



Post-synthetic isotopic labeling of an azamacrocyclic ligand

Mirko Pachioni,^a Andrea Bega,^a Antonio C. Fabretti,^a Donella Rovai^b and Andrea Cornia^{a,*}

^aDipartimento di Chimica and INSTM, Università di Modena e Reggio Emilia, via G. Campi 183, I-41100 Modena, Italy

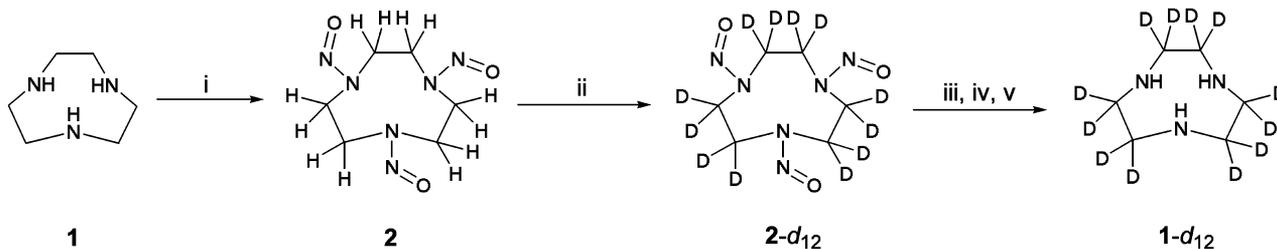
^bDipartimento di Chimica and INSTM, Università di Firenze, Via Maragliano 75/77, I-50144 Firenze, Italy

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Abstract—A simple post-synthetic method for the preparation of 1,4,7-triazacyclononane-*d*₁₂ (90% atom D) is reported. The macrocycle is first converted into 1,4,7-trinitroso-1,4,7-triazacyclononane, whose solid-state and solution properties are herein described. In CD₃OD/D₂O solution, the trinitroso derivative undergoes fast base-catalyzed H/D exchange on the whole set of methylene hydrogens and can be subsequently denitrosated by reduction with Ni/Al alloy. © 2002 Elsevier Science Ltd. All rights reserved.

Isotope exchange reactions have found prominent applications in many different branches of chemistry, physics and biology, ranging from the investigation of reaction mechanisms to the development of new functional materials.¹ Recently, isotopic substitution has emerged as a new tool for tuning the magnetic properties single-molecule magnets, a class of transition metal clusters showing hysteresis loops of purely molecular origin.² The rate at which magnetization relaxes at low temperature can be controlled via hyperfine and super-hyperfine interactions between electron and nuclear spins,^{2d} as first demonstrated in the octairon(III) cluster [Fe₈O₂(OH)₁₂(TACN)₆]Br₈·9H₂O (Fe₈), with TACN = 1,4,7-triazacyclononane (**1**). When ⁵⁶Fe (*I*=0) is replaced with ⁵⁷Fe (*I*=1/2) in the cluster a faster relaxation of the magnetization is observed due to the increased hyperfine contribution. By contrast, deuteration of the OH and NH groups induces slower dynam-

ics because of the smaller nuclear magnetic moment of ²H as compared with ¹H. Deuteration can thus be systematically used to enhance the properties of single-molecule magnets. For this reason, we have considered isotopic labeling of **1** on the six methylene groups. The simplest strategy for the synthesis of **1-d**₁₂ is a Richman–Atkins cyclization reaction with perdeuterated diethylenetriamine and ethyleneglycol.^{3a} The former can be synthesized either by ammonolysis of dichloroethane-*d*₄ in a ND₃/D₂O mixture (100–105°C, 25–30 bar, yield 11%)^{3b} or by amidation of glycine-*d*₅ and successive reduction (yield 22%).^{3c} Considering the very low yield and the large amount of deuterated chemicals required in both procedures, we have turned to post-synthetic methods for isotopic labeling. To our knowledge, H/D exchange of C–H protons in saturated azamacrocycles has not been reported to date. Base-catalyzed isotope exchange has been observed in a few



Scheme 1. Reagents and conditions: (i) NaNO₂, HCl, H₂O, 65°C, 6–7 h, rt, 12–18 h, 83–84%; (ii) NaOD 0.5 M, CD₃OD:D₂O 1:1 v/v, 70°C, 2 h, 45%; (iii) Ni/Al alloy, NaOD 0.5 M, CD₃OD:D₂O 1:1 v/v, rt, 12–18 h; (iv) HBr/AcOH, H₂O, 60%; (v) NaOH, toluene, 82%.

