A new synthetic route to substituted cyclam macrocycles

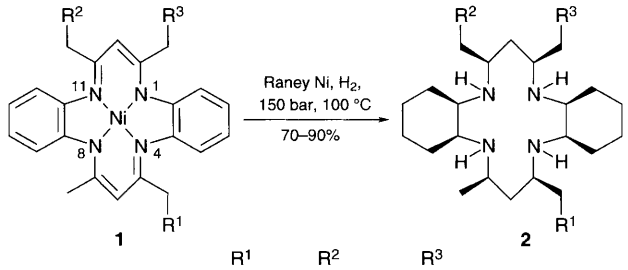
Burkhard König,*†[a] Mario Pelka,[a] Harald Zieg,[a] Peter G. Jones[b] and Ina Dix[b]

[a] *Institut für Organische Chemie der Technischen Universität Braunschweig, Hagenring 30, D-38106 Braunschweig, Germany*
[b] *Institut für Anorganische und Analytische Chemie der Technischen Universität Braunschweig, Hagenring 30, D-38106 Braunschweig, Germany*

Raney-nickel hydrogenation of macrocyclic phenylendiamine–dicarbonyl condensation products gives cyclam-type ligands in high yield with complete all-*cis* stereoselectivity.

Various new medicinal concepts for diagnosis and therapy, such as magnetic resonance imaging[1] or radioimmunotherapy,[1] utilize metal ions. To reduce their toxicity and adapt their physical properties to specific applications, a tight coordination of the metal ion with a functionalized ligand is necessary. In many cases aza-crowns, such as 1,4,7,10-tetraazacyclododecane (cyclen) or 1,4,8,11-tetraazacyclotetradecane (cyclam) and their N-alkylated derivatives have been employed as effective metal-ion binding sites.[2] Whereas several practical methods for the selective N-alkylation of commercial aza-crowns are available,[3] the synthesis of C-substituted derivatives[4] remains difficult. We report here a new economical strategy for the synthesis of C-substituted cyclams.

This strategy is based on unsaturated tetraaza macrocycles as starting materials. The parent system **1a** is readily accessible by metal-templated condensation[5] of phenylenediamine and acetylacetone.[6] Treatment of **1a** with 1 equiv. of Bu^{n}Li followed by an alkylation reagent then results in a clean substitution of one enamine position (**1b–e**), whereas 2 equiv. of base and alkylation reagent yield a 1 : 1 mixture of the 5′,12′- and 5′,14′-disubstituted products **1f–h**.‡ Hydrogenation of the compounds thus obtained on Raney nickel[7] finally leads to the fully saturated cyclam macrocycles. Reaction of **1a** with 150 × 10^5 Pa H_2 in methanol for 36 h at 100 °C renders **2a**§ in 74% isolated yield (Scheme 1). Under these conditions all hydrogens were 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 **1a** is not observed; higher temperatures and increased H_2-pressure give rise to a loss of stereoselectivity and lower yields.



	R^1	R^2	R^3
a	H	H	H
b	Me	H	H
c	C_6H_{13}	H	H
d	$C_{12}H_{25}$	H	H
e	CH_2OH	H	H
f	Me	H/Me	H/Me
g	C_6H_{13}	H/C_6H_{13}	C_6H_{13}/H
h	CH_2OH	H/CH_2OH	CH_2OH/H

Scheme 1

Single crystals of **2a** were collected from the crude reaction mixture upon treatment with chloroform. The X-ray analysis‖ reveals the proposed stereochemistry of the macrocycle (Fig. 1). Two chloroform molecules are weakly hydrogen bonded to nitrogen in the crystal. The diameter of the cavity of the macrocycle is 279 pm [N(1)···N(8)] × 385 pm [N(4)···N(11)].

The hydrogenation of the monosubstituted derivatives **1b–e** proceeds under the same conditions as described for the parent system, whereas disubstituted compounds call for longer reaction times and slightly higher temperatures.**

C-substituted cyclams, generated as described, display the expected metal-ion binding properties, as could be demonstrated in coordination experiments with **2a**. Metal complexes of **2a** with $Ni(OAc)_2$, $Fe(H_2O)_7SO_4$, $Cu(OAc)_2$, $La(OAc)_3$ and SmI_2 were prepared by simple mixing of the components in acetonitrile at room temperature. The X-ray structure analysis†† of [Ni(**2a**)]·2OAc·2MeOH·3H_2O, which displays crystallographic twofold symmetry, shows a square-planar coordination geometry of the nickel ion (Fig. 2). The coordinated metal ion is well protected in a pocket of hydrophobic residues, whereas the acetate counter ion is hydrogen bonded to the nitrogen atoms of the macrocycle.

In summary we have shown that the stereoselective *cis*-hydrogenation of substituted condensation products of phenylenediamine and acetylacetone yields new cyclam macrocycles in a single step. The functionalized aza-crown derivatives of defined all-*cis* stereochemistry thus accessible might facilitate the synthesis of new metal complexes for medicinal applications.

