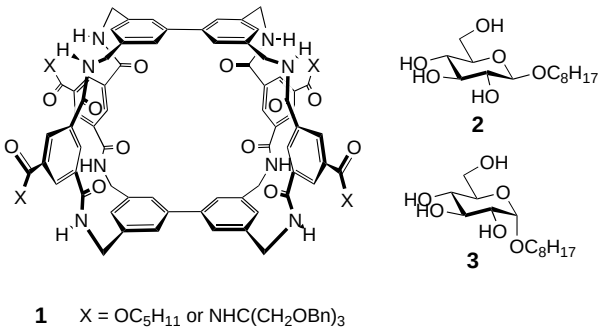
Morin, Jr., E. J. Salaski, *J. Am. Chem. Soc.* **1985**, *107*, 8066.
[19] We thank Professor Larry Overman for comparing NMR spectra of (±)-**1** with those of chiral **1**.[4]
[20] E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190.
[21] CCDC 185370 contains the supplementary crystallographic data for compound **19**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
[22] A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, J. Meienhofer, *J. Org. Chem.* **1978**, *43*, 4194.
[23] a) G. Lakshmaiah, T. Kawabata, M. Shang, K. Fuji, *J. Org. Chem.* **1999**, *64*, 1699; b) R. F. Borch, A. Hassid, *J. Org. Chem.* **1972**, *37*, 1673.



**1** X = $OC_5H_{11}$ or $NHC(CH_2OBn)_3$

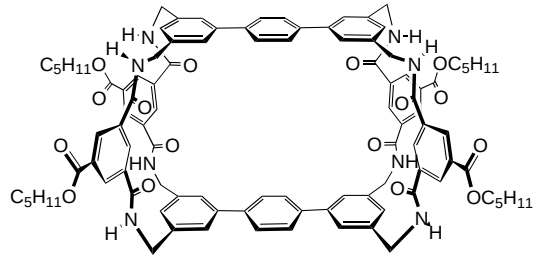
## Highly Selective Disaccharide Recognition by a Tricyclic Octaamide Cage**

Grégory Lecollinet, Andrew P. Dominey, Trinidad Velasco, and Anthony P. Davis*

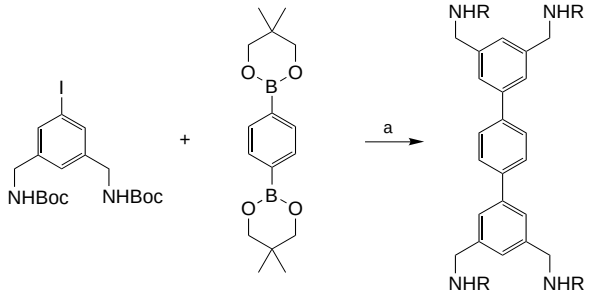
Carbohydrate recognition presents a continuing challenge to supramolecular chemistry,[1] fuelled by the growing awareness of saccharide structures as mediators of biological events.[2] However, while the biological interest is focussed largely on oligosaccharides, supramolecular chemists have concentrated mainly on monosaccharide substrates. A number of systems show preferential binding of di- versus monosaccharides,[1c–e,3] but only a few boron-based receptors show good selectivity between disaccharides.[1c,3a–3d] The latter employ covalent B–O bond formation, and are thus less relevant to biological carbohydrate recognition.

We recently described the tricyclic cage receptors **1**, which bind monosaccharide derivatives strongly and selectively even in the presence of a hydroxylic cosolvent.[4] Receptor **1** proved remarkably selective for the all-equatorial β-glucoside **2** as against the α-anomer **3**. We now report the synthesis and binding properties of **4**, an "extended analogue" of **1** designed to accommodate disaccharide substrates. Compound **4** has proved to be the first receptor capable of distinguishing clearly between disaccharides through noncovalent interactions.

