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Structure of the Stereoisomers of Tetrasubstituted *p*-*t*-Butylcalix[4]arene Containing a Morpholine Fragment: Data of 1D and 2D (NOESY) NMR Spectroscopy

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Abstract—The structure of three isomers of 5,11,17,23-tetra-*t*-butyl-25,26,27,28-tetrakis[(morpholidocarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene in conformations of *partial cone*, 1,3-*alternant* and *cone* was studied by the methods of 1D and 2D (NOESY) ^{1}H and ^{13}C NMR spectroscopy in conjunction with computational modeling (semiempirical quantum-chemical PM3 calculations). Characteristic cross-peaks for each conformer in the two-dimensional NOESY spectra were established. It is found that unsymmetrical conformation of *partial cone* is more "flattened" as compared with highly symmetrical 1,3-*alternant* and *cone* conformations, while $OCH_2C(O)NC_4H_8O$ substituent is located in the *exo*-position. Theoretical modeling is found to be more consistent with the experimental data for highly symmetrical conformations.

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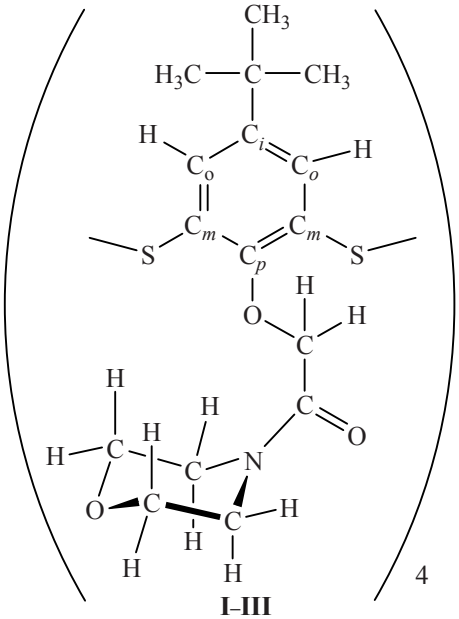
Unsubstituted *p*-*t*-butylthiacalix[4]arene is known to exist in cone conformation both in solution and in crystal [1-3]. Its functionalization at the lower rim can theoretically result in the formation of four conformational isomers: *cone*, *partial cone*, 1,2- and 1,3-*alternants* [1-5]. Therewith, deviation from actual (up/down) orientation is possible, e.g., aryl rings can be turned outside with formation of so-called *flattened* conformations. In addition, the substituents at the lower rim can occupy *endo*- and *exo*-positions.

The aim of this work is establishing the structure of *p*-*t*-butylthiacalix[4]arenes **(I–III)** by the methods of one- and two-dimensional (NOESY) NMR spectroscopy in conjunction with computational modeling using semiempirical methods of quantum chemistry.

The *p*-*t*-butylthiacalix[4]arene tetrasubstituted at the lower rim (**I**) is in *partial cone* conformation and contains arene rings of three types, A, B, and C, with two equivalent B rings (Fig. 1).

Analysis of ^{1}H and ^{13}C NMR spectra was carried out with accounting for the specificity of the *partial cone* structure, namely, the chemical equivalence of the nuclei in equivalent positions of two aromatic B rings and substituents at these rings leading to double intensity of the corresponding signals. Actually, in the ^{1}H NMR spectrum the signals of *t*-Bu^{A}, *t*-Bu^{B} and *t*-Bu^{C} protons are three singlets with the double intensity of *t*-Bu^{B} signal (Table 1, Fig. 2).



