CONFORMATIONAL ANALYSIS OF BENZO-15-CROWN-5 AND 2,3-(4'-BENZOYL)BENZO-15-CROWN-5

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The ability of macrocyclic polyethers to form stable complexes with various metals is finding broad applications in many different fields of application [1]. Deserving attention in this respect is the membranotropic activity of macrocyclic derivatives, which leads to the possibility of obtaining psychotropic and cardiotropic substances [2, 3]. Thus, benzo-crown-ethers manifest significant psychotropic properties [4]. A substantial factor in determining the effects on biological properties is the size of the macrocycle and the nature of the substituents on the benzene ring.

In the work reported here, we carried out a detailed conformational analysis of two benzo-crown-ethers that manifest different physiological properties – benzo-15-crown-5 (B15C5) and 2,3-(4'-benzoyl)benzo-15-crown-5 (BB15C5) – in the crystalline state and in solutions with different polarities. Also, an evaluation has been made of the character of conformational changes in these two macrocycles when they form complexes with calcium [5]. The studies were performed by a combination of x-ray structure analysis (XSA), IR spectroscopy, and conformational calculations within the framework of a mechanical model [6].

EXPERIMENTAL

2,3(4'-Benzoyl)benzo-15-crown-5. A solution of 2 g of B15C5 and 0.8 g of $(PHCO)_2O$ in 40 g of polyphosphoric acid (obtained at 60°C) was heated with mixing for 3 h at 70°C. The mixture was then decomposed with water and extracted with ether. The BB15C5 was purified by recrystallization from diethyl ether. Obtained 2.1 g, mp 104-106°C.

The BB15C5 was obtained in the form of transparent, yellow crystals, random in form; the elementary cell constants were determined by means of a retrograph camera and refined in a DRON-1 diffractometer on CuK_α radiation: $a = 15.75$, $b = 8.21$, $c = 8.31$ Å, $\alpha = 112.7$, $\beta = 105.9$, $\gamma = 77.8°$. The structure was determined by the direct method and refined using Rentgen-75 programs [7]. All nonhydrogen atoms were localized. The IR spectra were recorded in an IFS-113V Fourier transform spectrometer with a resolution of 1 cm^{-1}, over a range from 50 to 4000 cm^{-1}. The crystalline substances were prepared as suspensions in white mineral oil and as solutions in CCl_4, $CHCl_3$, Me_2CO, and MeCN (light path 0.1-1.0 mm, KBr cuvettes). The wavenumber calibration was performed on the basis of a helium–neon laser, with an accuracy of 0.1 cm^{-1}. The positions of the absorption bands were determined from the absorption maxima in the spectra, expressed in digital form with a reproducibility of 0.5 cm^{-1}.

The conformational calculations were performed using the MM-2 program [6] in the parametrization of [8]. The program was preadapted to a Nord-10 computer. It is indicated in [8] that there is no possibility of any accurate description of the torsion component U_{tors} in the strain energy function of a molecule U_{ms} for rotation around a C_{sp^2}–O bond. This reflects the ambiguity of the available experimental data. For example, in the case of p-fluoromethoxybenzene, experiments based on Kerr constants and dipole moments indicate a planar structure. At the same time, studies performed by microwave spectroscopy and electron diffraction indicate a planar conformation.* Moreover, the difference in values obtained for the energy of the barrier to rotation as obtained for this substance by differ-

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*As in Russian original – Translator.

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TABLE 1. Experimental and Calculated Values of Dihedral Angle (φ_n (n = 1-15), deg] of Macrocycles in Benzo-15-crown-5 and 2,3-(4'-Benzoyl)benzo-15-crown-5, Strain Energy (ΣU, kcal/mole), and Dipole Moment (μ, D) of Possible Structures

