ISSN 1070-3632, Russian Journal of General Chemistry, 2013, Vol. 83, No. 4, pp. 698–702. © Pleiades Publishing, Ltd., 2013.
Original Russian Text © F.Kh. Karataeva, R.R. Vagizova, I.I. Stoikov, I.S. Antipin, V.V. Klochkov, 2013, published in Zhurnal Obshchei Khimii, 2013, Vol. 83, No. 4, pp. 613–617.

One- and Two-Dimensional NMR Study of Structure of 1,2-Disubstituted *p-tert*-Butylthiacalix[4]arene Containing Amide Fragment

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Received March 23, 2012

Abstract—The structure of 5,11,17,23-tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis[*N*-(4'-nitrophenyl)aminocarbonylmethoxy]thiacalix[4]arene **I** was examined by 1D and 2D (NOESY) ^{1}H and ^{13}C NMR methods in a $CDCl_3$ solution using numerical simulation (semi-empirical quantum-chemical calculations, PM3 method). Compound **I** was found to exist in the 1,2-*alternate* conformation, where bulky substituents $OCH_2C(O)\cdot NHPhNO_2$ are in the *endo*-position relative to the macrocycle cavity.

DOI: 10.1134/S1070363213040154

It is known that calix[4]arenes are conformationally flexible in solutions [1, 2]. Introduction of bulky substituents into the lower rim of calix[4]arene structure hinders the macrocycle flexibility, resulting in the fixing of one of the four possible conformations (*cone*, 1,3-*alternate*, 1,2-*alternate*, and *partial cone*) depending on the substitution position, the size and nature of the substituents in the lower and upper rims [3, 4]. This raises the problem of studying the structure and flexibility of the substituents proper and their orientation with respect to the macrocycle cavity, which is important for the use of these substances as *host* molecules.

Previously [5], we have studied the structure of mono- and 1,3-disubstituted *p-tert*-butylthiacalix[4] arenes containing bulky substituent $OCH_2C(O)$ $NHPhNO_2$. It was found that both compounds in solution exist in a *cone* conformation with substituent (s) in the *exo*- and *endo*-positions with respect to the macrocycle cavity, respectively.

The aim of this work is to study the structure of 1,2-disubstituted *p-tert*-butylthiacalix[4]arene **I** by methods of one- and two-dimensional (NOESY) NMR spectroscopy involving the numerical simulation (semi-empirical quantum-chemical calculations).

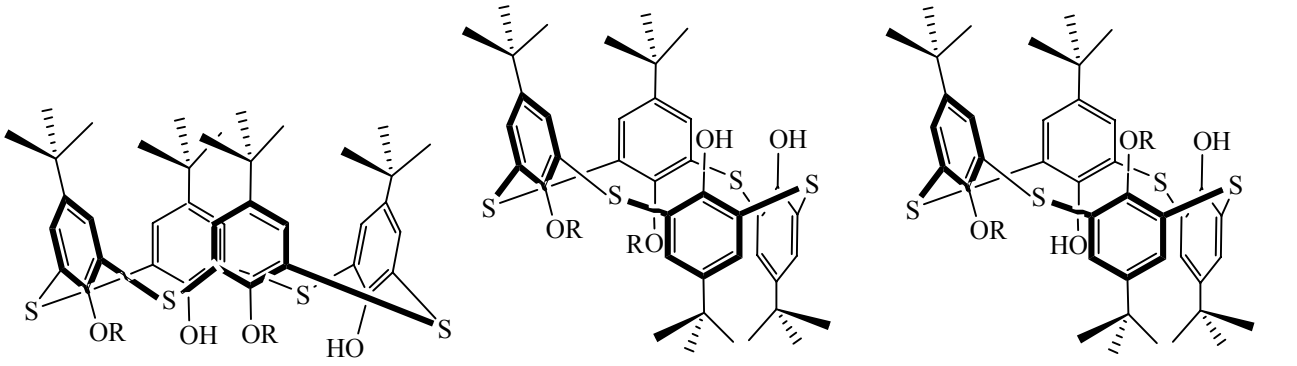
In the ^{1}H NMR spectrum of **I** (Fig. 1) the protons H^1 and H^2, H^3 and H^4 of two adjacent arene rings of the macrocycle, whose pairs form spin AB systems, appear as two quartets at δ 7.6 and 7.4 ppm, respectively, with the spin-spin coupling constant $^{4}J_{HH}$ 2.6 Hz.

