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Review Article

Synthesis of Functionalized Aza-macrocycles and the Application of Their Metal Complexes in Binding Processes

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Abstract. Although aza-macrocycles have been thoroughly investigated ever since their discovery because of their interesting binding properties, recent applications of their metal complexes in medical concepts or as binding sites for recognition in water have increased the demand for efficient syntheses of functionalized derivatives. We present here two approaches to functionalized aza-macrocycles: substituted cyclams have been obtained by heterogeneous hydrogenation of unsaturated heterocycles, and with established coupling methods from peptide chemistry the selective introduction of functional groups and tethering of cyclens was achieved. The ability of Lewis-acidic complexes of such substituted aza-macrocycles to reversibly form defined aggregates even in neutral aqueous solution was demonstrated with the synthesis of an electron donor – electron acceptor dyad, which is capable of undergoing a very efficient intramolecular photoinduced electron transfer.

Key words: aza-macrocycles, cyclen, cyclam, Lewis-acids, metal complexes, coordinative bonds

1. Introduction

Aza-crown compounds [1], such as 1,4,7,10-tetraaza-cyclododecane (cyclen) or 1,4,8,11-tetraaza-cyclotetradecane (cyclam), have been studied for a long time. Reliable procedures for their synthesis are known and in many cases coordination properties and pK_a-values have been reported. More recently the application of aza-crown compounds in medicinal concepts that utilize metal ions for diagnosis and therapy, such as magnetic resonance imaging or radioimmunotherapy [2], has received much attention. By tight coordination aza-macrocycles can reduce the otherwise high toxicity of metal ions [3] and adapt their physical properties to

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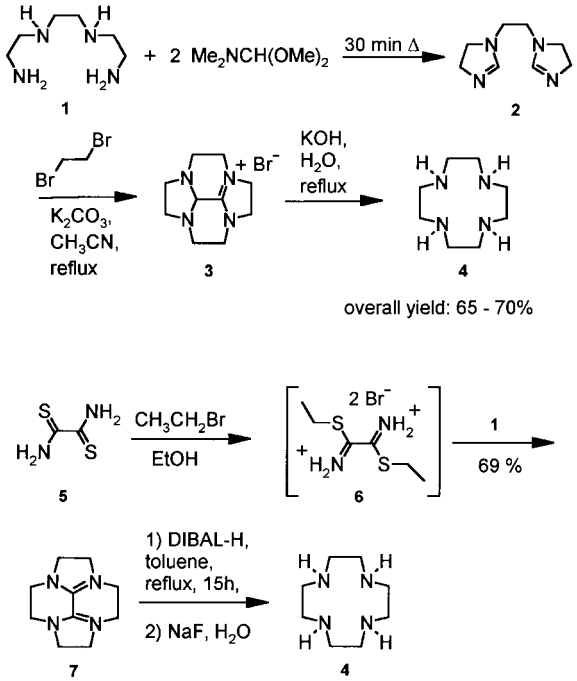


Scheme 1. Efficient, large scale syntheses of 1,4,7,10-tetraaza-cyclododecane (cyclen). Upper route: Dow Chemicals. Lower route: Synthesis reported by Weisman and Reed [4].

specific applications. However, to perform the desired function in most cases the ligand must bear the required functional groups. While recently developed large scale syntheses [4] (see Scheme 1) provide kilogram amounts of cyclen as starting material, and several practical methods for selective *N*-alkylation are available, the synthesis of C-substituted derivatives and defined oligomers of aza-macrocycles remains difficult. In this contribution we will summarize our recent efforts to provide new synthetic routes to functionalized aza-macrocycles and show examples of their use in supramolecular chemistry by the preparation of a photoactive aggregate in water.

2. Experimental

2.1. X-RAY STRUCTURE DETERMINATIONS

Crystal data for 13a: $C_{38}H_{55}H_5O_7S$, M = 725.93, crystals from acetone, triclinic, space group $P\bar{1}$, a = 1157.6 (4), b = 1168.5 (4), c = 1512.6 (4) pm, α = 89.63(3)°, β = 74.19 (3)°, γ = 86.83 (4)°, V = 1.9650(10) nm^3, Z = 2, D_c = 1.9650(10) g cm^{-3}, T = 143 K, F(000) = 780, crystal size: 0.48 × 0.42 × 0.38 mm, λ (Mo K_α) = 71.073 pm, 7497 reflections, 6931 independent, R_{int} = 0.035, $2\theta_{\max}$

50°. Refinement on F^2 (program ShelxL-97), 470 parameters, $wR_2 = 0.114$, $R_1 = 0.044$.

Crystal data for 9a: $C_{22}H_{44}N_4 \cdot \frac{1}{2}H_2O$, $M = 373.62$, crystals from acetone, triclinic, space group $P\bar{1}$, $a = 851.6$ (1), $b = 1081.9$ (1), $c = 1412.6$ (1) pm, $\alpha = 68.03(1)°$, $\beta = 79.40$ (1)°, $\gamma = 76.97$ (1)°, $V = 1.1687(2)$ nm^3, $Z = 2$, $D_c = 1.0620$ (1) g cm^{-3}, $T = 293$ K, F(000) = 418, crystal size: 0.25 × 0.20 × 0.15 mm, λ(Mo K_α) = 71.073 pm, 9323 reflections, 5078 independent, $R_{int} = 0.045$, $2\theta_{max}$ 54°. Refinement on F^2 (program ShelxL-97), 442 parameters, $wR_2 = 0.119$, R_1 (all data) = 0.070.

3. Synthesis

General: Melting points were taken on a Hot-plate microscope apparatus and are not corrected. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) in [D]-chloroform solutions unless otherwise stated. The multiplicity of the ^{13}C signals was determined with the DEPT technique and quoted as: (+) for CH_3 or CH, (−) for CH_2 and (C_{quat}) for quaternary carbons. CC means column chromatography on silica gel unless otherwise stated. All HPLC separations were performed on a RP-18 column, 10 × 200 mm. EE means ethyl acetate. Compounds **11a** [21b], **11b** [21a], **12** [5] and **14a** [24] have been prepared according to literature procedures.

General procedure A (GP-A): A mixture of the aza-macrocycle (1 mmol), the required equiv. of carboxylic acid and DCC in CH_2Cl_2 (10 mL) was stirred at room temperature under nitrogen for 15 h. The precipitated dicyclohexyl urea (DCU) was removed by filtration, the solvent was evaporated *in vacuo* and the crude product was purified by CC.

General procedure B (GP-B): A mixture of the aza-macrocycle (1 mmol), the required amount of carboxylic acid, DCC and *N*, *N*-dimethylaminopyridine (1.1 equiv./COOH) in CH_2Cl_2 (10 mL) was stirred under nitrogen at room temperature for 15 h. The precipitated DCU was filtered off, the CH_2Cl_2 solution was washed with aqueous NaOH (2 M) and HCl (1 M), dried over Na_2SO_4, and the solvent was removed *in vacuo.* The crude products were purified by CC.

