Cyclic Trimers and Tetramers with Piperazine and 2-Butyne as Building Blocks

Rolf Gleiter,*[a] Kirstin Hövermann,[a] Frank Rominger,[a] and Thomas Oeser[a]

Dedicated to Professor Richard Neidlein on the occasion of his 70th birthday

Keywords: Alkynes / Macrocycles / Inclusion compounds / Nitrogen heterocycles

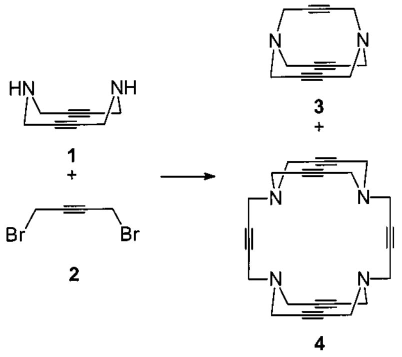
The reaction of piperazine with 2-butyne-1,4-ditosylate in a 1:1 ratio yields the cyclic trimer **7** and the cyclic tetramer **8**. ^{1}H NMR investigations on **7** and **8** reveal a dynamic process with $\Delta G^\ddagger$ = 13 kcal/mol. This process is attributed to an inversion of the piperazine rings. Single crystals of **7**·CH_3OH, **7**·2 $CF_3COOH{\cdot}H_2O$ and **8** have been isolated and investigated by X-ray diffraction. In the first two cases methanol, or water and $CF_3CO_2^-$, were included in the interior of the ring.

Introduction

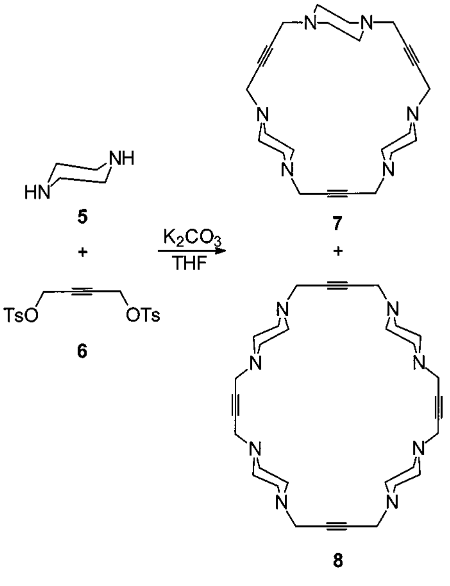
Macrocyclic systems and belt-like cavities are of considerable interest in view of the application of these species for the inclusion of ions and neutral molecules.[1,2] Frequently π-systems, diols and diamines have been employed as building blocks, to name but a few.[1,2] The latter are particular convenient due to their bifunctionality. Recently we examined the reactions of several cyclic diamines, such as 1,6-diazacyclodeca-3,8-diyne (**1**)[3] 1,8-diazacyclotetradeca-4,11-diyne,[4] and 1,10-diazacyclooctadeca-5,14-diyne,[5] with various α,ω-dibromides. In each case the intramolecular product (e.g. **3**) was preferred over the intermolecular product (e.g. **4**) (Scheme 1). This result was also observed when the bridge contained a rigid triple bond as shown in Scheme 1. We ascribed the preference for the intramolecular product to the high flexibility of the cyclic diamines mentioned above. For each of them we can assume an equilibrium between a boat and a chair conformation as was shown in detail for **1**.[6] To obtain macrocycles it seems necessary to employ a cyclic diaza compound in which the chair conformation was preferred. We chose piperazine because the versatility of this molecule as a supramolecular building unit has been demonstrated on several occasions.[7–9] In this paper we describe the syntheses of two macrocycles with three and four piperazine units, respectively.

Results and Discussion

The preparations of the macrocycles **7** and **8** were achieved under high dilution conditions from the reaction of piperazine (**5**) with the bistosylate of 2-butyne-1,4-diol (**6**)[10] in a one-pot procedure. The reaction was carried out in the presence of K_2CO_3 as base in THF at 50–60 °C. The resulting yields were 13% of the trimer **7** and 1% of the tetramer **8** (Scheme 2).



Scheme 1. Reaction of **1** with **2**



Scheme 2. Preparation of **7** and **8**

The separation of the reaction mixture of **7** and **8** with acetonitrile on Alox III turned out to be problematic because small amounts of acetamide were produced by hydrolysis of the solvent, yielding to an adduct with **7**. The separation could finally be achieved with chloroform/ethanol in a ratio of 200:1 on silica gel as adsorbent.

