Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters

Tetrahedron Letters 45 (2004) 9553–9556

The unusual course of the high-pressure reaction of 1,10-diaza-[18]-crown-6 with α,ω-diiodo ethers

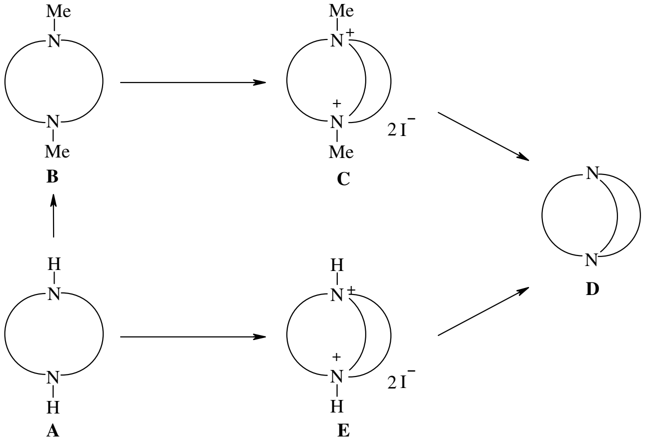
Aldona Tarnowska,[a] Piotr Tarnowski[a] and Janusz Jurczak[a,b,*]

[a]*Department of Chemistry, Warsaw University, Pasteura 1, 02-093 Warsaw, Poland*
[b]*Institute of Organic Chemistry PAS, Kasprzaka 44/52, 01-224 Warsaw, Poland*

Received 23 September 2004; revised 28 October 2004; accepted 2 November 2004

Abstract—Simple 1,10-diaza-[18]-crown-6 reacts smoothly with di(2-indoethyl)ether under high-pressure (10 kbar) to give a bis-quaternary spiro salt as a major product, whereas the analogous reaction with 1,8-diiodo-3,6-dioxaoctane leads to the expected precursor of a [2.2.2] cryptand.

Macrobicyclic molecular receptors, containing two bridgehead nitrogen atoms, are commonly called cryptands and their most distinguishing feature is their complexing behaviour.[1] They form stable complexes with a wide range of chemical species and therefore, since Lehn's discovery,[2] studies aimed at rational design and synthesis of more elaborated cryptand derivatives having the desired complexing properties have advanced considerably.[3] The first versatile procedure for the synthesis of cryptands, namely the high-dilution method, was developed by Lehn and co-workers.[2] This method is based on the condensation of diazacoronands of type A (Scheme 1) with an appropriate dicarboxylic acid dichloride. In the early 1980s, we proposed a novel high-pressure procedure for the synthesis of cryptands via the double-quaternization of *N*,*N*′-dimethyl diazacoronands of type B and α,ω-diiodo ethers (Scheme 1). We have successfully applied this method for the preparation of simple[4] and chiral bicyclic cryptands[5] as well as their tricyclic analogues.[6] Simple bicyclic cryptands have also been obtained from a high-pressure double-alkylation reaction involving diazacoronands of type A and α,ω-diiodo bridging components, followed by thermal decomposition of the cryptate formed during neutralization (Scheme 1),[7] but the yields were substantially lower compared with the double-quaternization/demethylation procedure.



Scheme 1.

This puzzling results, as well as recent developments in a new analytical tool, ESI-MS for precise analysis of complex reaction mixtures, prompted us to reinvestigate the reaction mentioned above.