General procedure for ester hydrolysis (GP-H): The ester (1 mmol) was dissolved in a mixture of aqueous NaOH (2 M) (10 mL) and methanol (10 mL) and stirred at room temperature for 15 h. Methanol was removed *in vacuo*, HCl (1 M) was added to adjust the reaction mixture to pH 1, the aqueous phase was extracted with CH_2Cl_2, the organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*.

General procedure for selective removal of Cbz protecting groups from 1,4,7,10-tetraaza-cyclododecane (GP-Cbz): The Cbz-protected derivative of 1,4,7,10-tetraaza-cyclododecane was hydrogenated on Pd/C in ethanol at a hydrogen pressure of 405 kPa for 12 h. Pd/C was removed by filtration and the solvent was evaporated *in vacuo*.

General procedure for selective removal of Boc protecting groups from 1,4,7,10-tetraaza-cyclododecane (GP-Boc): The Boc-protected derivative of 1,4,7,10-tetraaza-cyclododecane was mixed with CF_3COOH/CH_2Cl_2(1 : 1) under nitrogen or aqueous HBr (48%) in ethanol. The mixture was stirred for 3 h at room temperature, NaOH (2 M) was added to adjust the reaction mixture to pH 12, the aqueous phase was extracted with CH_2Cl_2, the organic layer dried was over Na_2SO_4 and the solvent was evaporated *in vacuo*.

10-(3-Phenothiazine-1-yl-propionyl)-1, 4, 7, 10-tetraaza-cyclododecane-1, 4, 7- tricarboxylic acid tri-tert-butyl ester (**13a**): A mixture of 3-phenothiazine-10-yl-propionic acid (**12**, 312 mg, 1.15 mmol), 1,4,7,10-tetraaza-cyclododecane-1,4,7-tricarboxylic acid tri-*tert*-butyl ester (**11a**, 472 mg, 1.15 mmol), DCC (237 mg, 1.15 mmol) and DMAP (140 mg, 1.15 mmol) was allowed to react in 12 mL CH_2Cl_2 according to *GP-B*. The crude product was purified by HPLC (CH_3CN, retention time = 3.5 min at a flow rate of 9 mL/min; TLC, EE, R_f = 0.7) to yield 760 mg (91%) **13a**, as a white solid, m.p. 78 °C; IR (KBr): 3446, 2975, 1646 cm^{-1}; UV/VIS (MeCN): λ_{max} (log ϵ): 192 (4.715), 256 (4.522), 308 (3.615); ^{1}H NMR (400 MHz, [D_6]-acetone) δ 7.11 (m, 2 H); 7.07 (m, 2 H), 7.03 (m, 2 H), 6.98 (m, 2 H), 4.20 (m, 2 H), 3.42 (m, 16 H), 2.05 (m, 2 H), 1.50 (s, 18 H), 1.33 (s, 9 H); ^{13}C NMR (100 MHz, [D_6]-acetone) δ), 157.6 (C_{quat}); 155.9 (C_{quat} 145.9 (C_{quat}), 128.4 (+), 128.0 (+), 125.2 (C_{quat}), 123.4 (+), 116.2 (+), 80.3 (C_{quat}), 51.7 (−), 51.0 (−), 50.5 (−), 50.2 (−), 43.9 (−), 31.6 (−), 29.6 (+), 28.6 (+); MS (70 eV, EI): *m/z* = 725 (100) $[M]^+$; $C_{38}H_{55}N_5O_7S$. Calcd.: C 62.87, H 7.64, N 9.65, S 4.4; found: C 62.59, H 7.87, N 9.12, S 4.4.

10-(3-Phenothiazin-1-yl-propionyl)-1, 4, 7, 10-tetraaza-cyclododecane-1, 4, 7-tricarboxylic acid tribenzyl ester (**13b**): A mixture of 3-phenothiazine-10-yl-propionic acid (**12**, 570 mg, 2.1 mmol), 1,4,7,10-tetraaza-cyclododecane-1,4,7-tricarboxylic acid tribenzyl ester (**11b**, 1.2 g, 2.1 mmol) and DCC (430 mg, 2.1 mmol) in 12 mL CH_2Cl_2 was allowed to react according to *GP-A*. The crude product was purified by CC (EE, R_f = 0.5) to yield 1.63 g (94%) **13b**, as a white solid, m.p. 84 °C; IR (KBr): 3065, 2931, 1735, 1542 cm^{-1}; UV/VIS (MeCN): λ_{max} (log ϵ): 192 (4.526), 256 (4.352), 308 (3.482); ^{1}H NMR δ 7.10 (m, 19 H), 6.90 (m, 4 H), 5.08 (s, 2 H), 5.05 (s, 2 H), 4.95 (s, 2 H), 3.10 (bs, 18 H), 2.80 (m, 2 H); ^{13}C NMR δ 171.1 (C_{quat}); 156.4 (C_{quat}), 145.9 (C_{quat}), 136.2 (C_{quat}), 128.1 (+), 127.4 (+), 127.1 (+), 127.0 (+), 126.9 (+), 125.6 (C_{quat}), 124.2 (+), 115.1 (+), 68.0 (−), 51.8 (−), 50.7 (−), 50.0 (−), 49.2 (−), 44.0 (−), 33.5 (−); MS (70 eV, EI): *m/z* = 827 (70) $[M^+]$, 91 (100).

1-(7-Acetyl-1,4,7,10-tetraaza-cyclododec-1-yl)-ethanone (**14b**): 1,4,7,10-Tetraaza-cyclo-dodecane (**4**, 100 mg, 0.58 mmol) was dissolved in a mixture of acetic acid (10 mL) and acetic acid anhydride (0.25 mL, 238 mg, 2.22 mmol). The mixture was stirred for 3 h at room temperature, the solvents were removed *in vacuo* and the residue was dissolved in a small amount of aqueous NaOH (2 M). The solution was evaporated *in vacuo*, the residue was extracted with CH_2Cl_2, the organic phase was dried over Na_2SO_4 and the solvent was again removed *in vacuo*

to yield 130 mg (88%) of **14b**, as a colorless oil; IR (KBr): 3425 cm^{-1}, 3417, 2934, 1635; – UV/Vis (CH_3CN): λ_{max} (log ϵ) = 198 nm (4.183), 228 (3.209), 242 (2.394), 302 (2.019); ^{1}H-NMR δ = 3.38 (m, 8 H), 2.76 (m, 8 H), 2.06 (s, 3 H), 2.04 (s, 3 H); ^{13}C-NMR δ = 172.0 (C_{quat}), 171.9 (C_{quat}), 51.5 (+), 51.2 (+), 49.5 (+), 49.2 (+), 49.0 (+), 48.3 (+), 48.0 (+), 47.8 (+), 22.3 (−), 22.2 (−); MS (EI) m/z (%): 256 (4) [M^+], 141 (100).

