DFT calculation of benzoazacrown ethers and their complexes with calcium perchlorate

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The complexation constants of several azacrown ethers with $Ca(ClO_4)_2$ were determined and turned out to be the higher, the large the macrocycle. The structures of free ligands and their complexes and the complexation energies were calculated by the DFT method. In the aza-12(15)-crown-4(5) ether complexes with $Ca(ClO_4)_2$, the metal cations lie outside the averaged plane of heteroatoms of the macrocycle, and the coordination of both counterions is V-like. In the complexes of aza-18-crown-6 ethers, the counterions are in the axial position relatively to the macrocycle in the center of which the Ca^{2+} ion is localized. The complexation energies increase with an increase in the size of the azacrown ether macrocycle. The involvement of the nitrogen atom in binding with the Ca^{2+} ion decreases with the expansion of the macrocycle. Two methods for quantitative estimation of the degree of pre-organization of ligands to complexation were considered: geometric and energetic methods. Benzoaza-15-crown-5 ether is a ligand which is more pre-organized to complexation than *N*-phenylaza-15-crown-5 ether.

Key words: benzoazacrown ethers, complexation, complexes with calcium perchlorate, quantum-chemical calculations, density functional theory.

Crown compounds are characterized by the pronounced ability to selective binding metal ions, organic cations, and neutral molecules. This ability forms a basis for the use of crown compounds as selective polydentate ligands for metal cations,[1,2] including fluorescent and photochromic ligands,[3—8] for extraction and separation of metal cations,[9,10] in ion transport through membranes, in ion-selective electrodes,[11] as phase transfer catalysts and synzymes simulating enzymatic activity,[12] *etc*. Presently, researchers are continuing an intensive search for new types of crown compounds capable of efficient and selective complexation in different media. Crown compounds containing the O and N atoms in the macrocycle are of permanent interest.[13,14] By their complexation ability, these compounds are intermediate between crown ethers, which strongly bind alkaline and alkaline-earth metals, and cyclames that form strong complexes with transition and heavy metal ions. Systems in which the nitrogen atom is conjugated with the chromophore, in particular, phenylazacrown ethers and 1-aza-2,3-benzocrown ethers, are of special interest from the viewpoint of using fragments of azacrown compounds in photosensitive ligands. 1-Aza-2,3-benzocrown ethers represent an almost unstudied but, in our opinion, very promising type of crown ethers, whose most functional derivatives are poorly accessible despite of their simple structures.[15—18] Published data on their complexation are virtually lacking. Our new approach developed for the synthesis of formyl derivatives of benzoazacrown ethers **1a—c** and **2a—c** [19,20] made it possible to study the specific features of their complexation by both experimental and theoretical methods.

In this work we determined the complexation constants (K_1) of formylbenzoazacrown ethers **1a—c** and **2a—c** and *N*-(phenylformyl)aza-15-crown-5 ether (**3**) as a reference compound with $Ca(ClO_4)_2$ and performed quantum-chemical calculations of the geometric and electronic structures and complexation energies (E_{compl}) of azacrown ethers **1a—c**, **2a—c**, and **3** and their complexes with the Ca^{2+} cation and one or two counterions. The purpose of the calculations is to determine the influence of the macrocycle size, number of counterions linked with the cations, and replacement of the H atom at the N atom by the methyl group on the complexation energy. A special attention was given to the elucidation of the role of pre-organization of the macrocycle to complexation*

* The ligand, whose coordination with a metal ion is accompanied by minimum structural changes, is considered pre-organized.