The ^{1}H NMR spectrum of **7** is rather simple, showing two singlets at δ = 2.61 and 3.22. The former signal corre-

---

[a] Organisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany

sponds to the piperazine protons, the latter to the propargylic protons. At lower temperatures the singlet at δ = 2.61 broadens and at 273 K (0 °C) it starts to split into two signals at δ = 2.3 and 2.9. Finally at 243 K an AA′XX′ pattern is observed. It is interesting to note that the ^{13}C NMR spectrum of **7** does not show any changes between 323 K (50 °C) and 223 K (−50 °C). At 213 K (−60 °C) a broadening of the signals at δ = 52.1 and 47.1 was observed whereas the signal at δ = 80.4 was still unchanged.

From the coalescence temperature at 273 K we were able to estimate the $\Delta G^{\ddagger}$ value for the corresponding dynamic process to be 13 kcal/mol. The ^{1}H NMR spectroscopic data of **8** are nearly identical to those of **7**. The temperature of coalescence of the signal at δ = 2.61 was found to be 275 K which also leads to a $\Delta G^{\ddagger}$ value of 13 kcal/mol for the dynamic process. To rationalize the temperature dependence of the ^{1}H NMR spectra we assume that, at lower temperature, the inversion of the piperazine rings is slowed down and finally frozen.

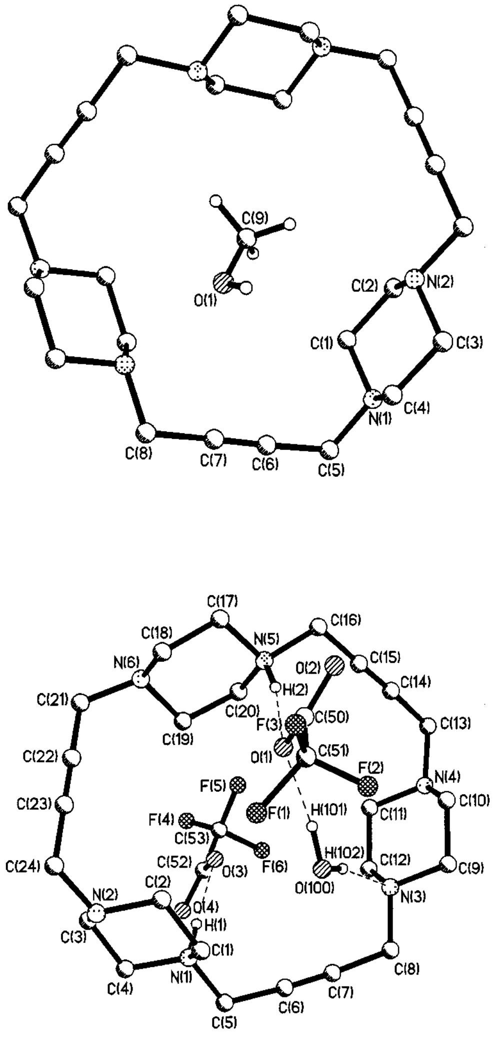


Figure 1 (top) solid state structure of **7a**; the hydrogen atoms of the host are omitted for clarity; due to the crystallographically imposed threefold symmetry the methanol guest molecule is disordered; two of the three superimposed methanol images are omitted for clarity; (bottom) solid state structure of **7b**; the hydrogen atoms bound to carbon atoms are omitted for clarity; the trifluoroacetate anions and the water molecule are connected to the host compound by a set of hydrogen bonds

The assumption that at lower temperatures the inversion of the piperazine rings is frozen is supported by the $\Delta G^{\ddagger}$ value reported for the ring inversion of *N,N′*-dimethylpiperazine (13 kcal/mol).[11]

Structural Investigations

By adding methanol to a solution of **7** in chloroform we could isolate single crystals of **7a** (**7**·CH_3OH). By adding trifluoroacetic acid we were able to isolate **7b** (**7**·2 $CF_3CO_2H \cdot H_2O$). In Figure 1 the molecular structures of **7a** and **7b** are shown. The triyne host includes one molecule of methanol in **7a**, located in the center of the ring system on a threefold rotation axis (Figure 1, top). The hydroxy group thereby suffers a threefold disorder. The O1···N2 distance of 2.986 Å is appropriate for an OH···N interaction.

