Synthesis of Calix[4]arene Bisporphyrin on the Basis of Biladiene-*a,c* Dihydrobromide

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A new calix[4]arene-bisporphyrin has been synthesized following a stepwise approach. The tetrapyrrolic precursor for bisporphyrin is 10-aryl substituted biladiene-a,c dihydrobromide. The preparation of the starting pyrrolic compounds has been optimized with respect to the previously reported methods.

Keywords: Dipyrromethane, biladiene-*a,c* dihydrobromide, calix[4]arene bisporphyrin.

Introduction

The synthetic organic chemistry of bisporphyrins is one of the most extensively developing fields of the chemistry of macroheterocyclic compounds. Up to now, dimeric porphyrins having a very complex structure have been synthesized. The orientation of porphyrin fragments therein may be determined by both flexible hydrocarbon or ether bridges and rigid aromatic structures, such as benzene, naphthalene, and anthracene nuclei.[1] Bisporphyrins in which 5-phenyl-10,15,20-trimesitylporphyrin macroheterocycles are attached to a calixarene spacer were prepared.[2] Introduction of calixarene fragment as a bridging entity connecting two porphyrin rings attracts a strong interest, taking into account the ability of calixarenes to form π-complexes with cationic species. This ability underlies their wide application as traps for various metals.[3]

The most common linear tetrapyrroles used for the synthesis of porphyrins are biladienes-*a,c*. Dolphin *et al.*[4] have prepared vinylporphyrins from 1-bromo-19-methylbiladienes-*a,c*. Lash *et al.*[5] have synthesized dinaphthoporphyrins from biladienes-*a,c*. Smith *et al.*[6] have carried out the cyclization of biladiene-*a,c* salts with 1,19-arylmethyl substituents. Recent achievements in the preparation of porphyrins from biladienes-*a,c* are presented by Smith in [7]. In this work, we have developed first synthetic approach for obtaining of a calix[4]arene-bisporphyrin conjugate from 10-substituted biladiene-*a,c* dihydrobromide.

Experimental

^{1}H NMR spectra were recorded on Bruker AC-200 spectrometer at 200 MHz. Chemical shifts are given in ppm from tetramethylsilane (TMS), solvent deuterochloroform. Electronic absorption spectra were obtained in toluene using Cary 100 spectrophotometer. The mass spectra (electronic impact, 70 eV) were obtained on MKh-1310 instrument (ion source temperature 150-200 °C). Reactions were monitored by thin layer chromatography and spectrophotometry. Neutral alumina (Merck; Brockmann activity grade III) was used for column chromatography.

Bis(3-ethyl-5-carboxy-4-methyl-2-pyrrolyl)-phenylmethane, **2.** 4-Ethyl-3-methyl-2-ethoxycarbonylpyrrole **1**[8] (0.60 g, 2.87 mmol) was dissolved in ethanol (30 ml) and added to a solution of benzaldehyde (0.20 g, 1.32 mmol) in ethanol (100 ml). The mixture was heated to boiling, and hydrochloric acid (0.1 ml) was added into the flask. The reaction mixture was refluxed for 2.5 h, cooled, and diluted with water (100 ml). The precipitate formed was filtered off, washed with water, and dissolved in ethanol (100 ml). The solution was heated to boiling, and potassium hydroxide (0.20 g) dissolved in water (10 ml) was added. The mixture was refluxed for 3 h more, then ethanol was distilled off in vacuum. The residue was diluted with 2 N hydrochloric acid until the reaction product solution was brought to p*H*=8.0, and the precipitated tarry substances were filtered off. The solution was neutralised further until p*H*=6.0, and the reaction product precipitated was filtered off. Yield 0.49 g (69%). *m/z*: 207.3 ($I_{rel.}$=71%) [*M*- $2CO_2$]$^+$. ^{1}H NMR ($CDCl_3$) δ ppm: 8.82 (s, 2H, NH), 6.92 (d, 2H, *phenyl*$_{ortho}$), 6.71 (d, 2H, *phenyl*$_{meta}$), 6.63 (t, 1H, *phenyl*$_{para}$), 5.37 (s, 1H, *meso*-H), 2.20 (q, 4H, *β*-$CH_2$$CH_3$), 2.34 (s, 6H, *β*-$CH_3$), 0.71 (t, 6H, *β*-$CH_2$$CH_3$).

