J Incl Phenom Macrocycl Chem (2007) 57:179–183
DOI 10.1007/s10847-006-9197-8

ORIGINAL ARTICLE

Synthesis and characterization of a persistent paramagnetic rotaxane based on α-cyclodextrin and α,ω-alkyl disulfides

Elisabetta Mezzina · Paola Franchi · Marco Lucarini

Received: 15 May 2006 / Accepted: 20 October 2006 / Published online: 19 January 2007

Abstract A new synthetic strategy for the preparation of persistent paramagnetic cyclodextrin-based rotaxanes is described. The method consists in the formation of inclusion complexes between α-cyclodextrin (α-CD) and α,ω-dithiols containing an octamethylene chain covalently trapped by bulky stoppers composed of 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) radical fragments. Interaction of α-CD (the bead) and 1,8-octanedithiol (the thread) occurs in aqueous alkaline media and encapsulation is obtained by nucleophilic substitution at both termini of the linear component with a bulky paramagnetic iodide [2,2,6,6-tetramethyl-4-(2-iodoacetamide)piperidine-N-oxyl]. Structure determination of the new [2]rotaxane by ^{1}H NMR is reported and the spectroscopic data are discussed.

Keywords α-Cyclodextrin · Inclusion complexes · Rotaxanes · Nitroxides · Free radicals

Introduction

Rotaxanes [1] represent a relatively new class of molecular architectures with adaptive functionality in which a cyclic component (bead) is threaded mechanically by a linear chain. The possibility of controlling the movement of the components in these systems by light, electrons, chemical reactions, pH, or temperature make rotaxanes typical prototype of molecular devices [2]. Among the bead components used in rotaxane chemistry, cyclodextrins (CDs) [3] represent the most versatile receptors because of their shape and binding properties [4]. These natural glucopyranose oligomers are characterized by a toroidal shape and a strong binding affinity in aqueous media for hydrophobic molecules forming a wide range of inclusion type complexes.

Very recently we reported the synthesis and the spectroscopic characterization of an α-CD based [2]rotaxane capped by persistent nitroxyl radicals [5]. The construction of such mechanical interlocked organic free radical represented the first example of a novel family of paramagnetic supramolecular structures whose properties could be exploited in many technological field., *i.e.* in biomedicine as spin traps [6], in chemical synthesis [7], and in the assembly of organic radical centers to control magnetic interaction in multispin molecular systems [8]. By using ESR spectroscopy we were able to demonstrate that the 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) group can be used as an end-cap group in a α-CD based [2]rotaxane because this radical fragment is large enough to prevent dethreading. Actually, complexation of sebacoyl chloride by α-cyclodextrin followed by reaction with the bulky 4-amino-TEMPO resulted in the trapping of the cyclodextrin, threaded by the alkyl chain, thus generating the rotaxane structure. The rotaxane was recovered in an overall 5% yield.

Here we report a new synthetic strategy for the preparation of a mechanical interlocked persistent nitroxide radical based on the reaction of α, ω-thiolates with 2,2,6,6-tetramethyl-4-(2-iodoacetamide)piperidine N-oxyl (4-iodoacetamide-TEMPO). The proposed procedure resulted in an increase of the yield of the desired product.

E. Mezzina · P. Franchi · M. Lucarini (✉)
Department of Organic Chemistry ''A. Mangini'', University of Bologna, Via San Giacomo 11, 40126 Bologna, Italy
e-mail: marco.lucarini@unibo.it

Experimental

Material and measurements

All reagents were commercially available and were used without further purification. 1D and 2D NMR spectra were recorded at 298 K on a Varian Inova spectrometer operating at 600 MHz in DMSO-d^6 solutions using the solvent peak as an internal standard (2.50 ppm). Chemical shifts are reported in parts per million (δ scale). ROESY data were collected using a 90° pulse width of 6.1 μs and a spectral width of 6000 Hz in each dimension, respectively. The data were recorded in the phase sensitive mode using a CW spin-lock field of 2 KHz, without spinning the sample. Acquisitions were recorded at mixing times 200–300 ms. Other instrumental settings were: 128 increments of 2K data points, 8 scans per t_1, 1.5 s delay time for each scan.