1,4,7,10-Tetraaza-cyclododecane-1,4,7-tricarboxylic acid 1,7-di-benzyl ester 4-tert-butyl ester (**15a**): A mixture of **14a** (500 mg, 1.13 mmol) and di-*tert*-butyl dicarbonate (248 mg, 1.13 mmol), dissolved in 75 mL of CH_2Cl_2, was stirred for 15 minutes at room temp. and the solvent was removed *in vacuo*. CC (SiO_2, EE) yielded 400 mg (65%) of **17a** (R_f = 0.35), as a white solid, m.p. 45 °C; IR (KBr): 3432 cm^{-1}, 1632, 1107; UV/Vis (CH_3CN): λ_{max} (log ϵ) 192 nm (4.889), 198 (4.542), 218 (3.968); ^{1}H NMR δ 7.33 (m, 10 H), 5.10 (s, 4 H), 3.3–3.6 (m, 12 H), 2.85 (s, 4 H), 1.35 (s, 9 H), 0.95 (s, 1 H); ^{13}C NMR δ 156.5 (C_{quat}), 155.4 (C_{quat}), 136.8 (C_{quat}), 128.4 (+), 128.2 (+), 127.9 (+), 79.0 (C_{quat}), 67.0 (−), 50.9 (−), 46.4 (−), 46.0 (−), 45.1 (−), 28.3 (+); MS (EI); m/z (%): 540 (10) [M]$^+$, 440 (5) [M–$C_5H_9O_2$]$^+$, 91 (100); $C_{29}H_{40}N_4O_6$ (540.66). Calcd.: C 64.42, H 7.46, N 10.36; found: C 64.36, H 7.66, N 10.19.

4,10-Diacetyl-1,4,7,10-tetraaza-cyclododecane-1-carboxylic acid tert-butyl ester (**15b**): Di-*tert*-butyl dicarbonate (484 mg, 2.22 mmol) was added to a solution of **14b** (569 mg, 2.22 mmol) in 15 mL of CH_2Cl_2 and the mixture was stirred for 15 minutes at room temperature. The solvent was removed *in vacuo* and the crude product was purified by CC (CH_2Cl_2 : MeOH, 95 : 5) to give 320 mg (41%) of **15b** (R_f = 0.10), as a white solid, m.p. 40 °C; IR (KBr): 3446 cm^{-1}, 2973, 1637; UV/Vis (CH_3CN): λ_{max} (log ϵ) = 194 nm (4.230), 234 (2.918), 246 (2.302); ^{1}H-NMR δ = 3.64 (m, 4 H), 3.35 (m, 8 H), 2.82 (m, 4 H), 2.00 (s, 3 H), 1.97 (s, 3 H), 1.41 (s, 9 H); ^{13}C-NMR δ = 170.3 (C_{quat}), 155.4 (C_{quat}), 80.2 (C_{quat}), 51.7 (−), 50.7 (−), 50.6 (−), 49.2 (−), 48.2 (−), 47.9 (−), 45.9 (−), 45.2 (−), 28.4 (+), 21.7 (+), 21.6 (+); MS (EI) m/z (%): 356 (8) [M^+], 141 (100).

10-[5-(Dimethylamino)-naphthalene-1-sulfonyl]-1, 4, 7, 10-tetraaza-cyclododecane-1, 4, 7-tricarboxylic acid 1,7-dibenzyl ester 4-tert-butyl ester (**17**): A mixture of **15a** (540 mg, 0.89 mmol) and dansyl chloride **(16)** (270 mg, 1.118 mmol) in 25 mL CH_2Cl_2 and 5 mL pyridine were stirred at room temperature under nitrogen for 3 h. The organic phase was washed three times with aqueous HCl (1 M), dried over Na_2SO_4, and the solvent was removed *in vacuo*. The crude product was purified by CC (CH_2Cl_2 : MeOH [95 : 5]) and yielded 451 mg (65%) of **17** (R_f = 0.75), as a yellow solid, m.p. 60 °C; IR (KBr): 3428 cm^{-1}, 3064, 2834; 1694 UV/Vis (CH_3CN): λ_{max} (log ϵ) 194 nm (4.884), 254 (4.155), 342 (3.629); ^{1}H NMR δ 8.58 (s, 1 H), 8.03 (m, 1 H), 7.48 (m, 2 H), 7.32 (m, 10 H), 7.18 (m, 2 H), 5.13 (s, 4 H), 3.65 (m, 4 H), 3.39 (m, 8 H), 3.24 (m, 4 H), 2.88 (s, 6 H), 1.32 (s, 9 H); ^{13}C NMR δ 156.0 (C_{quat}), 155.0 (C_{quat}), 136.3 (C_{quat}), 130.7 (+), 128.2 (+), 128.1 (+), 123.1 (+), 115.3 (+), 79.6 (C_{quat}), 67.3 (−), 50.3 (−), 49.9 (−), 45.4 (+), 28.2 (+); MS (FAB); m/z (%): 774 (8) [M + H]$^+$, 674 (30) [M–$C_5H_9O_2$]$^+$, 91 (100).

4-[5-(Dimethylamino)-naphthalene-1-sulfonyl]-1, 4, 7, 10-tetraaza-cyclododecane-1, 4, 7-tricarboxylic acid 1,7-dibenzyl ester (**18**): Compound **17** was reacted in 20 mL of ethanol with 10 mL of HBr (48% in H_2O) according to *GP-Boc* to yield 330 mg (84%) of **18**, as a yellow oil, (R_f = 0.4 (CH_2Cl_2 : MeOH [95 : 5]); IR (KBr): 3449 cm^{-1}, 2939, 1698; 1139; UV/Vis (CH_3CN): λ_{max} (log ϵ) 192 nm (4.976), 256 (4.115), 340 (3.666); ^{1}H NMR δ 8.44 (s, 1 H), 8.28 (m, 1 H), 7.99 (m, 2 H), 7.35 (m, 10 H), 7.15 (m, 2 H), 5.04 (s, 4 H), 3.67 (m, 4 H), 3.31 (m, 8 H), 3.24 (m, 4 H), 2.84 (s, 6 H), 2.78 (m, 4 H); ^{13}C NMR δ 156.0 (C_{quat}), 151.7 (C_{quat}), 136.6 (C_{quat}), 130.1 (+), 128.5 (+), 128.0 (+), 115.0 (+), 67.1 (−), 49.9 (−), 45.3 (+); MS (EI); m/z (%): 673 (10) $[M]^+$, 91 (100).

