

An Organometallic B₁₂-Rotaxane and a B₁₂-Dimer, Relaxed and Loaded Forms of a Molecular Spring

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Received July 11, 1996

Studies on catenanes, rotaxanes, and related topologically or sterically constrained oligomolecular supermolecules^{1,2} expand chemistry toward materials science as well as biology.^{2,3} Cyclodextrins have been versatile building blocks in this respect.⁴ We report here on synthetic and structural studies of non-natural B₁₂ derivatives, one of them an asymmetric organometallic rotaxane.⁵ These amphiphiles have a novel built-in, conformationally adaptable “hydrophobic gap”⁶ and appear to provide first examples of a structurally characterized “molecular spring”.⁷

From addition of a deoxygenated aqueous solution of (12'-bromododecyl)-cob(III)alamin (**3**) and of a 10-fold excess of α -cyclodextrin (α -CD) to an aqueous and oxygen-free solution of an equivalent of electrochemically produced cob(I)alamin (**2**⁻), the light-sensitive rotaxane **5** could be obtained in 50% yield (see Figure 2).⁸ NMR spectra (recorded at ambient temperature)⁹ revealed an asymmetric overall structure for this

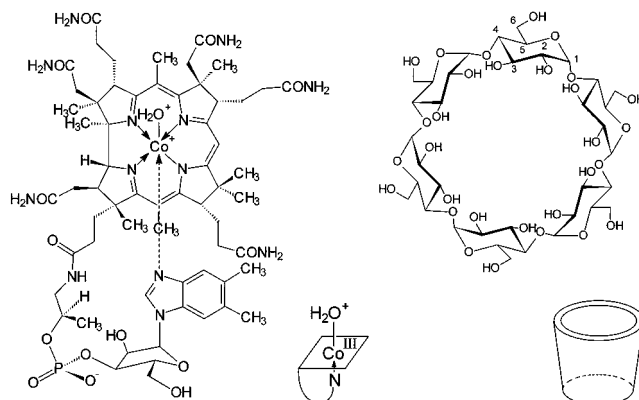


Figure 1. Structural formulas and symbols of aquocob(III)alamin cation (left) and of α -cyclodextrin (α -CD, right).

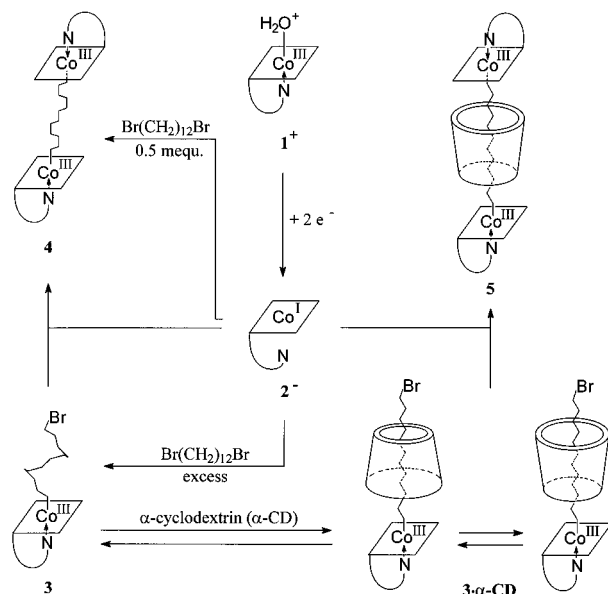


Figure 2. Schematic summary of the synthesis of (12'-bromododecyl)-cob(III)alamin (**3**), dodecamethylene-1,12-dicob(III)alamin (**4**), and rotaxane **5**.

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(1) (a) Schill, G. *Catenanes, Rotaxanes and Knots*; Academic Press: New York, 1971. (b) Sauvage, J. P., Ed. *Topology in Molecular Chemistry*. *New J. Chem.* **1993**, 17, No. 10/11. (c) Weber, C. In ref 1b, p 627. (d) Walba, D.; Homan, T. C.; Richards, R. M.; Haltiwanger, R. C. In ref 1b, p 661.

