Synthesis and properties of 3,6,10,13,16,19-ethanosarcophagine

Bohdan Korybut-Daszkiewicz*† and Jan Klimkiewicz

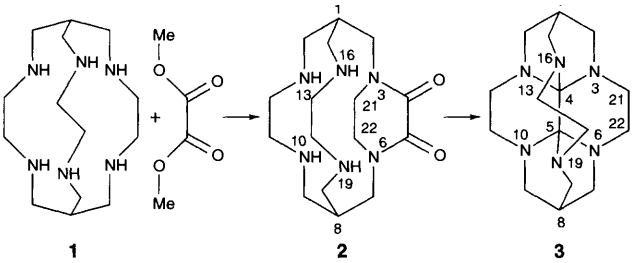
Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw 01-224, Poland

Dimethyl oxalate reacts with 3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane (sarcophagine) 1 to give oxamide 2 which subsequently is transformed into heptacyclic orthoamide 3.

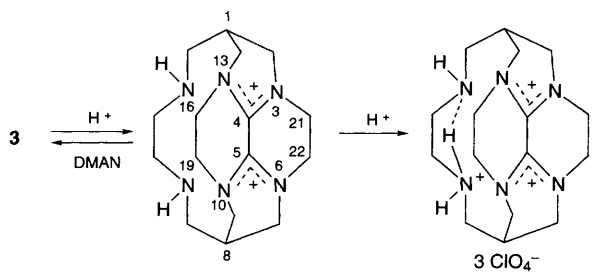
Several reports have described the use of macrocyclic polyamines in preparing stable polycyclic orthoamides *via* an 'insertion' of orthoesters, dimethylformamide dimethyl acetal or formamidnium acetate into the cavity of macrocycle.[1–3] It was found that the macrocyclic cage imparts high stability and unusual reactivity to the central moiety of those systems. Although this 'macrocyclic effect' has long been recognized and utilized in transition metal chemistry, it has not been fully exploited by organic chemists.

The present communication describes encapsulation of a carbon–carbon moiety inside the sarcophagine[4] **1** cage. Orthoamides cannot usually be prepared directly from amines and carboxylates,[5] therefore the reaction of dimethyl oxalate with sarcophagine was exceptional. Ethanosarcophagine **3**‡ was isolated with *ca.* 60% yield after 16 h reaction of equimolar mixture of substrates in methanol solution at room temperature. Compound **3** crystallizes as colourless plates after addition of acetonitrile to the concentrated methanolic solution. The crystals start to decompose at *ca.* 250 °C, but do not melt below 300 °C. The product gave satisfactory elemental analysis (C,H,N) as well as the mass spectrum, and no absorption in the region of N–H vibrations was observed in the IR spectra. The 500 MHz ^{1}H NMR spectrum ($CDCl_3$) consists of a sharp septet of C-1 and C-8 protons (δ 1.74, *J* 2.5 Hz), two broad signals of six cap CH_2 groups (δ 2.38 and 3.26) and also two broad signals of three ethylenediamine residues (δ 2.64 and 3.18). NMR signal broadening is probably due to the exchange between twisted and chair conformation of the six-membered rings of central 'propellane'[6] part of the molecule. The spectrum of solution of **3** containing three equivalents of optically active (+)-2,2,2-trifluoro-1-phenylethanol shows a 0.03 ppm splitting of signal at *ca.* δ 2.5 (2.64 in neat $CDCl_3$) indicating that no configuration inversion takes place during the dynamic process responsible for broadening of NMR signals. The ^{13}C NMR spectrum‡ is consistent with D_3 symmetry for compound **3**, since only four signals were observed.