ESI-MS measurements were recorded with Micromass ZMD ESI-MS spectrometer by using the following instrumental settings: positive ions; desolvation gas (N_2) 230 L/h; cone gas (skimmer): 50 l/h; desolvation temp. 150 °C; capillary voltage: 2.8 kV; cone voltage: 120 V; hexapole extractor: 3 V.

Synthesis of **4**

To an aqueous solution (5–10 ml) of α-CD (72 mg, 0.0740 mmol) was added in three portions 2,2,6,6-tetramethyl-4-(2-iodoacetamide)piperidine-N-oxyl (4-iodoacetamide-TEMPO) **2** (25 mg, 0.0737 mmol) at room temperature and the solution was sonicated after each addition. To the resulting solution 1,8-octanedithiol (6.8 μl, 0.0368 mmol) was added in 3 portions, at 2 min intervals, with stirring. The resulting mixture was adjusted at pH = 10 with 1 M NaOH and protected by light. The solution was stirred for 48 h at room temperature and extracted with $CHCl_3$ (4 × 5 ml) to remove the free thread **3**. The concentrated aqueous solution gave a white solid which was suspended twice in methanol (10 ml) with stirring for 24–72 h at room temperature for decreasing the amount of α-CD from the reaction mixture. The filtrate was concentrated (15 mg) and the powder was analyzed by ESI-MS spectrometry and by TLC. ESI-MS spectrum revealed peaks corresponding to rotaxane **4** and α-CD; rotaxane **4** was the most abundant peak in the spectrum. TLC was performed on RP18 F254 plates. The eluent was MeOH–H_2O 1:1 (v:v) and the spots were detected by UV lamp or by exposing the plates to iodine vapour (to detect the rotaxane), and then by charring with heat spraying the plate with 50% methanolic sulphuric acid. Charring is the indication for the presence of cyclodextrin moieties (R_f (α-CD): 0.72; R_f (**4**): 0.62). The crude obtained was separated by gel filtration over a Sephadex G-15 column (length 45 cm, i.d. 1.5 cm) using distilled water as eluent. In the chromatographic separation fractions of 1–2 ml were collected. Rotaxane **4** (11 mg) was recovered in 19% yield. Small amounts of the mono reducted *N*-hydroxy derivative of **4**, can also be present in the isolated product.

4: orange solid, ^{1}H NMR (DMSO-d^6) δ ppm: 5.60–5.95 (m, 12H, OH(2), OH(3)), 4.81 (broad s, 6H, H_1), 4.48 (broad s, 6H, OH(6)), 3.50–3.80 (m, 18H, H_3, H_5, H_6), 3.20–3.50 (m, 12H, H_4, H_2), 3.15 (broad s, 2H, CH_2 (α)), 2.97 (broad s, 2H, CH_2 (α′)), 1.54–1.70 (m, 6H, H_{eq}, H'_{eq}, CH_2 (b)), 1.20–1.50 (m, 14H, H_{ax}, H'_{ax}, CH_2 (c, d, b′, c′, d′)). Positive ESI-MS: m/z 1596.2 $[\mathbf{4} + Na]^+$, 799.0 $[\mathbf{4} + H + Na]^{2+}$, 809.5 $[\mathbf{4} + 2Na]^{2+}$. Negative ESI-MS: m/z 1572.1 $(\mathbf{4} - H)^-$.