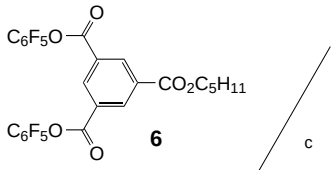
Receptor **4** was synthesized by two independent routes. In the first, the tetraaminoterphenyl **5** was prepared as shown in Scheme 1 and coupled under high dilution with bis(penta-



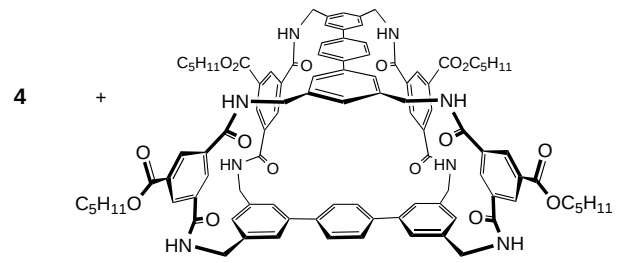
**4**



**5** R = Boc / R = H



**6**



**7**

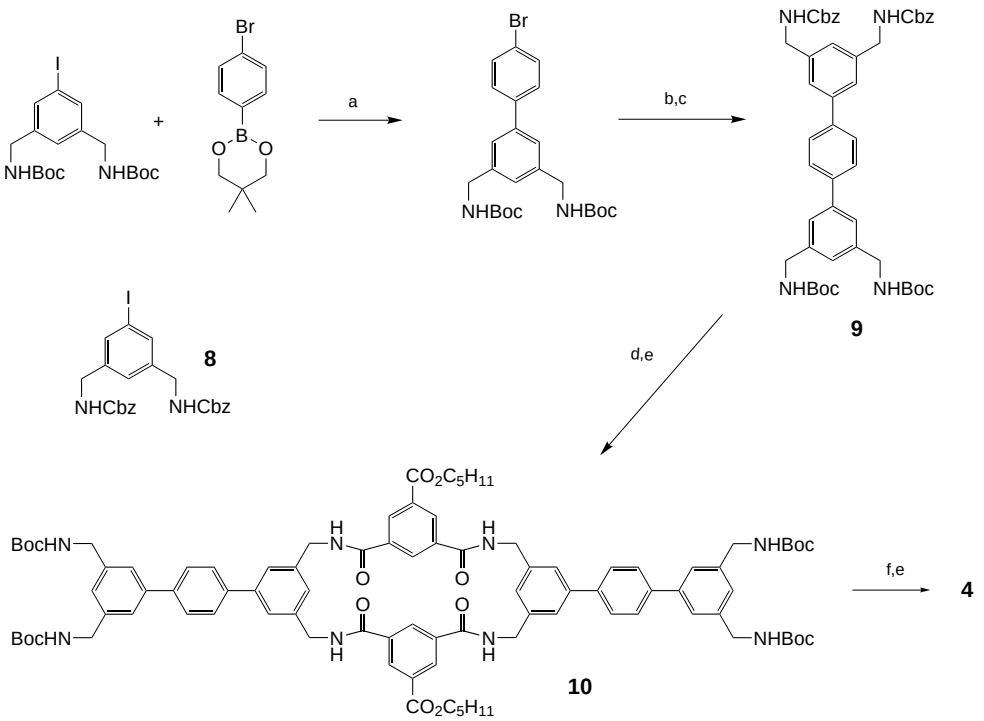
Scheme 1. Synthesis of **4** + **7**: a) [$PdCl_2$(dppf)], $Na_2CO_3$ aq. (2M), DMF, 80°C; b) trifluoroacetic acid (TFA), $CH_2Cl_2$; c) **6**, $iPr_2NEt$, THF/DMF, high dilution. dppf = diphenylphosphanylferrocene.

[*] Prof. A. P. Davis, Dr. G. Lecollinet, T. Velasco
School of Chemistry
University of Bristol
Cantock's Close
Bristol BS8 1TS (UK)
Fax: (+44) 117-929-8611
E-mail: Anthony.Davis@bristol.ac.uk
Dr. A. P. Dominey
Department of Chemistry
Trinity College, Dublin 2 (Ireland)

[**] Financial support for this work was provided by the European Commission (TMR contract ERB-FMRX-CT98-0231) and Enterprise Ireland.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