I–III

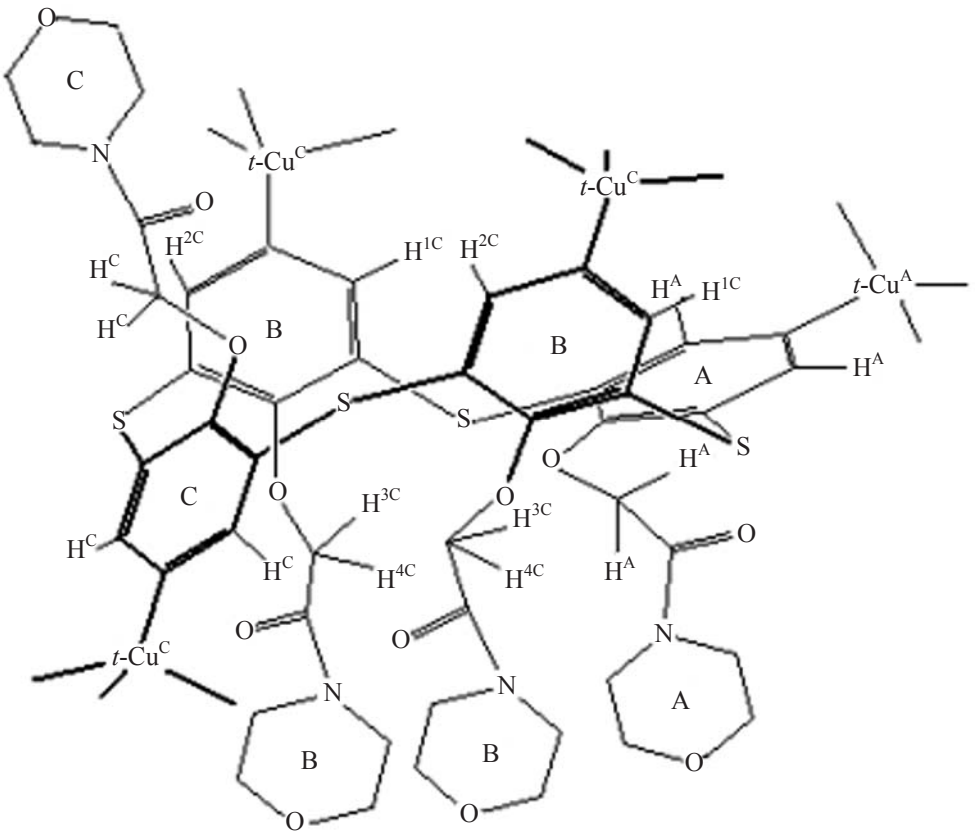


Fig. 1. Structure of compound **I**.

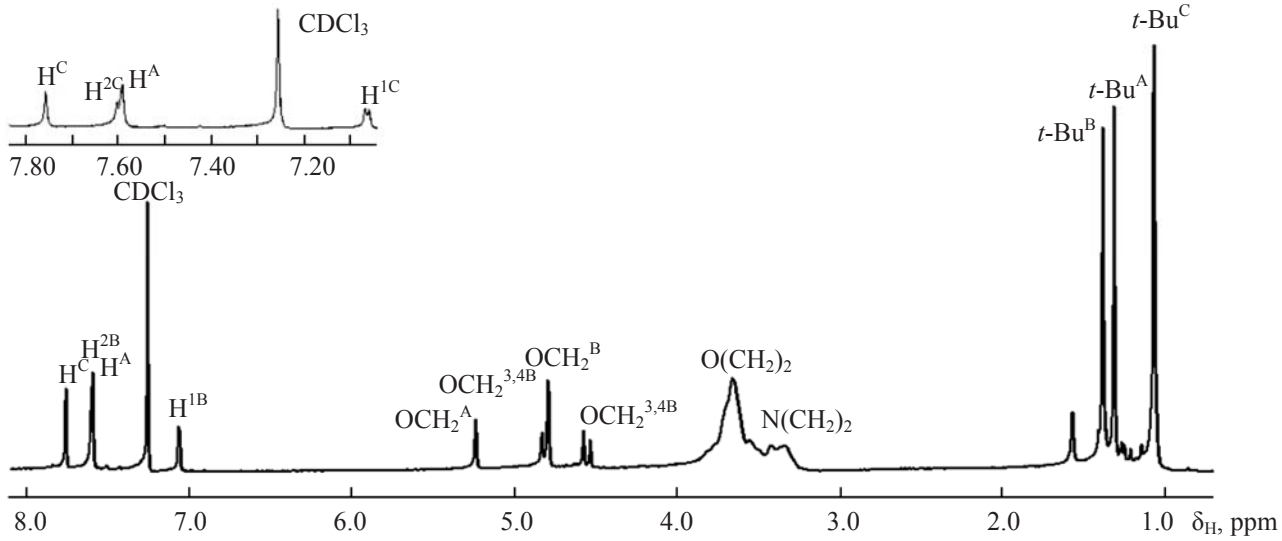


Fig. 2. The ^{1}H NMR spectrum of compound **I**, solution in $CDCl_3$.

The aromatic protons H^{1B} and H^{2B} forming an *AX* system (Δδ 0.54 ppm, Table 1), appear in the spectrum as two doublets (Fig. 2) while the protons H^A and H^B (the signal of the former is overlapped by the signal of H^{2B} proton of the neighboring aromatic ring) are characterized by two singlets with overall integral intensity (4H) reasonably the same as the intensity of four signals of aromatic rings B.

The magnetic nonequivalence of methylene protons in $OCH_2{}^B$ groups at the B rings (H^{3B} and H^{4B}, an *AB*-quadruplet, Fig. 2) is understandable due to the spatial

Table 1. The ^{1}H NMR spectra [δ, ppm (J_{HH}, Hz)] of compounds **I–III**, solvent $CDCl_3$

Protons[a]	Compound		
	I	**II**	**III**
H^A	~7.6	7.5	7.3
H^{2C}	7.6 (–2.5)		
H^{1C}	7.06 (–2.5)		
H^C	7.76		
t-Cu^A	1.3	1.3	1.1
t-Cu^C	1.15		
t-Cu^C	1.4		
$OCH_2{}^C$	4.8	4.7	5.3
$OCH_2{}^A$	5.2		
$OCH_2{}^{3,4C}$	4.8 (–12.5)		
	4.6 (–12.5)		
$O(CH_2)_2$ и $N(CH_2)_2$ in morpholine ring	~3.7 и ~3.3	~3.6–3.2	~3.7–3.6

[a] Superscript indices correspond to the ring type and the position of the proton in the ring.

approach of substituents at the B rings (Fig. 1) leading to steric hindrances to the rotation of the protons of these groups relatively to the magnetically anisotropic C=O group, while the absence of hindrances for the protons in $OCH_2{}^A$ and $OCH_2{}^C$ groups makes them magnetically equivalent (two singlets, Fig. 2).

