A COVALENTLY BOUND TEMPLATE IN THE REGIOSELECTIVE SYNTHESIS OF BIS(TETRAAZACROWN)S

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The two-carbon core in the tricyclic bis(aminal)s arising by condensation of linear tetramines with biacetyl serves as a template in the regioselective alkylation with 1,2,4,5-tetrakis(bromomethyl)benzene.

Key words: Amines; Crown compounds; Cyclization; Macrocycles; Azacrown compounds; *N*-Ligands; Bis(aminals).

Recently, bis(tetraazacrown)s containing *p*-xylylene spacer have been shown to exhibit a remarkable anti-HIV activity[1]. An extensive synthetic scrutiny following this discovery has been directed to the bis(tetraazacrown) compounds distinguished by anchoring the individual macrorings to the spacer unit *via* a single covalent bond (one-point anchor; Fig. 1a)[2]. We are interested in synthesis of analogous compounds differing in that the individual macrorings are appended to the spacer *via* two covalent bonds (two-point anchor; Fig. 1b). To this end, we have chosen 1,2,4,5-tetrakis(bromomethyl)benzene (**1**) as a convenient building block which on reaction with appropriately protected linear tetramines **2** could provide the target compounds.

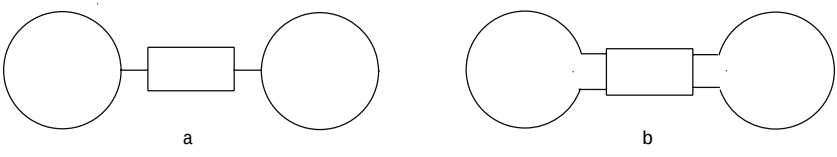
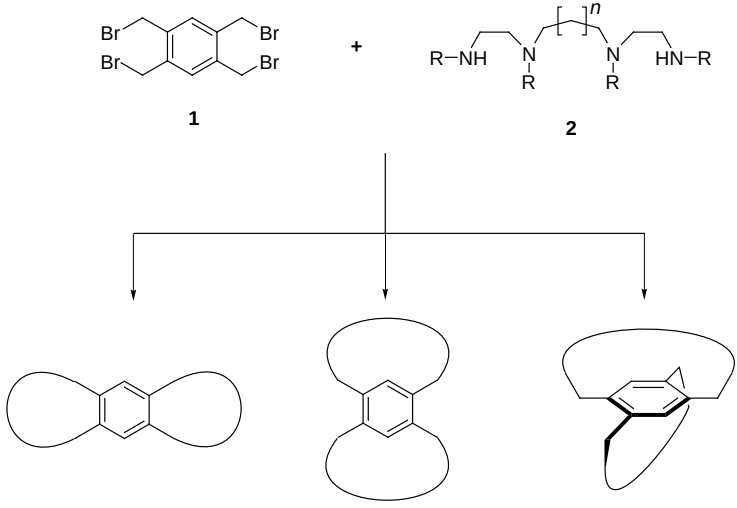


FIG. 1
One- and two-point anchoring of macrorings to an aromatic platform

Regioselectivity presents a difficult problem in the alkylation allowing, in principle, *ortho* as well as *meta* and *para* annulation (Scheme 1). With the tosylated tetramine (**2**; R = Ts), a mixture of *ortho* and *meta* isomers was obtained[3].