Bis(3-ethyl-4-methyl-2-pyrrolyl)-phenylmethane, **3**. In a sealed ampule dipyrromethane **2** (0.49 g, 1 mmol), hydrazine hydrate (1 ml) and an aqueous solution of potassium hydroxide (10 %, 8 ml) were heated to 180°C for 5 h. On cooling, compound **3** was filtered off, washed with water and dried. Yield 0.30 g (75%). *m/z:* 207.3 ($I_{rel.}$ = 87%) [*M*]$^+$. ^{1}H NMR ($CDCl_3$) δ ppm: 9.02 (s, 2H, NH), 6.90 (d, 2H, *phenyl*$_{ortho}$), 6.68 (d, 2H, *phenyl*$_{meta}$), 6.59 (t, 1H, *phenyl*$_{para}$), 5.42 (s, 1H, *meso*-H), 2.22 (q, 4H, *β*-$CH_2$$CH_3$), 2.14 (s, 6H, *β*-$CH_3$), 0.72 (t, 6H, *β*-$CH_2$$CH_3$).

7,13-Dimethyl-2,3,8,12,17,18-hexaethyl-10-phenylbiladiene-a,c dihydrobromide, **4.** 2-Formyl-3,4-diethylpyrrole (0.45 g, 3 mmol)[9] and dipyrromethane **3** (0.61 g, 1.5 mmol) were dissolved in methanol (300 ml) with stirring. Then, hydrobromic acid (46 %, 1 ml) was added, and the mixture was stirred at ambient temperature for 1 h. The precipitated biladiene-*a,c* dihydrobromide **4** was filtered off, washed with methanol and diethyl ether, and dried. Yield 0.80 g (64%). Found: C 61.14, H 6.39, N 7.28 %. $C_{39}H_{49}Br_2N_4$ requires C 61.18, H 6.41, N 7.32 %. *m/z:* 580.5 ($I_{rel.}$ = 78%) [*M* – 2HBr]$^+$. UV-vis λ_{max} nm (lg ε): 373 (3.92), 452.4 (4.39), 521.7 (4.84). ^{1}H NMR ($CDCl_3$) δ ppm: 13.42 (s, 2H, NH), 13.30 (s, 2H, NH), 7.12 (s, 2H, =CH), 6.88 (d, 2H, *phenyl*$_{ortho}$), 6.36 (d, 2H, *phenyl*$_{meta}$), 6.27 (t, 1H, *phenyl*$_{para}$), 5.27 (s, 1H, CH), 3.30, 3.12 (m, 12H, *β*-$CH_2$$CH_3$), 2.71 (s, 3H, *β*-$CH_3$), 2.41 (s, 3H, *β*-$CH_3$), 1.01, 0.87 (m, 18H, *β*-$CH_2$$CH_3$).

5,7-Bis(15-phenyl-2,3,7,8,13,17-hexaethyl-12,18-dimethylporphyrinyl)-25,27-bishydroxy-26,28-bismethoxy-calix[4]arene,