To get information about the mechanism of orthoamide **3** formation the reaction was performed in CD_3OD solution (0.084 mol dm^{-3}) and followed by ^{1}H and ^{13}C NMR measurements (Fig. 1). During the first 10 minutes of the experiment all dimethyl oxalate disappeared from the reaction mixture (methoxy group signal at δ 3.85) and only methanol signal at δ 3.34 was observed. In the same time oxamide **2**§ was formed and reached the highest concentration after *ca.* 20 minutes (75–80%). The oxamide **2** was then transformed in a much slower intramolecular reaction into orthoamide **3**. The final reaction mixture after 17 h consisted of 17.3% of sarcophagine **1** and 82.7% of orthoamide **3**. This result indicates that simultaneously with formation of oxamide **2** about 17% of dimethyl oxalate was hydrolysed in the strongly basic reaction medium. A substantial low field shift of all three sarcophagine signals from δ 1.79 (CH), 2.73 (en-CH_2) and 2.91 (cap-CH_2) in



1 **2** **3**



4 **5**

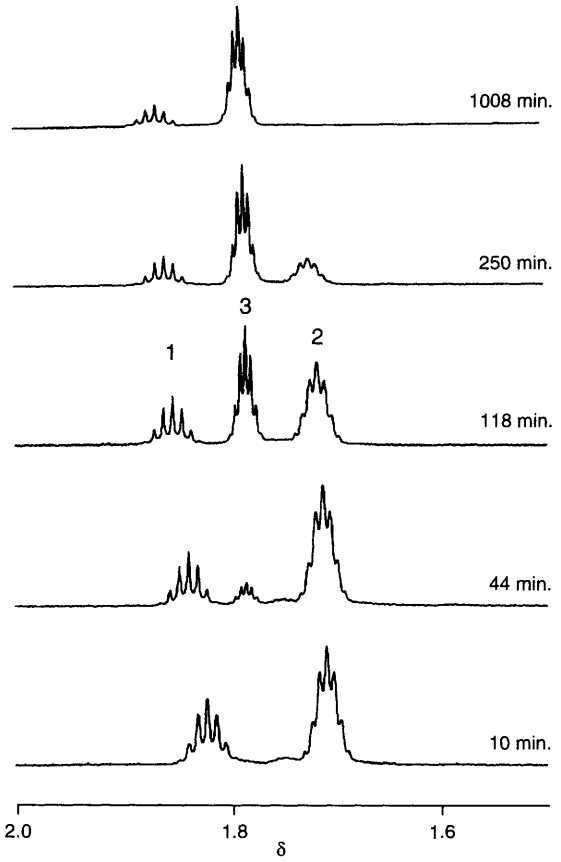


Fig. 1 1,8-CH absorption region of 500 MHz ^{1}H NMR spectrum of dimethyl oxalate and sarcophagine (1 : 1) reaction mixture in CD_3OD solution

neat CD_3OD to δ 1.86, 2.82 and 2.99, respectively, after the reaction indicates a partial protonation of amine **1**.

This assumption was confirmed by a similar experiment carried out in [$^2H_8$]toluene solution where formation of oxamide **2** was slower, and only about 50% of sarcophagine **1** was converted into product **3**.

An addition of 2 equiv. of trifluoroacetic acid to CD_3OD solution of **3** resulted in formation of oxamidinium salt **4**.¶ Protonation of **3** was accompanied by two C–N bond cleavages and no monoprotonated species was detected in the ^1H NMR spectrum. Consecutive addition of 'proton sponge' [1,8-bis-(dimethylamino)naphthalene (DMAN)] resulted in a slow reverse reaction. However, only a 2 : 3 ratio of **3** : **4** was obtained in the equilibrium with 1.75 fold excess of DMAN ($DMANH^+$: DMAN = 1 : 5) after 48 h at 25 °C. The overall protonation constant calculated from these values (β_{3H_2} = 37.5 $K_{aDMAN}{}^{-2}$) shows that ethanosarcophagine is a stronger base than DMAN. A further protonation occurred at amino nitrogen atoms of compound **4** and the insoluble in methanol triperchlorate **5**‖ was isolated and characterized.

