Pergamon

Tetrahedron Letters, Vol. 38, No. 11, pp. 1911-1914, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00241-4

Synthesis and Characterization of a New Series of [12]aneN3 Type Macrocycles. Structures of two Protonated Metal-Free Ligands

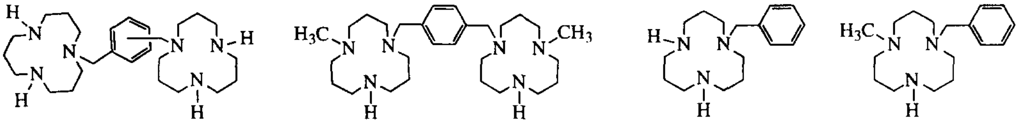
Patricia Hubsch-Weber and Marie-Thérèse Youinou*

Laboratoire de Chimie des Métaux de Transition et de Catalyse, associé au C.N.R.S., Université Louis Pasteur, Institut Le Bel,
4 rue Blaise Pascal, 67000 Strasbourg, France.

Abstract. The synthesis of a family of monotopic and ditopic ligands possessing a [12]aneN$_3$ synthon and different spacers is described. The characterization of two of them by X-ray diffraction is also reported.

Our current interest in modelling hydrolytic enzymes has prompted us to design new polyamine ligands. In order to ascertain the role of metal ions in promoting hydrolytic activity, considerable efforts have been centered on developing synthetic metal complexes of Zn^{2+}, Cu^{2+}, Co^{2+}/Co^{3+} and Ni^{2+}.[1] Furthermore, whether one or two metal ions might be preferred to effect hydrolysis is still a debated question. The choice of our ligand system was primarily based upon the reported efficiency of a zinc complex of 1,5,9-triazacyclododecane ([12]aneN$_3$) towards hydrolysis of esters.[2] Secondly the design of flexible binucleating ligands and their mononucleating analogues, both possessing a [12]aneN$_3$ synthon was initiated in order to investigate the potential cooperativity between two adjacent metal ions. Finally, nitrogen methylation of polyazamacrocycles affecting the catalytic properties of their complexes,[3] selective attachment of a methyl group on the triamine synthon was of interest. We wish to report here our investigations concerning the synthesis and the characterization of a new family of ditopic (**1-4**) and monotopic (**5-6**) ligands shown in Scheme I.

Scheme I



1-3 **4** **5** **6**
para, meta, ortho-xylyl

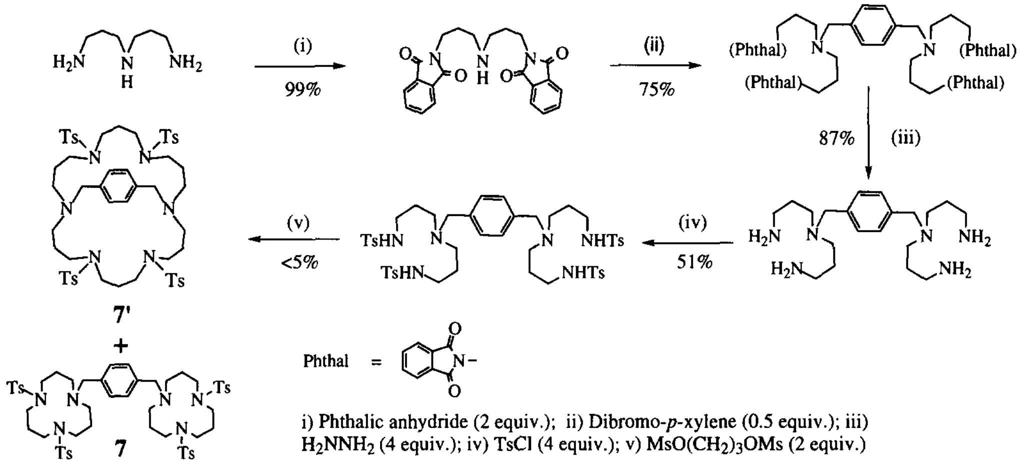
Extensive studies have been carried out on the chemistry of 1,4,7-triazacyclononane over the last decade.[4] However, much less is known on the synthesis and coordination properties of [12]aneN$_3$ derivatives, although branched mononucleating ligands of this type have been developed recently along with their coordination

Fax: 33-(0)3-88-41-61-71. E-mail: youinou@chimie.u-strasbg.fr

chemistry.[5] The literature is even much less documented when considering the area of ditopic ligands in which two [12]aneN$_3$ subunits are linked together by a given spacer between nitrogen bridgeheads, such as **1-4**.