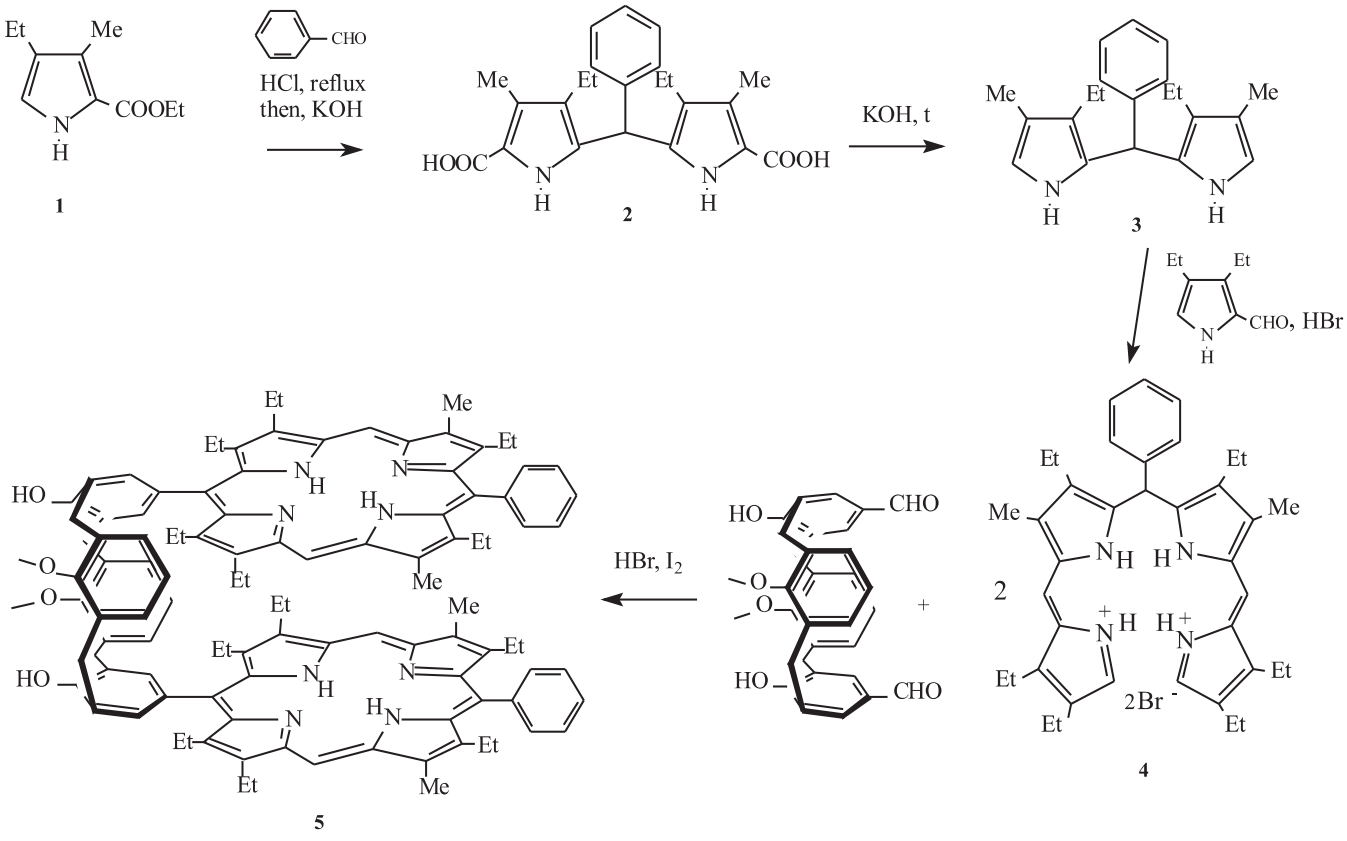
5. A solution of biladiene-*a,c* **4** (1.0 g, 1.2 mmol), of *bis*-formyl calix[4]arene[10] (0.31 g, 0.6 mmol) and hydrobromic acid (46 %, 1 ml) was heated under reflux for 4 h in methanol-methylene chloride mixture (50 ml, 2:1). Iodine (0.10 g) was then added and the mixture was refluxed for an additional 15 min. After cooling, the precipitate was filtered off, washed with methanol and dried. The crude calix[4]arene-*bis*-porphyrin was dissolved in methylene chloride and subjected to chromatography on alumina (Brockmann activity grade III), with methylene chloride–methanol mixture (1:1) as the eluent. The eluate was partly evaporated, and the calix[4]arene-bisporphyrin **5** was precipitated with methanol. Yield 0.57 g (52%). Found: C 84.41, H 8.09, N 3.41 %. $C_{114}H_{132}N_4O_4$ requires C 84.44, H, 8.15, N 3.46 %. *m/z* 1621.1 ($I_{rel.}$ = 96%) $[M]^+$. UV-vis λ_{max} nm (lg ε): 621.4 (3.49), 574.7 (3.71), 542.5 (3.61), 508.0 (4.01), 410.1 (5.14). ^{1}H NMR ($CDCl_3$) δ ppm: 10.12 (s, 4H, *meso*-H), 7.96 (m, 4+4H, *phenyl*$_{ortho}$+*calix.*), 7.68-7.49 (m, 4+4H, *phenyl*$_{meta}$+ *calix.*), 7.31 (t, 2H, *phenyl*$_{para}$), 7.11 (t, 2H, calix.), 4.47 (s, 6H, OCH_3), 4.01 d (4 H, $ArCH_2Ar$), 3.97 q (16 H, CH_2CH_3), 3.89 s (2 H, OH), 3.86 m (8 H, CH_2CH_3), 3.42 d (4 H, $ArCH_2Ar$), 2.41 s (12 H, CH_3), 1.03 t (24 H, CH_2CH_3), 0.92 t (12 H, CH_2CH_3), –2.42 (s, 4H, NH).