Ethanosarcophagine can be included among the Vögtle's 'fascinating molecules',[6] and further studies of its structure and properties will be presented in a full paper.

Footnotes

† E-mail: bkd@ ichf.edu.pl

‡ **3** (3,6,10,13,16,19-hexaazaheptacyclo[6.6.6.$3^{3,6}$.$0^{4,13}$.$0^{4,16}$.$0^{5,10}$.$0^{5,19}$]-docosane); *m/z* = 302 (M^+); ^{13}C NMR (125.7 MHz; $CDCl_3$): δ 28.8 (1,8-CH), 51.3 (cap-CH_2), 55.2 (en-CH_2) and 78.5 (4,5-C). All NMR assignments were made and confirmed using reported shift data and 2D homonuclear, heteronuclear and selective INEPT experiments on a Bruker AM 500 instrument (b - broad, sp - septat, d - doublet, m - multiplet).

§ **2** (3,6,10,13,16,19-hexaazatricyclo[6.6.6.$2^{3,6}$]docosa-4,5-dione); ^{13}C NMR (125.7 MHz; CD_3OD): δ 39.7 (1,8-C), 46.5 (21,22-C), 51.1 and 51.2 (11,12-C and 17,18-C), 53.4 (2,7-C), 53.7 and 54.7 (9,14-C and 15,20-C), 162.7 (4,5-C); ^1H NMR (500 MHz, CD_3OD; *J* in Hz): δ 1.71 (sp, *J* 3.5, 1,8-CH), 2.47 and 2.61, 2.64 and 2.84 (m, two AA′XX′ spin systems of 11,12- and 17,18-CH_2), 3.60 and 4.21 (m) (AA′XX′ of 21-CH_2 and 22-CH_2 in six membered ring), 4.53 and 2.98 (dd, *J* 14.3, 2,7-CH_2), 3.18 and 2.79 (dd, *J* 12.6), 3.00 and 2.97 (m, 9,14- and 15,20-CH_2).

¶ **4** (3,6-diazonium-10,13,16,19-tetraazapentacyclo[6.6.6.$0^{4,13}$.$0^{5,10}$.$2^{3,6}$]-docosa-3,5-diene ditrifluoroacetate); ^{13}C NMR (125.7 MHz; CD_3OD): δ 28.7 (1,8-C), 47.4 (11,12,21,22-C), 54.4 (2,7,9,14-C), 53.6 and 54.7 (17,18- and 15,20-C), 146.1 (4,5-C); ^1H NMR (500 MHz; CD_3OD; *J* in Hz): δ 2.28 (m, 1,8-CH), 2.57 (s, 17,18-CH2), 3.05 (d, *J* 2.8, 15,20-CH_2), 3.69 and 4.04 (dd, *J* 12.8, 4.8, 2,7,9,14-CH_2) 3.93 (b, 11,12-CH_2 and 21,22-CH_2).

‖ **5** (3,6,16-triazonium-10,13,19-triaazapentacyclo[6.6.6.$0^{4,13}$.$0^{5,10}$.$2^{3,6}$]-docosa-3,5-diene triperchlorate); IR (Nujol, cm^{-1}): 1695, 1645 (v. strong), 1598; ^{13}C NMR (125.7 MHz; CD_3CN; *J* in Hz): δ 26.7 (1,8-C), 47.1 (11,12,21,22-C), 49.8 (17,18-C), 51.7 (15,20-C), 53.2 (2,7,9,14-C), 145.8 (4,5-C); ^1H NMR (500 MHz, CD_3CN): δ 2.80 (b, 1,8-CH), 3.05 (b, 17,18-CH_2), 3.12 (b, 15,20-CH_2), 3.69 and 4.04 (dd, *J* 14, 2,7,9,14-CH_2) 3.85 and 4.01 (m, AA′ and XX′ spin system of 11,12-CH_2 and 21,22-CH_2), 4.98 (b, three 16,19-NH).

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