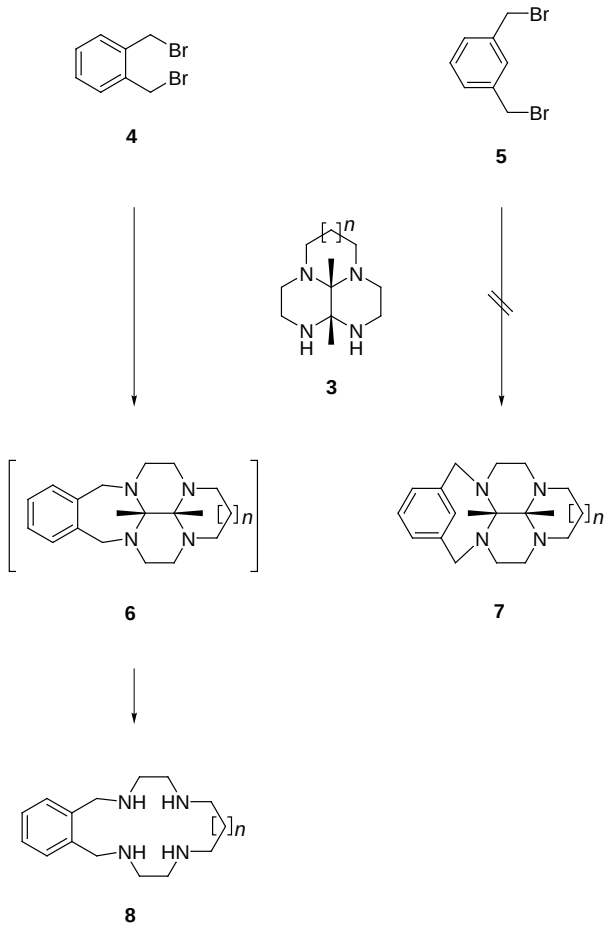


SCHEME 1

In order to achieve an exclusive *ortho* annulation, we have now proposed tricyclic bis(aminal)s **3** (ref.[4]) arising by condensation of linear tetramines (**2**; R = H) with biacetyl to serve as a regioselective partner in the reaction. The bis(aminal) grouping is known to provide a selective protection of the inner (tertiary) *vs* the outer (secondary) nitrogens in the alkylation[5]. Moreover, the two-carbon core involved in the bis(aminal) is expected to enforce such an arrangement of the reactive nucleophilic sites which can lead to the preferential displacement of the bromide substituents, which are located at the *ortho* carbons of the tetrabromide **1**, in the proposed reaction.

To test this concept, we have investigated first the behaviour of the bis(aminal)s **3** with the *ortho* and *meta* substituted bifunctional models **4** and **5** in the cyclization reaction (Scheme 2). The key step in the alkylation with the *ortho* isomer **4** gave rise to the pentacyclic bis(aminal) **6** (ref.[6]) and on the subsequent hydrolysis the tetraazacrown ether **8**.

After confirmation that only the *ortho* dibromide **4** undergoes the expected cyclization, while the *meta* isomer **5** gives rise only to straight-chain



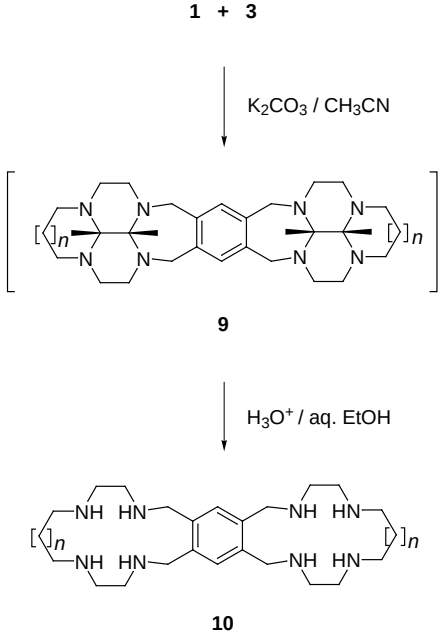
In formulae **3**, **6**, **7** and **8**: **a**, n = 0
b, n = 1

SCHEME 2

oligomers, we have accomplished the corresponding alkylation of the bis(aminal)s **3a** and **3b** with the tetrabromide **1** (Scheme 3). The target octaamines **10** resulting after hydrolysis of the alkylation products **9** were isolated as hydrochlorides and assigned the structure of the *ortho* annulated bis(tetraazacrown)s.

In this way, it has been demonstrated that the two-carbon core in the tricyclic bis(aminal)s **3** can serve as a covalent template in the regioselective

alkylation with the tetrabromide **1**. This methodology could be advantageously used for the synthesis of the higher homologues with an expanded aromatic (*e.g.* 2,3,6,7-tetrakis(methylene)naphthalene or 2,3,6,7-tetrakis(methylene)anthracene) platform, representing potentially interesting ligands[7].