n	Benzo-15-crown-5						
	experiment	calculation					
		conformation of macrocycle					
		(I)	(II)	(III)	(IV)	(V)	(VI)
1	167	165	154	−160	163	−115	−160
2	0	0	0	3	0	4	−4
3	−166	−166	−159	−89	−156	163	105
4	171	171	170	167	172	−166	−164
5	−71	−69	−62	−68	−51	66	67
6	167	165	174	175	−76	−171	−154
7	−85	−85	−169	180	−170	173	168
8	−66	−62	63	66	−77	−60	−53
9	168	178	−168	−164	92	167	−173
10	−171	180	171	77	178	−170	−167
11	72	63	−63	53	70	84	98
12	81	87	169	−173	107	−81	−70
13	−163	−164	−175	176	−162	−82	−79
14	70	69	62	−60	75	167	93
15	−170	−171	−168	178	−162	61	170
μ	–	2,5	0,9	2,9	1,2	2,4	1,9
U_{ms}	–	33,0	32,6	30,5	30,9	30,1	30,3
U_{tors}	–	−0,1	−2,0	2,4	2,7	4,0	5.6

n	2,3-(4'-Benzoyl)benzo-15-crown-5						
	experiment	calculation					
		conformation of macrocycle					
		(I)	(II)	(III)	(IV)	(V)	(VI)
1	165	169	165	175	167	−146	−166
2	3	−1	0	4	0	1	−4
3	−170	−159	−150	93	−160	135	96
4	179	165	172	166	171	−145	−163
5	−51	−71	−61	−68	−51	70	68
6	−64	166	173	175	−63	−172	−150
7	−179	−87	−168	179	−171	−177	170
8	−78	−63	63	66	−82	−63	−53
9	89	178	−170	−164	87	170	−175
10	171	−179	171	77	176	−175	−166
11	76	62	−63	52	71	87	96
12	95	86	169	−171	100	−66	−72
13	−155	−164	−174	176	−157	−73	−75
14	75	70	61	−59	78	161	98
15	−164	−170	−170	179	−162	63	176
μ	–	3,0	2,5	4.5	1,5	4.3	4,1
U_{ms}	–	46.8	47,0	44,1	47,1	46,0	46,4
U_{tors}	–	6,7	4,0	8,9	8,8	9,8	9,9

ent methods (IR, Raman, electron diffraction) amounts to 3.0 kcal/mole. In this connection, the accuracy in estimating the barrier to rotation around a C_{sp^2}—O bond is no better than ±1 kcal/mole. Therefore, U_{ms} is listed in Table 1 without accounting for U_{tors}; the contribution of U_{tors} is listed separately, and will not be included in the subsequent discussion.

RESULTS AND DISCUSSION

The presence of 15 axes of internal rotation in the B15C5 and 17 axes in the BB15C5 (Fig. 1) indicates great conformational mobility of these molecules. Even if we restrict our examination to the structure of the macrocycle in which the COCCOC unit has trans-gauche-trans (TGT) and trans-gauche-gauche (TGG) conformations, stabilized in crystalline B15C5 and in various complexes of this compound [9-11], we will need to consider several tens of structures. Under these conditions, it is necessary to arrive at some reasonable limitation of the number of possible variants to be considered. In the present work, we used for such a procedure conformational calculations within the framework of a mechanical model. Using as the zero approximation structures with "classical" dihedral angles (60° and 180°), we calculated these structures, with subsequent optimization of bond lengths, bond angles, and dihedral angles. As a result of these calculations, we established that it is actually

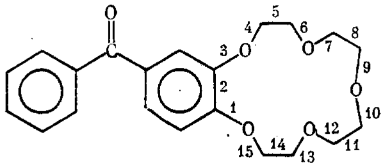

Fig. 1. Axes of internal rotation φ_n (n = 1-15) in B15C5 and BB15C5.

necessary to consider only six structures of the molecules of B15C5 and BB15C5 with different sets of dihedral angles. The other structures are considerably overloaded in energy and can be eliminated from consideration.

In Table 1 we have listed calculated values of the dihedral angle of the macrocycles φ_1-φ_{15} in the six indicated structures (I)-(VI), as well as values of the strain energy in the molecule U_{ms} and the molecular dipole moment μ of these structures. Also included in Table 1 are data on the molecular structure of B15C5 [9] and BB15C5 in the crystalline phase, obtained in the present work by x-ray structure analysis (XSA).