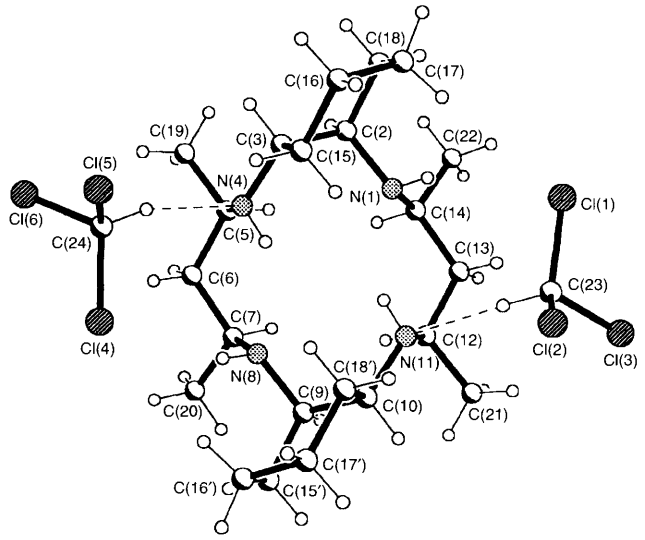


Fig. 1 Structure of **2a**·2$CHCl_3$ in the crystal. Selected bond lengths (pm) and bond angles (°): N(1)–C(2) 146.6(4), N(1)–C(14) 146.9(4), C(2)–C(3) 154.5(4); C(2)–N(1)–C(14) 117.0(3), N(1)–C(2)–C(3) 110.2(2), N(1)–C(2)–C(18) 113.7(3). Distance of N atoms from best N_4 plane: ±24 pm.

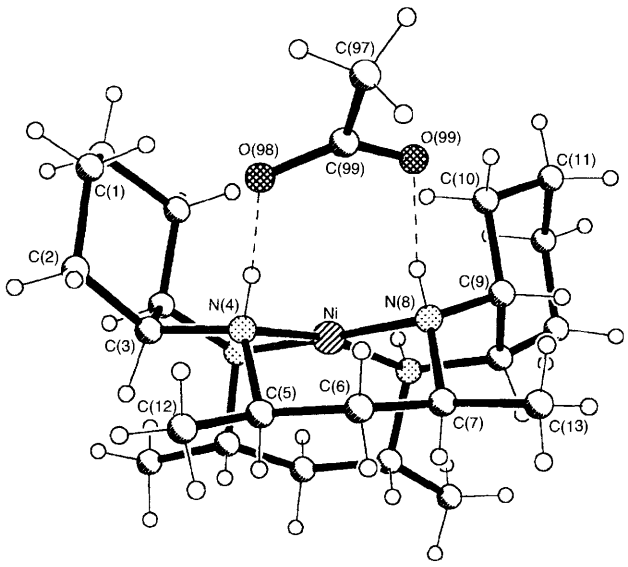


Fig. 2 Structure of **2a**·Ni(OAc)$_2$ in the crystal (solvent molecules not shown). Selected bond lengths (pm) and bond angles (°): Ni–N(8) 189.9(1), Ni–N(4) 193.5(1), N(4)–C(3) 151.0(2), N(4)–C(5) 151.7(2); N(8)–Ni–N(8′) 178.31(8), N(8)–Ni–N(4′) 88.23(6), N(8)–Ni–N(4) 91.95(6), N(4)–Ni–N(4′) 167.71(8), C(7)–C(6)–C(5) 118.29(1). Distance of N atoms from best N_4 plane: ±12 pm.

We thank Mr A. Weinkauf for the X-ray data collection of **2a**. Financial support from the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

Footnotes

† E-mail: Koenig@SGI3.ORG-CHEM.NAT.TU-BS.DE

‡ Treatment of **1a** with excess base followed by an alkylation reagent yields mainly twofold alkylation products. However, substantial amounts of the three-and even four-fold alkylated cycle could be detected in the crude product mixture.

§ *Selected analytical data* for **2a**: mp 60 °C. IR (KBr): $\tilde{\nu}$/cm^{-1} 3292, 2950, 1474, 761. UV–VIS (MeCN) λ_{max} (lg ε) 192 nm (3.957), 250 (2.523). ^{1}H NMR ($CDCl_3$) δ 0.98 (m, 14 H), 1.38 (m, 22 H), 2.68 (brs, 4 H), 2.96 (brs, 4 H). MS (70 eV) *m/z* (%): 364 (26) [M$^+$], 125 (100) (Found: C, 72.38; H, 12.40; N 15.18. Calc. for $C_{22}H_{44}N_4$: C, 72.47; H, 12.16; N, 15.37%).