The signals of the protons of methylene groups $N(CH_2)_2$ and $O(CH_2)_2$ in morpholine fragment of substituents forming two four-spin systems of *AA'XX'* type are strongly broadened, that can result from the close δ_H values of the same groups in A, B, and C substituents and also by ring inversion.

In the ^{13}C NMR spectrum we expected a triplication of the signals of carbon atoms for each structural fragment**.** One such signal in each group should be of double intensity (two B rings), and this can be clearly traced in the regions of resonance of the carbon atoms in C–*t*-Bu, C=O and OCH_2 groups (Fig. 3, Table 2).

Let us analyze the^{13}C NMR spectrum in the region of resonance of aromatic rings, each of them including four sorts of nonequivalent carbon atoms: one C_I, connected directly with *t*-Bu group, two C_o atoms, two equivalent C_m atoms, and one C_p carbon atom connected with the substituent at the lower rim.

Triplication of signals is observed in the cases of C_p and C_i carbon atoms (Fig. 3, Table 2). The C_m carbon atoms due to coincidence of chemical shifts of $C_m{}^{A,B}$ gives in the spectra two singlets. Four signals of C_o

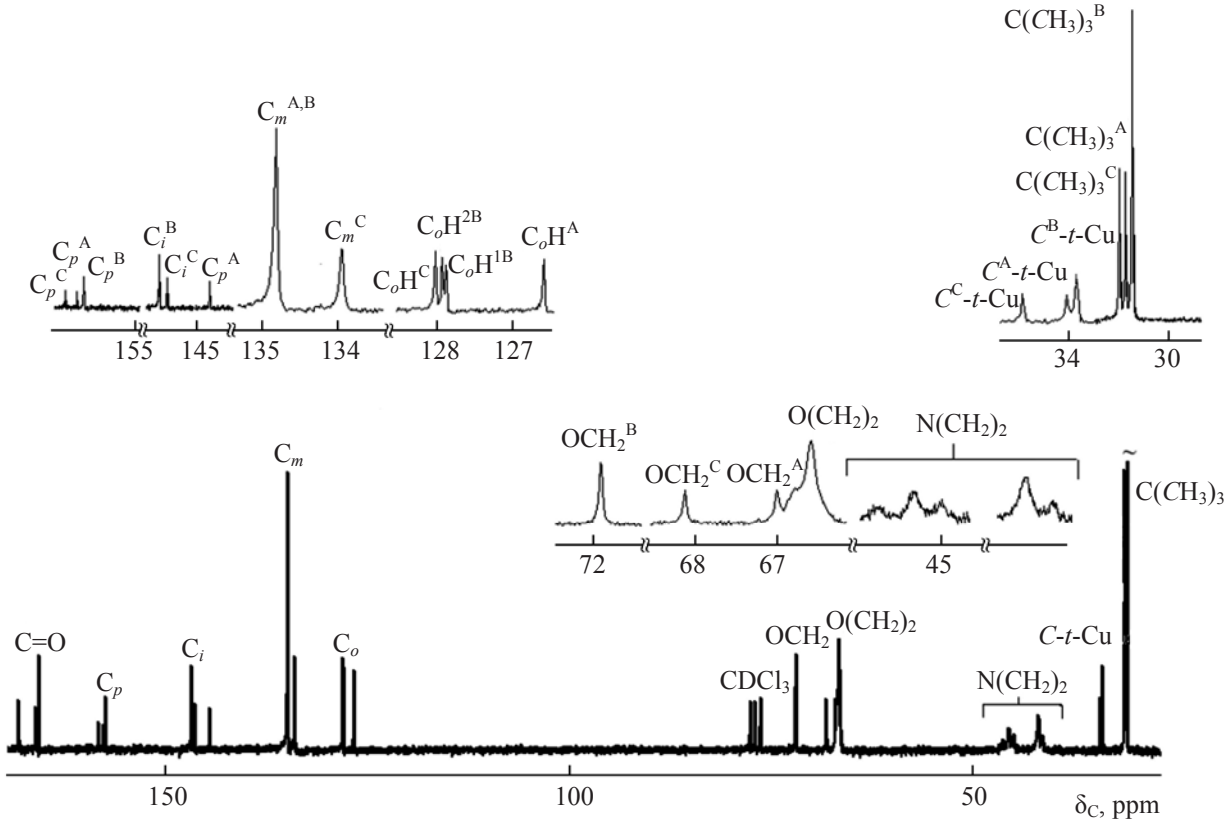


Fig. 3. The ^{13}C NMR spectrum of compound **I**, solvent $CDCl_3$.

atoms instead of expected three are due to a small nonequivalence of C_o^B in different B rings (Δδ 0.05 ppm, Table 2) owing to the difference in location of these rings relative to the neighboring rings A and B and substituents in these rings (Fig. 1). Note that the same reasons define the nonequivalence of aromatic protons H^{1B} and H^{2B} (see above).