Our initial procedure described in Scheme II involved, as previously reported for analogous examples,[6] the attachment of the *p*-xylene unit in an early stage of the synthesis, followed by hydrolysis of the phthalic derivative and reprotection with tosyl chloride. Finally, the ring closure by the classical Richman-Atkins cyclisation method gave,[7] after standard work-up and chromatography, a fraction with the expected molecular peak (Chemical Ionization, *i*-butane, *m/z* = 1060.4). However, ^{1}H NMR data suggested that a competition reaction between the unfavorable 12-membered ring **7** and the 19-membered ring **7'** occurred, yielding **7'** preferably. Such a conclusion is supported by other examples described in the literature.[8]

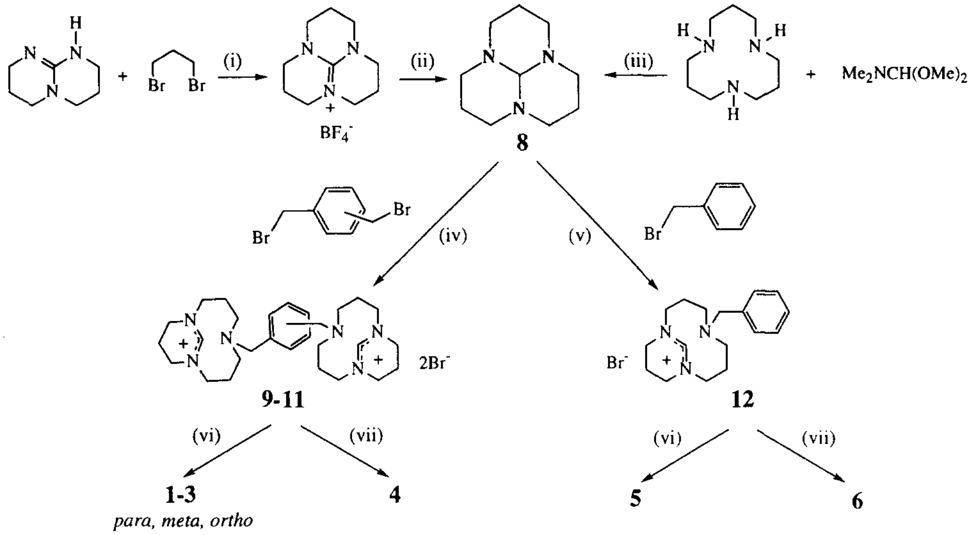
Scheme II



i) Phthalic anhydride (2 equiv.); ii) Dibromo-*p*-xylene (0.5 equiv.); iii) H_2NNH_2 (4 equiv.); iv) TsCl (4 equiv.); v) $MsO(CH_2)_3OMs$ (2 equiv.)

As an alternative strategy, we examined the methodology described by Weisman, based on selective N-protection of [12]ane N$_3$.[9] Such a method was indeed very effective when the spacer group between the two subunits involves an aliphatic chain. We found that the tricyclic orthodiamide **8** was also easily monoalkylated with α,α'-dibromo-*p*-xylene or *m*-xylene and *o*-xylene derivatives ($CHCl_3$, 40-50° C, 24h) alike with $PhCH_2Br$ ($CHCl_3$, 25° C, 1.5h). Hydrolysis of the bicyclic amidinium salts **9-11** under basic conditions (NaOH 0.1M, reflux, 24h) afforded the bismacrocycles **1-3** as well as the previously unreported compound **5** in good yields. When instead a reduction reaction of the amidinium salts was carried out in presence of sodium borohydride in refluxing EtOH for 4 hours, the corresponding methyl ligands **4** and **6** were obtained. In the early stage of this work,[10] the key orthodiamide **8** was rather prepared as previously reported,[11] using the [12]aneN$_3$ synthesized from a modified literature procedure,[12] although lengthy, than from the commercially available source. The alternative route, proposed later by Weisman,[13] allowed a very efficient two-step synthesis of **8**, via a guanidinium salt obtained from inexpensive starting materials, as opposed to [12]aneN$_3$ itself (scheme III). All new compounds **1-6** as well as their intermediates were fully characterized on the basis of microanalytical results and of their ^{1}H, ^{13}C NMR and MS spectra. Furthermore, whilst attempting to prepare complexes of manganese and nickel, respectively in presence of **1** and **5**, colourless crystals with the composition $[\mathbf{1}\cdot H_2](ClO_4)_2$ and $[\mathbf{5}\cdot H_2](NO_3)_2$ were obtained from the reaction mixture,[14,15] although a competitive 1:1 ligand/metal complex formation was also observed in the case of **5**.