A comparison of the experimental XSA data shows that, in the crystal state, the conformational state of the macrocycles in B15C5 differ substantially from that in BB15C5. The main difference is related to the realization, in the BB15C5, of not two TGT conformations and two TGG conformations, but rather a single TGT conformation, two TGG conformations, and one TGG' conformation (the conformation of the COCCOC fragment with $\varphi_7 - \varphi_9$ differs from the traditional TGG in rotations in different directions). In general form, the structures that are realized in the crystal phase correspond to the calculated conformers (I) for B15C5 and (IV) for BB15C5.

In order to judge the conformational state of B15C5 and BB15C5 in solution, we used IR spectroscopy with a detailed examination of the 1050-1300 $\mathrm{cm^{-1}}$ region. Within this interval of wavenumbers, symmetric and antisymmetric stretching vibrations of C—O—C (ν_s and ν_{as}) are realized. Here it was established that the ν_{as}C—O—C vibrations are extremely sensitive to the conformational state of the COCCOC fragments, while they are affected hardly at all by the phase state of the ligand or by complexation of the ligand with various metal salts [12-14]. In Fig. 2 we show IR spectra of B15C5 and BB15C5 in the crystal state (spectra *a* and *a'*), in CCl_4 solutions (spectra b and b'), and in MeCN solutions (spectra c and c'), as well as solutions of B15C5 and BB15C5 together with $Ca(NCS)_2 \cdot 2H_2O$ in MeCN (spectra d and d'). We also obtained and examined spectra of crystalline complexes of B15C5 and BB15C5 with $Ca(NCS)_2$ (spectra e and e').

According to the XSA data on the B15C5 in the crystalline phase, the structure that is stabilized is that in which, apart from the trans-cis-trans conformation of the $COC_{ap}C_{ap}OC$ fragment, two COCCOC units have the TGT conformation and two units have the TGG conformatin [9]. In the IR spectra of crystalline B15C5 in the 1100-1200 $\mathrm{cm^{-1}}$ region, there are two significant absorption bands with maxima at 1108 and 1121 $\mathrm{cm^{-1}}$; according to the data of [12-14], these can be assigned to ν_{as}COC vibrations in COCCOC fragments with TGT and TGG conformations, respectively. In the IR spectrum of crystalline BB15C5 in the 1100-1200 $\mathrm{cm^{-1}}$ region, the most intense absorption band is observed at 1130 $\mathrm{cm^{-1}}$. We can assume that this band corresponds to the ν_{as}COC vibration in the TGG' conformation, which exists in the crystal phase according to the XSA data.

Passage of these ligands into the dissolved state is accompanied by substantial changes in the spectra. For example, in CCl_4, for both the B15C5 and BB15C5, the 1100-1200 $\mathrm{cm^{-1}}$ region exhibits three bands with maxima at 1137, 1130, and 1110 $\mathrm{cm^{-1}}$. The third band corresponds to the TGT conformer of the COCCOC unit. The low intensity of this band may be regarded as evidence that this conformation is not predominant for the COCCOC units of the macrocycles in B15C5 and BB15C5 dissolved in CCl_4. The first two bands are quite intense. The relative intensities of these two bands change considerably upon going from B15C5 to BB15C5: In the B15C5, the second band is much stronger than the first, whereas in the BB15C5, the second band appears as a shoulder on an intense first band. The positions of these two bands enable us to assign the absorption at 1137 $\mathrm{cm^{-1}}$ to ν_{as}COC in the TGG' conformer of the COCCOC fragment, and the absorption at 1130 $\mathrm{cm^{-1}}$ to the same type of vibration in the TGG conformer. The slight shift in maxima of these bands toward higher wavenumbers when the change is made from solid phase to solution can be attributed to the influence of the crystalline phase. The difference in relative intensities of these bands in the spectra of B15C5 and BB15C5 indicates differing contributions of the TGG and TGG' conformations to the conformational state of the macrocycles of these ligands. According to the results of calculations presented in Table 1, out of the possible structures (I)-(VI), the TGG' conformation