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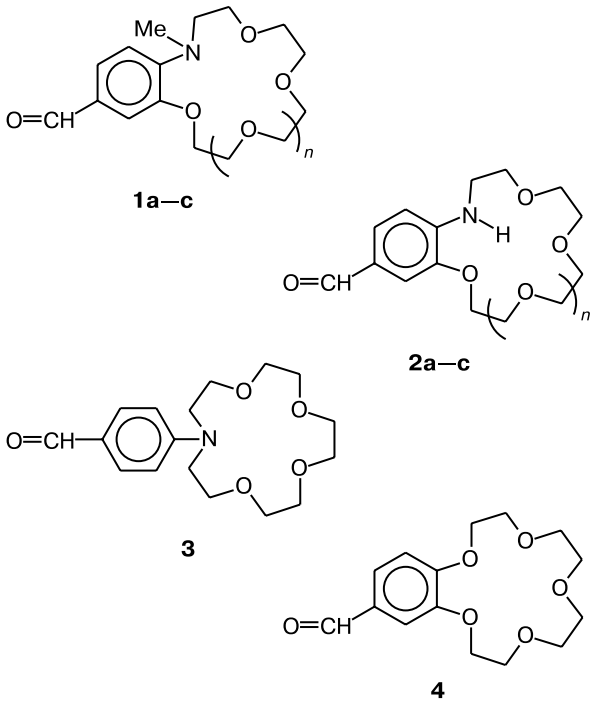


1, 2: n = 0 (**a**), 1 (**b**), 2 (**c**)

as a driving force resulting in relatively high complexation constants of compounds **1a—c** compared to that of compound **3**. In addition, the dependence of the degree of charge transfer on the macrocycle size and number of counterions at the Ca^{2+} ion was observed.

Results and Discussion

Complexation constants. To obtain quantitative characteristics for binding of benzoazacrown ethers **1** and **2** with Ca^{2+} ions, we measured the stability constants of the complexes in CD_3CN using the ^1H NMR titration method (the titration procedure will be described in detail elsewhere). The stability constants of the 15-crown-5 ether complex **3**, which, as complexes **1b** and **2b**, contains the N atom in the macrocycle but the phenylformyl substituent is at the N atom, and compound **4** were determined under the same conditions for comparison. In all cases except compound **1b**, the dependences found for changes in chemical shifts ($\Delta\delta_H$) of protons of the crown ethers on the amount of added $Ca(ClO_4)_2$ corresponded to the formation of the 1 : 1 complex

$$L + Ca^{2+} \overset{K_1}{\rightleftharpoons} [L \cdot Ca]^{2+}, \qquad (1)$$

where L is crown ether, and K_1/mol^{-1} is the stability constant of the 1 : 1 complex. For compound **1b**, the experimental plots corresponded to the 1 : 1 complexes

Table 1. Stability constants (K_1) of the complexes of crown ethers **1a—c**, **2a—c**, **3**, and **4** with $Ca(ClO_4)_2$*

Ligand	$\log(K_1/mol^{-1})$	Ligand	$\log(K_1/mol^{-1})$
1a	2.1±0.1	**2a**	1.0±0.1
1b	4.8±0.4,	**2b**	2.0±0.1
	4.7±0.3**	**2c**	4.1±0.2
1c	>5,	**3**	2.4±0.1
	6.8±0.6**	**4**	3.8±0.1

* In CD_3CN at 30 °C.
** From the competitive ^1H NMR titration with compound **4**.

1b·Ca^{2+} with the K_1 complexation constant (Eq. (1)) and the 2 : 1 complexes

$$[\mathbf{1b} \cdot Ca]^{2+} + \mathbf{1b} \overset{K_2}{\rightleftharpoons} [(\mathbf{1b})_2 \cdot Ca]^{2+}, \qquad (2)$$

where K_2/mol^{-1} is the stability constant of the 2 : 1 complex ($\log K_2 = 2.3 \pm 0.3$). The K_1 and K_2 constants were calculated by the HYPNMR program.[21] The results of calculations are presented in Table 1.