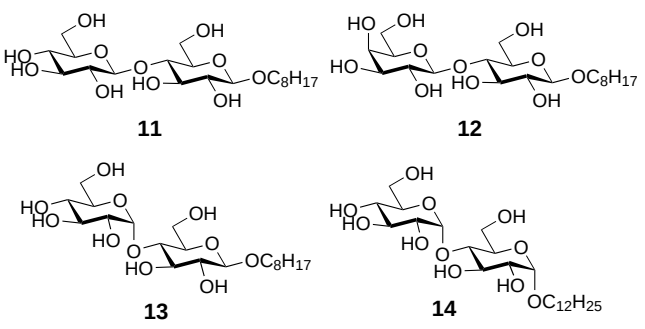
  0044-8249/02/4121-4093 $ 20.00+.50/0 




Scheme 2. Synthesis of **4**: a) [$PdCl_2$(dppf)], $Na_2CO_3$ aq. (2 M), DMF, 80 °C; b) bis(pinacolato)diboron, [$PdCl_2$(dppf)], KOAc, DMF, 80 °C; c) **8**, [$PdCl_2$(dppf)], $Na_2CO_3$ aq. (2 M), DMF, 80 °C; d) $H_2$, 10 % Pd/C, $CH_3OH/CH_2Cl_2$; e) **6**, *i*$Pr_2$NEt, THF/DMF, high dilution; f) TFA, $CH_2Cl_2$.

fluorophenyl) ester **6**. This direct route seemed viable as, for steric and geometric reasons, no [1+1] cyclization is possible between **5** and **6**. The smallest unstrained rings (favored at high dilution) result from [2+2] cyclizations, as required for **4**. However, a regioisomeric macrotricycle **7** is also possible, and two cyclized products were indeed formed. Mass spectrometric and NMR spectroscopic data were consistent with a mixture of **4** + **7**, but unfortunately the two could not be separated. Pure **4** was therefore prepared by a longer but unambiguous sequence (Scheme 2) in which orthogonal protection in tetracarbamate **9** allowed sequential [2+2] cyclizations, leading specifically to **4** via **10**.

In common with receptor **1**, macrotricycle **4** possesses extended, parallel apolar surfaces linked through spacers containing hydrogen-bond donor and acceptor groups. This geometry should be compatible with equatorially substituted carbohydrate derivatives.[4a] Accordingly, the all-equatorial *n*-octyl-β-D-cellobioside **11**[5,6] was employed for initial binding studies. In the first instance, **11** was added to the mixure of **4** and **7** in $CDCl_3/CD_3OH$ (92:8) (the solvent used for NMR




binding studies on **1**[4]). As hoped, we observed changes in the $^1$H NMR spectrum of just one of the macrotricycles (later identified as **4**). However, instead of signal movements with minor splittings (as observed for **1** + **2**[4a]), the spectrum of **4** was replaced by a new set of resonance signals implying loss of all symmetry (see Figure S1 in the Supporting Information). Titration of **11** into pure **4** confirmed this result, revealing progressive loss of receptor and growth of the new spectrum (Figure 1), and clearly implying complex formation with slow exchange. Integration of bound versus uncomplexed receptor proved unworkable, but the growth of the new signals could be monitored by integration versus an internal standard. The data was consistent with 1:1 binding (Figure 2) with a binding constant ($K_a$) of

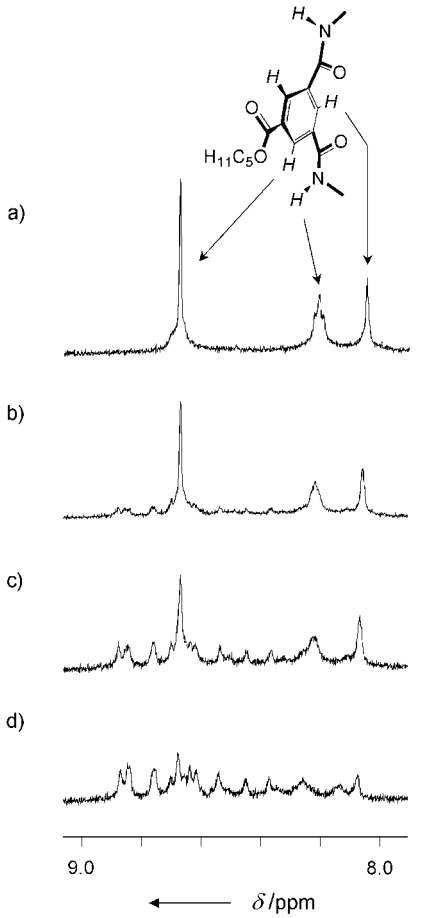



Figure 1. Partial $^1$H NMR spectra in $CDCl_3/CD_3OH$ (92:8) of receptor **4** after addition of a) 0, b) 0.4, c) 1, and d) 5 equivalents of **11**.