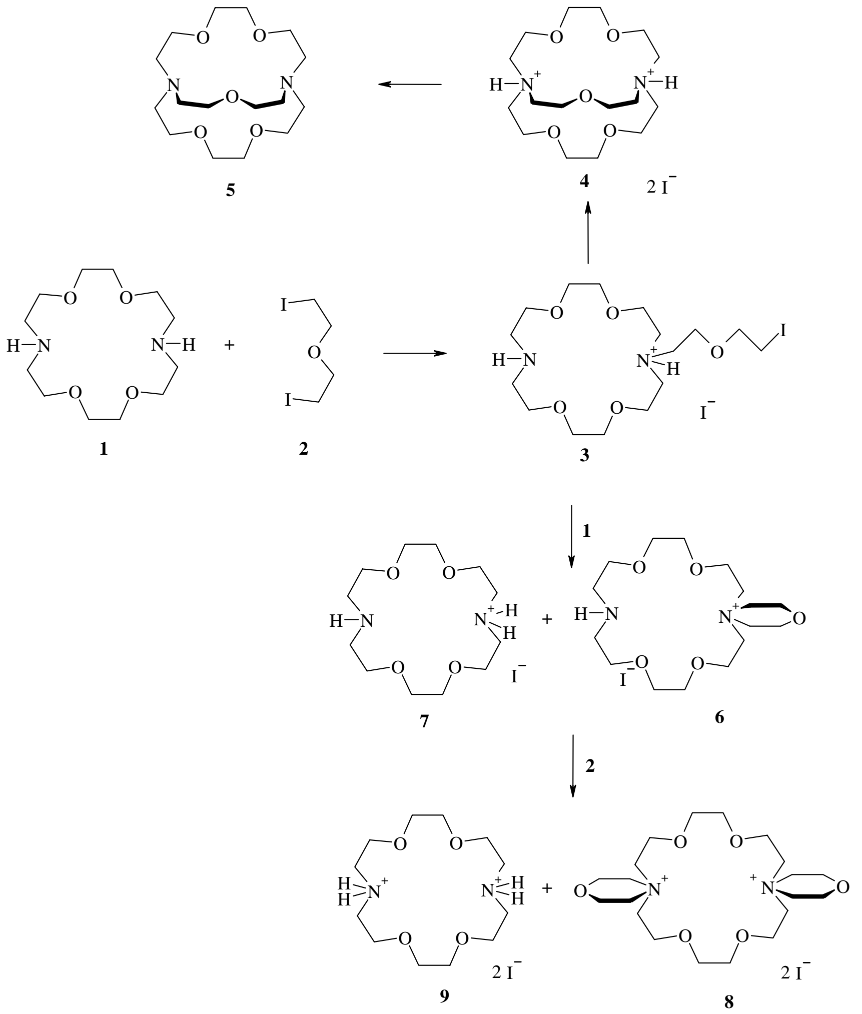
Of many possible substrates already employed in our laboratory, we chose 1,10-diaza-[18]-crown-6 **1**, and di(2-indoethyl)ether **2** as a bridging unit, for the preliminary studies. Equimolar amounts of these compounds were subjected to the high-pressure alkylation reaction (10 kbar, 50 °C, acetonitrile, 72 h, Scheme 2). Following decompression, we found that complete conversion had occurred. The resulting products precipitated from the solution as a colourless solid, which was subjected

---

Keywords: High pressure; Double quaternization; Macrocycles; Spiro salts.

[*] Corresponding author. Tel./fax: +48 22823 0944; e-mail: acybul@chem.uw.edu.pl

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.11.014



Scheme 2.

to ESI-MS analysis. The spectrum obtained made it possible to determine the qualitative composition of the product mixture. Contrary to our expectations, the *m*/*z* peaks corresponding to the ammonium salt **4** were not the most intense signals. The major peaks came from the product of double quaternization, which led to the salt **8** (Scheme 2).

A thorough analysis of the ESI-MS spectrum of the solid obtained provided valuable information concerning the course of the reaction. Based on these findings, we propose the reaction course presented in Scheme 2. We assume that the first step is attack of the electrophile **2** on one of the nucleophilic nitrogen atoms of the diazacoronand **1**, resulting in formation of the ammonium salt **3**, which is a generally acknowledged intermediate leading to the bicyclic ammonium salt **4** and, consequently, to the cryptand **5**. In fact, the reaction course is completely different from this point; namely, the free end of the diiodo ether chain attacks the same nitrogen atom, to form a stable quaternary ammonium salt **6** in the form of a six-membered morpholine ring spiro to the macrocyclic ring. The evidence indicates that formation of the product **6** is accompanied by formation of an equimolar amount of the salt **7**. Although **6** is positively charged, diminishing its nucleophilic character, the high-pressure conditions favour attack of the second molecule of the diiodo ether **2** on the other nitrogen atom, resulting analogously in formation of the salts **8** and **9**. The former should be characterized by an extraordinary stability. Indeed, fractional crystallization of the crude reaction product made it possible to isolate pure salt