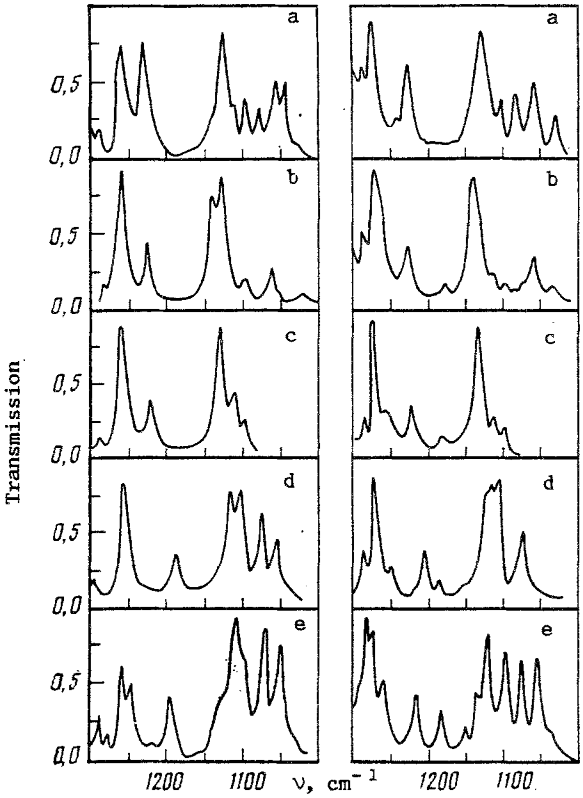

Fig. 2. IR spectra of B15C5 (a-d) and BB15C5 (a'-d') in crystalline state (a, a'), in CCl_4 solution (b, b'), in MeCN solution (c, c') and in MeCN solution with added $Ca(NCS)_2 \cdot 2H_2O$ (d, d'), and crystalline complexes of B15C5 and $Ca(NCS)_2 \cdot 2H_2O$ (e) and BB15C5 and $Ca(NCS)_2 \cdot 2H_2O$ (e').

is represented in structures (IV)-(VI) and the TGG conformation in structures (I) and (III); this suggests that an quilibrium of structures from these two groups is realized in CCl_4 solution. In view of the substantial differences in dipole moment for structures (IV)-(VI), selection among these structures can be facilitated by examining the spectra of B15C5 and BB15C5 in media with various polarities. A comparison of the spectra of these ligands in CCl_4 (Fig. 2, spectra b and b'), MeCN (c and c'), $CHCl_3$ and Me_2CO shows that the relative intensities of the bands with maxima at 1137 and 1130 cm^{-1} are considerably redistributed in favor of the lower-frequency bands as the dielectric constant of the medium increases. Such behavior is characteristic for structures differing widely in dipole moment. The structures (I) and (III), and also (V) and (VI), differ only slightly in polarity, but are conisiderably more polar than the structure (IV). This suggests that one of the partners in the equilibrium in CCl_4 solutions, both for B15C5 and BB15C5, is structure (IV), which has a relatively low dipole moment. The second partner in the equilibrium in a nonpolar medium may be the structure (I) or (III). In MeCN solutions, there are no spectral indications of structure (IV). The similarity of spectra of MeCN solutions of B15C5 and BB15C5 to the spectra of crystalline B15C5 suggests that in this polar medium, the predominant structure is (I).

The addition of $Ca(NCS)_2$ to solutions of B15C5 and BB15C5 is accompanied by substantial spectral changes as a result of complexation. In the 1000-1300 cm^{-1} region, changes take place not only with the ν_{as}COC bands, but also with ν_{as}C—O—C$_{ap}$. According to [14], the first type of vibration can be used to judge the conformational state of the COCCOC fragments, and the second to establish the fact of complexation. In Fig. 2 (d, d'), we show spectra of solutions of B15C5 and BB15C5 in MeCN with the addition of $Ca(NCS)_2$ up to complete disappearance of the bands with maxima at 1220 cm^{-1}, assigned to ν_{as}C—O—C$_{ap}$ vibrations of the free ligands. Thereby we obtain spectra of solutions of the undissociated complexes of B15C5 and BB15C5 in MeCN. The character of absorption by these complexes in MeCN in the region of manifestation of ν_{as}COC was considerably different from that exhibited in the spectra of B15C5 and BB15C5 in this solvent. Here we must note first of all the substantial increase in absorption intensity in the 1100-1110 cm^{-1} region. It is in this precise interval that $\nu_{as}COC$ is manifested in the TGT conformation. Also, in place of absorption at 1130 cm^{-1}, we observe bands at 1110-1120 and 1120-1125 cm^{-1} in the spectra of solutions of B15C5 and BB15C5 complexes in MeCN. A most striking fact is that the ratio of intensities of all three bands in the 1100-1125 cm^{-1} region changes upon variation of ligand and salt concentrations, even after the $\nu_{as}C{-}O{-}C$ bands of the free ligands have disappeared. These facts can be regarded as spectral confirmation of the existence of complexes in such systems with metal/ligand ratios of 1/1 and 1/2, as established by titration [15]. As regards the conformational state of the ligand in these complexes, according to the spectra that have been obtained, we can asssume on the basis of the intense bands in the 1100-1110 cm^{-1} region that TGT conformations of the COCCOC fragments make a large contribution to the structure. The structure (III) has such properties. The new bands in the 1110-1120 and 1120-1125 cm^{-1} regions, which are absent in the spectra of B15C5 and BB15C5, either in the crystalline state or in solution, are probably related to structures of ligands that are not included in Table 1, structures that have considerably greater strain energies