In the case of benzoazacrown ethers **1b,c**, the K_1 values are close or exceed the upper threshold of applicability of the direct method of ^1H NMR titration. For more exact determination of the constants, we carried out the competitive ^1H NMR titration of the complexes of these compounds with $Ca(ClO_4)_2$, using compound **4** with the known (from direct titration) K_1 constant as a competitor. The stability constants found for the complexes increase with an increase in the macrocycle size in the homological series of benzoazacrown ethers **1a—c** and **2a—c**, and *N*-methyl derivatives **1a—c** are much more strongly linked with the Ca^{2+} ions than benzoazacrown ethers **2a—c** with the same size. In our opinion, the differences in constants depend on the degree of participation of a lone electron pair (LEP) of the N atom in cation binding. For example, as compared to compounds **2b** and **3** providing, possibly, the maximum conjugation of the LEP of the N atom with the π-system of the benzene ring and, hence, the minimum participation of the LEP in binding, the stability constants in compound **1b** increase by 500 and 200 times, respectively. This fact can be explained by an increase in accessibility of the LEP of the N atom for the formation of a coordination bond with the metal cation due to a decrease in the LEP conjugation with the benzene ring in crown ethers **1a—c**. It should be noted that, being in the 1 : 1 complex, compound **1b** binds the Ca^{2+} ions by an order of magnitude more strongly even compared with its oxygen analog **4**, indicating a high electron-donating ability of the N atom in compound **1b** and, perhaps, the better pre-organization of the macrocycle in this compound to complexation (see below).

Calculation method. The conformers of azacrown ethers **1a—c**, **2a—c**, and **3**, the structures of their com-

plexes with $Ca(ClO_4)_2$ and $Ca(ClO_4)^+$, and the complexation energies were calculated using the density functional theory (DFT) by the PRIRODA program (version 110),[22] the Perdew—Burke—Ernzerhof (PBE) functional,[23] and the three-exponent basis set of Gaussian functions specially optimized for DFT calculations.[24] The PBE functional has no empirical parameters and reliably predicts the equilibrium geometry, bond energies, and vibrational frequencies.[25] The geometry was completely optimized for all compounds, and corrections to zero-point energies (ZPE) were calculated in the harmonic approximation. All structures discussed for free crown ethers, calcium cations with one and two perchlorate ions, and their complexes correspond to local minima in the potential energy surface, because they have 3N-6 real vibrational frequencies. The complexation energies (E_{compl}) were calculated, taking into account ZPE, as heats of reaction (3).

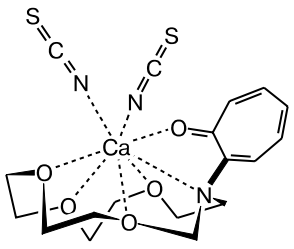
$$E_0(\text{crown}) + E_0(Ca(ClO_4)_n) \rightleftharpoons E_0(\text{complex})$$

$$E_0 = E_{tot} + \text{ZPE} \qquad (3)$$

$n = 1, 2$

Note that all E_{tot} and E_0 values are negative. According to the calculation, the formation of all complexes is energetically favorable and, hence, E_{compl} is negative.

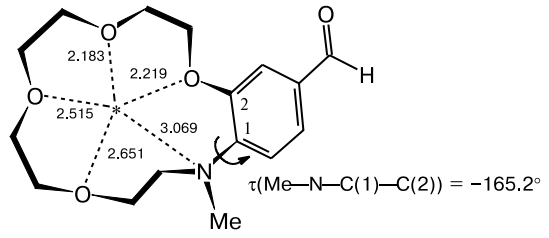
Calculation of the model compound. Calcium complex **5**, whose structure was determined by X-ray diffraction analysis,[26] was calculated as a model system.



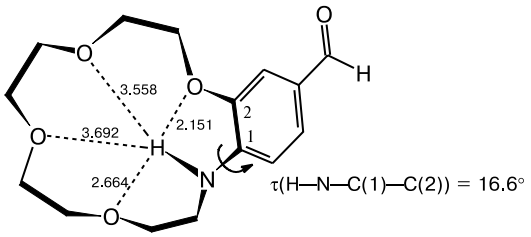
5

In this complex, the calcium ion does not go in the cavity of the 15-membered macrocycle and is localized outside the averaged plane of heteroatoms to form short contacts with the O and N atoms of the macrocycle, and two SCN^- ions acting as counterions are coordinated with calcium to form the V-like configuration. The calculation of the model system **5** showed that the DFT/PBE method reflects correctly the specific features of binding of the calcium ion with the aza-15-crown-5 derivative in the presence of two anions.