10-(3-Methoxycarbonyl-propionyl)-1, 4, 7, 10-tetraaza-cyclododecane-1, 4, 7-tricarboxylic acid 1,7-di-benzyl ester 4-tert-butyl ester (**20**): Succinic acid 1-methyl ester (**19**, 49 mg, 0.37 mmol), DCC (84 mg, 0.41 mmol) and **15a** (200 mg, 0.37 mmol) were allowed to react according to *GP-A*. CC (EE) yielded 201 mg (83%) of **20** (R_f = 0.50), as a white solid, m.p. 70 °C; IR (KBr): 3450 cm^{-1}, 2950, 1620; UV/Vis (CH_3CN): λ_{max} (log ϵ) 192 nm (4.963), 198 (4.885), 226 (3.956); ^{1}H NMR δ 7.30 (m, 10 H), 5.13 (s, 2 H), 5.11 (s, 2 H), 3.67 (s, 3H), 3.14–3.48 (m, 16 H), 2.04 (m, 4 H), 1.40 (s, 9 H); ^{13}C NMR δ 176.2 (C_{quat}), 155.9 (C_{quat}), 155.4 (C_{quat}), 136.3 (C_{quat}), 136.1 (C_{quat}), 128.7 (+), 128.5 (+), 128.4 (+), 128.2 (+), 80.4 (C_{quat}), 67.3 (−), 51.6 (+), 51.3 (−), 49.8 (−), 49.7 (−), 49.2 (−), 33.9 (−), 28.9 (−), 28.3 (+); MS (EI); m/z (%): 654 (10) $[M]^+$, 554 (30) $[M–C_5H_9O_2]^+$, 91 (100).

10-(3-Carboxy-propionyl)-1, 4, 7, 10-tetraaza-cyclododecane-1, 4, 7-tricarboxylic acid 1,7-dibenzyl ester 4-tert-butyl ester (**21**): Hydrolysis of **20** (430 mg, 0.66 mmol) following GP-H gave 390 mg (93%) of **21** (R_f = 0.30), as a white solid, m.p. 75 °C; IR (KBr): 3391 cm^{-1}, 3033, 1736; UV/Vis (CH_3CN): λ_{max} (log ϵ) 192 nm (4.858), 198 (4.544), 218 (3.341); ^{1}H NMR δ 7.32 (m, 10 H), 5.12 (s, 2 H), 5.10 (s, 2 H), 3.10–3.50 (m, 16 H), 1.90 (m, 2 H), 1.72 (m, 2 H), 1.40 (s, 9 H); ^{13}C NMR δ 176.1 (C_{quat}), 155.7 (C_{quat}), 155.3 (C_{quat}), 136.3 (C_{quat}), 136.1 (C_{quat}), 128.8 (+), 128.6 (+), 128.5 (+), 80.6 (C_{quat}), 67.4 (−), 51.2 (−), 49.5 (−), 49.7 (−), 49.2 (−), 33.7 (−), 29.5 (−), 28.4 (+); MS (FAB); m/z (%): 663 (30) $[M + Na]^+$, 91 (100); $C_{33}H_{44}N_4O_9 + CH_3OH$ (672.78). Calcd.: C 60.70, H 7.19, N 8.33; found: C 61.15, H 7.32, N 8.11.

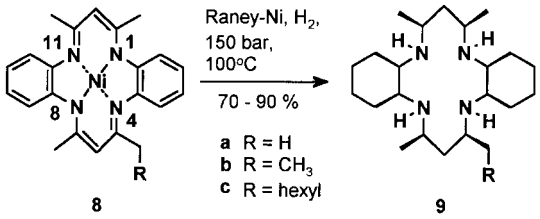
Diamide **22**: Compound **20** (1 g, 1.53 mmol) was treated with 25 mL of CF_3COOH in 25 mL of CH_2Cl_2 according to *GP-Boc* to give 669 mg (79%) of 10-(3-methoxy-carbonyl-propionyl)-1,4,7,10-tetraaza-cyclododecane-1,4,7-tricarboxylic acid 1,7-di-benzyl ester. A mixture of 10-(3-methoxycarbonyl-propionyl)-1,4,7,10-tetraaza-cyclododecane-1,4,7-tricarboxylic acid 1,7-di-benzyl ester (600 mg, 1.08 mmol), **21** (688 g, 1.08 mmol), DCC (222 mg, 1.08 mmol) and DMAP (131 mg, 1.08 mmol) was allowed to react in 50 mL of CH_2Cl_2 according to *GP-B*. The crude product was purified by CC (EE, R_f = 0.45) to yield 1.02 g (81%) of **22**, as a white solid, m.p. 85 °C; IR (KBr): 3436 cm^{-1}, 3007, 1585; UV/Vis (CH_3CN): λ_{max} (log ϵ) 192 nm (5.124), 198 (4.841), 224 (3.724); ^{1}H NMR δ 7.3 (m, 20 H), 5.28 (s, 2 H), 5.13 (s, 2 H), 5.12 (s, 2 H), 5.07 (2 H), 3.68 (s, 3 H),

3.2–3.6 (m, 32 H), 2.34 (m, 4 H), 1.92 (m, 4 H), 1.40 (s, 9 H); ^{13}C NMR δ 173.1 (C_{quat}), 155.0 (C_{quat}), 154.5 (C_{quat}), 136.2 (C_{quat}), 128.6 (+), 128.5 (+), 128.4 (+), 128.3 (+), 128.0 (+), 127.7 (+), 81.0 (C_{quat}), 67.2 (−), 51.6 (+), 51.5 (−), 50.6 (−), 49.8 (−), 48.7 (−), 33.9 (−), 29.6 (−), 28.3 (+); MS (MALDI-TOF); m/z (%): 1201 (50) $[M + Na]^+$, 555 (100).

4, 10-Bis-(5-methoxycarbonyl-pentanoyl)-1, 4, 7, 10-tetraaza-cyclododecane-1, 7-dicarboxylic acid dibenzyl ester (**24**): A mixture of **14a** (267 mg, 0.608 mmol), 8-methoxy-7-oxo-octanoyl chloride (**23**, 10.5 mL, 0.9 mmol) and 1 mL of pyridine in 40 mL of CH_2Cl_2 was allowed to react at room temperature for 12 h and worked up as described in GP-B. CC (EE) yielded: 400 mg (91%) of **24** (R_f = 0.25), as a white solid, m.p. 45 °C; IR (KBr): 2958 cm^{-1}, 1736, 1465; UV/Vis (CH_3CN): λ_{max} (log ϵ) 194 nm (4.808), 224 (3.562), 232 (3.017); ^{1}H NMR δ 7.35 (m, 10 H), 5.13 (s, 4 H), 3.66 (s, 6 H), 3.45 (s, 8H), 3.25 (s, 4H), 3.07 (s, 4H), 2.28 (s, 8 H), 1.57 (s, 8 H); ^{13}C NMR δ 173.6 (C_{quat}), 155.0 (C_{quat}), 136.0 (C_{quat}), 128.7 (+), 128.6 (+), 67.4 (−), 51.4 (+), 50.4 (−), 33.7 (−), 24.56 (−), 24.49 (−); MS (EI); m/z (%): 724 (20) $[M]^+$, 693 (40) $[M–OCH_3]^+$, 91 (100).