In formulae **9** and **10**: **a**, $n = 0$
b, $n = 1$

SCHEME 3

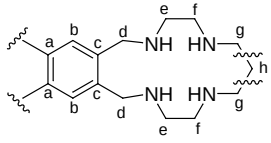
EXPERIMENTAL

NMR spectra were measured on a Varian UNITY 500 spectrometer (^{1}H at 499.9 MHz, ^{13}C at 125.7 MHz) in D_2O with TSP as an internal reference[8]. Mass spectra were recorded on a ZAB-EQ (VG Analytical) instrument using the FAB (Xe, 8 kV) technique. Thin-layer chromatography (TLC) was carried out on Kieselgel 60 F254 (Merck) plates. Bromomethyl compounds **1**, **4** and **5** were purchased from Aldrich. Bis(aminal)s **3a** and **3b** were prepared according to literature procedures[4,5].

General Procedure

A suspension of finely ground potassium carbonate (6.91 g, 50 mmol) in acetonitrile (15 ml) was stirred under nitrogen and separate solutions of an appropriate bromide (2.5 mmol) and of bis(aminal) **3** (2.5 mmol with dibromide **4** or **5**; 5 mmol with tetrabromide **1**), both in acetonitrile (80 ml), were added simultaneously during 4 h at room temperature. The reaction mixture was stirred overnight, the deposited salts were removed by filtration and the solution was evaporated. The residue was subjected to a column chromatography (silica gel; methanol–acetone–triethylamine, 19 : 19 : 1), the eluate was taken down on a vacuum evaporator, dissolved in ethanol (4 ml) and hydrolyzed on standing with 10% aqueous HCl (16 ml) at room temperature for 2 days. The product was taken to dryness and recrystallized from aqueous EtOH. The obtained salts are hydrates, which decompose gradually on heating. The NMR spectra are summarised in Table I.

TABLE I
^{1}H and ^{13}C NMR data of hydrochlorides of azacrowns **6** and **7** in D_2O



Compound	^{1}H NMR						
	H(a)	H(b)	H(d)	H(e)	H(f)	H(g)	H(h)
8a·3 HCl	7.63 m		4.48 s	3.58 m	3.44 m	3.26 s	–
8b·4 HCl	7.58 m		4.51 s	3.63 b	3.63 b	3.58 bt	2.32 b
10a·6 HCl	–	7.83 s	4.47 s	3.52 m	3.38 m	3.22 s	–
10b·8 HCl	–	7.68 s	4.42 bs	3.43 b	3.43 b	3.29 b	2.09 b

	^{13}C NMR[a]							
	C(a)	C(b)	C(c)	C(d)	C(e)	C(f)	C(g)	C(h)
8a·3 HCl	134.07	134.76	133.67	49.91	48.16	45.95	47.94	–
8b·4 HCl	133.61	133.90	134.17	51.69	46.82	46.11	48.54	24.70
10a·6 HCl	137.39	137.96	137.39	50.65	48.58	46.70	47.81	–
10b·8 HCl	137.39	137.96	137.39	52.65	48.00	47.11	50.23	24.88

[a] At 50 °C.

*3,6,9,12-Tetraazabicyclo[12.4.0]octadeca-14,16,18(1)-triene trihydrochloride (**8a**·3 HCl)*. Yield: 29%. For $C_{14}H_{27}Cl_3N_4$ (357.7) calculated 47.00% C, 7.61% H, 15.66% N, 29.73% Cl; found 46.16% C, 7.63% H, 15.29% N, 29.15% Cl. FAB MS, *m/z*: 249 ([M – 3 HCl + H]$^+$).

*3,6,10,13-Tetraazabicyclo[13.4.0]nonadeca-15,17,19(1)-triene tetrahydrochloride (**8b**·4 HCl)*. Yield: 50%. For $C_{15}H_{30}Cl_4N_4$ (408.2) calculated 44.13% C, 7.41% H, 13.73% N, 34.74% Cl; found 43.83% C, 7.25% H, 13.54% N, 34.21% Cl. FAB MS, *m/z*: 299 ([M – 3 HCl + H]$^+$).

*5,8,11,14,20,23,26,29-Octaazatricyclo[16.12.0.0^{3,16}]triaconta-1,3(16),17-triene hexahydrochloride hexahydrate (**10a**·6 HCl·6 H_2O)*. Yield: 9%. For $C_{22}H_{60}Cl_6N_8O_6$ (745.5) calculated 35.44% C, 8.11% H, 15.03% N, 28.53% Cl; found 35.68% C, 7.87% H, 14.96% N, 28.49% Cl. FAB MS, *m/z*: 455 ([M – 5 HCl + H]$^+$).