Structure of macrocycles. The results of calculations of the structures of macrocycles **1a** and **2c** agree with those obtained by X-ray diffraction analysis.[27] The theoretical and experimental $C_{Ar}—C_{Ar}$ bond lengths of the



1b



2b

Fig. 1. Structures of benzoazacrown ethers **1b** and **2b** calculated by the DFT/PBE method. The geometric center of the macrocycle is marked by asterisk (**1b**), and the distances to the H atom are presented for structure **2b**.

aromatic cycles included into the macrocycles correlate as follows: in **1a**, $r(C_{Ar}—C_{Ar}) = 1.422$ Å (experiment) and 1.443 Å (calculation); in **2c**, $r(C_{Ar}—C_{Ar}) = 1.435$ Å (experiment) and 1.434 Å (calculation). The torsion angles are rather close and show that the LEP of the N atom is not virtually involved in the conjugation with the aromatic ring and, therefore, can form a coordination bond. For example, in **1a**, the $C_{Ar}—C_{Ar}—N—C_{macrocycle}$ angle is −139.7° (experiment) and −152.8° (calculation); in **2c**, the $C_{Ar}—C_{Ar}—N—C_{macrocycle}$ angle is −139.0° (experiment) and −127.8° (calculation). If the LEP of the N atom was conjugated with the aromatic ring, then this angle would be close to 180°. The calculated spatial structures of formylbenzoazacrown ethers **1b** and **2b** are presented in Fig. 1.

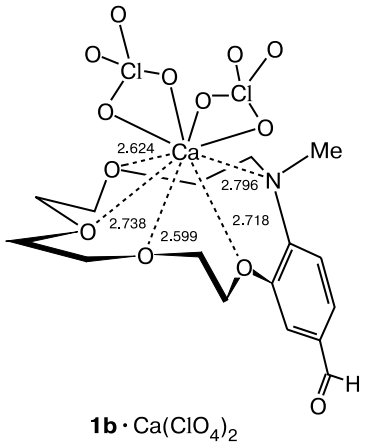
In both series (**1a—c** and **2a—c**), the cavity size, which is characterized by the distance from the geometric center of the macrocycle to the heteroatoms, increases. In addition, crown ethers containing the Me group at the N atom differ from those containing no such a group by the cavity size: for example, in **1b** the size of the cavity is 2.527 Å, whereas in **2b** it is 2.511 Å. In structure **2b**, the conformation of the macrocycle favors the efficient conjugation of the LEP of the N atom with the aromatic ring. This is a direct consequence from the insertion of the rigid aromatic ring into the macrocycle.

Structures **1c** and **2c** resemble each other to a greater extent than structures **1b** and **2b**. In molecule **1c**, the angle between the C—N bond of the Me group and the average plane of heteroatoms of the macrocycle is equal

to ~65°, and the angle between the plane of the aromatic ring and the average plane of heteroatoms of the macrocycle is 153.7°. In structure **2c**, the angle between the N—H bond and the average plane of heteroatoms of the macrocycle is ~75°, and the angle between the plane of the aromatic ring and the average plane of heteroatoms of the macrocycle is 145.1°. The sizes of the cavities also differ slightly. For example, the average distance from the geometric center to heteroatoms in molecule **1c** is 2.504 Å, and that in molecule **2c** is 2.526 Å.

Structures of the complexes. The calculated structures of the calcium complexes of benzoazacrown ethers **1b** and **2b** are presented in Fig. 2.

Considering the complexes of benzoaza-15-crown-5 ethers **1b** and **2b**, one can see that the calcium cation is localized in the vertex of a distorted pyramid, whose base is the averaged plane passing through the O and N atoms of the macrocycle, and the arrangement of two perchlorate anions above the calcium ion is V-like. The pyramid height (*h*) is presented in Table 2.