(2) Lehn, J.-M. *Supramolecular Chemistry*; Verlag Chemie: Weinheim, Germany, 1995.

(3) (a) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 1154–1196. (b) Dietrich-Buchecker, C. O.; Sauvage, J.-P. *Bioorganic Chemistry Frontiers*; Dugas, H., Ed.; Springer-Verlag: New York, 1991; pp 195–248.

(4) (a) Isnin, R.; Kaifer A. E. *Pure Appl. Chem.* **1993**, 65, 495–498. (b) Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1992**, 31, 846–848. (c) Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 803–822. (d) Ogino, H. *J. Am. Chem. Soc.* **1981**, 103, 1303–1304.

(5) For other organometallic rotaxanes (with ferrocene stoppers), see ref 4a; for early work on rotaxanes with cyclodextrins and Co(III)–amine centers, see ref 4d.

(6) A “hydrophobic gap”, as used here, is generated within a molecule by a hydrophobic segment placed between spacious hydrophilic moieties. The B₁₂ derivatives **4** and **5** appear to be monomeric in solution; they have a shorter lipophilic bridge than “bola-amphiphiles” (ref 6a,b). (a) Fuhrhop, J.-H.; Köning, J. *Membranes and Molecular Assemblies: The Synergetic Approach*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, U.K., 1994; p 26. (b) Escamilla, G. H.; Newkome, G. R. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 2013–2016.

(7) The macrobiomolecular composites of muscle fibers have been described to act as “dual-stage molecular springs”: Wang, K.; McCarter, R.; Wright, J.; Beverly, J.; Ramirez-Mitchell, R. *Biophys. J.* **1993**, 64, 1161–1177.

(8) Syntheses. **3**: 100 mg (72.3 μ mol) of **1** and 2.37 g (7.23 mmol) of dibromododecane in 10 mL of 0.1 M TBAPF₆ in CH₃OH/THF (1:1), reduced at -1.1 V (Hg) vs 0.1 NCE (protection from light, air, consumption: 2.00 F/mol of **1**), afforded 89.5 mg (78.5%) of **3**. **4**: 100 mg (72.3 μ mol) of **1** was reduced at -1.1 V (Hg) vs 0.1 NCE in 4 mL of 0.1 M TBAPF₆ in CH₃OH; 11.8 mg (36.2 μ mol) of 1,12-dibromododecane (in 1 mL of 0.1 M TBAPF₆ in THF) was added, and electrolysis continued at -1.0 V for 2 h (total consumption: 2.00 F/mol of **1**) to afford 82.8 mg (72.5%) of **4**. **5**: 40 mg (28.9 μ mol) of **1** was reduced at -1.1 V (Hg) vs 0.1 NCE in 5 mL of 0.1 M KCl in H₂O. After 3 h, 3 mL of a deoxygenated solution of 45.6 mg (28.9 μ mol) of **3** and 281 mg (289 μ mol) of α -CD was added with protection from light, electrolysis at -1.0 V for 1 h (total consumption: 2.12 F/mol of **1**), to give 54.2 mg (49.4%) of **5**.