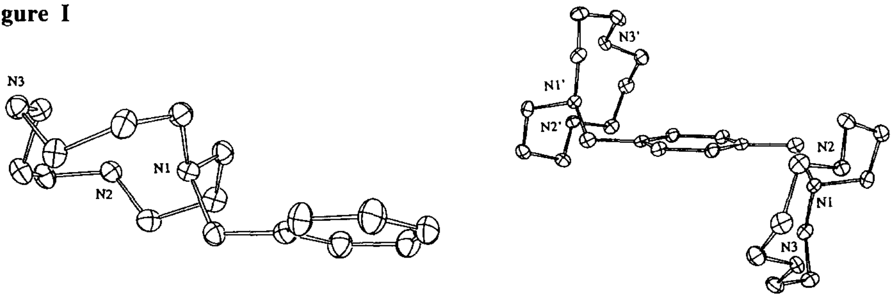
Scheme III



i) and (ii) ref. 13; iii) EtOH, reflux, 3h. ref. 11; iv) and v) Dibromo-xylene (0.5 equiv.) or $PhCH_2Br$ (1 equiv.) $CHCl_3$, 45 °C, 24h. (instead of conditions of ref. 9), yields of 90, 86, 57, 92 % for **9-12**; vi) 0.1 M-NaOH, reflux, 1h., yields of 90, 82, 50 % for **1-3** and 92 % for **5**; vii) $NaBH_4$ (10 equiv.) in EtOH, reflux, 3h., crude yields of 93, 96 % for **4**,**6**

The X-ray crystal analysis of $[\mathbf{1}\cdot H_2](ClO_4)_2$ reveals an *anti* conformation of the two macrocycles, related to each other by an inversion center coinciding with the center of the *para*-xylyl group. In both structures of the diprotonated forms of **1** and **5** depicted in Figure I,[16,17] the methylene carbons are located either above or below the mean plane formed by the three nitrogen atoms, as opposed to the situation observed in $[Me_3[9]aneN_3H](ClO_4)$ where a smaller separation between the nitrogen atoms allowed all carbon atoms to be on one side of the nitrogen plane as well as internal hydrogen bonding.[18] The stabilization is now achieved via a network of intra- and intermolecular hydrogen bonds [NH---O] between the cation and the anion, of 2.37(1) Å (H25--O4) and of 2.288(6) or 2.419(6) Å (H23--O2 or H25--O1) respectively in $[\mathbf{1}\cdot H_2](ClO_4)_2$ and as short as 1.797(3) or 1.864(3) Å (for H29--O2 or H26--O5) and of 1.998(3) or 2.015(3) Å (for H28--O2 or H28--O1) in $[\mathbf{5}\cdot H_2](NO_3)_2$.

Figure I



In presence of zinc(II), dinuclear complexes of general formula "Zn_2L^{n+}" (n = 2, 3 or 4 depending upon the nature of the additional ligand) and mononuclear complexes such as $[ZnL'(CH_3CO_2)](ClO_4)$ or $[ZnL'(NO_3)](NO_3)$ have been synthesized and characterized for these ligands (L = **1-4** and L' = **5**, **6**) and will be reported separately along with their activity towards hydrolysis of esters.

Acknowlegements

We thank Pr. C. J. Burrows for fruitful discussions, Pr. J. A. Osborn for his support and the C.N.R.S. for funding.