The crystal structure analysis of **7b** reveals the inclusion of one molecule of water and two trifluoroacetate anions (Figure 1, bottom). The water is situated in the center of the cavity and forms hydrogen bonds to one oxygen atom of one $CF_3CO_2^-$ unit (O100···O1 2.826 Å/O100···O1A 2.850 Å; O1 and O1A being equally populated, in disordered positions) and to a nonprotonated nitrogen atom of the host (O100···N3 2.890 Å). Two of the six nitrogen atoms of **7b** are protonated and the accompanying negatively

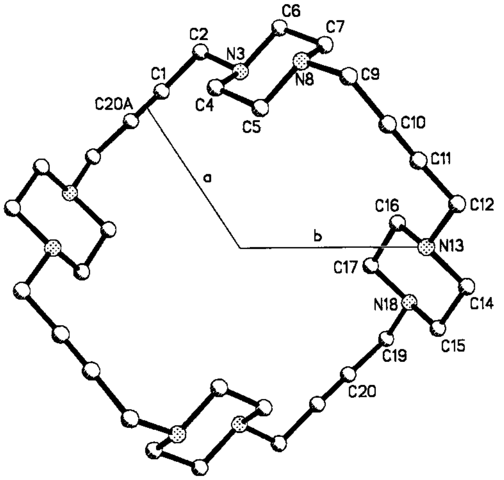


Figure 2. Solid state structure of **8**; hydrogen atoms are omitted for clarity

Table 1. Selected bond lengths [Å] and angles [°]. Listed are average values

	7a	7b	8
C(sp)−C(sp)	1.182(3)	1.181(4)[a]	1.188(2)[a]
C(sp)−C(sp^3)	1.472(3)[a]	1.465(4)[a]	1.476(2)[a]
N−C(sp^3)	1.459(2)[a]	1.471(3)[a]	1.464(2)[a]
C(sp^3)−C(sp)−C(sp)	178.5(2)[a]	177.2(3)[a]	178.0(2)[a]
a[b]	4.31	4.33	4.92
b[b]	4.01	3.60/4.32	4.48/4.98

[a] average values. – [b] average distances between the centers of gravity and the centers of triple bonds (**a**) and the nitrogen atoms (**b**).

charged $CF_3CO_2^-$ units are located near the positively charged nitrogen atoms and fixed by hydrogen bonds (distances O1···N5 2.762 Å and O1A···N5 2.652 Å and O3···N1 2.725 Å). In Figure 2 the molecular structure of **8** is presented. The tetrayne is located on a twofold crystallographic rotation axis perpendicular to the plane of the ring. In contrast to the triynes, the centers of the triple bonds are not all situated at the same height referring to the plane of the ring. Opposite pairs of triple bonds are situated above or below the plane forming a boat shape. The piperazine units serve as vertical spacers. Although this molecule offers a larger cavity than the triynes (see Table 1) no guest molecule is present. In Table 1 several average distances and angles, as well as some quantities describing the cavity sizes, are listed. As anticipated, the distances **a** and **b** of **7a** and **7b** are very similar and smaller than those found for **8**.

Conclusion

We have been able to selectively direct the assembly of bifunctional piperazine rings and butyne units towards intermolecular couplings which led to the isolation of cyclic trimers and tetramers. Both molecules possess large cavities which are capable of hosting smaller molecules. In the case of **7** this was achieved with water and methanol as well as aqueous trifluoroacetic acid.

Experimental Section

General Procedures: Reactions were carried out in oven-dried (120 °C) glassware under argon and with magnetic stirring. Solvents were dried and distilled under argon before use. ^1H and ^{13}C NMR: Bruker AS 200. The spectra were recorded in $CDCl_3$ at 200 MHz (^1H), the ^{13}C NMR spectra at 50 MHz using the solvent as internal standard (δ). High resolution mass spectra (HRMS) were obtained with a ZAB high resolution mass spectrometer (Vacuum Generators). Microanalyses: Analytical Laboratory of the Chemische Institute der Universität Heidelberg.