  0044-8249/02/4121-4094 $ 20.00+.50/0 *Angew. Chem. Int. Ed.* **2002**, *41*, No. 21

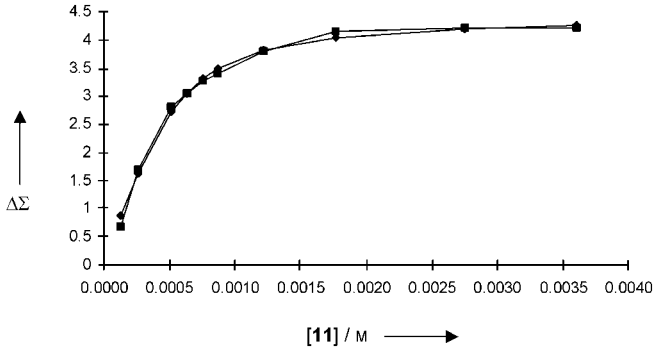



Figure 2. Experimental (■) and calculated (◆) values for the $^1$H NMR binding study of **4** + **11** in $CDCl_3/CD_3OH$ (92:8). [**4**] = 0.5 mM, [**11**] = 0.13–3.6 mM. $T$ = 278 K. Experimental points were obtained by integration of the signal at $\delta$ = 8.8–8.9 (see Figure 1) versus an internal standard (pentafluorobenzaldehyde, $\delta$ = 10.27). The data were analyzed by using a nonlinear least-squares curve-fitting program implemented within Excel 2000.

7000 $M^{-1}$, slightly higher than the value of 980 $M^{-1}$ measured for **1** + **2** under these conditions.[4a] In a control experiment, glycoside **11** was added to macrocycle **10** under the same conditions; as expected, no change was observed in the spectrum of **10**.To investigate the selectivity of **4**, similar experiments were performed with octyl glucosides **2** and **3**, octyl β-D-lactoside **12**,[6,7] octyl β-D-maltoside **13**,[6,8] and dodecyl α-D-maltoside **14** as substrates. Remarkably, none of these compounds produced any detectable effect on the NMR spectrum of the receptor. Moreover, addition of **12** to (**4** + **11**) had no effect on the spectrum of the complex. The implied selectivity was confirmed by two further techniques. First, irradiation of **4** at $\lambda$ = 285 nm caused fluorescence emission in the ranges 350–450 nm and 650–750 nm. Addition of **11** caused substantial increases in the intensities of both bands (see Figure S2 in the Supporting Information). Analysis of the data supported a 1:1 binding model, with $K_a$ = 2500 $M^{-1}$ (Figure 3).[9] In contrast, experiments with **2**, **3**, and **12**–**14** showed no sign of complex formation. In each case, addition of 10 equivalents of glycoside (to 0.3 mM) produced no effect on the fluorescence of **4**. The fluorescence titration of **4** versus **11** was repeated in a less competitive solvent system, $CHCl_3$/MeOH (98:2), yielding a binding constant of 64000 $M^{-1}$ (see Figures S3 and S4 in the Supporting Information). Even under these conditions, addition of lactoside **12** or β-maltoside **13** caused no change in emission (see Figure S5 in the Supporting Information). Second, weak but unambiguous induced circular dichroism was observed when **11** was added to **4** in $CHCl_3$/MeOH (92:8) (see Figure S6 in the Supporting Information). The spectra were too noisy for quantitative analysis, but saturation was clearly observed with increasing [**11**]. Once again, negative results were obtained with **12** or **13**, the receptor remaining CD-silent.