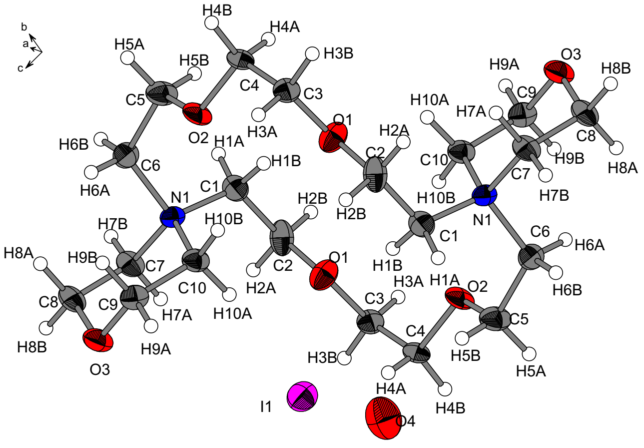
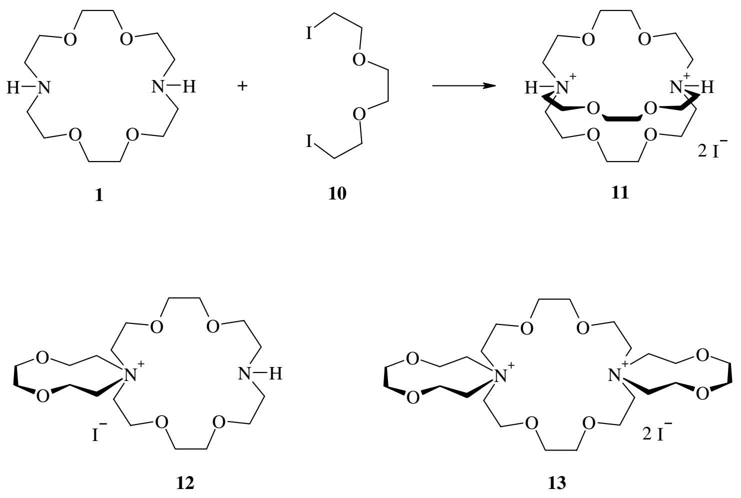


Figure 1. Crystal structure of **8**: ORTEP plot with atom labels.



Scheme 3.

8[8] (25% yield based on substrate **1**) as monocrystals suitable for X-ray structure analysis.[9] The results of this analysis are shown in Figure 1.

Referring back to the analysis of the ESI-MS of the reaction product, we would like to point out the possibility that compound **1** is not only a substrate for the reaction, but also a scavenger for hydrogen iodide. This second role diminishes the overall yield of the process, which cannot exceed 50% based on **1**.

These preliminary results prompted us to study an analogous reaction of the substrate **1** with 1,8-diiodo-3,6-dioxaoctane (**10**) (Scheme 3).

As in the former case, an ESI-MS spectrum was recorded for the crude solid reaction product. The major peaks were attributable to the salt **11**, which can be readily converted to the free [2.2.2] cryptand. This agrees well with our previously published findings.[7] As a consequence, only minute amounts of the spiro systems **12** and **13** are formed. Such a result agrees well with the generally accepted rule that formation of nine-membered rings (e.g., in compounds **12** and **13**) is not favoured in contrast to formation of the six-membered rings (e.g., in compounds **6** and **8**).

These preliminary results cast a new light on the scope and limitations of the high-pressure synthesis of cryptands making use of double alkylation of secondary and tertiary macrocyclic diamines.

Further studies, involving other substrates, both macrocyclic rings and α,ω-diiodo bridging units, appear to be necessary to confirm unequivocally the reaction course proposed in this paper. Work towards this end is in progress in our laboratory.