Theoretical calculation of energy (heat of formation) and calculation of interproton distances in the stereoisomers **I–III** were carried out by semiempirical PM3 method.

The data in Table 3 show that highly symmetrical cone and 1,3-*alternant* conformations are energetically preferable. The *cone* conformation has the lowest heat of formation, but in this case we can suggest only the principal preference of this conformation for the calculations are carried out only for the gas phase. In solutions an interaction exists of the molecules of substance with the molecules of the solvent, that is, solvation effects affecting geometry and stability of dissolved molecules [6]. This can lead to discrepancies between the experimental (NMR) data and results of theoretical simulation that should be taken into consideration.

For experimental measurement of the respective interproton distances in each stereoisomer **I–III** we choose the method of nonstationary nuclear Overhauser effect (two-dimensional NOESY experiment) [7–9]. This experiment allows establishing the interproton distance with an error less than 8% [10, 11]. For each compound we carried out a series of NOESY experiments differing by the mixing time (0.1 to 0.8 s). Then for each observable cross-peak a plot was constructed of its integral intensity vs the mixing period. The obtained plot was approximated by a straight line and its slope was measured. This slope, or, in other words, the rate of change of the nuclear Overhauser effect is directly related to the distance between the interacting nuclei [12]. The distance between the relaxing nuclei r_i was calculated from the relation $r_i = r_k (v_k/v_{ij})$, where r_k is the distance between the reference pair of protons, v_k is the rate of the change in intensity of reference cross-peak, v_{ij} is the rate of the change in intensity of the analyzed cross-peak. Then the obtained distances were compared with the geometric parameters of structures **I–III** obtained by PM3 calculation.

The ^{1}H NOESY NMR spectrum of compound **I** in $CDCl_3$ at room temperature contains 9 pairs of cross-peaks (Fig. 4). Therewith, each aromatic proton in the rings A, B, and C has a cross-peak with related *t*-Bu group. Besides:

– non-equivalent protons in B ring give cross-peaks with each other and proton H^{2B} with the protons of OCH_2^B group of the substituent in B ring, in

Table 2. ^{13}C NMR spectra (δ_C, ppm) of compounds **I–III**, solvent $CDCl_3$

Carbon nuclei[a]	Compound		
	I	**II**	**III**
$C(CH_3)^A$	31.083	31.080	31.072
$C(CH_3)^B$	30.911		
$C(CH_3)^C$	31.238		
C^A-*t*-Bu	34.013	34.205	34.010
C^B-*t*-Bu	33.955		
C^C-*t*-Bu	34.295		
$N(CH_2)_2$ and $O(CH_2)_2$ (morpholine ring)	66.995–41.37	66.526–41.931	66.616–41.683
OCH_2^A	66.997	67.766	66.719
OCH_2^B	71.916		
OCH_2^C	68.130		
C_oH^A	126.62	127.445	128.607
C_oH^{1B}	127.89		
C_oH^{2B}	127.94		
C_oH^C	128.04		
$C_m^{A, B}$	133.97	132.169	134.342
C_m^C	134.83		
C_i^A	144.47	146.348	145.942
C_i^B	146.39		
C_i^C	146.73		
C_p^A	157.65	156.790	157.637
C_p^B	157.34		
C_p^C	158.22		
C^A=O	165.620	166.125	167.245
C^B=O	166.047		
C^C=O	168.19		

[a] Superscript indices show the ring type.

Table 3. Heat of formation of compounds **I–III** calculated by PM3 method

Conformation	Δ*H*, kJ mol^{-1}
Cone	–1390.509
Partial cone	–1105.493
1,3-*alternant*	–1123.097
1,2- *alternant*	–1094.466

Table 4. Interproton distances in compound **I** obtained in NOESY experiment and by quantum-chemical PM3 calculation

Proton pair	Distance *r*, Å (NOESY)	Error Δ*r*, Å	Distance *r*, Å (calculation)
H^3–H^4 (OCH_2^B)	1.77		1.77
H^{1B}–H^{2B}	2.80	0.13	2.38
H^{1B}–*t*-Bu^B	2.64	0.09	2.60
OCH_2^B–*t*-Bu^B	3.10	0.12	4.32
H^{2B}–OCH_2^C	2.64	0.09	3.25
H^A–*t*-Bu^A	2.81	0.07	2.85
H^{2B}–*t*-Bu^B	2.87	0.07	2.66
H^C–H^{3B}	2.85	0.09	2.72
H^C–*t*-Bu^C	2.69	0.11	2.67

correspondence with the structural relations in the *partial cone* (**I**) stereoisomer (Fig. 1);

– the protons H^B in B aromatic ring show cross-peaks with each proton H^3 and H^4 in the OCH_2^B of the substituent in B ring;

– in its turn, the protons of OCH_2^B group of the substituent in C ring show the cross-peaks with the protons of the morpholine ring.