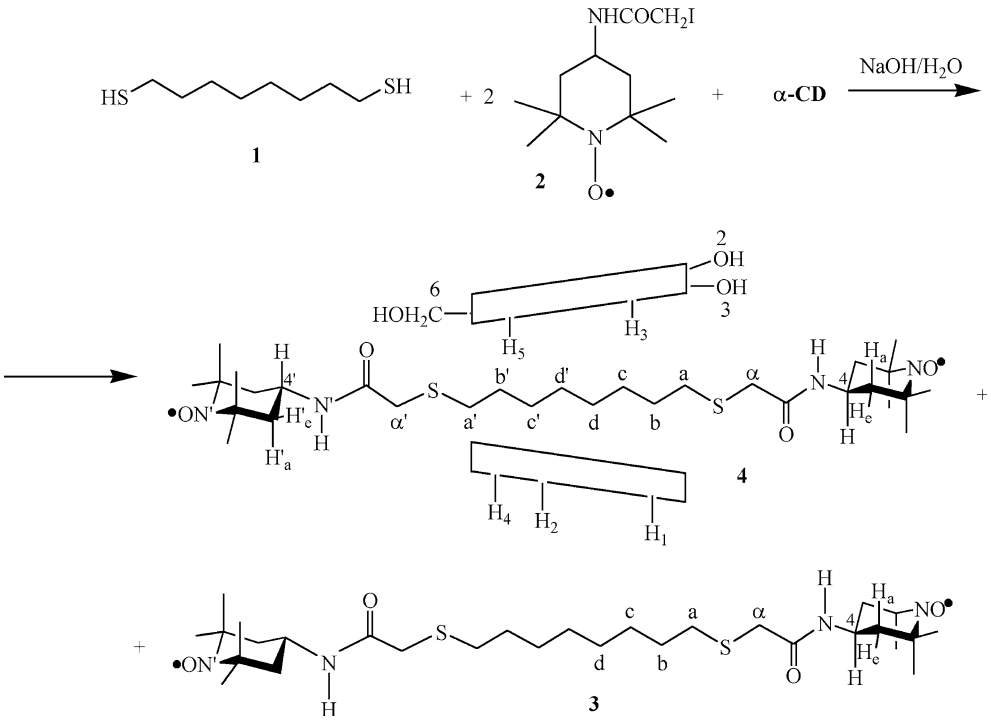
In order to increase the NMR spectral resolution compound **4** has been converted into the diamagnetic N–OH derivative (**4**-OH) by adding directly inside the NMR tube a small amount of phenylhydrazine [9].

4-OH: ^{1}H NMR (DMSO-d^6) δ ppm: 7.82 (d, J = 7.8 Hz, 1H, NHCO), 7.76 (d, J = 7.8 Hz, 1H, N′HCO), 7.09 (s, 1H, NOH), 7.08 (s, 1H, NOH), 5.81 (broad s, 6H, OH(2)), 5.70 (broad s, 6H, OH(3)), 4.80 (d, J = 3.0 Hz, 6H, H_1), 4.48 (m, 6H, OH(6)), 3.82–3.96 (m, 2H, 4-H, 4′-H, overlapped with NH_2 of phenylhydrazine), 3.74 (t, J = 9.3 Hz, 6H, H_3), 3.54–3.72 (m, 18H, H_5, H_6), 3.44 (t, J = 9.0 Hz, 6H, H_4), 3.29 (m, 6H, H_2), 3.15 (s, 2H, CH_2 (α)), 2.97 (s, 2H, CH_2 (α′)), 2.58 (t, J = 7.8 Hz, CH_2 (a)), 2.47 (t, J = 7.8 Hz, CH_2 (a′)), 1.64–1.68 (m, 4H, H_{eq}, H'_{eq}), 1.59–1.64 (m, 2H, CH_2 (b)), 1.37–1.45 (m, 2H, CH_2 (b′)), 1.18–1.36 (m, 12H, H_{ax}, H'_{ax}, CH_2 (c, d, c′, d′)), 1.05 (s, 24H, Me_{ax}, Me_{eq}).

