One-pot Synthesis of a 1,3,7,9-Tetraazacyclododecane Derivative and an Investigation of its Complexation Properties†

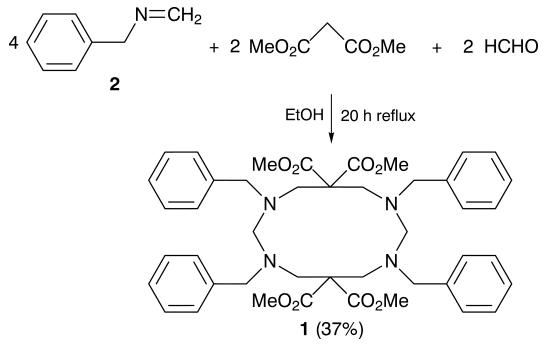
J. Chem. Research (S), 1998, 712–713†

Andreas Axén, Helena Grennberg and Adolf Gogoll*

Department of Organic Chemistry, University of Uppsala, Box 531 751 21 Uppsala, Sweden

A one-pot synthesis of a 1,3,7,9-tetraazacyclododecane macrocycle in 37% yield from inexpensive starting materials is described, and its complexation properties with metal cations are investigated.

Aza-crown macrocycles have been investigated for their properties as strong and selective complexing agents for metal cations and other charged and uncharged guest molecules.[1] Practical applications include their use as phase transfer agents,[2] NMR shift reagents,[3] MRI contrast reagents[4] or as catalysts.[5] They often also show a wide range of biological activity.[6] This has motivated the synthesis of a great variety of aza-crown macrocycles with varying ring size and different spacers between the heteroatoms.[7]



Scheme 1 Synthesis of 1,3,7,9-tetrabenzyl-5,5,11,11-tetramethoxycarbonyl-1,3,7,9-tetraazacyclododecane

In general, synthesis is performed by cyclisation of diamines with dialdehydes, diepoxides, dihalides or activated diacid derivatives.[8] In spite of the many preparation methods, the NCH_2N linkage in such macrocycles is still considered a challenge due to its low stability.[8] A common way to overcome this problem is to complex the amine to a transition metal cation which is used as a template.[9] This seems to be a limitation, since the only preparation of such 1,3,7,9-tetraazacyclododecane derivatives found in the literature was for *N*,*N*′,*N*″,*N*‴-tetramethyl-1,3,7,9-tetraazacyclododecane which could not be fully characterised due to its low stability.[10] In contrast, the corresponding 1,4,7,10-tetraaza macrocycles are well characterised.[11]

In the course of our investigations aimed at finding ligands suitable for NMR investigations of organic palladium complexes[12] we serendipitously found a one-pot synthesis for the backbone of a 1,3,7,9-tetraazacyclododecane derivative. The compound, 1,3,7,9-tetrabenzyl-5,5,11,11-tetramethoxycarbonyl-1,3,7,9-tetraazacyclododecane **1**,[13] is stable, can be chromatographed on silica, and stored in solution for weeks without any notable decomposition. Our synthesis (Scheme 1) is based on a Mannich reaction, mixing the preformed Schiff base **2**[14] of benzylamine with dimethyl malonate and formaldehyde. No protection/deprotection scheme or addition of template ions is needed, and since the starting materials are all cheap and readily available chemicals, the moderate yield (37%) should be acceptable for most purposes.

Attempts to improve the yield by increasing the excesses of *N*-methylenebenzylamine or formaldehyde gave no improvement. Prolonged reaction times lead only to increased polymer formation. Increasing the amount of solvent had no effect. Addition of formaldehyde in the form of aqueous solution instead of paraformaldehyde increased the yield considerably (from *ca.* 20 to 37%).