As the reference (calibration) pair we choose the protons H^3 and H^4 in the methylene group of OCH_2^B, because distance between these protons is constant, being equal to 1.77 Å (Table 4).

The values of integral intensities of these cross-peaks are negative owing to the Overhauser effect. The exchange cross-peaks with positive values of integral intensity are not considered in this work.

The data in Table 4 demonstrate good agreement between experimental and theoretical results for the most pairs of protons in compound **I**. The experimental distance in two pairs of proton groups, OCH_2^B–*t*-Bu^B and H^{2B}–OCH_2^C, is considerably smaller than calculated one that points to deviation of substituent at the C ring from the plane of the macrocycle (*exo*-position). This can be connected with the rotation of methylene protons in OCH_2^B group around C–C(O) bond that is

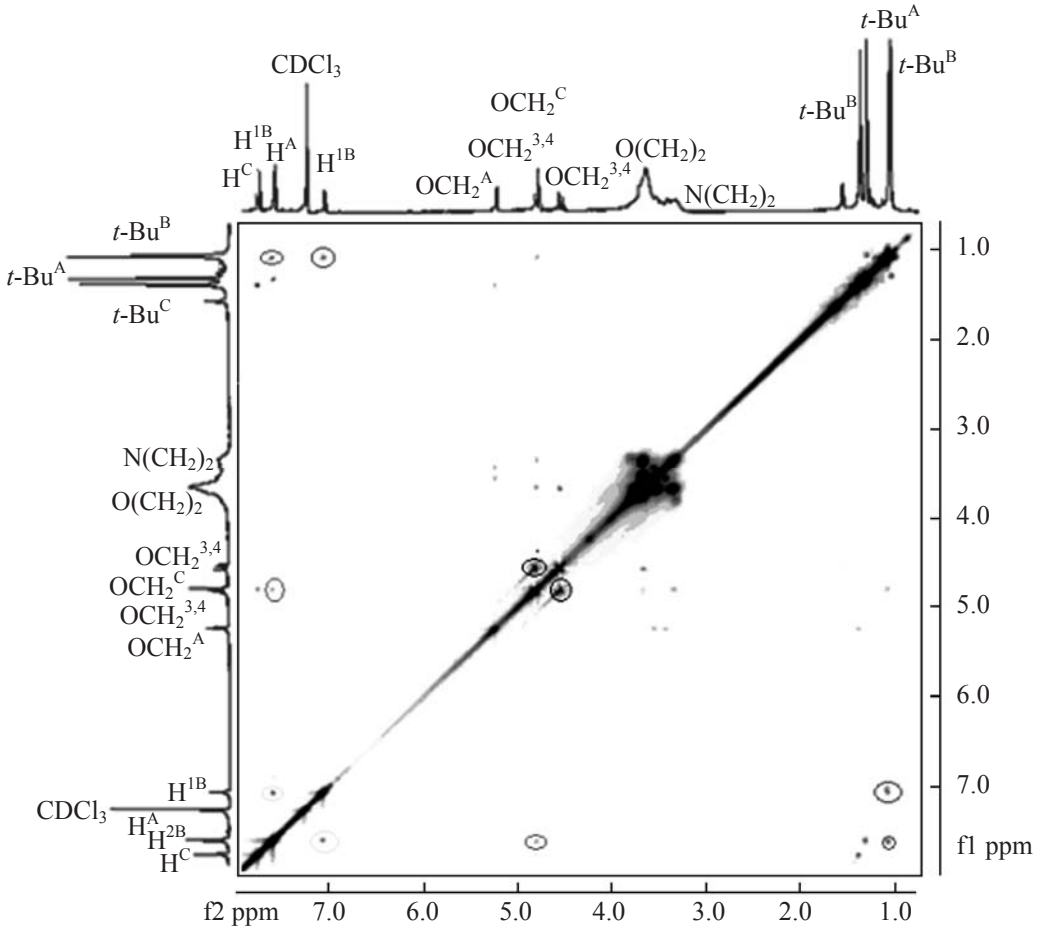


Fig. 4. ^{1}H NOESY NMR spectrum of compound **I** (solvent $CDCl_3$). Mixing duration $\tau_{mix} = 0.5$.