The same phenyl protons H^7 and H^8 in two equivalent substituents on adjacent arene rings resonate as two doublets at δ 7.1 and 8.0 ppm (AX system), respectively. The signals of these protons are

somewhat broadened in comparison with the well-resolved signals of similar protons in the spectrum of 1,3-disubstituted analog showing AA'XX system [5]. This fact will be discussed later when comparing the calculated and NOESY experimental data.

Magnetic nonequivalence of the protons H^{5A} and H^{5B} within each of the methylene groups of the substituents is apparently connected with an asymmetric arrangement of these protons relative to the adjacent magnetically anisotropic C=O group at hindered rotation around the C–C(O) bond. Therefore, in contrast to the 1,3-disubstituted analog, where the protons resonate as a singlet [5], in this case the AB-quartet at δ 4.72 ppm ($^2J_{HH}$ 14.5 Hz)is observed. The signals of the protons NH^6 and OH^9 are at δ 6.75 and 8.5 ppm, respectively.

In principle, the above characteristics of the ^1H NMR spectrum of compound **I** correspond to any of the four fundamentally different conformations. However, the presence of two singlets of *tert*-butyl groups at δ 1.12 and 0.86 ppm in the upfield region of the spectrum indicate the high degree of symmetry of the molecule. Only three conformations have such symmetry: *cone*, 1,2-*alternate*, and 1,2-*alternate*'.



R = $CH_2C(O)NHPhNO_2$.

As expected, in the ^{13}C NMR spectrum there are 16 signals of the phenyl atoms. Six of these belong to the signals of similar carbon atoms of two substituted rings of the macrocycle. Also 6 signals correspond to six carbon atoms of two unsubstituted rings. In this resonance region there are also four signals of the carbon atoms of the phenyl rings of two equivalent substitutes.

Unambiguous assignment of the signals in the resonance region has been possible for the following carbon atoms: COH^9 (δ 155.06 ppm), CNO_2 (δ 150.64 ppm). The signals of the rest carbon atoms are interpreted as follows: δ 34.45 [C(*t*-Bu^1)], 31.08 [CH_3(*t*-Bu^1)], 34.31 [C(*t*-Bu^2)], 31.61 [CH_3(*t*-Bu^2)], 67.70 (CH_2^5) and 165.15 ppm (C=O). The ^{13}C NMR spectrum, as well as the ^1H NMR spectrum, indicate the high symmetry of the molecule of **I**, but it does not allow to select from the three the preferred conformation.

Theoretical calculation of the heats of formation of the different conformations of compound **I** was carried out using the PM3 method with the software Hyperchem Professional 7. The heats of formation (Table 1) and interproton distances (Table 2) for each of the conformations were calculated.

1,3-*Alternate* conformation has the lower heat of formation (Table 1), which is inconsistent with the ^1H and ^{13}C NMR spectral data on the existence of the symmetric structure. The heats of formation of two

