REGIOSELECTIVE DOUBLE CYCLISATION OF 1,2,4,5-TETRAKIS-(BROMOMETHYL)BENZENE WITH TOSYLATED DIETHYLENE-TRIAMINE. TOWARDS CONFORMATIONALLY BIASED BIS(PERAZACROWN) RECEPTORS

Jana HODAČOVÁ[a1,*], Jiří ZÁVADA[a2] and Peter C. JUNK[b]

[a] *Institute of Organic Chemistry and Biochemistry, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic; e-mail: [1] hodacova@uochb.cas.cz, [2] zavada@uochb.cas.cz*

[b] *Department of Chemistry, James Cook University, Townsville, QLD, 4811, Australia; e-mail: peter.junk@jcu.edu.au*

Received September 3, 1999
Accepted October 1, 1999

Dedicated to Professor Otto Exner on the occasion of his 75th birthday.

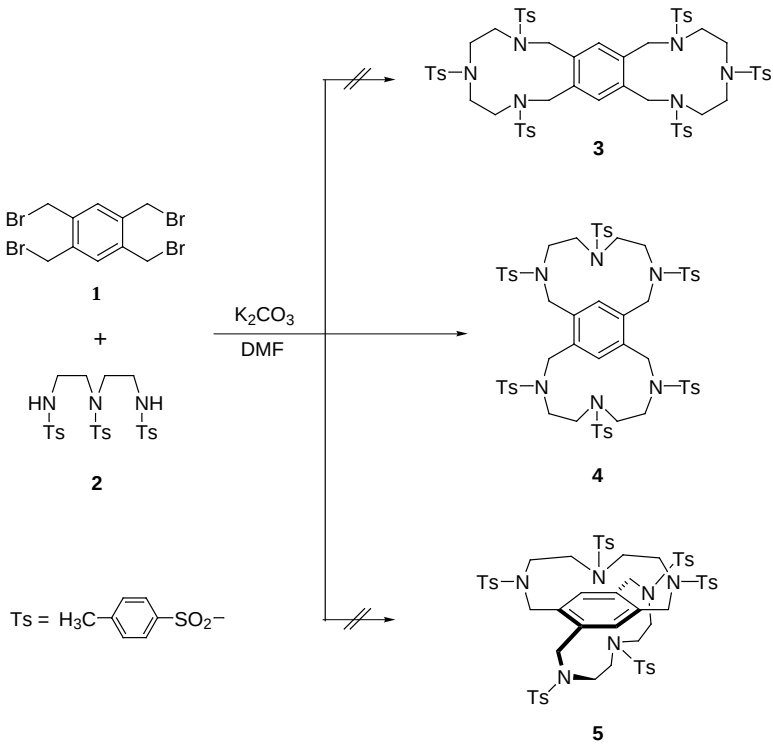
Of three possible tricyclic regioisomers, the reaction of 1,2,4,5-tetrakis(bromomethyl)benzene with tosylated diethylenetriamine affords selectively a single product which has been assigned structure 4,7,10,15,18,21-hexakis(4-methylbenzenesulfonyl)-4,7,10,15,18,21-hexaazatricyclo[11.9.1.1^{2,12}]tetracosa-1(23),2(24),12-triene with the aid of X-ray crystal analysis.

Key words: Crown compounds; Azacrown compounds; Amines; Cyclisations; Macrocycles; N-Ligands; X-Ray diffraction.

Synthetic design of bis(perazacrown)s has recently aroused a considerable interest owing to the unique ability of some of these ligands to catalyse RNA hydrolysis[1] and also to inhibit efficiently HIV replication[2,3]. We are interested in synthesis of novel bis(perazacrown) ligands, whose individual branches are two-point anchored to a central durene platform. This hitherto almost unexplored design[4,5] is aimed at conformational control of the receptors. Herein we report some pertinent results obtained on alkylation of 1,2,4,5-tetrakis(bromomethyl)benzene with tosylated linear polyamines. Cyclisation of the tetrabromide **1** with two equivalents of the tosylated diethylenetriamine **2** has been employed as the model reaction (Scheme 1).

In principle, three isomeric tricyclic products of the double cyclisation **3**–**5** may arise in the reaction, resulting alternatively from ortho, meta and para annelation. However, under standard conditions of the Richman–Atkins cyclisation[6], a single isomer **4** has been preferably produced in a sur-

prisingly high yield (63% after crystallisation). Structure assignment to the tricyclic product has been attained with the X-ray crystal structure analysis demonstrating meta annelation[7] of the individual diethylenetriamido branches to the central aromatic platform (Fig. 1).