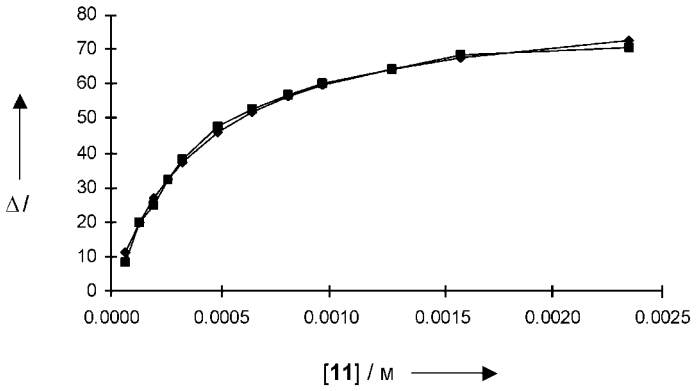



Figure 3. Experimental (■) and calculated (◆) values for the fluorescence binding study of **4** + **11** in $CHCl_3/CH_3OH$ (92:8). [**4**] = 0.03 mM, [**11**] = 0.065–2.3 mM.

In conclusion, these experiments seem to reveal an interaction of unusual specificity between a synthetic receptor **4** and a biomolecular substrate **11**. We cannot be absolutely certain that **4** does not bind the other glycosides, as complex formation might not induce a change in spectroscopic properties in these cases. However, the complete absence of any signal from any other substrate, on employing three quite different techniques, provides strong evidence for extreme selectivity. The substrates, moreover, are only subtly different from each other. For example, **11** and **12** are related by inversion at a single asymmetric center, at one end of the structure. Finally, the design strategy seems to have been validated. The geometry of **4** does indeed favor the "flat" all-equatorial substrate, supporting the notion that selective receptors for at least some complex biomolecules are accessible through rational design and synthesis.

Received: June 6, 2002 [Z19486]

[1] Reviews: a) A. P. Davis, R. S. Wareham, *Angew. Chem.* **1999**, *111*, 3160; *Angew. Chem. Int. Ed.* **1999**, *38*, 2978; b) T. D. James, K. R. A. S. Sandanayake, S. Shinkai, *Angew. Chem.* **1996**, *108*, 2038; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1911; recent examples: c) A. Sugasaki, K. Sugiyasu, M. Ikeda, M. Takeuchi, S. Shinkai, *J. Am. Chem. Soc.* **2001**, *123*, 10239; d) A. S. Droz, U. Neidlein, S. Anderson, P. Seiler, F. Diederich, *Helv. Chim. Acta* **2001**, *84*, 2243; e) O. Rusin, K. Lang, V. Král, *Chem. Eur. J.* **2002**, *8*, 655; f) R. D. Hubbard, S. R. Horner, B. L. Miller, *J. Am. Chem. Soc.* **2001**, *123*, 5810; g) W. Yang, H. He, D. G. Drueckhammer, *Angew. Chem.* **2001**, *113*, 1764; *Angew. Chem. Int. Ed.* **2001**, *40*, 1714; h) S. Tamaru, M. Yamamoto, S. Shinkai, A. B. Khasanov, T. W. Bell, *Chem. Eur. J.* **2001**, *7*, 5270; i) M. Mazik, H. Bandmann, W. Sicking, *Angew. Chem.* **2000**, *112*, 562; *Angew. Chem. Int. Ed.* **2000**, *39*, 551; j) J. Bitta, S. Kubik, *Org. Lett.* **2001**, *3*, 2637; k) S. Arimori, M. L. Bell, C. S. Oh, K. A. Frimat, T. D. James, *Chem. Commun.* **2001**, 1836; l) N. Sugimoto, D. Miyoshi, J. Zou, *Chem. Commun.* **2000**, 2295; m) M. Inouye, J. Chiba, H. Nakazumi, *J. Org. Chem.* **1999**, *64*, 8170.

[2] R. A. Dwek, T. D. Butters, *Chem. Rev.* **2002**, *102*, 283 (and succeeding articles); I. Capila, R. J. Linhardt, *Angew. Chem.* **2002**, *114*, 426; *Angew. Chem. Int. Ed.* **2002**, *41*, 390; T. Feizi, B. Mulloy, *Curr. Opin. Struct. Biol.* **2001**, *11*, 585 (and succeeding articles); C. R. Bertozzi, L. L. Kiessling, *Science* **2001**, *291*, 2357; J. K. Bashkin, *Chem. Rev.* **2000**, *100*, 4265 (and succeeding articles).