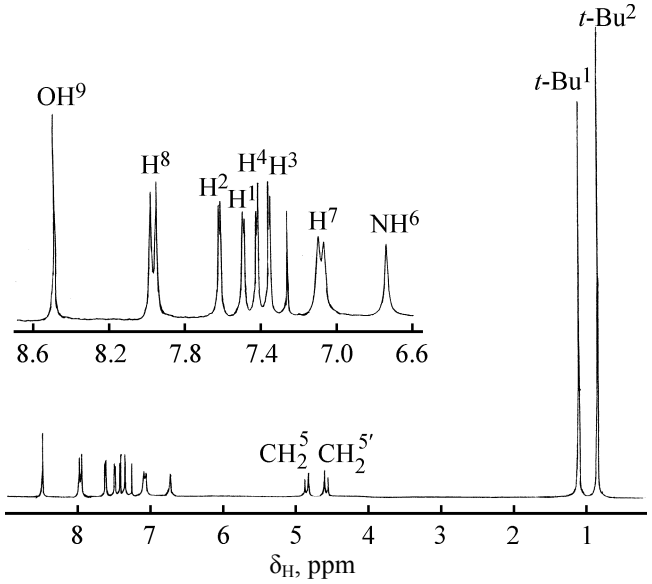


Fig. 1. The ^1H NMR spectrum of compound **I** in $CDCl_3$.

Table 1. The heats of formation of compounds **I** calculated by the PM3 method

Conformation	ΔH^0, kJ mol^{-1}
Cone	–14129.0199
Partial cone	–14126.6836
1,2-*Alternate*	–14130.8057
1,2-*Alternate*'	–14129.5894
1,3- *Alternate*	–14133.7429

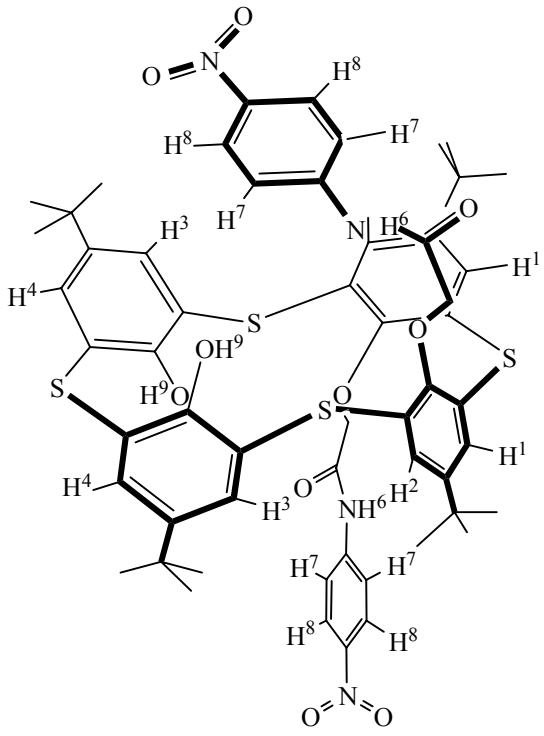
Table 2. Experimental (NOESY) and calculated (PM3) values of interproton distances (r_{ij}, Å) in compound **I**

Bond	NOESY	1,2-*Alternate*'	1,2- *Alternate*	*Cone*
OH^9–H^8	3.23	4.42	6.61	2.42
OH^9–H^2	3.73	4.82	3.27	4.86
OH^9–H^1	4.55	5.58	5.48	6.40
OH^9–H^3	4.25	4,60	4.56	4.55
OH^9–H^7	2.94	2.48	8.84	3.62
OH^9–NH^6	2.58	3.045	6.61	5.78
OH^9–CH_2^{5B}	3.38	3.23	4.76	3.35
H^8–H^2	3.31	5.87	8.04	7.81
H^8–H^1	3.21	7.96	10.15	9.52
H^8–H^3	3.87	4.52	9.32	11.15
H^7–H^8	2.45	2.45	2.45	2.45
H^2–H^1	3.29	4.30	4.29	4.29
H^2–CH_2^{5B}	3.18	4.62	4.57	4.61
H^2–H^3	3.45	1.86	5.45	2.45
H^4–H^3	3.54	4.30	4.30	4.30
H^1–NH^6	3.49	4.72	6.22	6.24
H^7–H^3	3.54	4.62	6.90	6.61
H^7–NH^6	2.32	2.34	2.39	2.33
H^4–NH^6	3.34	5.81	5.29	6.22
H^4–CH_2^{5A}	2.87	6.11	3.15	7.78
NH^6–CH_2^{5A}	3.68	2.66	2.59	2.53
NH^6–CH_2^{5B}	3.99	3.65	3.69	3.64
CH_2^{5A}–CH_2^{5B}	1.78	1.79	1.78	1.80

symmetrical 1,2-*alternate* conformations have similar values (Table 1). Therefore the next step in the study of the structure of this compound was a two-dimensional ^{1}H NMR experiment NOESY.