SCHEME 1

It is known that template effects may provide an extra energy bonus favouring ortho over meta (or para) macrocyclisation occurring on the benzene ring[8]. Such an effect is however absent in the investigated reaction. Presumably, internal strain involved in the macrocyclisation step controls regioselectivity of the alkylation. A molecular mechanics calculation performed on the corresponding (unsubstituted) thia analogues[5] of **3** and **4** suggests that meta cyclisation is energetically more advantageous (by >30 kJ/mol) than the corresponding ortho annelation. Examination of molecular models suggests that the alternative para annelation must be much more difficult.

It should be noted that such a conclusion is valid only for the bis(crown) derivatives involving the $–X–(CH_2)_2–X–(CH_2)_2–X–$ chains. For larger chains, the analysis predicts that ortho annelation may become the energetically more favourable process[5a]. Accordingly, we have found that the reaction of the tetrabromide **1** with the tosylated triethylenetetramine, a higher homologue of **2**, proceeds non-selectively affording two main products which have been tentatively assigned structure of ortho and meta annelated bis(crown) derivatives[9].

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. ^{1}H NMR spectra were measured on a Varian Gemini 300HC spectrometer at 300.07 Hz using tetramethylsilane as an internal standard (coupling constants *J* are given in Hz). Mass spectra were recorded on a ZAB-EQ (VG Analytical) instrument using the FAB (Xe, 8 kV) techniques. Thin-layer chromatography (TLC) was carried out on Kieselgel 60 F_{254} (Merck) plates. HPLC analyses were performed on an ECOM chromatograph with a UV detector operating at 254 nm.

4,7,10,15,18,21-Hexakis(4-methylbenzenesulfonyl)-4,7,10,15,18,21-hexaazatricyclo-[11.9.1.1^{2,12}]tetracosa-1(23),2(24),12-triene (**4**)

1,2,4,5-Tetrakis(bromomethyl)benzene (0.45 g, 1 mmol), triamide[10] **2** (1.13 g, 2 mmol) and potassium carbonate (0.62 g, 4.5 mmol) were stirred in dry dimethylformamide (20 ml) under a nitrogen atmosphere. The mixture was heated to 100 °C until all intermediates containing the bromomethyl moiety disappeared (1 h). Progress of the reaction was monitored using TLC (silica gel, toluene–10% acetone, sprayed with 1% alcoholic solution of 4-(4-nitrobenzyl)pyridine and visualised in a triethylamine atmosphere). After cooling to room temperature, the reaction mixture was poured into water (250 ml) and vigorously stirred for 15 min. The white precipitate was isolated by filtration, thoroughly washed with excessive amount of water and dried. Crystallisation from acetone produced colourless crys-

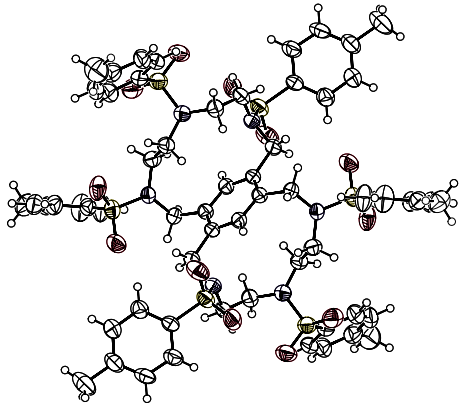


FIG. 1
Perspective ORTEP drawing of **4**. Thermal ellipsoids are shown at the 50% probability level

tals of **4** as an acetone solvate in 63% yield (0.86 g). The reverse-phase HPLC analysis (C_{18}, 10 μm, 4 × 250 mm; acetonitrile–water) of the product showed only a single peak. Analysis of the crude reaction mixture exhibited in addition to the main product (84% of total peak area) several minor components, at least one representing the positional isomer **3** or **5** (according to FAB MS). M.p. 169–172 °C (desolvation) and 314–315 °C. ^{1}H NMR (dimethylformamide-d_6): δ 2.40 (s, CH_3, 6 H); 2.48 (s, CH_3, 12 H); 2.91 (br m, CH_2, 8 H); 3.26 (br m, CH_2, 8 H); 4.53 (br s, CH_2, 8 H); 7.47 (d, *J* = 8.2, ArH-Ts, 4 H); 7.56 (d, *J* = 8.2, ArH-Ts, 8 H); 7.65 (d, *J* = 8.2, ArH-Ts, 4 H); 7.86 (d, *J* = 8.2, ArH-Ts, 8 H); 7.95 (s, ArH, 2 H). HR-FAB MS, *m/z*: 1 257.3332 ([M + H]$^+$); for $C_{60}H_{69}N_6O_{12}S_6$ calculated: 1 257.3298. For $C_{60}H_{68}N_6O_{12}S_6 \cdot 2\ CH_3COCH_3$ (1 373.7) calculated: 57.70% C, 5.87% H, 6.12% N, 14.00% S; found: 57.65% C, 5.93% H, 5.99% N, 14.04% S.