References and notes

1. Lehn, J.-M. *Science* **1985**, *227*, 849–856.
2. (a) Dietrich, B.; Lehn, J.-M.; Sauvage, J.-P. *Tetrehedron Lett.* **1969**, 2885–2888; (b) Dietrich, B.; Lehn, J.-M.; Sauvage, J.-P.; Blanzat, J. *Tetrahedron* **1973**, *29*, 1629–1645.
3. (a) An, H.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1992**, *92*, 543–572; (b) Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, 1995.
4. (a) Pietraszkiewicz, M.; Sałański, P.; Jurczak, J. *Bull. Pol. Acad. Chem.* **1985**, *33*, 433–436; (b) Pietraszkiewicz, M.; Sałański, P.; Jurczak, J. *Heterocycles* **1985**, *23*, 547–548; (c) Pietraszkiewicz, M.; Sałański, P.; Ostaszewski, R.; Jurczak, J. *Heterocycles* **1986**, *24*, 1203–1204.
5. (a) Pietraszkiewicz, M.; Sałański, P.; Jurczak, J. *Tetrahedron* **1984**, *40*, 2971–2973; (b) Pietraszkiewicz, M.; Jurczak, J. *J. Carbohydr. Chem.* **1985**, *4*, 429–434; (c) Ostaszewski, R.; Jacobsson, U.; Jurczak, J. *Bull. Pol. Acad. Chem.* **1989**, *37*, 347–352.
6. (a) Jurczak, J.; Ostaszewski, R.; Pietraszkiewicz, M.; Sałański, P. *J. Inclusion Phenom.* **1987**, *5*, 553–561; (b) Ostaszewski, R.; Jurczak, J. *Tetrahedron* **1997**, *53*, 7967–7974.
7. Jurczak, J.; Ostaszewski, R.; Sałański, P. *Bull. Pol. Acad. Chem.* **1991**, *39*, 275–277.
8. Selected data for **8**: mp 261–264 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.56 (t, J = 4.5 Hz, 8H), 3.62 (s, 8H), 3.82–3.87 (m, 8H), 3.88–3.92 (m, 8H), 3.95 (t, J = 4.5 Hz, 8H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 58.19, 58.97, 59.59, 63.63, 70.17; HRMS (ESI) $(M-I)^+$ calcd for $C_{20}H_{40}N_2O_6I$: 531.1926, found: 531.1943.
9. X-ray single-crystal diffraction was carried out on an Enraf-Nonius-CAD4 diffractometer (CAD4-EXPRESS program[10]) with CuK$_\alpha$ radiation (1.5478 Å) and the $\omega/2\theta$ scanning mode. The standard reflections were measured every 50 min, and a maximum of 68% of decay was detected. Data were corrected for decay and Lorenz and polarization effects. The structure was solved by direct methods[11] and refined using SHELXL.[12] Formula $C_{20}H_{40}I_2N_2O_6$, M 658.35; monoclinic, $a = 7.656$, $b = 18.357$, $c = 9.830$ Å, $\alpha = 90$, $\beta = 94.98$, $\gamma = 90.01°$, $V = 1376.4$ Å^{-3}, space group $P2_1/c$, $Z = 4$, $D_x = 1.666$ Mg/m^3; $\mu(\mathrm{CuK}_\alpha) = 18.309$ mm^{-1}; reflections collected/unique 2072/1934 [$R_{\mathrm{int}} = 0.0526$]. Data/restraints/parameters 1934/0/146. Final $R = 0.0594$, $wR = 0.1526$ [$I > 2\sigma(I)$]. Largest diff. Peak and hole 1.503 and -1.797 e Å^{-3}. Crystallographic data (excluding structural factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 247198. Copies of the data can be obtained free of charge on application to

CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: Int code + (1223)336-033; E-mail:deposit@ccdc.cam.ac.uk).

10. Nonius, B.V. 'CAD4-EXPRESS v. 5.1. Nonius B.V.'; Delft, The Netherlands, 1994.
11. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467–473.
12. Sheldrick, G. M. *SHELXL, Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1993.