The room temperature ^{1}H NMR spectrum of the macrocycle **1** shows broad methylene proton signals due to a slow conformational equilibrium, probably similar to those of other tetraazacyclododecanes.[15]

The complexing properties of this new macrocycle **1** have been tested with sodium and cobalt(II) ions in non-aqueous solvents using NMR methods.[16] For sodium ions (solvent acetone or THF) the ^{23}Na chemical shift variation with ligand concentration was measured. No complexation at all could be detected in acetone solution whereas in THF a weak complexation was indicated.[17] For the paramagnetic cobalt(II) ion the chemical shift change of the macrocycle ring methylene protons ($\Delta\delta_{CH_2}$) upon variation of the metal ion concentration in acetone solution was measured. A plot of the relative concentration of the metal ion and ligand *versus* δ_{CH_2} (Fig. 1) shows a linear increase of δ_{CH_2} until a ratio of approximately 1:1 is reached. Further addition of metal ion does not change the resonance frequency. This behaviour indicates the formation of a stable 1:1 complex.[18] Chemical shift changes (ambient temperature, 300 MHz) for the other protons in the molecule were negligible.

Polyamine macrocycles often show a reduced ability to complex alkali and alkaline earth metal cations,[19] and are more effective in complexing divalent transition

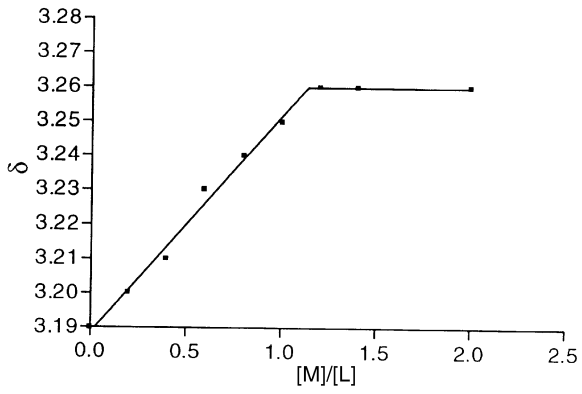


Fig. 1 Chemical shift variation for 2,8-methylene protons (δ_{CH_2}) of compound **1** as a function of the cobalt(II) concentration. Addition of cobalt(II) chloride solution (0.01 M) to a solution of **1** (0.001 M) in acetone

*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

metal cations.[20] However, 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid (DOTA) does complex sodium ions,[21] and mixed nitrogen–oxygen ligands commonly complex alkali metal cations.[22] A model for the size-match relation between the ion and the macrocyclic ligand has been proposed,[23] although it can be difficult to apply because of the many variables (nature of the donor atom, ring size and number of chelating atoms, relative position of the donor atoms, nature of the ligand backbone) that affect the system.[3] In conclusion, the new macrocycle **1** should be of general interest as a model compound due to its simple synthesis and unexpected stability as well as that of its metal complex.

The Swedish Natural Science Research Council and Magn. Bergvalls Stiftelse are gratefully acknowledged for financial support.