Results and Discussions

The reaction of 5-unsubstituted pyrrole **1** with benzaldehyde in ethanol in the presence of hydrochloric acid results in the formation of *meso*-phenyldipyrromethane diester, which was converted in a one-pot procedure into the dicarboxy derivative **2** (Scheme 1). If the dipyrromethane has different substituents at the β-positions of the pyrrole ring, a mixture of isomeric products can be formed on decarboxylation due to cleavage and recombination of the fragments. To avoid this, we've investigated several ways to obtain 5,5'-diunsubstituted dipyrromethane **3** from **2**. Firstly, the carboxy groups were substituted by iodine and then the iodo-derivative was reduced with tin(II) chloride to afford **3** in 60% yield. Alternatively, dipyrromethane dicarboxylic acid **2** was decarboxylated with trifluoroacetic acid (TFA). It was found that 5,5'-diunsubstituted dipyrromethane **3**, thus formed in 70% yield, is stable in TFA at room temperature for a week. Finally, heating of **3** in aqueous base in the presence of hydrazine as a stabilizer appears to be the method of choice for decarboxylation of β-alkylated dipyrromethanes. In this case, the yield of the target product reaches 75%.

10-Phenyl substituted octaalkyl-biladiene-*a,c* dihydrobromide was then prepared by addition of two equivalents of 2-formylpyrrole to *meso*-phenyldipyrromethane 3 in methanol. Hydrobromic acid was used to provide a good yield (61%) of the crystalline 1,19-unsubstituted-10-phenyl-biladiene-*a,c* **4**. The reaction of **4** with bis-formyl-calix[4] arene methanol-methylene chloride mixture (2:1) gives a new calix[4]arene-bisporphyrin conjugate **5**. The strength of the organic acids (trifluoroacetic acid, chloroacetic acid, acetic acid) used as the catalyst for this condensation only slightly affects the yield of the target product **5**, but hydrobromic acid is the most convenient and provides the optimum yield (52%). The overall yield of the four-step transformation of pyrrole **1** into the calixarene substituted bisporphyrin **5** is satisfying (15%).

The spectral characteristics of **5** and pyrrolic compounds **2-4** are in full agreement with the proposed structures. In the ^{1}H NMR spectra of biladiene-*a,c* dihydrobromide **4** there are two sets of signals for the NH- and *meso*-CH groups, due to the lower symmetry of biladiene-*a,c* molecule and the presence of the 10-phenyl group.



Scheme 1.

The ^{1}H NMR spectra of **5** contain signals of protons of the calix[4]arene and the porphyrin macroheterocycles. The presence of distinct signals from bridging methylene groups in the cyclophane moiety (two symmetric doublets at 4.01 and 3.42 ppm) indicates that the calix[4]arene macroheterocycle in **5** adopts a cone conformation. Upfield shift (≈1.0 ppm) of signal of the pyrrolic methyl groups in **5** as compared with monomeric porphyrin of similar structure is the result of a strong mutual effect of π-electron systems of the stacked tetrapyrrolic macroheterocycles in bisporphyrin.

With a view to design sterically preorganized complexing cavities for selective binding of anions we also examined the effect of acid–base equilibria on the spectral parameters of **5**. According to obtained experimental data and the results of our previous investigations spectrophotometric titration of the calix[4]arene-bisporphyrin in the system **5**-C_2H_5OH-H_2SO_4 could be represented by equilibria (1) and (2).

$$H_4P + 2H^+ \overset{K_b}{\rightleftarrows} H_6P^{2+} \quad (1)$$

$$H_6P^{2+} + 2H^+ \overset{K_{b2}}{\rightleftarrows} H_8P^{4+} \quad (2)$$

The equilibrium constants calculated according to a standard procedure[11] were $\log(K_{b1}) = 10.31 \pm 0.01$ (Equation 1) and $\log(K_{b2}) = 7.97 \pm 0.01$ (Equation 2). That finding seems to be fairly promising from the viewpoint of the design of supramolecular receptors for anions selective binding. It provides a means for optimization of the geometric parameters of receptor cavity to match substrate's parameters.

Conclusions

10-Phenyl-*a,c*-biladiene can be used as a stable intermediate for new calix[4]arene-bisporphyrin conjugate. Firstly, dipyrromethane is formed from 5-unsubstituted pyrrole and benzaldehyde, and then it is transformed to biladiene-*a,c* dihydrobromide **4**. Finally, **4** is condensed with bis-formyl-calix[4]arene, introducing the calix[4]arene functional part into the macroheterocycle.

It was found out that each of the tetrapyrrolic macroheterocycles in calix[4]arene-bisporphyrin can undergo two steps of protonation to form tetraprotonated molecule. The molecule with two positive charges on the pyrrolenic (–N=) and the pyrrolic (–NH–) nitrogens could serve as the host sites for anions complexation. This finding reveals the possibility of using of calix[4]arene-bisporphyrin as receptors for anions of different nature.

Acknowledgments. This work was supported by Russian Foundation for Basic Research (grant № 08-03-00009).

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Received date 27.12.08
Accepted date 02.02.09
First published on the web 02.04.2009