(9) Selected spectral data (see also Table 1). **4**: UV/vis (H₂O) λ_{\max} (log ϵ) = 290 (4.49), 316 (4.42), 347 (4.36), 511 (4.19); CD (H₂O) λ ($\Delta\epsilon$) = 271 (12.0), 318 (10.2), 330 (−5.3), 358 (−14.1), 388 (13.5), 440 (−11.2), 500 (12.7), 554 (−14.1). FAB-MS (NOBA) m/z (%) = 2829.4 (6), 2828.4 (10), 2827.4 (11), 2826.4 (9), (M + 1)⁺ = C₁₃₆H₂₀₁Co₂N₂₆O₂₈P₂⁺, 1329.3 (100). **5**: UV/vis (H₂O) λ_{\max} (log ϵ) = 289 (4.44), 316 (4.42), 347 (4.25), 511 (4.08); CD (H₂O) λ ($\Delta\epsilon$) = 272 (13.5), 318 (8.4), 330 (−5.4), 358 (−11.9), 386 (10.8), 438 (−10.1), 498 (9.0), 552 (−13.6); FAB-MS (NOBA) m/z (%) = 3801.6, 3800.6 (0.1), 3799.7 (0.09), 3798.8 (0.07), (M + 1)⁺ = C₁₇₂H₂₆₁Co₂N₂₆O₅₈P₂⁺, 2722.4 (6), 1329.6 (100). For complete ¹H and ¹³C NMR data see the Supporting Information.

diamagnetic [2]-rotaxane, with an effectively 6-fold symmetric α -cyclodextrin torus, an axis provided by a dodecamethylene chain and stoppered by two cob(III)alamin units. UV/vis and CD spectra⁹ exclude conformationally perturbed organometallic B₁₂ moieties, indicated by ROESY spectra to be both bound at their β -side. From such spectra of solutions of **5** in H₂O or in D₂O, time-averaged close contacts of alkyl chain and of cyclodextrin endo-hydrogens can also be deduced (see Figure 3), while they do not indicate any contact of these hydrogens with bulk water.

The dimer **4** was obtained as a side product of **5** or, in over 70% yield, from reaction of cob(I)alamin (**2**⁻) with 0.5 mol equiv of 1,12-dibromododecane.⁸ Of the spectroscopic data for **4**, the positions of the ¹³C signals of the dodecamethylene chain are notable (see Table 1). When compared to the corresponding signals of rotaxane **5** in aqueous solution, in the ¹³C spectrum of **4**, all signals of the alkyl chain are shifted upfield (up to 3.2 ppm, see Figure 3), in a position-dependent manner. These ¹³C chemical shift differences can be quantitatively accounted for by a conformational model, revealing the presence of characteristic conformational differences within the alkyl chains of **4** and of **5**.¹⁰ Rotaxane **5** largely accommodates the dodecamethylene chain of its organometallic moiety with anti conformations, but with a high probability of a gauche conformation at the (C δ /C ϵ) or (C ϵ /C ξ) bond, near the wider opening of the α -CD torus. In contrast, in the amphiphilic dimer **4**, gauche confor-

Table 1. Selected Signal Assignments from ^1H -NMR (500 MHz)^a and ^{13}C -NMR (125 MHz)^b Spectra of Dimer **4** and Rotaxane **5**

	dimer 4 (D ₂ O)		dimer 4 (CD ₃ OD)		rotaxane 5 (alkyl chain) (D ₂ O)				rotaxane 5 (α -CD moiety) (D ₂ O)		
	^{13}C	^1H	^{13}C	^1H	^{13}C unprimed ^c	^{13}C primed ^c	^1H unprimed ^c	^1H primed ^c		^{13}C	^1H
α	28.43	0.57/1.42	31.94	0.65/1.45	31.60	31.04	0.29/1.39	0.36/1.19	CD6	62.13	3.39/3.63
β	33.38	0.13/−0.40	34.31	0.22/−0.30	34.21	34.29	0.23/−0.49	0.10/−0.44	CD5	74.20 ^d	3.51
γ	32.01	0.95	32.28	0.85/1.00	32.30	34.98	0.65/0.97	0.47/0.50	CD3	76.34	3.67
δ	31.09 ^e	0.87 ^d	32.0	1.01 ^d	32.39	34.33	1.02	0.81/0.90	CD4	84.11	3.50
ϵ	31.42 ^e	0.99 ^d	32.0	1.06 ^d	32.91 ^e	33.23 ^e		1.09/1.12 ^f	CD2	74.07 ^d	3.51
ζ	31.20 ^e	0.93 ^d	32.0	1.03 ^d	32.51 ^e	32.70 ^e		0.92/0.93 ^f	CD1	104.88	4.90