The NOESY spectrum of **I** in $CDCl_3$ (Fig. 2) contains twenty-three pairs of cross-peaks. The protons of the amide group NH^6 show the cross-peaks with each of methylene protons $CH_2^{5A,B}$ and aromatic protons H^7 of the substituents, as well as with the macrocycle protons H^4, H^1, OH^9. The protons CH_2^5 of the substituent show a cross-peak with each other. The protons OH^9 have seven cross-peaks: with the protons H^1, H^2, H^3 of the macrocycle and the protons H^7, H^8, NH^6 and CH_2^5 of the substituent. The protons H^1, H^2, H^3, and H^4 of the macrocycle show the cross-peaks with each other (H^2 with H^1 and H^3, H^4 with H^3), with phenyl protons of the "tail" part of the substituent (H^2 with H^8, H^1 with H^8, H^3 with H^8), with protons NH^6 of the amide group (H^1 with NH^6, H^4 with NH^6), and with the methylene protons (H^2 with CH_2^{5A}, H^4 with CH_2^{5B}). The values of the integral intensities of all the cross-peaks are negative, indicating the absence of chemical exchange effects in **I** in solutions. Thus, all the cross-peaks are due to the Overhauser's effect. The pair of aromatic protons H^7–H^8 of the substituent was chosen as a calibration pair of protons [6].

This view of the NOESY spectrum, in which there are cross-peaks of the proton NH^6 with the aromatic macrocycle protons H^1 and H^4 of the differently substituted rings (i.e., containing and not-containing the amide substituents), as well as the cross-peaks of each of the aromatic protons H^2 and H^4 of the



macrocycle with one of the protons of the methylene groups of substituents (CH_2^{5A} and CH_2^{5B}, respectively), satisfies only one conformation – 1,2-*alternate*', in which the substituents of two adjacent rings of the macrocycle have the opposite orientation relative to the macrocycle cavity.

Comparative analysis of the experimental and calculated interproton distances (Table 2) for the possible conformations of **I** showed that the best convergence of the results is also observed for the 1,2-*alternate*' conformation. However, the experimentally determined values of the distances between the aromatic protons H^1, H^2, H^3 of the macrocycle and the protons NH^6, H^7 and H^8 of the substituent were less than those calculated for this conformation. This refers largely to the distances between the H^8 proton, which is important from the point of view of the formation and identification of 1,2-*alternate*' conformation, and the protons H^1, H^2 and H^3 (Table 2). Reduced distances are likely due to the fact that the bulky substituents $OCH_2C(O)NHC_2H_4NO_2$ are turned into the macrocycle cavity, i.e., they are in the *endo*-position and quite rigidly fixed in space.

In this steric case there is a rapprochement of steric aromatic protons H^4 of the unsubstituted arene rings of the macrocycle with the protons NH^6 and CH_2^{5A} of substituents (Table 2). Inhibition of the rotation of the methylene protons $CH_2^{5A,B}$ around the C–C(O) bond, leading to their magnetic nonequivalence in the ^1H NMR spectrum (Fig. 1), is due to the steric hindrance in the molecule. Finally, a rapprochement of one of the protons H^7 of the substituent with aromatic protons of the macrocycle is also possible. It causes the corresponding broadening of the signals of H^7 in the ^1H NMR spectrum (Fig. 1). The signals of remote protons H^8 of a "tail" part, which are less sterically hindered, are narrower.

Thus, based on the analysis of the one- and two-dimensional ^1H and ^{13}C NMR spectral data and quantum-chemical calculations, it is concluded that compound **I** in solution exists in a 1,2-*alternate* conformation, where the substituents $OCH_2C(O)\cdot NHPhNO_2$ are present in the *endo*- position.