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* Corresponding author. Tel.: +39-59-2055032; fax: +39-59-373543; e-mail: acornia@unimo.it

unsaturated azamacrocycles upon complexation.⁴ We have now found that the acidity of methylene protons α to nitrosamino groups⁵ can be exploited to synthesize **1-d**₁₂ via H/D exchange,⁶ as summarized in Scheme 1. In the first step (i) macrocycle **1** is converted into 1,4,7-trinitroso-1,4,7-triazacyclononane (**2**) in 83–84% yield by standard treatment with NaNO₂/HCl.⁷ The NMR spectral properties of this compound in CD₂Cl₂ solution (Fig. 1a, b) clearly point to the presence of two isomers, **I** (symmetric) and **II** (asymmetric),⁸ as expected from the hindered rotation of the NO group around the N–N bond (Scheme 2).^{8b}

The **I:II** ratio determined from the relative areas of ¹H NMR signals is 42:58, with a slight prevalence of the statistically-favored asymmetric isomer. Colorless rod-like crystals of **2** suitable for a single-crystal X-ray investigation⁹ have been grown by slow evaporation of CH₂Cl₂ solutions. The molecular structure of **2** is shown in Fig. 2, while selected interatomic distances and interbond angles are gathered in Table 1.

The ring conformation is very similar to that found in formyl and benzoyl derivatives of **1**.^{8a} Among the three NO groups, one lies above and two below the average ring plane, leading to minimal C–H bond eclipsing. Since the NO groups have the same orientation around the ring, the solid-state conformation corresponds to

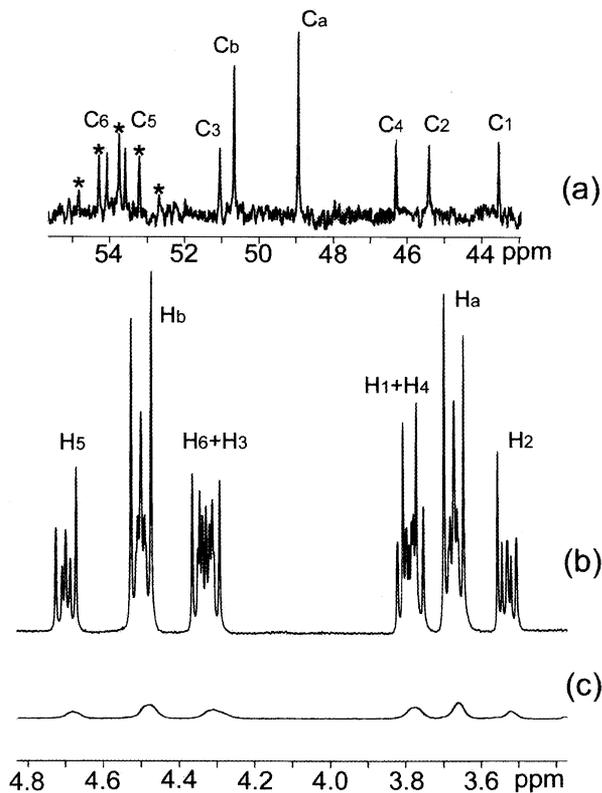
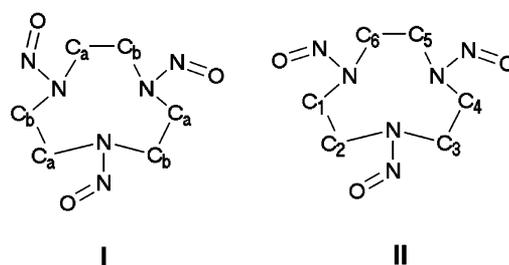


Figure 1. ¹³C (a) and ¹H NMR (b) spectra of **2** in CD₂Cl₂ (assignments based on 2D spectra). The ¹H NMR spectrum of **2-d**₁₂ in CD₂Cl₂ is shown in (c) for comparison (see Scheme 2 for atom labeling). Solvent peaks are marked with an asterisk.

symmetric isomer **I** (Scheme 2). The C2–C3–N2–N5–O2, C1–C6–N1–N4–O1 and C4–C5–N3–N6–O3 moieties are essentially planar (max. dev.: 0.090 Å). The N–N and N–O distances are all equal within experimental error [1.318(2) and 1.239(2) Å, respectively] and are typical for *N*-nitroso amines,¹⁰ with partial π -electron delocalization over the N–NO fragments. The crucial H/D exchange step (ii) is carried out with 0.5 M NaOD in CD₃OD/D₂O (70°C, 2 h) and leads to **2-d**₁₂ in 45% yield. The NMR spectrum of the deuterated compound (Fig. 1c) shows the same pattern of resonances



Scheme 2. Symmetric (**I**) and asymmetric (**II**) isomers of **2** with the atom labeling scheme.