*5,8,12,15,21,24,28,31-Octaazatricyclo[17.13.0.0^{3,17}]dotriaconta-1,3(17),18-triene octahydrochloride dihydrate (**10b**·8 HCl·2 H_2O)*. Yield: 22%. For $C_{24}H_{58}Cl_8N_8O_2$ (774.4) calculated 37.22% C, 7.55% H, 14.47% N, 36.62% Cl; found 37.29% C, 7.25% H, 14.37% N, 36.33% Cl. FAB MS, *m/z*: 483 ([M – 7 HCl + H]$^+$).

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REFERENCES AND NOTES

1. a) De Clercq E., Yamamoto N., Pauwels R., Balzarini J., Witvrouw M., De Vreese K., Debyser Z., Rosenwieth B., Peichl P., Datema R., Thornton D., Skerlj R. T., Gaul F., Padmanabhan S., Bridger G. J., Fricker S., Henson G. W., Abrams M. J.: *Antimicrob. Agents Chemother.* **1994**, *38*, 668; b) De Clercq E.: *Pure Appl. Chem.* **1998**, *70*, 567; c) De Clercq E.: *Collect. Czech. Chem. Commun.* **1998**, *63*, 449.
2. a) Bridger G. J., Skerlj R. T., Thornton D., Padmanabhan S., Martellucci S. A., Henson G. W., Abrams M. J., Yamamoto N., De Vreese K., Pauwels R., De Clercq E.: *J. Med. Chem.* **1995**, *38*, 366; b) Joao H. C., De Vreese K., Pauwels R., De Clercq E., Henson G. W., Bridger G. J.: *J. Med. Chem.* **1995**, *38*, 3865.
3. Hodačová J., Závada J., Junk P. C.: *Collect. Czech. Chem. Commun.* **1999**, *64*, 1827.
4. a) Stetter H.: *Chem. Ber.* **1953**, *86*, 69; b) Jażwiński J., Koliński R. A.: *Tetrahedron Lett.* **1981**, *22*, 1711; c) Jażwiński J., Koliński R. A.: *Bull. Pol. Acad. Sci. Chem.* **1988**, *36*, 215.
5. a) Hervé G., Bernard H., Le Bris N., Yaouanc J.-J., Handel H., Toupet L.: *Tetrahedron Lett.* **1998**, *39*, 6861; b) Hervé G., Bernard H., Le Bris N., Le Baccon M., Yaouanc J.-J., Handel H.: *Tetrahedron Lett.* **1999**, *40*, 2517.
6. The bis(aminal) **6b** was isolated. M.p. 121–123 °C (hexane). For $C_{19}H_{28}N_4$ (312.5) calculated 73.04% C, 9.03% H, 17.93% N; found 73.13% C, 9.04% H, 17.65% N. FAB MS, *m/z* (rel.%): 311 (100), 313 (85). ^{1}H NMR ($CDCl_3$): 1.10 m, 1 H (CH_2); 1.37 s, 3 H (CH_3); 1.45 s, 3 H (CH_3); 1.86 m, 1 H (CH_2); 2.19–2.48 m, 4 H (CH_2); 2.56–2.90 m, 6 H (CH_2); 3.20–3.32 m, 1 H (CH_2); 3.27 d, 1 H, *J* = 15 ($ArCH_2$); 3.51 d, 1 H, *J* = 15 ($ArCH_2$); 3.84 m, 1 H (CH_2); 4.15 d, 1 H, *J* = 15 ($ArCH_2$); 4.59 d, 1 H, *J* = 15 ($ArCH_2$); 6.98–7.17 m, 4 H (ArH). ^{13}C NMR ($CDCl_3$): 11.85, 11.96, 18.55, 45.26, 45.95, 47.59, 50.17, 51.26, 52.73, 55.42, 59.85, 76.07, 79.17, 127.34, 127.40, 128.59, 130.55, 138.85, 140.83.
7. a) Joung 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.

8. The proton as well as carbon signals were broadened probably due to a medium rate of conformational exchange of alicyclic systems. Sharper lines were obtained in ^{13}C NMR spectra when measured at a higher temperature (50 °C). Structure assignment of proton signals is based on characteristic chemical shifts, multiplicities and intensities of individual signals. Carbon signals were assigned using ^{1}H–^{13}C correlated HMQC spectra.