4, 10-Bis-(5-carboxy-pentanoyl)-1, 4, 7, 10-tetraaza-cyclododecane-1, 7-dicarboxylic acid dibenzyl ester (**25**): Hydrolysis of **24** (340 mg, 0.47 mmol) according to *GP-H* yielded 320 mg (97%) of **25** (R_f = 0.15), as a white solid, m.p. 55 °C; IR (KBr): 3429 cm^{-1}, 2944, 1731, 1456; UV/Vis (CH_3CN): λ_{max} (log ϵ) 192 nm (4.900), 202 (4.456), 228 (3.143); ^{1}H NMR δ 9.50 (s, 2 H), 7.27 (m, 10 H), 5.05 (s, 4 H), 3.42 (s, 8 H), 3.26 (s, 4 H), 2.97 (s, 4 H), 2.32 (s, 8 H), 1.49 (s, 8 H); ^{13}C NMR δ 179.0 (C_{quat}), 155.0 (C_{quat}), 136.5 (C_{quat}), 128.9 (+), 128.6 (+), 67.0 (−), 50.9 (−), 50.4 (−), 34.0 (−), 24.6 (−); MS (EI); m/z (%): 696 (5) $[M]^+$, 91 (100); $C_{36}H_{48}N_4O_{10}$(696.80). Calcd.: C 62.05, H 6.94, N 8.04; found: C 61.65, H 7.09, N 7.62.

Tetraamide **26**: A mixture of **15a** (95 mg, 0.22 mmol), **25** (50 mg, 0.1 mmol), DCC (45 mg, 0.22 mmol) and DMAP (27 mg, 0.22 mmol) was allowed to react according to *GP-B*. The crude product was purified by HPLC chromatography ($CH_3CN : H_2O$, 90 : 10) to yield: 92 mg (53%) of **26** (R_f(EE) = 0.15, retention time = 4.5 min at 9 mL/min), as a white solid, m.p. 50 °C; IR (KBr): 3432 cm^{-1}, 2926, 1648, 1366; UV/Vis (CH_3CN): λ_{max} (log ϵ) 192 nm (5.388), 224 (3.978), 258 (3.289); ^{1}H NMR δ 7.30 (m, 30 H), 5.13 (s, 4 H), 5.12 (s, 4 H), 510 (s, 4 H), 3.0–3.7 (m, 56 H), 2.11 (s, 8 H), 1.39 (s, 18 H); MS (FAB); m/z (%): 1742 (20) $[M]^+$, 1642 (15) $[M–C_5H_9O_2]^+$, 91 (100); $C_{94}H_{124}N_{12}O_{20}$ (1742.90). Calcd.: C 64.81, H 7.17, N 9.65; found: C 64.50, H 7.45, N 9.71.



Scheme 2. Stereoselective hydrogenation of nickel macrocycles to substituted cyclams.

4. Results and Discussion

4.1. STEREOSELECTIVE SYNTHESIS OF SUBSTITUTED 1,4,8,11-TETRAAZA-CYCLOTETRADECANES BY HYDROGENATION OF UNSATURATED PRECURSORS

This strategy is based on unsaturated tetraaza-macrocycles [6] as starting materials. The parent system **8a** is readily accessible by metal-templated condensation of phenylendiamine and acetylacetone [7]. Compound **8a** allows further functionalization by lithiation of the acidic methyl groups followed by the addition of an electrophile [8]. Treatment of **8a** with 1 equiv. of *n*-BuLi in THF followed by an alkylation reagent results in a clean substitution of one methyl group (**8b–c**), whereas 2 or more equiv. of base and electrophile yield a 1 : 1 mixture of the 5′,12′- and 5′,14′-substituted products [9]. Hydrogenation of **8a–c** on Raney nickel [10] leads to fully saturated cyclam macrocycles. Reaction of **8a** with 150×10^5Pa H_2 in ethanol for 36 h at 100 °C renders **9a** in 74% isolated yield. Under these conditions all hydrogens are transferred to the macrocycle from one side, resulting in the exclusive formation of the *all-cis-R,S,R,S* compound. At lower temperatures hydrogenation of **8a** is not observed; higher temperatures and increased H_2-pressure give rise to a loss of stereoselectivity and lower yields. The stereochemistry of the saturated product was confirmed by X-ray analysis [8].

Depending on the solvent used for recrystallization two different crystals of the saturated product are obtained. The X-ray analysis of the single crystals of **9a** from chloroform solution revealed the *all-cis* stereochemistry and showed two chloroform molecules weakly hydrogen bonded to nitrogen in the crystal [8]. The X-ray analysis of single crystals obtained from wet acetone shows an arrangement of two molecules in the unit cell which are bridged by a disordered water molecule [11].

Although the detailed mechanism of the heterogeneous perhydrogenation remains speculative, the central nickel(II) atom in **8a** seems to be important. Hydrogenation of the analogous metal-free macrocycle [7, 8] under the same conditions gives a mixture of several partially hydrogenated products without a defined stereochemistry. The hydrogenation of the monosubstituted derivatives **8b–c** proceeds at slightly higher temperatures than given for the parent system [12]. Alkylation of the sterically hindered nitrogen atoms of **9a** with electrophiles, such