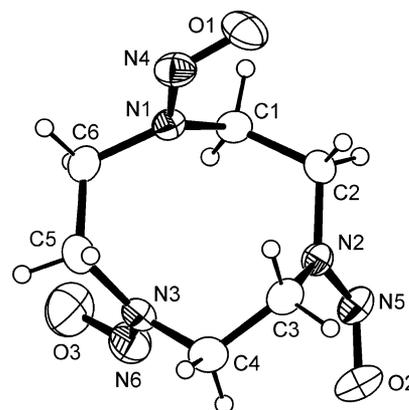


Figure 2. Structure of **2** with the atom numbering scheme.

Table 1. Bond distances (Å) and interbond angles (°) for **2**, with estimated standard deviations in parentheses

C1–N1	1.465(2)	C1–C2	1.512(3)
C2–N2	1.459(2)	C3–N2	1.460(2)
C3–C4	1.509(3)	C4–N3	1.454(3)
C5–N3	1.459(3)	C5–C6	1.510(3)
C6–N1	1.460(2)	N1–N4	1.319(2)
N2–N5	1.318(2)	N3–N6	1.316(2)
N4–O1	1.237(2)	N5–O2	1.240(2)
N6–O3	1.240(3)		
N1–C1–C2	116.20(15)	N2–C2–C1	114.86(15)
N2–C3–C4	113.07(17)	N3–C4–C3	113.20(16)
N3–C5–C6	115.07(17)	N1–C6–C5	114.19(17)
N4–N1–C6	114.94(16)	N4–N1–C1	120.97(15)
C6–N1–C1	122.17(16)	N5–N2–C2	115.53(14)
N5–N2–C3	122.21(15)	C2–N2–C3	121.72(15)
N6–N3–C4	115.18(18)	N6–N3–C5	122.28(18)
C4–N3–C5	122.28(19)	O1–N4–N1	114.89(16)
O2–N5–N2	114.92(16)	O3–N6–N3	114.68(19)

observed in **2** (Fig. 1b), with six broad peaks from residual protons.^{5c} The relative areas of the resonances are retained, showing that *all* methylene hydrogens in **2** undergo isotopic substitution. The final isotopic enrichment, as determined from the integrated intensity of the residual proton resonances, is ca. 90%. The yield of the H/D-exchange reaction is mainly limited by the concomitant decomposition of the trinitrosomacrocycle in alkaline solution.¹¹ However, a higher degree of deuteration (with lower yield) can in principle be obtained by using longer reaction times or higher temperatures. The successive step (iii) involves denitrosation of **2-d**₁₂, for which several methods have been tested. Treatment with 2 M HCl in water at 90°C (2 h),^{12a} as well as reduction with NiCl₂·6H₂O/NaBH₄ in THF at room temperature (6 h)^{12b} are totally ineffective. By contrast, reduction with Ni/Al alloy in alkaline solution, with *in situ* generation of Raney-Ni,¹³ leads to complete removal of the three nitroso groups. As a major advantage, the Ni/Al alloy can be directly added to the reaction mixture resulting from the H/D-exchange step (ii) without intermediate isolation of **2-d**₁₂. As the reduction proceeds, the liquid phase progressively turns to a pink color typical of nickel(II) hexaamino complexes.¹⁴ The white trihydrobromide **1-d**₁₂·3HBr can be isolated in 60% yield from the filtered reaction mixture by removing the solvent *in vacuo* and treating the solid residue with aqueous HBr/AcOH (iv). Finally, the free perdeuterated ligand **1-d**₁₂ (90% atom D) can be recovered by following standard methods (v).

In summary, we have individuated a convenient post-synthetic route for isotope exchange in a saturated azamacrocycle. The effect of deuteration on the magnetic properties of Fe₈ is currently under investigation and the results will be published soon.