^a HDO and CHD₂OD as internal reference: $\delta(\text{HDO}) = 4.68$ ppm, $\delta(\text{CHD}_2\text{OD}) = 3.39$ ppm. ^b Sodium 3-(trimethylsilyl)propionate as the external reference. $\delta(\text{CH}_3) = 0$ ppm. ^c Primed, unprimed indicates position of the specified atoms with respect to α -CD moiety. ^d No individual assignment. ^e Tentative assignment. ^f No individual assignment to primed, unprimed position.

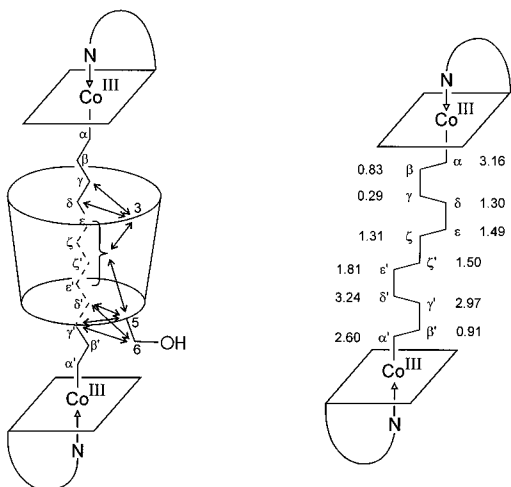


Figure 3. (left) Symbol for **5** and NOE contacts of the aliphatic chain with the cyclodextrin moiety (arrows). (right) Symbol for **4** and differences in ^{13}C chemical shifts of the signals of the corresponding carbons of the aliphatic chain in **4** and in **5** [$\Delta\delta = \delta(\mathbf{5}) - \delta(\mathbf{4})$].

mations are indicated¹⁰ to prevail at all four (pairwise equivalent) $\text{C}\beta/\text{C}\gamma$ and $\text{C}\delta/\text{C}\epsilon$ bonds of the alkyl chain.¹¹

Indeed, amphiphilic dimers, such as **4**, are molecules with a unique built-in “hydrophobic gap”.⁵ Dimer **4** is indicated to be contracted in aqueous solution (but less so in methanol)¹² and to behave as a “loaded molecular spring”. In water, the solvent exposed surface of the contracted lipophilic alkyl chain of **4** appears to be reduced¹³ at the expense of about 3 kcal/mol of gauche strain.¹⁴ On the other hand, in rotaxane **5**, the organometallic moiety (**4**) is threaded by the α -CD torus and shielded significantly from exposure to solvent water. Indeed, it is indicated to contain a conformationally relaxed and more extended dodecamethylene chain and accordingly, in **5**, the threaded **4** now represents a “relaxed molecular spring”.

Related effects of hydrophobic contacts may contribute to the assembly of the reactants, crucial for the synthesis of the

(10) For the conformation dependence of ^{13}C chemical shifts of oligomethylene carbons, see e.g.: (a) Saito, H. *Magn. Reson. Chem.* **1986**, *24*, 835–852. (b) Cheney, B. V.; Grant, D. M. *J. Am. Chem. Soc.* **1967**, *89*, 5319–5327.

(11) In 1,4-bis($\text{Co}\beta$ -cobalaminy)butane, a $\text{C}\beta/\text{C}\beta'$ -gauche conformation is indicated for the tetramethylene bridge, see: Kräutler, B.; Dérier, T.; Liu, P.; Mühlecker, W.; Puchberger, M.; Gruber, K.; Kratky, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 84.

(12) For ^{13}C chemical shift data see Table 1.

(13) Van der Waals’ surfaces of the dodecamethylene chain: 244 Å² (all-trans conformation) and 232 Å² (with four gauche conformations). ($\text{Co}-\text{Co}$) distances: 14.1 and 11.1 Å, respectively (Sybyl 6.2; Tripos Associates).