¶ The crude reaction mixture was analysed by HPLC to verify that only a single diastereomer of **2a** was obtained.

‖ *Crystal data* for **2a**·2$CHCl_3$: $C_{24}H_{46}Cl_6N_4$: M = 603.35, crystal size 0.9 × 0.8 × 0.7 mm, monoclinic, space group $P2_1/n$, a = 1120.0(2), b = 1863.2(3), c = 1566.6(3) pm, β = 106.11(2)°, U = 3.1407(10) nm^3, Z = 4, D_c = 1.276 Mg m^{-3}, λ(Mo-Kα) = 71.073 pm, μ = 0.57 mm^{-1}, F(000) = 1280, Stoe STADI-4 diffractometer, scan type ω–θ to 2θ = 55°, T = 143 K, 8893 reflections, 7204 unique (R_{int} = 0.0345), refined[8] on F^2, 323 parameters, $R(F)$ = 0.081, $R_w(F^2)$ = 0.198.

** Disubstituted compounds were hydrogenated at 130 °C, H_2 pressure 150 × 10^5 Pa, for 48 h.

†† *Crystal data* for [Ni(**2a**)]·2OAc·2MeOH·3H_2O: $C_{28}H_{64}N_4NiO_9$: M = 659.54, crystal size 0.8 × 0.7 × 0.4 mm, orthorhombic, space group *Pnna*, a = 1389.61(12), b = 2102.7(3), c = 1181.07(12) pm, U = 3.4511(7) nm^3, Z = 4, D_c = 1.269 Mg m^{-3}, λ(Mo-Kα) = 71.073 pm, μ = 0.62 mm^{-1}, F(000) = 1440, Siemens P4 diffractometer, scan type ω to 2θ = 55°, T = 173 K, 6711 absorption-corrected reflections, 3966 unique (R_{int} = 0.0198), 205 parameters, $R(F)$ = 0.032, $R_w(F^2)$ = 0.0838.

Atomic coordinates, bond lengths and angles, and thermal parameters of both structures have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1. Additionally, full details of the structure determinations have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlichtechnische Information mbH, 76344 Eggenstein-Leopoldshafen, Germany. Any request for this material should quote a full literature citation and the reference number CSD 404463 (ligand), 404464 (nickel complex).

References

1 For recent applications of aza-crowns as metal ion binding sites see: S. Aime, M. Botta, S. G. Crich, G. B. Giovenzana, G. Jommi, R. Pagliarin and M. Sisti, *J. Chem. Soc., Chem. Commun.*, 1995, 1885; T. J. Norman, D. Parker, F. C. Smith and D. J. King, *J. Chem. Soc., Chem. Commun.*, 1995, 1877, 1879.

2 T. A. Kaden, *Pure Appl. Chem.*, 1988, **60**, 1117; P. V. Bernhardt and G. A. Lawrence, *Coord. Chem. Rev.*, 1990, **104**, 297; A. S. de Sousa and R. D. Hancock, *J. Chem. Soc., Chem. Commun.*, 1995, 415.

3 B. Broitrel, B. Andrioletti, M. Lachkar and R. Guilard, *Tetrahedron Lett.*, 1995, **36**, 4995; J. E. Richman, *Tetrahedron Lett.*, 1977, 559; A. Dumont, V. Jacques, P. Qixiu and J. F. Desreux, *Tetrahedron Lett.*, 1994, **35**, 3707; W. J. Kruper, P. R. Rudolf and C. A. Langhoff, *J. Org. Chem.*, 1993, **58**, 3869; J.-J. Yaouanc, N. LeBris, G. LeGall, J.-C. Clement, H. Handel and H. des Abbayes, *J. Chem. Soc., Chem. Commun.*, 1991, 206; A. Bencini, A. Bianchi, C. Bazzicalupi, M. Ciampolini, P. Dapporto, V. Fusi, M. Micheloni, N. Narda, P. Paoli and B. Valtancoli, *J. Chem. Soc., Perkin Trans. 2*, 1993, 715.

4 M. L. Garrity, G. M.Brown, J. E. Elbert and R. A. Sachleben, *Tetrahedron Lett.*, 1993, **34**, 5531.

5 B. Dietrich, P. Viout and J.-M. Lehn, *Macrocyclic Chemistry*, VCH, Weinheim, 1993; E.-G. Jäger, H. Keutel, M. Rudolph, B. Krebs and F. Wiesemann, *Chem. Ber.*, 1995, **128**, 503 and references therein.

6 L. F. Tietze and Th. Eicher, *Reaktionen und Synthesen*, Thieme, Stuttgart, 1991.

7 For the preparation of Raney nickel see: A. A. Parlic and H. Adkins, *J. Am. Chem. Soc.*, 1946, **68**, 1471.

8 G. M. Sheldrick, SHELXL-93, a program for refining crystal structures, University of Göttingen, 1993.

Received, 22nd November 1995; Com. 5/07635H