Preparation of 7 and 8: To a suspension of K_2CO_3 (80 g) in dry THF (1.5 L) were added simultaneously under reflux piperazine (20.4 g, 0.2 mol) in THF (1 L) and 2-butyne-1,4-ditosylate[10] (93.2 g, 0.2 mol) in THF (1 L) within 9.5 h. The addition was carried out with syringe pumps, to guarantee a synchronous addition. After completion of the addition the mixture was stirred at 50 °C for 3 days. To isolate the products the solvent volume was reduced to 1 L and the organic phase was filtered from the residue. The organic phase was extracted with 10 N HCl, saturated with NaCl. Subsequently the water was neutralized with 10 N NaOH saturated with NaCl and subsequently reextracted with $CHCl_3$. The chloroform solution was dried with K_2CO_3 and, after removal of the solvent, chromatographed on Alox III with $CHCl_3$/EtOH (300:1). This procedure yielded a mixture of **7** and **8** (4.9 g). To separate these substances further chromatography was carried out on Alox III with $CHCl_3$/EtOH (400:1). This yielded **7** (4.1 g, 0.01 mol, 12.6%). After changing the solvent to $CHCl_3$/EtOH (200:1) we could isolate **8** (0.3 g, 0.6 mmol, 0.9%). The trimer was recrystallized from $CHCl_3$/diethyl ether at −30 °C and yielded colorless needles, m.p.

Table 2. Crystallographic data of **7a**, **7b** and **8**.

Compound	7a	7b	8
Empirical formula	$C_{24}H_{36}N_6 \cdot MeOH$	$C_{24}H_{36}N_6 \cdot 2\ F_3C_2O_2H \cdot H_2O$	$C_{32}H_{48}N_8$
Molecular mass [g/mol]	440.6	654.7	544.8
Crystal size [mm]	0.4 × 0.38 × 0.3	0.44 × 0.40 × 0.33	3.0 × 1.3 × 0.6
Crystal color	colorless	colorless	colorless
Crystal shape	prism	irregular	needle
Space group	*P*-3	$P2_1/c$	$C2/c$
a [Å]	12.355(3)	20.408(4)	24.867(2)
b [Å]	12.355(3)	10.471(1)	5.9359(4)
c [Å]	9.680(2)	16.701(3)	24.598(2)
α [°]	90	90	90
β [°]	90	113.24(1)	112.97(1)
γ [°]	120	90	90
V [Å^3]	1279.7(4)	3279.2(9)	3343.2(4)
$D_{calcd.}$ [Mg/m^3]	1.14	1.33	1.08
Z	2	4	4
F (000)	480	1376	1184
Temperature [K]	223	293	200
h_{min}/h_{max}	0/16	−22/22	−29/29
k_{min}/k_{max}	−14/0	0/13	−7/7
l_{min}/l_{max}	−12/12	0/22	−28/28
$(\sin \Theta/\lambda)_{max}$ [Å^{-1}]	0.66	0.66	0.61
μ [mm^{-1}]	0.07	0.11	0.07
Refl. collected	2335	7644	11627
Refl. unique	2054	7391	2856
Refl. observed $[I > 2\sigma(I)]$	1206	3567	2029
Variables	140	663	277
$(\Delta/\sigma)_{max}$	<0.01	0.01	<0.01
R	0.051	0.048	0.039
R_w	0.130	0.107	0.086
S (Gof)	1.15	1.24	1.04
$(\Delta\rho)_{max}$ [e Å^{-3}]	0.17	0.15	0.18
$(\Delta\rho)_{min}$ [e Å^{-3}]	−0.17	−0.17	−0.19

145 °C (decomp.). − ^{1}H NMR: δ = 2.61 (br. s, 24 H), 3.22 (s, 12H). − ^{13}C NMR: δ = 47.0 (t), 51.9 (t), 80.3 (s). − MS-FAB: *m/z* (%): 409 (17.8) [$M^+ + 1$], 407 (7.0) [$M^+ - 1$]. − HRMS ($C_{24}H_{37}N_6^+$): calcd. 409.3079; found 409.3063. − $C_{24}H_{36}N_6$·MeOH (449.6): calcd. C 68.15, H 9.15, N 19.07; found C 67.99, H 8.97, N 19.12.

The tetramer **8** crystallized from $CHCl_3$ as colorless needles: M.p. 145 °C (decomp). − ^{1}H NMR: δ = 2.60 (br. s, 32 H), 3.26 (s, 16 H). − ^{13}C NMR; δ = 47.3 (t), 52.2 (t), 80.1 (s). − HRMS: *m/z* [M + 1] = calcd. 545.4086, found 545.4073.