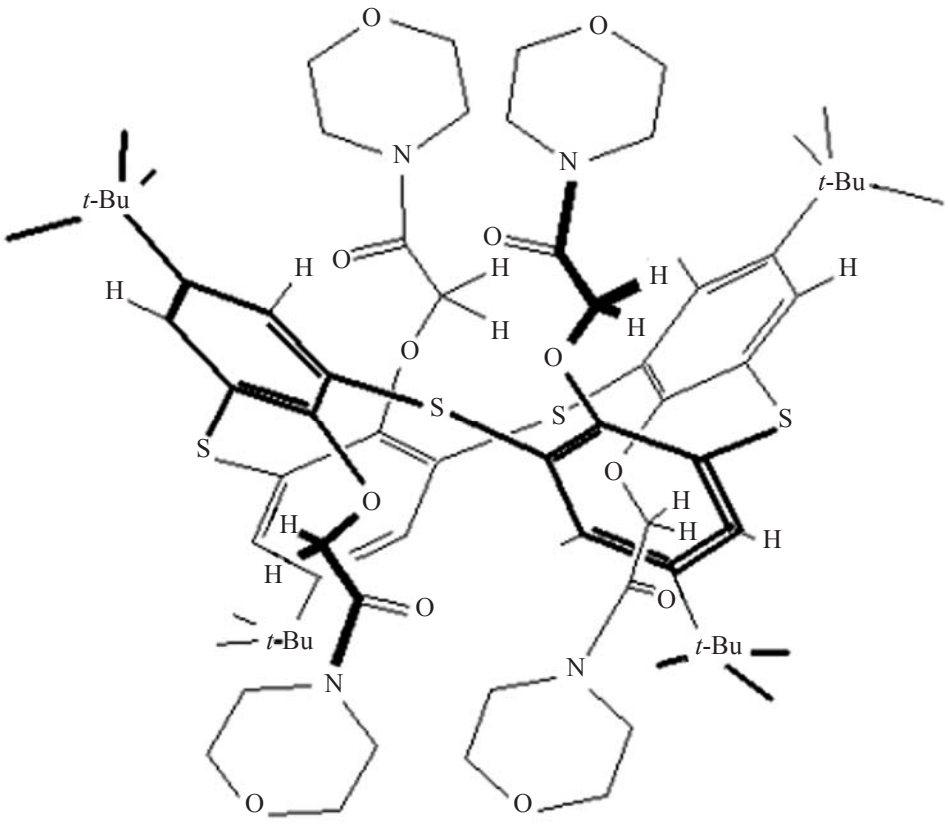


Fig. 5. Structure of compound **II**.

confirmed indirectly by apparent magnetic equivalence of these protons in the ^{1}H NMR spectrum (Fig. 2).

The stereoisomers **II** and **III** that are in 1,3-*alternant* and *cone* conformations are characterized by high symmetry leading to simplicity of their ^{1}H and ^{13}C spectra. Actually, ^{1}H NMR spectrum of 1,3-*alternant* isomer **II** (Fig. 5) consists of five signals (Fig. 6, Table 1), that is, related protons in four aromatic rings and in respective substituents are equivalent.

The ^{13}C NMR spectrum of compound **II** (Fig. 7, Table 2) also corresponds to a symmetrical structure: four groups of non-equivalent carbon nuclei appear as four signals and the carbon nuclei in C=O, C(CH_3) and OCH_2 groups resonate as singlets.

The signals of morpholine rings in both ^{1}H and ^{13}C NMR spectra are strongly broadened, like in the spectra of compound **I**.

Figure 8 depicts 2D ^{1}H NOESY NMR spectrum of compound II in $CDCl_3$. The spectrum contains 3 pairs of cross-peaks:

– between aromatic protons and *t*-Bu groups,

– between aromatic protons in two opposite rings and the protons in OCH_2 substitents in the other pair of opposite rings.

– exact the same, between *t*-Bu groups in one pair of ring and OCH_2 sibstituents in another one.

Two last cross-peaks are characteristic ones for 1,3-*alternant* conformation.

The spectrum also contains exchange cross-peaks between the protons of morpholine attributable to the ring inversion. Besides, the protons of this ring show

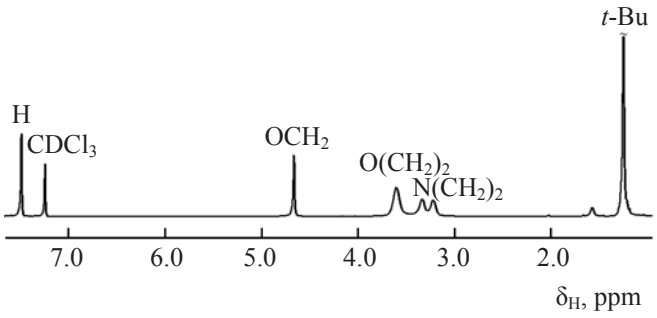


Fig. 6. ^{1}H NMR spectrum of compound **II** (solvent $CDCl_3$).

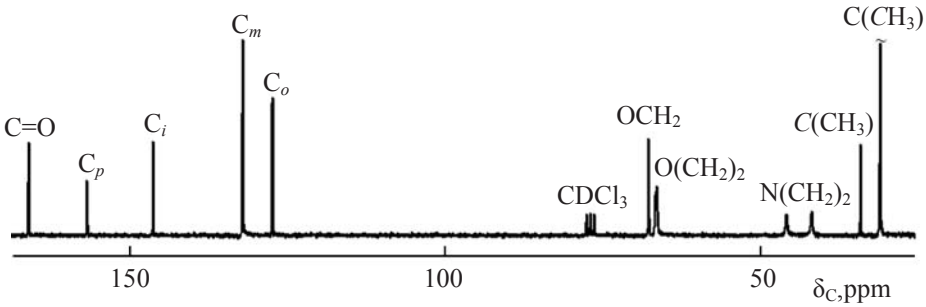


Fig. 7. ^{13}C NMR spectrum of compound **II** (solvent $CDCl_3$).