Results and discussion

The reaction was carried out treating 1,8-octanedithiol **1** with an excess of α-CD in alkaline water and two equivalents of the bulky paramagnetic iodide named 2,2,6,6-tetramethyl-4-(2-iodoacetamide)piperidine-N-oxyl (4-iodoacetamide-TEMPO) **2**, giving rise to the free **3** and the desired interlocked thread **4**, together with unreacted α-CD (Scheme 1). The formation of rotaxane **4** was evidenced by recording the ESI-MS spectrum of the reaction crude, showing intense signals at 1596.2 m/z ($[\mathbf{4} + Na]^+$) and 809.5 m/z ($[\mathbf{4} + 2Na]^{2+}$). It should be remarked that ESI-MS analysis of a mixture containing the separate components of the rotaxane (**3** and α-CD) resulted only in the

Scheme 1



signal due to the free rod and the uncomplexed α-CD. From the resulting reaction mixture the rotaxane **4** was isolated in 19% yield by using a Sephadex G-15 exclusion column.

Complete structural assignment of the interlocked molecule was obtained by analysis of 1D and 2D NMR spectra. Because paramagnetic species yield NMR spectra of very low resolution making structural assignment rather difficult, NMR spectra were recorded by converting **4** into the analogous N-hydroxyl amine derivative (**4**-OH) by adding directly inside the NMR tube a stoichiometric amount of phenylhydrazine. Figure 1 reports spectra of **4** (trace **a**) and of the reducted product (trace **b**), which are indicative of the inclusion and the locking of the nitroxide diradical in the cyclodextrin. Assignment of the signals is obtained on the basis of 2D ROESY spectral data by using the labels reported in Scheme 1.

The spectra show some methylene resonances of the guest separate into couples of signals (see spectrum (**b**) of Figure 1) indicating that the linear guest is mechanically blocked in a rotaxane assembly. In particular α, *a* and *b* protons located at the external parts of the rod are splitted into signal couples separated by of 0.11, 0.18 and 0.22 ppm, respectively. A similar behaviour is shown by the amidic protons which display two different doublets as a consequence of the presence of α-CD (range 0.06 ppm). The signals due to the inner methylene protons (*c* and *d*) and the heterocyclic protons of the axle molecule are not splitted, but the corresponding signals are significantly broadened.

This behaviour is the consequence of the different environment experienced when the non symmetrical cavity of the cyclodextrin wraps the thread, making the protons of the axle molecule magnetically unequivalent. In particular, the methylene protons far from the centre of the rod show a different chemical environment depending if they are located near the largest rim or are close to the minor edge of the macrocycle. On the other hand, internal alkyl protons of the rod, being located at the center of the internal cavity of α-CD, experience a similar environment and the corresponding signals appears only as a broadened singlet.

An interesting aspect of the threading of the alkyl chain into CD cavity is the significant displacement of the proton signals of the macrocyclic host respect to those of the free α-CD (data not shown).

If the 1D spectra provide evidence of the formation of the rotaxane, proof of the actual occurred complexation is based on ^{1}H-^{1}H ROESY experiments which show spatial interactions between protons of the guest and the internal H_3 and H_5 of the host. In Fig. 2 is reported a spectral region of the contour plot pointing out the strong intermolecular interactions connecting methylene protons of the thread and the internal sugar protons.

In particular, H_3 proton of α-CD correlates exclusively with the external alkyl protons of the axle molecule resonating downfield (protons *a* and *b*), while the H_5 and H_6 protons of the macrocycle shows