[3] a) A. Sugasaki, M. Ikeda, M. Takeuchi, S. Shinkai, *Angew. Chem.* **2000**, *112*, 3997; *Angew. Chem. Int. Ed.* **2000**, *39*, 3839; b) M. Ikeda, S. Shinkai, A. Osuka, *Chem. Commun.* **2000**, 1047; c) H. Kijima, M. Takeuchi, S. Shinkai, *Chem. Lett.* **1998**, 781; d) K. Sandanayake, K. Nakashima, S. Shinkai, *J. Chem. Soc. Chem. Commun.* **1994**, 1621; e) A. S. Droz, F. Diederich, *J. Chem. Soc. Perkin Trans. 1* **2000**, 4224; f) J. Otsuki, K. Kobayashi, H. Toi, Y. Aoyama, *Tetrahedron Lett.* **1993**, *34*, 1945.

[4] a) A. P. Davis, R. S. Wareham, *Angew. Chem.* **1998**, *110*, 2397; *Angew. Chem. Int. Ed.* **1998**, *37*, 2270; b) T. J. Ryan, G. Lecollinet, T. Velasco, A. P. Davis, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4863.

[5] Y. D. Ma, A. Takada, M. Sugiura, T. Fukuda, T. Miyamoto, J. Watanabe, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 346.

  0044-8249/02/4121-4095 $ 20.00+.50/0 

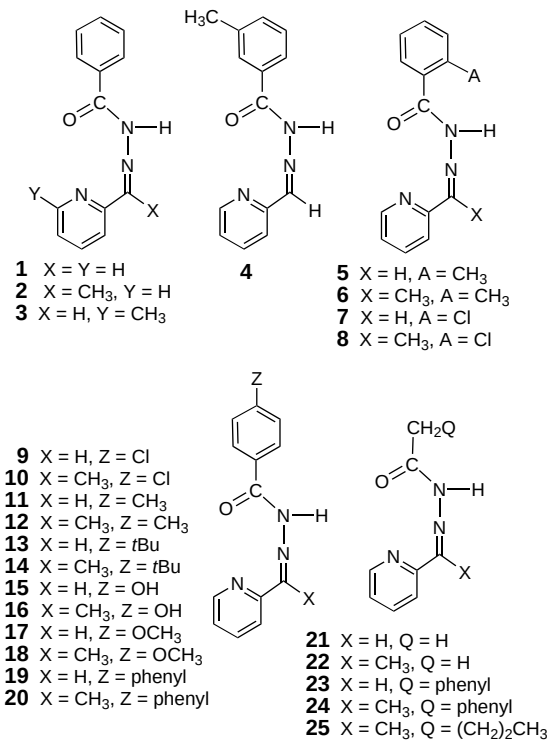
[6] Glycosides **11–13** were synthesized by using the method of Vill et al.; V. Vill, T. Bocker, J. Thiem, F. Fischer, *Liq. Cryst.* **1989**,*6*, 349.
[7] G. Pohlenz, M. Trimborn, H. Egge, *Glycobiology* **1994**, *4*, 625.
[8] H. Alpes, K. Allman, H. Plattner, J. Reichert, R. Riek, S. Schulz, *Biochim. Biophys. Acta* **1986**, *862*, 294.
[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

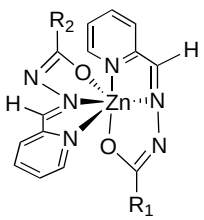



Scheme 1. Acylhydrazone ligands used in this study.

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.




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

[*] Prof. J. R. Morrow, Dr. S. Choudhary
Department of Chemistry
University at Buffalo
State University of New York
Amherst, NY 14260 (USA)
Fax: (+1) 716-645-6963
E-mail: jmorrow@acsu.buffalo.edu

[**] This work was supported by the American Chemical Society Petroleum Research Fund (34358-AC3) and by the Environment and Society Institute of the University at Buffalo.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  0044-8249/02/4121-4096 $ 20.00+.50/0 