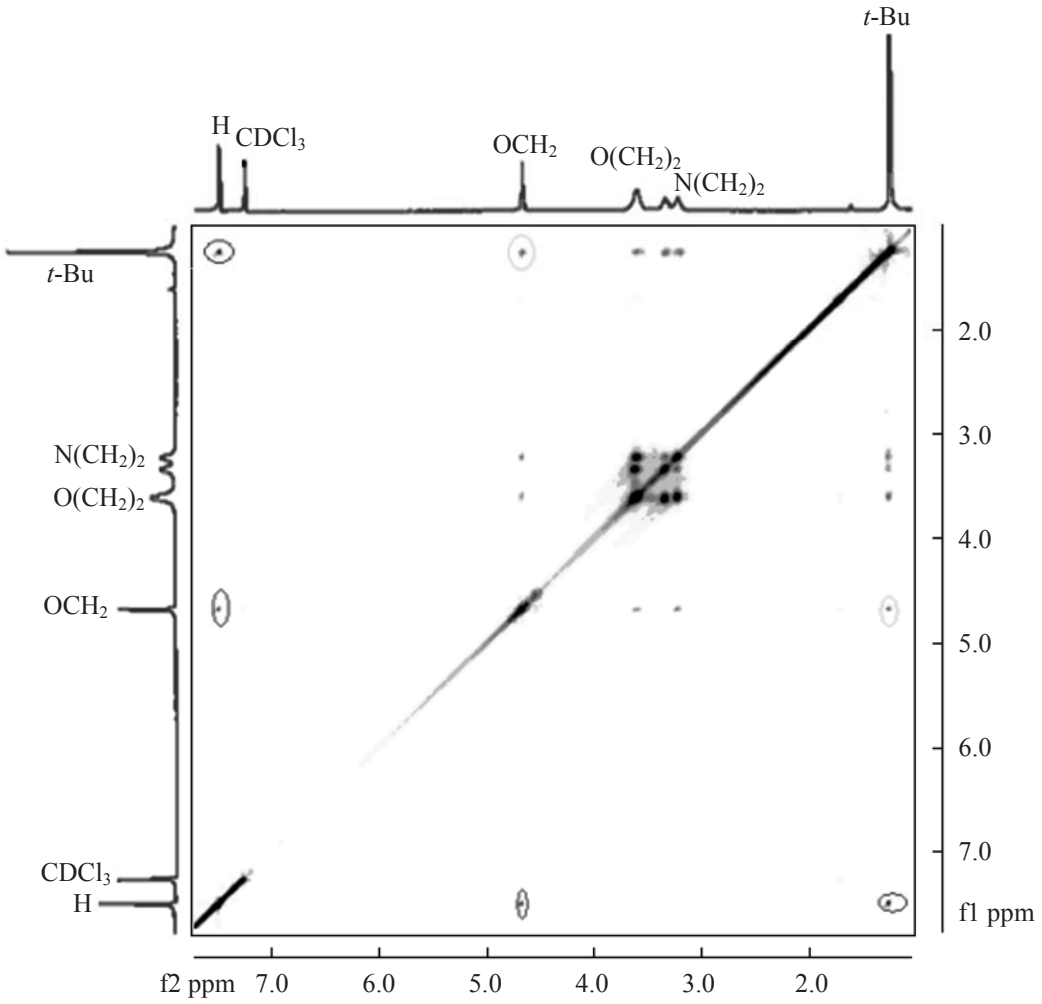


Fig. 8. 2D NMR ^1H NOESY spectrum of compound **II** (solvent $CDCl_3$).

exchange cross-peaks with the other protons of the molecule (Fig. 8). These facts indicate the flexibility of 1,3-*alternant* stereoisomer.

The data in Table 5 indicate that experimental and theoretical results are well consistent. As the reference pair we chose the protons of aromatic ring and methylene groups, the H–CH_2 distance $r_c = 2.65$ Å.

The comparative analysis of experimental inter-proton distances in *partial cone* (**I**) (Table 4) and 1,3-*alternant* (**II**) conformations (Table 5) shows that

nonsymmetrical conformation is more flattened, as first of all is shown by the presence of a great number of cross-peaks in the spectrum of compound **I** and diminishing of $r_i(H^A–t\text{-}Bu^B)$ (2.64 and 2.96 Å, that is, closeness of rings A and B) and r_i (OCH_2–*t*-Bu) (3.10 and 3.927 Å) values in the former.