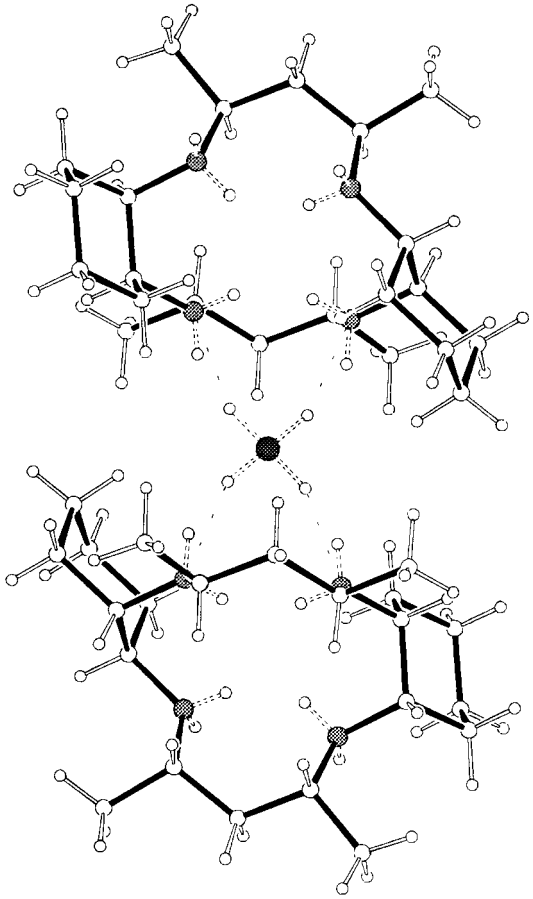
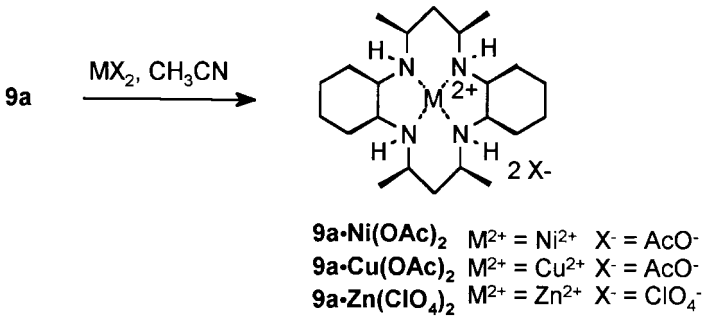


Figure 1. Structure of **9a** in the crystal that was obtained from acetone. Water molecule and H-N protons are disordered.

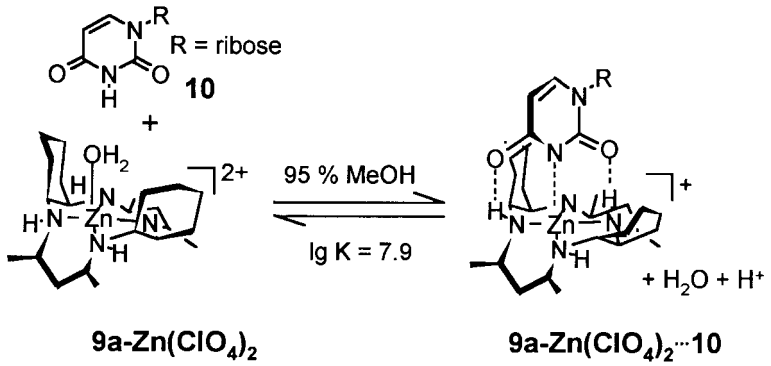
as benzyl bromide, *N*, *N*-diethylchloroacetamide or ethyl bromoacetate, did not proceed under standard conditions [13].

As expected, **9a** coordinates metal ions tightly. With $Ni(OAc)_2$ and $Cu(OAc)_2$ the corresponding complexes **9a** • **Ni(OAc)**$_2$ and **9a** • **Cu(OAc)**$_2$ are obtained from methanol solution at room temperature. For the preparation of the zinc perchlorate complex **9a** • **Zn(ClO**$_4$**)**$_2$ it was necessary to reflux the reaction mixture overnight. All complexes were characterized by X-ray analysis [14].

Metal complexes of the cyclam **9a** thus obtained show a distorted square planar coordination geometry in the solid state. Their redox and binding properties in solution are significantly different from the parent cyclam complexes: The copper(II) and nickel(II) complexes of **9a** are easier to reduce and more difficult to oxidize than the analogous cyclam complexes. The binding constant of the zinc complex of **9a** was determined as 5 orders of magnitude smaller than the parent cyclam



Scheme 3. Formation of highly substituted cyclam transition metal ion complexes.

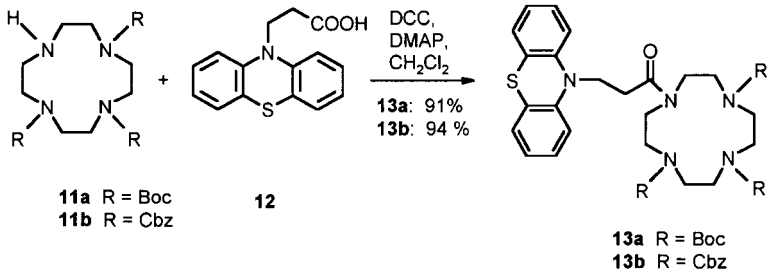


Scheme 4. Binding of uridine (**10**) by **9a** • **Zn(ClO**$_4$**)**$_2$ in aqueous methanol.

zinc complex, whereas the Lewis acidity of the zinc ion is higher if coordinated by **9a**. This is illustrated by the high binding constant of **9a** • **Zn(ClO**$_4$**)**$_2$ to uridine, which was determined by potentiometric titration to log K = 7.9 in 95% aqueous methanol [14]. The lipophilic character of **9a** and its metal complexes together with good availability renders it a suitable ligand for many applications directed towards metal ion coordination. The attempts to extend the procedure to other starting materials, such as condensation products of ethylendiamine and acetylacetone [15] or phthalocyanins unfortunately have failed so far.

4.2. SELECTIVE FUNCTIONALIZATION AND EFFICIENT COUPLING OF 1,4,7,10-TETRAAZACYCLODECANE USING METHODS FROM PEPTIDE CHEMISTRY

Recently several structures with two or three tetraaza-cyclododecane and -cyclotetradecane units have been reported [16], with some of them showing interesting physiological properties, such as strong HIV protease inhibition [17]. The synthesis of such complex and extended aza-macrocycles requires selective functionalization and linkage. Alkylation at nitrogen of aza-crowns or their partially protected derivatives is the major synthetic route to compounds of this kind and several pro-



Scheme 5. DCC-mediated coupling of partially protected cyclen.

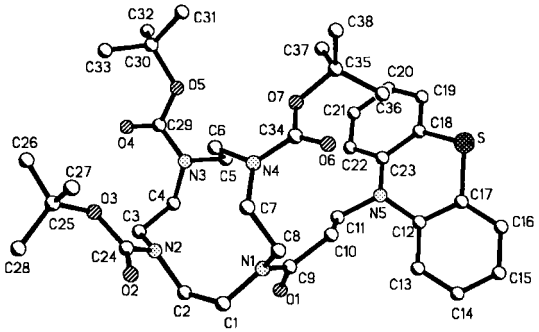
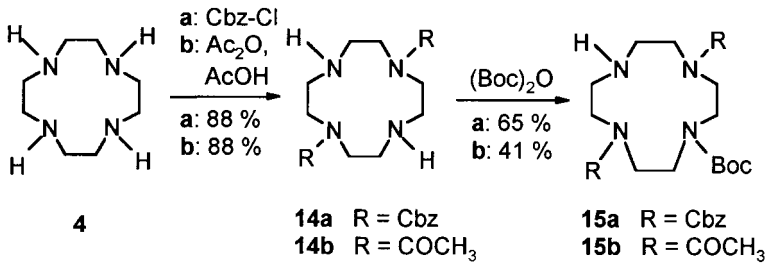


Figure 2. Structure of **13a** in the crystal (H atoms omitted for clarity) [23].

cedures are available [18], but in many cases yields are unsatisfactory. In addition, problems arise from the very long reaction times and the difficult isolation of the highly polar products. Surprisingly, the acylation of aza-crowns to amides, which may subsequently be reduced to amines, has been much less studied [19]. We summarize here our recent attempts to synthesize functionalized mono- and oligo-1,4,7,10-tetraaza-cyclododecanes using amine protecting groups and dicyclohexyl carbodiimide (DCC) amide coupling procedures [20].