In Fig. 2 (e, e') we show spectra of crystalline complexes of B15C5 and BB15C5 with $Ca(NCS)_2$. As regards the spectra of the B15C5 complex, they are entirely consistent with the available x-ray structure data [16] with respect to stabilization of the 1/1 complex, in which the ligand has the structure of the macrocycle (III). The basically different spectra of the isolated crystalline complexes of B15C5 and BB15C5 poses the question of nonsimilarity of structures of these complexes (all the way to a difference in composition and conformational state of the macrocycles). Since spectral differences in the crystal phase may be occasioned by various factors, the question of structure of the BB15C5 complex with $Ca(NCS)_2$ will best be discussed separately, following x-ray structure analysis of its single crystals.

CONCLUSIONS

1. An x-ray structure analysis has revealed substantial diferrences in the conformational states of 2,3-(4'-benzoyl)benzo-15-crown-5 and benzo-15-crown-5 in the crystal phase, differences related to realization of a trans-gauche-gauche' conformation in one COCCOC fragment in the 2,3-(4'-benzoyl)benzo-15-crown-5.

2. In nonpolar solvents, an equilibrium of several structures is realized in both compounds, an equilibrium with the participation of trans-gauche-trans, trans-gauche-gauche and trans-gauche-gauche' conformations. In a polar medium, there are no indications of the trans-gauch-gauche' conformation.

3. Upon complexation of the ligands with calcium thiocyanate in acetonitrile, there are spectral indications of complexes with differing stoichiometry, with a large contribution of the structure from trans-gauche-trans conformations.

LITERATURE CITED

1. M. Hiraoka, Crown Compounds: Their Characteristics and Applications, Elsevier, New York (1982).
2. N. V. Lukoyanov, O. A. Raevskii, A. S. Shtepanek, and T. N. Kudrya, Biol. Membrany, 1, 379 (1984).
3. N. V. Lukoyanov, G. I. Van'kin, L. V. Zhuravleva, et al., Biol. Membrany, 2, 71 (1985).
4. N. V. Lukoyanov, (Likojanov), G. I. Vankin, V. A. Panarin, and O. A. Raevskii (Raevsky), Proceedings of 11th International Symposium on Macrocyclic Chemistry, Florence (1986), p. 63.
5. M. N. Hughes, The Inorganic Chemistry of Biological Processes, Wiley-Interscience, New York (1981).
6. U. Burkert and N. L. Allinger (eds.), Molecular Mechanics, American Chemical Society, Washington, D.C. (1982).
7. V. I. Andrianov, Z. Sh. Safina, and E. L. Tarnopol'skii, Instructions for Operation with Rentgen-75 Program [in Russian], OIKhF Akad. Nauk SSSR, Chernogolovka (1975).
8. H. Dodziuk, H. von Voithenberg, and N. C. Allindger, Tetrahedron, 38, 2811 (1982); H. D. Beckhaus, Chem. Ber., 116, 86 (1983).
9. I N. Hanson, Acta Crystallogr. B, 34, 1026 (1978).
10. M. A. Buch and M. R. Truter, J. Chem. Soc., Perkin Trans. 2, 341 (1972).
11. P. R. Mallinson and M. R. Truter, J. Chem. Soc., Perkin Trans. 2, 1818 (1972).
12. J. Ogava, M. Ohta, M. Sakaribara, et al., Bull. Chem. Soc. Jpn., 50, 650 (1977); H. Matsuura and T. Miyazzawa, J. Chem. Soc., Perkin Trans. 2, 41, 1798 (1968).