(14) A gauche conformation in an oligomethylene chain is associated with about 0.8 kcal/mol strain (see e.g.: Quinkert, G.; Egert, E.; Griesinger Ch. *Aspekte der Organischen Chemie*; Verlag Chemie: Weinheim, Germany, 1995).

rotaxane: from NMR spectra (D₂O, 26 °C) for **3** and α -CD, a mean association constant K could be estimated ($\log K = 3.3 \pm 0.3 \text{ M}^{-1}$).¹⁵ This value, and the dependence of the yield of **5** and of **4** upon the concentration of α -CD, indicates the threaded complex **3**· α -CD to alkylate cob(I)alamin (**2**[−]) about one-third as rapidly as the uncomplexed monomer **3** itself. Accordingly, the α -CD moiety of **3**· α -CD hardly inhibits the reaction of the complexed organometallic bromoalkane with the bulky cob(I)alamin (**2**[−]). In **3**· α -CD, the threaded bromododecyl chain therefore appears to adopt an extended conformation to a significant extent (see Figure 3).

The asymmetric photolabile¹⁶ organometallic⁴ [2]-rotaxane **5** and the alkyl-bridged dimer **4** are remarkable low molecular weight amphiphiles that have built-in “hydrophobic gaps”.⁶ This latter structural feature provides the oligomethylene-bridged B₁₂ dimer **4** with the properties of a “molecular spring”, which may be “loaded” (as in **4**) or “relaxed” (as in **5**). Studies of such molecules should contribute to the understanding of “hydrophobic forces”^{17a} and “hydrophobic bonds”.^{17b} Conformationally adaptable groups that induce a “solvophobic contraction”¹⁸ (and the corresponding (re-)expansion) may enlarge the existing repertoire of functional compounds² and of synthetic strategies.³ The examination of such effects may contribute to the understanding of structures and reactivity of artificial supramolecular² and natural biomolecular assemblies.⁷

Acknowledgment. We would like to thank Prof. Dr. G. Schill (University of Freiburg, Germany) and Dr. F. Winkler (Hoffmann-La Roche, Basel, Switzerland) for helpful discussions, M. Tollinger for NMR spectra, Dr. H. Münster (Finnigan-MAT, Bremen, Germany) and Doz. Dr. K.-H. Ongania for FAB mass spectra, and Prof. H. Scheer (Botanical Institute, University of München, Germany) for circular dichroism spectra. This work was supported by the Austrian National Science Foundation (Proj. No. P09334 & P10816). Dedicated to Prof. Vladimir Prelog on the occasion of his 90th birthday.

Supporting Information Available: Experimental details, ROESY spectra, and ^1H - and ^{13}C -NMR signal assignments (6 pages). See any current masthead page for ordering and Internet access instructions.

JA962376B

(15) ROESY spectra indicate **3**· α -CD to exist in both orientations of **3** and α -CD in aqueous solution.

(16) At room temperature, rotaxane **5** and dimer **4** are not decomposed thermally, but readily so by visible light.

(17) (a) Zimmermann S. C. *Bioorganic Chemistry Frontiers*; Dugas, H., Ed.; Springer-Verlag: New York, 1991; Vol. 2, pp 33–71. (b) Fersht, A. *Enzyme Structure and Mechanism*; W. H. Freeman: New York, 1985.

(18) “Solvophobic contraction”: conformational changes leading to a reduction of the surface area of solvophobic parts of an amphiphile, exposed to solvent (for “hydrophobic collapse”, see e.g. ref 18a; for “hydrophobic expansion”, see ref 18b). (a) Newcomb, L. F.; Haque, T. S.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 6509–6519. (b) Machleidt, H.; Roth, S.; Seeman, P. *Biochem. Biophys. Acta* **1992**, *255*, 178–189.