The ^1H and ^{13}C NMR spectra of seteroisomers **II** and **III** (*cone*, Fig. 9), have similar patterns. Therefore they do not allow to assign undoubtedly certain conformation (1,3-*alternant* or *cone*) exclusively from the data of one-dimensional spectra. The answer gives a two-dimensional spectrum 2D NMR ^1H NOESY of compound **III** in $CDCl_3$ that contains cross-peaks between the protons of the following groups:

– *t*-Bu – H;

– OCH_2–$O(CH_2)_2$ and $N(CH_2)_2$ in morpholine;

– $O(CH_2)_2$–$N(CH_2)_2$ in morphopline ring.

The spectrum contains characteristic for *cone* conformation cross-peaks between the protons in the substituents at the lower rim, that is, the protons of methylene OCH_2 groups and morpholine rings that naturally are absent in the two-dimensional spectra of stereoisomers **I** and **II**.

Thus, applying the methods of ^1H and ^{13}C 1D and 2D (NOESY) NMR spectroscopy combined with simulation (semiempirical quantum-chemical PM3 calculations) we confirmed steric structures of three stereoisomer of 5,11,17,23-tetra-*t*-butyl-25,26,27,28-tetrakis[(morpholidocarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene existing in conformation *partial cone* (with *exo*-substituent), 1,3-*alternant* and *cone*. Characteristic cross-peaks of each conformer in the two-dimensional NOESY spectra were revealed.

EXPERIMENTAL

The stereoisomers of 5,11,17,23-tetra-*t*-butyl-25,26,27,28-tetrakis[(morpholidocarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene in conformations *partial cone* (**I**), 1,3-*alternant* (**III**), and *cone* (**III**) were synthesized at the Organic Chemistry Chair of Kazan State University in the group headed by Assistant Professor I.I. Stoikov.

The Registration of ^1H (300 MHz), ^{13}C (75.43 MHz), and ^{31}P (121.42 MHz) NMR spectra was carried out at varied temperature and concentration of solutions on a Varian UNITY-300 spectrometer. The spectrometer operated in the regime of internal stabilization on the ^2H resonance signal and was equipped with a device for maintaining temperature of the sample. At the registration of ^{31}P NMR spectra were commonly used 10°–15° pulses with the delay between the pulses *RD* = 1–2 s. The spectrum width *SW* 100 ppm, number of pulses *NT* from 10 to 100, digital filtration was not applied. For the registration of ^{13}C NMR spectra were commonly used 20°–30° pulses and broad-band proton decoupling, *RD* = 0, *SW* = 200 ppm, *NT* from 400 to 1000, digital exponential filtration was applied, *LC* = 2–4 Hz.

Table 5. Interproton distances in compound **II** from NOESY experiment and PM3 semiempirical calculations

Proton pair	Distance r, Å (NOESY)	Error Δr, Å	Distance r, Å (calculated)
$H^{ar}CH_2$	2.65		2.65
H^{ar}-*t*-Bu	2.96	0.03	2.91
OCH_2-*t*-Bu	3.93	0.06	3.97

At the registration of two-dimensional spectra were applied recommendation from the user manual. Number of acquisitions *nt* for NOESY spectra no less than 8. The number of repetitions *ni* on the time interval t_2 for obtaining the second frequency axis was chosen from the condition *ni* > (*sw* 1/2), where sw is the width of the spectral window. At the registration of NOESY spectra phase sensitive pulse sequence was applied. At the construction of two-dimensional spectra Fourier transform algorithm, algorithm of linear prediction for reproducing cut off FID and weighted Gauss function as a digital filter were applied. For

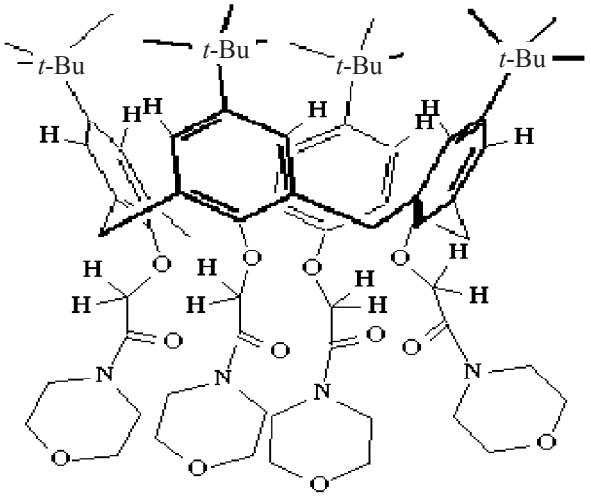


Fig. 9. Structure of compound **III**.

obtaining 2048×2048 points spectrum a procedure of supplementing FID with zeros was applied.

The samples were solutions of 3–5 wt. % concentration at the registration of ^{1}H NMR spectra and 10–15 wt. % for ^{13}C and ^{31} P spectra. Chemical shits were measured from the resonance signals of dissolved in the samples reference substances (internal references).

Theoretical calculation of energy (heat of formation) of three stereoisomers: *partial cone,* 1,3-*alternant* and *cone* was carried out in the framework of semiempirical approach in Gaussian 03 program with application of PM3 method.

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