Received, 1st June 1998; Accepted, 20th July 1998
Paper E/8/04077J

References

1 K. Bowman-James, in *Encyclopedia of Inorganic Chemistry*, ed. R. B. King, Wiley, Chichester, 1994, vol. 4, pp. 1999–2016.
2 D. Landini, A. Maia, F. Montanari and P. Tundo, *J. Am. Chem. Soc.*, 1979, **101**, 2526.
3 V. Alexander, *Chem. Rev.*, 1995, **95**, 273.
4 R. B. Lauffer, *Chem. Rev.*, 1987, **87**, 901.
5 E. Kimura, *Pure Appl. Chem.*, 1993, **65**, 355; R. Hettich and H.-J. Schneider, *J. Am. Chem. Soc.*, 1997, **119**, 5638.
6 J.-P. Behr and J.-M. Lehn, in *Design of Synthetic Molecular Receptors and Catalysts in Structural and Functional Aspects of Enzyme Catalysis*, ed. H. Eggerer and R. Huber, Springer, Berlin, Heidelberg, New York, 1981.
7 Reviews: H.-Y. An, J. S. Bradshaw and R. M. Izatt, *Chem. Rev.*, 1992, **92**, 543; K. E. Krakowiak, J. S. Bradshaw and R. M. Izatt, *Synlett*, 1993, 611.
8 A. V. Bordunov, J. S. Bradshaw, V. N. Pastushok and R. M. Izatt, *Synlett*, 1996, 933.
9 M. C. Thompson and D. H. Busch, *J. Am. Chem. Soc.*, 1964, **86**, 3651.
10 H. Krässig, *Makromol. Chem.*, 195/196, **17,** 77.
11 M. K. Moi and C. F. Meares, *J. Am. Chem. Soc.*, 1988, **110**, 6266; M. L. Garrity, G. M. Brown, J. E. Elbert and R. A. Sachleben, *Tetrahedron Lett.*, 1993, **34**, 5531.
12 A. Gogoll, H. Grennberg and A. Axén, *Organometallics*, 1997, **16**, 1167.
13 Synthesis: *N*-methylenebenzylamine (0.60 g, 5 mmol), dimethyl malonate (0.33 g, 2.5 mmol) and paraformaldehyde (30% aq. solution) (0.5 g, 5 mmol) were mixed in ethanol (30 mL) then refluxed with stirring for 20 h. The solvent was removed and the product **1** purified by column chromatography (Silica 60; pentane–diethyl ether, 7:3); yield 0.7 g, 37%, clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.20 (m, 20 H), 3.71 (s, 12 H), 3.61 (s, 8 H), 3.22 (br s, 4 H), 3.02 (br s, 8 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.4, 137.5, 128.7, 123.0, 126.9, 74.3, 59.0, 55.5, 54.0, 52.4; IR ($CDCl_3$) 3061, 2819, 1736, 1495, 1453, 1263 cm^{-1}; calc. for $C_{44}H_{52}N_4O_8$ C 69.09, H 6.85, N 7.32; found C 69.00, H. 6.87, N 7.22%; MS (electrospray, methanol solution), $m/z = 765$ ($[M + H]^+$).
14 Synthesis: Benzylamine (10.9 mL, 0.1 mol) and formaldehyde (0.1 mol, 8.6 mL 35% aq. solution) were mixed in ethanol (50 mL) and refluxed overnight. The solvent was removed yielding compound **2** as a clear oil that crystallised over time (10.1 g, 85%), mp 49–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5 H), 3.70 (s, 2 H), 3.45 (s br, 2 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.3, 128.8, 128.1, 126.9, 73.7, 57.0; IR ($CDCl_3$) 3050, 2900, 1490, 1450 cm^{-1}.
15 At lower temperatures (–60 °C) the methylene proton signals (two br s) separate into two pairs of doublets. Compare, *e.g.*, I. Lazar, D. C. Hrncir, W. D. Kim, G. E. Kiefer and A. D. Sherry, *Inorg. Chem.*, 1992, **31**, 4422.
16 E. Mei, L. Liu, J. L. Dye and A. I. Popov, *J. Solution Chem.*, 1977, **6**, 771; Y. Jayathirtha and V. Krishnan, *Indian J. Chem., Sect-A*, 1979, **18**, 311.
17 ^{23}Na NMR (ambient temperature, 39.35 MHz); sodium perchlorate (0.05 M, solvent THF or acetone), addition of ligand **1** (0.50 M in the respective solvent). Acetone solution: no chemical shift change of ^{23}Na, indicating absence of complexation. THF solution: small, continuous increase of ^{23}Na chemical shift, indicating a weak complexation.[18]
18 J. D. Lin and A. I. Popov, *J. Am. Chem. Soc.*, 1981, **103**, 3773.
19 R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb and J. J. Christensen, *Chem. Rev.*, 1985, **85**, 271.
20 M. Kodama, E. Kimura and S. Yamaguchi, *J. Chem. Soc., Dalton Trans.*, 1980, 2536.
21 J. F. Desreux, E. Merciny and M. F. Loncin, *Inorg. Chem.*, 1981, **20**, 987.
22 J.-M. Lehn and F. Montavon, *Helv. Chim. Acta*, 1978, **61**, 67.
23 R. D. Hancock, *Acc. Chem. Res.*, 1990, **23**, 253.