Acknowledgements

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 - 1,4,7-Triazacyclononane (**1**) was synthesized by a literature procedure (Ref. 3a). CAUTION: all the nitrosamines are *carcinogenic* and/or *mutagenic* and should be handled with due care using gloves in a properly functioning chemical fume hood. The reductions with Ni/Al alloy generate hydrogen and should be done in an efficient hood. The residual alloy is potentially *pyrophoric* and should be allowed to dry on a metal tray in the absence of flammable solvents for 24 h before being discarded as solid waste.
- All new compounds gave satisfactory analytical and spectral data in accordance with their structures. Selected data are as follows: **2**: mp 188°C (colorless crystals from CH₂Cl₂), yield 83–84%. Elemental analysis, found: C, 33.3; H, 5.8; N, 38.5; calcd for C₆H₁₂N₆O₃: C, 33.3; H, 5.6; N, 38.9%; *M*, 216; ¹H NMR (200 MHz, CD₂Cl₂, Me₄Si) δ 3.54 (2H, m, CH₂), 3.67 (4.4H, m, CH₂), 3.79 (4H, m, CH₂), 4.34 (4H, m, CH₂), 4.51 (4.4H, m, CH₂), 4.71 (2H, m, CH₂); ¹³C NMR (50 MHz, CD₂Cl₂, Me₄Si) δ 43.57 (s), 45.44 (s), 46.33 (s), 48.96 (s), 50.70 (s), 51.07 (s), 53.61 (s), 54.10 (s); MS-EI: *m/z* 186 (*M*-NO, 9.5) 156 (*M*-2NO, 7.9), 126 (*M*-3NO, 100), 97 (28.6), 85 (18.3), 84 (13.5), 70 (8.7), 56 (46), 55 (19.8), 44 (4.8). **2-d**₁₂: mp 188°C (colorless crystals from CH₂Cl₂), yield 45%; ¹H NMR (200 MHz, CD₂Cl₂, Me₄Si) δ 3.52 (2H, s, CHD), 3.66 (4.4H, s, CHD), 3.78 (4H, s, CHD), 4.31 (4H, s, CHD), 4.48 (4.4H, s, CHD), 4.68 (2H, s, CHD); MS-EI: *m/z* 197 (8), 167 (8), 137 (44), 123 (6), 106 (20), 92 (28), 74 (6), 60 (54), 46 (100). **1-d**₁₂·3HBr: yield 60%; ¹H NMR (200 MHz, D₂O, Me₄Si) δ 3.51 (s, CHD). **1-d**₁₂: mp 42–44°C (colorless crystals from diethylether), yield 82%; ¹H NMR (200 MHz, CDCl₃, Me₄Si) δ 2.70 (m, CHD), 2.73 (s, CH₂); MS-EI: *m/z* 166 (13), 151 (11), 142 (37), 134 (18), 121 (56), 106 (35), 92 (70), 75 (35), 61 (100), 46 (81).
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- Crystal data for **2**: C₆H₁₂N₆O₃, *M*=216.20, monoclinic, space group: *P*₂₁/*c*, *a*=12.3314(13), *b*=5.7996(3), *c*=13.7077(14) Å, β=94.446(12)°, *U*=977.39(15) Å³, *Z*=4, *D*_{calcd}=1.469 g cm⁻³, *T*=298 K, λ=0.71069 Å, absorption coefficient=0.119 mm⁻¹, *F*(000): 456, crystal size:

- 0.40×0.15×0.10 mm³; $\theta=1.66\text{--}25.94^\circ$, index ranges $-15 \leq h \leq 15$, $0 \leq k \leq 7$, $0 \leq l \leq 16$, reflections collected 1993, independent reflections: 1902 ($R_{\text{int}}=0.0158$), refinement method: full-matrix least-squares on F^2 , data/restraints/parameters: 1902/0/184, goodness-of-fit on F^2 : 1.017, final R indices [$I > 2\sigma(I)$]: $R_1=0.0388$, $wR^2=0.0902$, R indices (all data): $R_1=0.0718$, $wR^2=0.1031$. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Crystallographic Data Centre as supplementary publication number CCDC 174902. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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 14. The soluble nickel(II) complex $[\text{Ni}(\mathbf{1-d}_{12})_2]^{2+}$ is likely to be the main product of the denitrosation reaction. In fact, addition of KBr to the concentrated liquid phase leads to precipitation of $[\text{Ni}(\mathbf{1-d}_{12})_2]\text{Br}_2 \cdot 4\text{H}_2\text{O}$ in ~60% yield.