References and notes

1. Chin, J. *Acc. Chem. Res.* **1991**, *24*, 145-152.
2. a) Kimura, E.; Shiota, T.; Koike, T.; Shiro, M.; Kodama, M. *J. Am. Chem. Soc.* **1990**, *112*, 5805-5811. b) Breslow, R.; Berger, D.; Huang, D-L. *J. Am. Chem. Soc.* **1990**, *112*, 3686-3687.
3. Andrés, A.; Aragó, J.; Bencini, A.; Bianchi, A.; Domenech, A.; Fusi, V.; García-España, E.; Paoletti, P.; J. M.; Ramírez, J. A. *Inorg. Chem.* **1993**, *32*, 3418-3424.
4. Chaudhuri, P.; Wieghardt, K. *Progress in Inorg. Chem.* **1987**, *35*, 329-436.
5. a) Rawle, S. C.; Clarke, A. J.; Moore, P.; Alcock, N. W. *J. Chem. Soc., Dalton Trans.* **1992**, 2755- 2757. b) Rawle, S. C.; Harding, C. J.; Moore, P.; Alcock, N. W. *J. Chem. Soc., Chem. Commun.* **1992**, 1701-1703. c) Alcock, N. W.; Benniston, A. C.; Moore, P.; Pike, G. A.; Rawle, S. C. *J. Chem. Soc., Chem. Commun.* **1991**, 706-708. d) Koike, T.; Kimura, E.; Nakamura, I.; Hashimoto, Y.; Shiro, M. *J. Am. Chem. Soc.* **1992**, *114*, 7338-7345. e) Kimura, E.; Nakamura, I.; Koike, T.; Shionoya, M.; Kodama, Y.; Ikeda, T.; Shiro, M. *J. Am. Chem. Soc.* **1994**, *116*, 4764-4771.
6. a) Yuen Ng, H.; Motekaitis, R.J.; Martell, A.E. *Inorg. Chem.* **1979**, *18*, 2982-2986. b) Xu, D.; Mattner, P. G.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **1996**, *37*, 5301-5304.
7. Richman, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 2268-2270.
8. Dietrich, B.; Viout, P.; Lehn, J. M. *Macrocyclic Chemistry: Aspects of Organic and Inorganic Supramolecular Chemistry*; VCH: Weinheim, **1993**; pp. 3-37.
9. Weisman, G. R.; Vachon, D. J.; Johnson, V. B.; Gronbeck, D. A. *J. Chem. Soc., Chem. Commun.* **1987**, 886-887.
10. This research was first presented at the *Concoord XXII* Meeting, Paris, **1992**.
11. a) Atkins, T.J. *J. Am. Chem. Soc.* **1980**, *102*, 6364-6365. b) Weisman, G. R.; Johnson, V.; Fiala, R.E. *Tetrahedron Lett.* **1980**, *37*, 3635-3638.
12. Atkins, T. J.; Richman, J. E.; Oettle, W. F. *Org. Synth.* **1978**, *58*, 86-98.
13. Alder, R. W.; Mowlam, R. W.; Vachon, D. J.; Weisman, G. R. *J. Chem. Soc., Chem. Commun.* **1992**, 507-508.
14. To a solution of 0.304 g ($0.683\text{x}10^{-3}$ mol) of **1** in distilled MeOH (5ml) was added 0.118 g ($0.325\text{x}10^{-3}$ mol) of $Mn(ClO_4)_2.6H_20$ as a solid and the resultant yellow solution was stirred for 1 h. Addition of $Na(CH_3CO_2)$ (0.059 g, $0.715\text{x}10^{-3}$ mol) did not produce any color change, even after stirring for an extra hour. After partial evaporation of the solvent, a white crystalline solid was obtained; it was filtered off, washed with Et_2O and dried under vacuum, yielding $[\mathbf{1}.H_2](ClO_4)_2$ (0.333 g, 76%). NMR ^1H (200MHz, CD_3OD, 25 °C) δ (ppm): 7.33 (s, 4H, aromatic), 3.63 (s, 4H, NCH_2Ph), 3.07 (t, 8H, $HNCH_2CH_2CH_2NH$), 2.84 (t, 8H, $HNCH_2CH_2CH_2N$), 2.57 (t, 8H, $HNCH_2CH_2CH_2N$), 1.80 (m, 12H, $CH_2CH_2CH_2$). IR (KBr, ν cm^{-1}): ν(NH) 3304 and 3204 (m), ν(CH) and ν(NH--) 3000-2700 (br. and sharp), ClO_4: ν_3 1095 (s) and ν_4 623 (m). Found: C 48.20, H 7.64, N 12.87; calc. for $[C_{26}H_{50}N_6](ClO_4)_2$: C 48.37, H 7.81, N 13.02.