Derivatives of 1,4,7,10-tetraaza-cyclododecane in which three out of four nitrogens are protected as carbamates [21] are suitable starting materials for the introduction of one additional group at nitrogen [22]. Alkylation reactions with activated halides [18] and acylation with simple acid chlorides [19] have been reported. In order to avoid the prior preparation of acid chlorides we have used carboxylic acids for acylation, which were activated *in situ* by DCC for amide formation. As illustrated by the reaction of **12**, aliphatic carboxylic acids react with threefold protected 1,4,7,10-tetraaza-cyclododecane **11** (*R* = Cbz or Boc) smoothly in the presence of 1 equiv. DCC and 1 equiv. of 4-*N*, *N*-dimethylaminopyridine (DMAP, Steglich's base) at room temperature to give the corresponding coupling products in good yield. The connectivity of the amide is confirmed by an X-ray structure analysis (Figure 2) [23]. Suitable crystals for X-ray analysis are obtained by slow evaporation of an acetone solution of the compound.

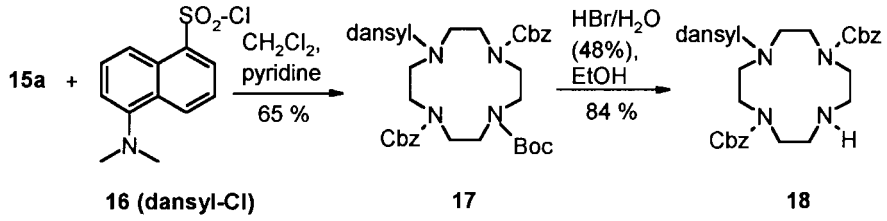


Scheme 6. Synthesis of partially protected cyclens, which allow a selective deprotection of amino groups.

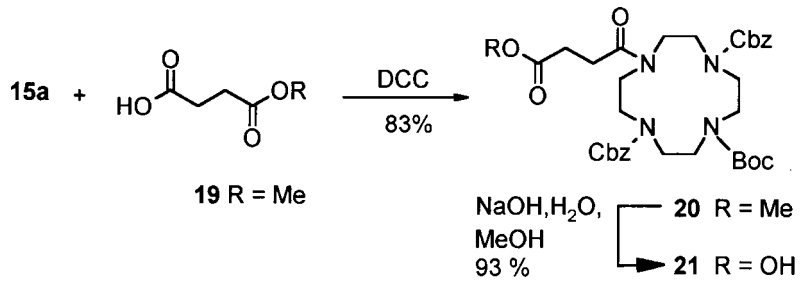
Amide coupling of threefold protected derivatives of 1,4,7,10-tetraaza-cyclododecane, such as **11a** or **11b**, is restricted to the formation of mono-substituted or bis-1,4,7,10-tetraaza-cyclododecanes. If more extended or non-symmetric compounds are required, differentiation of nitrogen protecting groups is necessary, which is achieved by combination of Boc- and Cbz-groups. According to previously reported procedures 1,4,7,10-tetraaza-cyclododecane (**4**) was transformed into the 1,7-Cbz-protected derivative **14a** [24]. Reaction of **14a** with di-*tert*-butyl dicarbonate in dichloromethane solution at room temperature for 15 min gave compound **15a** in 65% yield. Similarly **14b** [25], which is obtained selectively by reaction of **4** with acetic anhydride in acetic acid, yields **15b** if treated with di-*tert*-butyl dicarbonate.

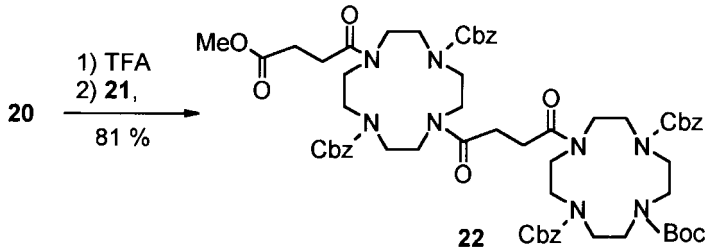
Compound **15a** allows, as do **11a** or **11b**, the selective introduction of one substituent at nitrogen. This is illustrated by the reaction of **15a** with dansyl chloride (**16**) or monomethyl succinate and DCC. By selective removal of the Boc protecting group with trifluoroacetic acid (TFA) or HBr a second substitution reaction at nitrogen can be performed selectively at position 7. The synthesis of unsymmetrically substituted bis-1,4,7,10-tetraaza-macrocycles, such as **20** and **21**, is readily achieved from **15a**. Compound **21** was obtained by hydrolysis of the ester group of **20** under standard conditions. Removal of the Boc protecting group of **20** and DCC-mediated coupling of the resulting product with **21** leads to covalently tethered aza-macrocycles, which might be extended further. The reactions demonstrate the advantage of compound **15a**, compared to **11a**, which does not allow the selective introduction of additional substituents or the synthesis of non-symmetrical bis-1,4,7,10-tetraza-macrocycles.

Fewer synthetic steps (starting from **4**) are necessary to prepare dicarboxylic acid **25**, which contains a protected 1,4,7,10-tetraaza-macrocycle. The compound is readily obtained by the reaction of **14a** with 5-chlorocarbonyl-pentanoic acid methyl ester (**23**) and subsequent hydrolysis. DCC-mediated coupling of **15a** to **25** yields a linear arrangement **26** of three 1,4,7,10-tetraaza-macrocycles in a fully protected form. The molecule allows further functionalization or extension by selective removal of the protecting groups or reduction of the amide moieties.