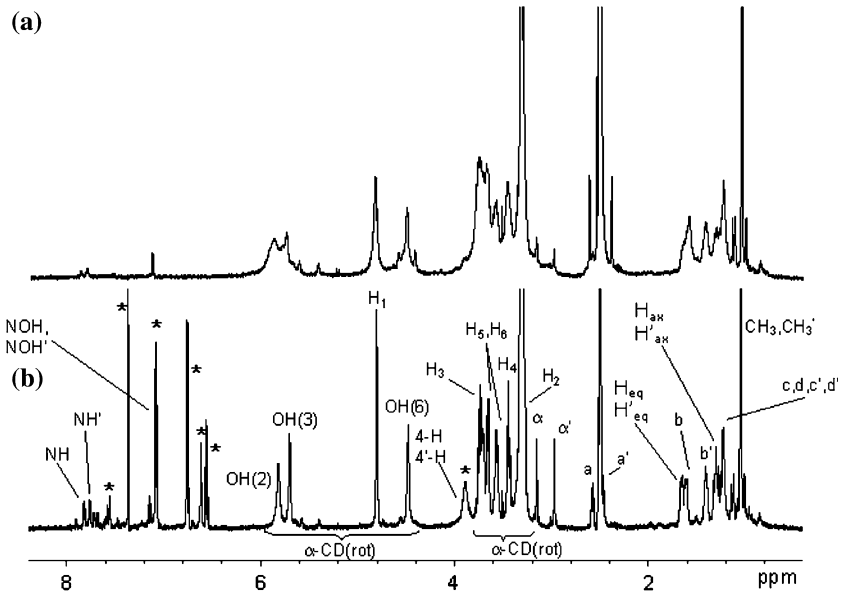


Fig. 1 ^{1}H NMR spectra (600 MHz, DMSO-d^6, 298 K) (**a**) of rotaxane **4**, (**b**) rotaxane **4**-OH obtained after in situ reduction of **4** with phenylhydrazine. Star symbols refer to the signals of phenylhydrazine (some peaks overlap the signals of rotaxane). The spectral region labeled with α-CD (rot) refers to the signals of the interlocked cyclodextrin. The signals were assigned on the basis of 2D ROESY experiments by using the labels reported in Scheme 1

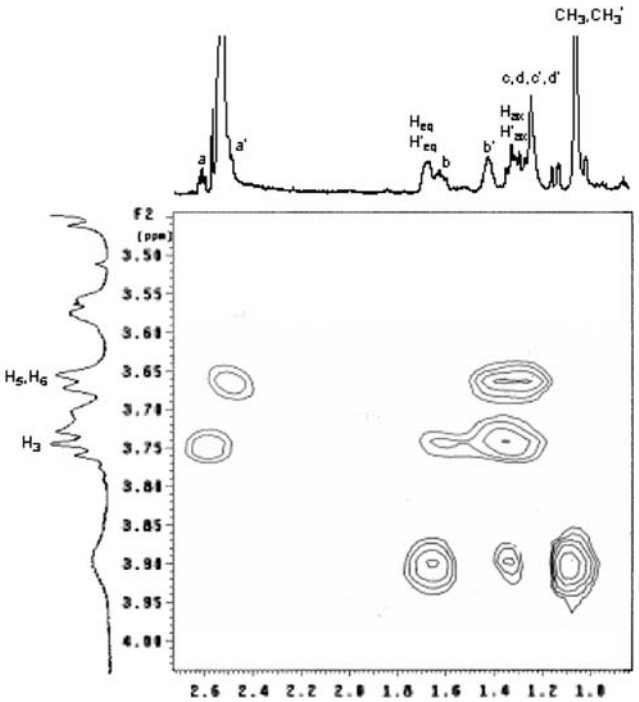


Fig. 2 2D ROESY region (600 MHz, DMSO-d^6) of rotaxane **4**-OH. The contour plot reflects the intermolecular cross peaks connecting the methylene protons of the thread and the protons of α-CD (H_3, H_5 and H_6, see Scheme 1 for label definitions). Each resonance corresponding to the external alkyl protons of the thread is split into a pair of signals, one shielded and the other deshielded respect to the signal of the free thread **3**. Apex letters represent the proton signals facing the smaller rim of α-CD rotor

a cross peak only with the upfield shifted protons, labeled with *a′* and *b′*, of the thread. The central protons of the thread (*c*, *c′*, *d*, *d′*) show, instead, a strong correlation with both H_3 and H_5 internal protons of α-CD. These results clearly confirm the formation of the interlocked molecule with the cyclodextrin being positioned symmetrically respect to the thread.

The complete proton assignment of the thread was obtained by ROE intramolecular cross peaks connecting the heterocyclic 4-H/4′-H protons of the axle molecule centred at 3.90 ppm with 3-H/3′-H protons and methyl substituents in 2-position of the TEMPO fragment (see Fig. 2) and the amidic protons (data not shown).