15. The reaction of **5** (0.060g, $0.232\text{x}10^{-3}$ mol) with an excess of $Ni(NO_3)_2.6H_20$ (0.101 g, $0.347\text{x}10^{-3}$ mol) in ethanol (12 ml) produced a green solution which upon stirring (24 h) gave a white solid; at this time, the product was removed by filtration, washed with ethanol and recrystallized from MeOH/Et_2O (1/10), yielding $[\mathbf{5}.H_2](NO_3)_2$ (0.021 g, 24%). NMR ^1H (200MHz, CD_3OD, 25 °C) δ (ppm): 7.36 (m, 5H, aromatic), 3.75 (s, 2H, NCH_2Ph), 3.20-3.0 (t partly masked by CD_3OD, $HNCH_2CH_2CH_2NH$ and $HNCH_2CH_2CH_2N$), 2.72 (t, 4H, $HNCH_2CH_2CH_2N$), 2.19 and 1.97 (br., 2H and 4H, $CH_2CH_2CH_2$). MS-FAB$^+$ (*m*-nitrobenzylalcohol matrix) *m/z* 262.42 (100%, expected value for $[M+H]^+$ 262.2). IR (KBr, ν cm^{-1}): ν(CH) and ν(NH--) 3200-2600 (br. with sharp peaks), NO_3: $\nu_1+\nu_4$ 1756 (vw), ν_3 1383 (s) and ν_2 825 (w). Found: C 49.60, H 7.86, N 17.78; calc. for $[C_{16}H_{27}N_3H_2](NO_3)_2$: C 49.60, H 7.54, N 18.08. If stirring of the filtrate was maintained for a much longer period of time (3 weeks), a blue solid of $[Ni(\mathbf{5})(NO_3)(H_2O)](NO_3)$ was formed (0.024 g, 24%).
16. Data were collected at 173° K using a Philips PW1100/16 diffractometer with Ni-filtered Cu Kα radiation ($\lambda = 1.5418$ Å). Crystal data for $[\mathbf{1}\cdot H_2](ClO_4)_2$: $C_{26}H_{50}N_6O_8Cl_2$, $M = 645.6$, colorless crystals, monoclinic, $P2_1/c$, $a = 13.931(5)$, $b = 7.960(3)$, $c = 14.397(5)$ Å, $\beta = 97.80(2)°$, $V = 1581.7$ Å^3, $Z = 2$, $D_c = 1.356$ (gcm^{-3}), $F(000) = 692$, $\mu = 23.291$ cm^{-1}. The structure was solved by direct methods. In the disordered perchlorate group, two positions with half occupancy were detected for two of the oxygen atoms. Difference Fourier maps revealed maxima at positions expected for the hydrogen atom H23 attached to N2 and for H24 and H25 attached to N3; these hydrogen atoms were introduced and refined by using a riding model. All other hydrogen atoms were introduced in structure factor calculations by their computed coordinates (C-H = 0.95 Å) and isotropic structure factors such as $B(H) = 1 + Be_q(C)$ Å^2 but not refined. Out of the 1982 independent reflections, 1359 reflections having $I > 3\sigma(I)$ were used. Full least-squares refinements converged to the conventional R(F) and R_w(F) of 0.061 and 0.084 respectively, with 212 variables and a highest final difference peak of 0.07 eA^{-3}.
17. Crystal data for $[\mathbf{5}\cdot H_2](NO_3)_2$: $C_{16}H_{29}N_5O_6$, $M = 387.4$, colorless crystals, monoclinic, $P2_1/c$, $a = 15.689(5)$, $b = 8.096(3)$, $c = 15.436(5)$ Å, $\beta = 91.58(2)°$, $V = 1959.9$ Å^3, $Z = 4$, $D_c = 1.313$ (gcm^{-3}), $F(000) = 832$, $\mu = 8.070$ cm^{-1}. The structure was solved by direct methods and refined using full-matrix least squares. Difference Fourier maps also revealed maxima at positions expected for the hydrogen atoms H26 and H27 attached to N2 and for H28 and H29 attached to N3. These atoms and all other hydrogen atoms were introduced as above. 2485 independent reflections of which 1373 reflections having $I > 3\sigma(I)$ were used in the final refinement; R(F)= 0.045 and R_w(F) = 0.066; 249 variables; highest final difference peak, 0.05 eA^{-3}. Further details of both crystal structure determinations can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ (UK) on quoting the full journal citation.
18. Wieghardt, K.; Brodka, S.; Peters, K.; Peters, E. M.; Simon, A. *Z. Naturforsch.* **1987**, *42b*, 279-281.

(*Received in France* 16 *December* 1996; *accepted* 30 *January* 1997)