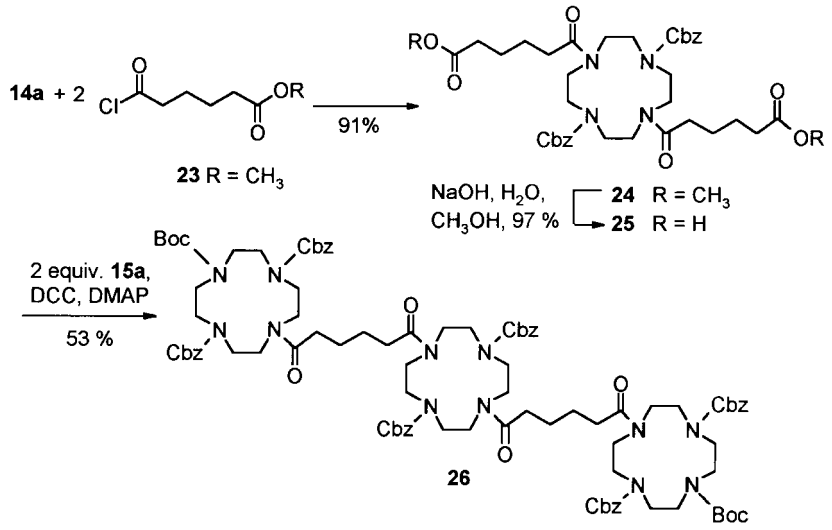


Scheme 7. Functionalization of cyclen by a dansyl moiety.

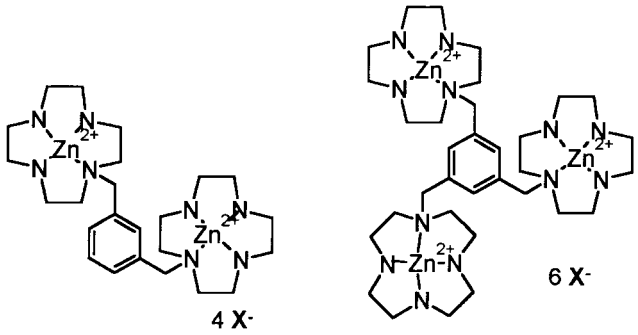




Scheme 8. Synthesis of covalently tethered cyclens.



Scheme 9. Synthesis of a protected tris-cyclen.



27 **28**

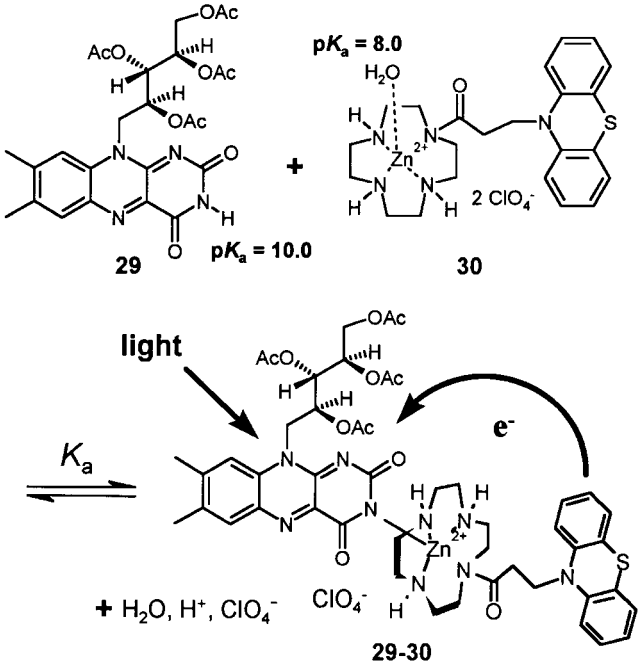
Scheme 10. Bis- and tris-cyclen zinc(II) complexes developed by Kimura *et al*. for binding of barbiturates or phosphates in aqueous solution [28].

The examples illustrate that the use of protecting groups and DCC-coupling procedures is a valid strategy to synthesize even complex functionalized or tethered 1,4,7,10-tetraaza-macrocycles. The extension of the procedures to solid phase reactions [26], which will allow automatization, is currently under investigation.

4.3. ASSEMBLY OF A PHOTOACTIVE DYAD BY ZINC-CYCLEN-IMIDE COORDINATION IN WATER

The control of reversible intermolecular bonds in organic solvents for recognition or self-assembly is now possible as illustrated by many reported examples. The use of intermolecular interactions to generate properties in water, however, remains a challenge. Kimura and coworkers [27] have recently demonstrated that the interaction of Lewis-acidic complexes of zinc-cyclen with Lewis-basic moieties, such as phosphates or deprotonated imides, provides sufficient binding strength even in water. By covalent linkage of two and three zinc aza-macrocycles they obtained receptors (**27** and **28**) for the selective binding of barbiturates and hydrogen phosphate in water [28].

We have adopted their concept to assemble in water a dyad that is suitable for showing photoinduced electron transfer (PET) [29]. To obtain the electron donor part with binding site, compound **13a**, which was synthesized as described above, was deprotected and converted into the corresponding zinc(II) complex **30**. The photoinduceable electron acceptor with binding site is provided by nature as riboflavin (vitamin B2), which was used for reasons of better photostability and solubility as the tetraacetate **29** [30]. Upon mixing in either organic solvents, such as acetonitrile or methanol, or buffered water at pH 7.4, the phenothiazine riboflavin dyad **29–30** is spontaneously obtained by formation of the zinc imide coordinative bond. Detailed photophysical studies, in particular transient spectroscopy, have shown that irradiation of the complex leads to a charge separated state after PET.



Scheme 11. Assembly of a riboflavin phenothiazine electron donor acceptor dyad *via* zinc(II) imide coordination. Hydrogen bonds between carbonyl oxygen and N—H groups may support the assembly.

In conclusion, we have demonstrated that functionalized aza-macrocycles are available *via* heterogeneous hydrogenation of unsaturated heterocycles or by the introduction of substituents using established coupling methods from peptide chemistry. Lewis-acidic zinc complexes of such ligands have been employed for binding of imides, such as uridine or riboflavin, in polar solvents. We hope that our efforts, together with the excellent contributions of many other groups, will pave the way for more applications of complexes of aza-macrocycles in medicine, biology and material science.

Acknowledgements

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9. Small amounts of mono- and of trisubstituted products were detected in the reaction mixtures by HPLC. The isomeric disubstituted products could not be separated by column chromatography. The use of more than 2 equiv. of BuLi and electrophile still yields a reaction mixture with isomeric disubstituted compounds as the major products. However, substantial amounts of trisubstituted and small amounts of mono- and tetrasubstituted products were detected.
10. For the preparation of Raney-nickel see: A. A. Parlic, H. Adkins, *J. Am. Chem. Soc.* **68**, 1471 (1946).
11. Full details of the crystal structure determination (except structure factors) have been deposited under the number 114671 at the Cambridge Crystallographic Data Centre. Copies may be obtained free of charge from: The Director, CCDC, 12 Union Road, GB-Cambridge CB2 1EZ (Telefax: Int. + 1223/336-033; E-mail: deposit@ccdc.cam.ac.uk)

12. The less clean Raney–Nickel hydrogenation of disubstituted compounds call for longer reaction times and higher temperatures.
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