TABLE I
Crystal data and structure refinement for **4**·2 CH_3COCH_3

Empirical formula	$C_{66}H_{80}N_6O_{14}S_6$
Formula weight	1 373.72
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, *P*21/*c*
Unit cell dimensions	*a* = 15.766(3) Å, α = 90°
	b = 14.145(3) Å, β = 105.55(3)°
	c = 16.411(3) Å, γ = 90°
Volume	3 526.0(12) Å^3
Z, calculated density	2, 1.294 Mg/m^3
Absorption coefficient	0.259 mm^{-1}
F(000)	1 452
Crystal size	0.2 × 0.3 × 0.1 mm
Θ range for data collection	1.93 to 23.29°
Reflections collected/unique	16 039/5 071 [*R*(int) = 0.0906]
Completness to Θ = 23.29	99.6%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5 071/0/417
Goodness-of-fit on F^2	0.976
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0624, *wR*2 = 0.1587
R indices (all data)	*R*1 = 0.1154, *wR*2 = 0.1991

X-Ray Structural Analysis

The crystal used for the data collection was obtained by recrystallisation of **4** from acetone and a suitable specimen was mounted on a glass fibre using epoxy resin. X-Ray data were collected at room temperature on a Bruker SMART CCD diffractometer using the omega scan mode. Data were corrected for absorption using the program SADABS. The structure was solved using direct methods in SHELXS and refined using SHELXL97-2 (ref.[11]). All non-hydrogen atoms were located and refined with anisotropic thermal parameters. The hydrogen atoms were placed at calculated positions and their thermal parameters were not refined. Crystal data and a summary of data collection appear in Table I. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-134116. Copies of the data can be obtained free of charge on application to CCDC, e-mail: deposit@ccdc.cam.ac.uk or from the author (P. C. J.) by e-mail.

We thank the Grant Agency of the Czech Republic for financial support of this research (grant No. 203/98/0726).

REFERENCES AND NOTES

1. a) Young M. J., Chin J.: *J. Am. Chem. Soc.* **1995**, *117*, 10577; b) Williams N. H., Takasaki B., Wall M., Chin J.: *Acc. Chem. Res.* **1999**, *32*, 485.
2. Bicyclam derivatives containing two cyclam moieties tethered through aromatic bridge rank among the most potent and selective anti-HIV agents described so far[3].
3. a) De Clercq E.: *Pure Appl. Chem.* **1998**, *70*, 567; b) De Clercq E., Yamamoto N., Pauwels R., Baba M., Schols D., Nakashima H., Balzarini J., Debyser Z., Murrer B. A., Schwartz D., Thornon D., Bridger G., Fricker S., Henson G., Abrams M., Picker D.: *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 5286; c) Joao H. C., De Vreese K., Pauwels R., De Clercq E., Henson G. W., Bridger G. J.: *J. Med. Chem.* **1995**, *38*, 3865; d) De Clercq E.: *Collect. Czech. Chem. Commun.* **1998**, *63*, 449.
4. Two-point anchoring to the durene platform has been already employed in the synthesis of thia and oxa analogues of **4** and **5** (refs[5,7]).
5. a) Loeb S. J., Shimizu G. K. H.: *Synlett* **1992**, 823; b) Loeb S. J., Shimizu G. K. H.: *J. Chem. Soc., Chem. Commun.* **1991**, 1119; c) Loeb S. J., Shimizu G. K. H.: *Inorg. Chem.* **1993**, *32*, 1001.
6. a) Chavez F., Sherry A. D.: *J. Org. Chem.* **1989**, *54*, 2990; b) Richman J. E., Atkins T. J.: *J. Am. Chem. Soc.* **1974**, *96*, 2268.
7. An entirely analogous situation has been recently found in the reaction of the positionally isomeric 1,2,3,4-tetrakis(bromomethyl)benzene with 2,4-bis[(4-methylbenzenesulfonylamino)methyl]benzene-1,5-dicarboxylic acid diethylester, which also yielded almost exclusively the corresponding product of meta annelation[12]. Notably, in both the compared instances, the participating ring chains are of the same length.
8. Lee Y., Sim W., Park O. S.: *Synlett* **1992**, 157.
9. Hodačová J., Závada J.: Unpublished results.
10. Atkins T. J., Richman J. E., Oettle W. F.: *Org. Synth.* **1978**, *58*, 86.

11. *SHELXL97. Program for Crystal Structure Refinement, release 97-2*. University of Göttingen, Göttingen 1997.
12. Harren J., Sobanski A., Nieger M., Yamamoto C., Okamoto Y., Vögtle F.: *Tetrahedron: Asymmetry* **1998**, *9*, 1369.