13. M. Fouassier and J. S. Lasseques, J. Chem. Phys., 75, 865 (1978).
14. O. A. Raevskii, S. V. Trepalin, V. E. Zubareva, and D. G. Batyr, Izv. Akad. Nauk SSSR, Ser. Khim., No. 7, 1574 (1985).
15. R. M. Izatt, J. S. Bradshaw, A. S. Nielson, et al., Chem. Rev., 85, 271 (1985).
16. J. D. Owen, J. Chem. Soc., Dalton Trans., 1418 (1978).

CONFORMATIONAL STUDY OF SOME α-AMINOKETONES

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Conformational studies of α-aminoketones have comprised mainly the determination of the mutual orientation of the C—N and C=O bonds by IR spectroscopy, involving the resolution of the absorption band of the carbonyl group [1]. Quantum-mechanical calculations on aminoacetaldehyde have shown that the global energy minimum corresponds to a configuration with the C—N and C=O bonds eclipsed and an anti orientation of the C—C bond and the unshared pair on the nitrogen [2]. The adoption of this form does not depend on the release of energy on account of the formation of a hydrogen bond. In this connection it is of interest to establish the conformational structure of α-aminoketones, which have a fully substituted nitrogen atom. We have therefore carried out a structural investigation of α-N-morpholyl acetone (I), α-N-piperidylacetone (II), α-N-dimethylaminocyclohexanone (III), α-N-piperidylcyclohexanone (IV), and α-N-morpholylcyclohexanone (V), using dipole moments (DM) and the Kerr effect, together with IR spectroscopic data.

The conformation of α-aminoketones is determined by two torsional angles about the bonds C—C(O) and C—N, and also by the axial or equatorial orientation of the acyl moiety in the amine ring. In describing the conformational state of a molecule we have used the first index to define rotation about the bond C—C(O), i.e., the conformation of the carbonyl group relative to the C—N bond: syn-periplanar (sp) when they are eclipsed (in compounds (III)–(V) this corresponds to an equatorial orientation of the C—N bond in the cyclohexanone ring) and anticlinal (ac) when the carbonyl group and the C—H bond are eclipsed (for compounds (III)-(V) this is equivalent to an axial orientation of the C—N bond in the cyclohexanone ring) (see Fig. 1). The second index refers to rotation about the C—N bond, i.e., the conformation of the acyl moiety relative to the unshared pair of the nitrogen. The index T indicates their mutual trans position. The index G refers to the orientation of the unshared pair of nitrogen and the C=O group on the same side of the plane of the bonds C—C—N, and the index G' to the orientation on different sides of the same plane. For syn-periplanar orientation about the C—C(O) bond in the aminoketones (I) and (II) the positions G and G' are energetically degenerate on account of the formation of a dℓ pair. In the aminocyclohexanones there is no degeneracy, and the positions G and G' differ in the orientation of the unshared pair: between the C—C and C—H bonds in the first case and between the C—C bonds of the cyclohexanone ring in the second.

The theoretical calculation of the dipole moments and of the Kerr constants employed an additive scheme with the parameters given in Table 1. Analysis of the calculated values showed that the axial or equatorial orientation of the acyl moiety in the amine ring is reflected only in the Kerr constant (Table 2). For the calculated values these orientationn are denoted by a third index a or e.

In order to exclude from consideration sterically unrealistic structures we modelled the steric situations by molecular mechanics, without optimizing the geometry and without allowing for electrostatic energy. The conformers ac-T-e and ac-T-a in which the acyl fragment is oriented with its methyl group inside the six-membered ring, were found to be less stable by more than 100 kcal mole^{-1} than the corresponding gauche forms for all values of the torsional angle corresponding to the ac form (90-180°). This means that it is quite safe to exclude them from consideration when analyzing the experimental data. Conformers with smaller energy differences were not excluded from the analysis.

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