EXPERIMENTAL

The NMR spectra were recorded on a multifunctional pulsed NMR spectrometer with Fourier transform Unity-300 (Varian Associates Inc., USA) with an operating frequency of 299.94 MHz

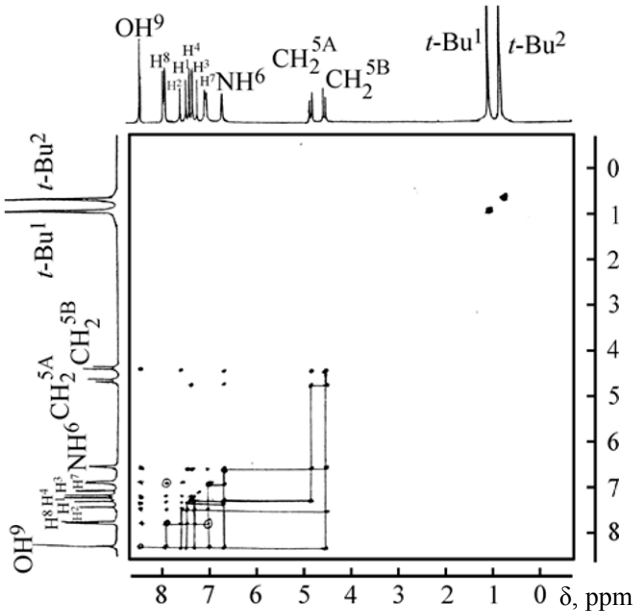


Fig. 2. The NOESY spectrum of compound **I** in $CDCl_3$. A pair of the calibration cross-peaks is encircled.

(^1H) and 75.42 MHz (^{13}C). The 1D-spectra were registered using 10°–15° pulses and 2 seconds delay between scans. The spectral width was 15 ppm, the number of accumulations was from 16 to 150 depending on the sample solubility. The ^{13}C NMR spectra were recorded with use of 30°–45° pulses and broadband decoupling of protons. The delay between scans was 0.2 sec, the spectral width 200 ppm, the number of accumulations was from 300 to 4000. The digital exponential filtering with lb = 1–3 Hz was used.

Stabilization of the magnetic field was carried out by the deuterium signals of the solvent.

When recording two-dimensional spectra, we used the pulse sequences with phase cycles to reduce the pulses calibration uncertainty. Accumulation number n_t for NOESY spectra was at least 8. The number of repetitions n_i on the time interval t_2 to obtain the second frequency axis were chosen from the relation $n_i = (sw\ 1/2)$, where sw is the width of the spectral window. The NOESY spectra were recorded with theuse of the phase-sensitive pulse sequence. When recording the NOESY spectrum, we used the Fourier transform algorithm of the linear prediction to restore the truncated FID, the weighing Gaussian function was applied as a digital filter. The FID was added with zeros to obtain the 2D-spectra of dimension of 2048× 2048 points. Algorithms to align the baseline were not

used because of possible errors in the measurement of the integral intensities of the peaks in the 2D NMR spectra.

The interproton distances were determined by a series of NOESY experiments with different mixing time (from 0.2 to 0.7 ms). Then, for each of the observed cross-peak we build its dependence of the integral intensity of the mixing time. The resulting dependence was approximated to calculate the slope. This angle or the rate of change of the nuclear Overhauser effect is directly related to the distance between the interacting nuclei. The distances between the relaxing nuclei were calculated from the relation $r_i = r_k \cdot (\delta_k/\delta_{ij})$, where r_{ij} is the distance between the relaxing nuclei, r_k is the distance between the calibration pair of the protons, δ_k is the rate of change of the intensity of calibration cross-peak, δ_{ij} is the rate of change of the intensity of the analyzed cross-peak.

Theoretical calculation of energy (heat of formation) of compound **I** was carried out within the semi-empirical approach using the software GAUSSIAN-03 (PM3 method).

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis[*N*-(4'-nitrophenyl)aminocarbonylmethoxy]thiacalix[4]arene **I** was synthesized at the Department of Organic Chemistry, Kazan State University [7].

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