In conclusion, this work reports the synthesis of a new radical [2]rotaxane. The rotaxane was obtained in an improved yield by double substitution using an α, ω-dithiolate anion as nucleophile. The alkylating reagent was a iodide containing a bulky paramagnetic nitroxide acting as a stopper. The new structure has been determined by ESI-MS and by 1D and 2D NMR. We believe that the reported procedure could be of interest to people involved in the assembly of organic radical centers to control magnetic interaction in multispin molecular systems.

References

1. Sauvage, J.-P.: Molecular catenancs, rotaxanes and knots: a journey through the world of molecular topology. In: Dictrich-Buchecker, C. (ed.) Wiley-VCH, Weinheim (1999)
2. (a) Balzani, V., Credi, A., Raymo, F.M., Stoddart, J.F.: Artificial molecular machines. Angew. Chem. Int. Ed. **39**, 3348–3391 (2000); (b) Balzani, V., Venturi, M., Crodi, A.: Molecular Devices and Machines—A Journey into the Nanoworld. Wiley-VCR, Weinheim (2003); (c) Flood, A.U.,

Ramirez, R.J.A., Deng, W.-Q., Muller, R.P., Goddard, W.A., Stoddart J.F.: Meccano on the nanoscale-a blueprint for making some of the world's tiniest machines. Aust. J. Chem. **57**, 301–322 (2004); (d) Kay, E.R., Leigh, D.A.: Synthetic Molecular Machine in Functional Artificial Receptors. In: Schrader, T., Hamilton, A.D. (eds.) Wiley-VC1, Weinheim (2005)

3. Ogino, H.: The first example of a cyclodextrin-based rotaxane has been reported by Ogino in 1981. Relatively high-yield syntheses of rotaxanes. Syntheses and properties of compounds consisting of cyclodextrins threaded by α,ω-diaminoalkanes coordinated to cobalt(III) complexes. J. Am. Chem. Soc. **103**, 1303–1304 (1981)
4. Nepogodiev, S.A., Stoddart, J.F.: Cyclodextrin-based catenanes and rotaxanes. Chem. Rev. **98**, 1959–1976 (1998)
5. Mezzina, E., Fanì, M., Ferroni, F., Franchi, P., Menna, M., Lucarini, M.: Synthesis and characterization of a persistent paramagnetic rotaxane based on α-cyclodextrin. J. Org. Chem. **71**, 3773–3777 (2006)
6. Mason, R.P.: Using anti-5,5-dimethyl-1-pyrroline N-oxide (anti-DMPO) to detect protein radicals in time and space with immuno-spin trapping. Free Radical Bio. Med. **36**, 1214–1223 (2004)
7. (a) Hawker, C.J., Bosman, A.W., Harth, E.: New polymer synthesis by nitroxide mediated living radical polymerizations. Chem. Rev. **101**, 3661–3688 (2001); (b) Hawker, C.J.: ''Living'' free radical polymerization: a unique technique for the preparation of controlled macromolecular architectures. Aec. Chem. Res. **30**, 373–382 (1997); (c) Studer, A.: The persistent radical effect in organic synthesis. Chem. Eur. J. **7**, 1159–1164 (2001); (d) Minisci, F., Recupero, F., Pedulli, G.F., Lucarini, M.: Transition metal salts catalysis in the aerobic oxidation of organic compounds. Thermochemical and kinetic aspects and new synthetic developments in the presence of Nhydroxyderivative catalysts. J. Mol. Cat. A. **63**, 204–205 (2003)
8. Amabilino, D.B., Veciana J.: Magnetism, Molecules to Materials II, In: Miller, J.S., Drillon M. (eds.) vol. II, pp. 1–60. Wiley-VCII, Weinheim (2001)
9. Lee, T.D., Birrell, G.B., Keana, J.F.W.: A new series of minimum steric perturbation nitroxide lipid spin labels. J. Am. Chem. Soc. **100**, 1618–1619 (1978)