X-ray Structural Analysis: The measurements were performed with a Nonius-CAD4-diffractometer (**7a**, **7b**) or a Bruker SMART CCD X-ray diffractometer (**8**) with Mo-K_α radiation and a graphite monochromator. Intensities were corrected for Lorentz and polarization effects. All structures were solved by direct methods (SHELXS 86[12]). The structural parameters of the non-hydrogen atoms were refined anisotropically according to a full-matrix least-squares technique (F^2) (Table 2). The parameters of the hydrogen atoms of **7a** were treated with retainment of the atomic positions and fixed thermal parameters. The triyne is situated on a crystallographic threefold rotation axis, and as a result, the hydroxy group of the methanol guest in **7a** is disordered around this axis. The parameters of the hydrogen atoms of **7b** were refined isotropically. The isotropic thermal parameters of the hydrogen atoms of the water molecule in **7b** were assigned to values of 1.2 times that of the equivalent parameter of the corresponding oxygen atom. The trifluoroacetic acid anions are disordered. The atoms F1, F2 and F3 of the first anion adopt three orientations with occupancies of 0.4, 0.3 and 0.3. The atoms O1 and O2 are disordered over two positions with equal occupancies. The atoms F4, F5 and F6 of the second trifluoroacetic acid anion are similarly in two orientations located with equal occupancies. Two of the nitrogen atoms of **7b** are protonated by the protons of the trifluoroacetic acid molecules. The hydrogen atoms of **8** were refined isotropically. Refinement of all structures was carried out with SHELXL-93.[13] Further crystallographic data (excluding structure factors) for the structures included in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no CCDC-147092 (**7a**), -147093 (**7b**) and -147094 (**8**). Copies of the data can be obtained free of charge on application to CCDC, Union Road, Cambridge CB 21E2, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

We are grateful to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the BASF Aktiengesellschaft, Ludwigshafen, for financial support. We thank Mrs. U. Wiesinger for crystal preparation and her help at the X-ray data collection and Mrs. A. Reule for preparing the manuscript.

---

[1] F. Vögtle, *Supramoleculare Chemie,* B. G. Teubner, Stuttgart **1989**; F. Diederich, Cyclophanes, The Royal Society of Chemistry, Cambridge, **1991**; J. M. Lehn, *Supramolecular Chemistry*, VCH Weinheim **1995**; B. Dietrich, P. Viout, J. M. Lehn, *Macrocyclic Chemistry*, VCH Weinheim **1993** and references therein.

[2] A. Schröder, H. B. Mekelburger, F. Vögtle, *Topics Curr. Chem.* **1994**, *172*, 179−201; R. M. Izatt, K. Pawlak, J. S. Bradshaw, R. L. Bruening, *Chem. Rev.* **1991**, *91*, 1721−2085.

[3] R. Gleiter, K. Hövermann, J. Ritter, B. Nuber, *Angew. Chem.* **1995**, **107**, 867−869; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 789−791.

[4] V. Wolfart, R. Gleiter, H. Irngartinger, T. Oeser, C. Krieger, *Eur. J. Org. Chem.* **1998**, 2803−2809:

[5] T. v. Hirschheydt, V. Wolfart, R. Gleiter, H. Irngartinger, T. Oeser, F. Rominger, F. Eisenträger, *J. Chem. Soc., Perkin 2* **2000**, 175−183.

[6] J. Ritter, R. Gleiter, H. Irngartinger, T. Oeser, *J. Am. Chem. Soc.* **1997**, *119*, 10599−10607.

[7] K. E. Krakowiak, J. S. Bradshaw, W. Jiang, N. K. Dalley, G. Wu, R. M. Izatt, *J. Org. Chem.* **1991**, *56*, 2675−2680.

[8] C. Bazzicalupi, A. Bencini, V. Fusi, M. Micheloni, B. Valtancoli, *Chem. Commun.* **1994**, 1119−1120.

[9] J. Huuskonen, K. Rissanen, *Liebigs. Ann.* **1995**, 1611−1615 and references cited therein.

[10] G. Eglinton. M. C. Whiting, *J. Chem. Soc.* **1950**, 3650−3656.

[11] F. A. L. Anet, R. Anet, in *Dynamic Nuclear Magnetic Resonance Spectroscopy*, L. M. Jackman, F. A. Coton, Edit, *Academic Press*, New York **1975**, 543−619; R. K. Harris, R. A. Spragg, *Chem. Commun.* **1966**, 314−316; L. W. Reeves, K. O. Strømme, *J. Chem. Phys.* **1961**, *34*, 1711−1714.

[12] G. M. Sheldrick, SHELXS-86, Universität Göttingen, Germany 1986.

[13] G. M. Sheldrick, SHELXL-93, Universität Göttingen, Germany 1993.

Received July 5, 2000
[O00332]