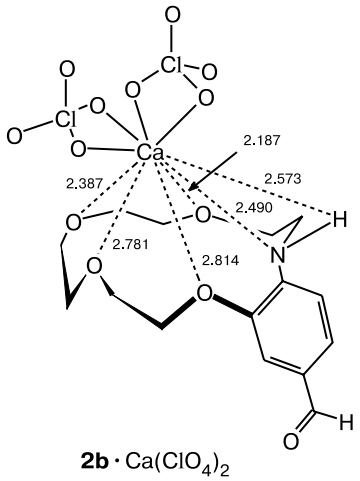


Fig. 2. Structures of the complexes of benzoaza-15-crown-5 ethers **1b** and **2b** with $Ca(ClO_4)_2$ calculated by the DFT/PBE method.

Table 2. Distance between the Ca^{2+} cation and averaged plane of heteroatoms of the azacrown ether (*h*) in the complexes of compounds **1a—c**, **2a—c**, and **3** with $Ca(ClO_4)^+$ and $Ca(ClO_4)_2$

Compound	*h*/Å	
	$Ca(ClO_4)^+$	$Ca(ClO_4)_2$
1a	1.893	1.893
1b	1.108	1.498
2a	1.629	1.949
2b	1.096	1.491
3	1.104	1.465

When the cycle size increases, the *h* value decreases, *i.e.*, the calcium cation drops to the middle of the macrocycle, and in the 12-membered cycles the pyramid with Ca^{2+} in the vertex is higher by ~0.4 Å than that in the 15-membered macrocycles. This spatial structure of the complexes is explained by the sizes of the cavities in the 12- and 15-membered cycles insufficient for calcium cation "immersing" into the middle of the cycles. This result agrees with the structure of complex **5**.[26] In the macrocycles of benzoaza-18-crown-6 ethers **1c** and **2c**, the cavity size is sufficient for inclusion of the calcium ion and, therefore, two ClO_4^- counterions are axially arranged at different sides from the macrocycle.

Complexation energies of crown ethers with calcium perchlorate calculated by the DFT method are presented in Table 3. The calculation of E_{compl} of the complexes with $Ca(ClO_4)^+$ has to simulate a possible influence of dissociation on the properties of the complexes.

The E_{compl} values presented in Table 3 were obtained as follows. The E_0 values for free ligands are needed for the calculation of E_{compl} by Eq. (3). However, it is diffi-

Table 3. Complexation energies (E_{compl}) of azacrown ethers **1a—c**, **2a—c**, and **3** with the Ca^{2+} ions coordinated with one and two perchlorate ions*

Compound	E_{compl}/kcal mol^{-1}	
	$Ca(ClO_4)_2$	$Ca(ClO_4)^+$
1a	30.1	74.4
1b	43.5 (37.0)	105.0
1c	40.4 (55.4)	112.1
2a	28.3	68.8
2b	40.6 (31.7)	97.7
2c	43.1 (56.4)	111.8
3	39.9 (37.7)	103.4

* Complexation energies are indicated for the V-like (in parentheses, for axial) orientation of the counterions.

cult to optimize the geometry of benzoazacrown ethers, because the total number of conformations of molecules **1a—c** and **2a—c** is equal to 2^m, where m is the number of independent torsion angles (τ) in macrocycles **a**, **b**, and **c** (m = 11, 14, and 17, respectively). Compared to the simplest crown ethers (12-crown-4, 15-crown-5, and 18-crown-6), the number of independent torsion angles in the benzocrown ethers is smaller by unity because of the condensation of the macrocycle with the rigid benzene ring, due to which the dihedral angle $\tau(O—C_{Ar}—C_{Ar}—N)$ is always close to 0°. Nevertheless, the number of independent torsion angles in molecules **1a—c** and **2a—c** remains too great to reckon on the reliable determination of the global minimum for the more exact calculation of E_{compl}. At the same time, since isolated molecules and complexes were calculated and all their properties were studied in solutions, tendencies of changing E_{compl} rather than their absolute values are of greater interest. Therefore, for each benzoazacrown ether, we started from the calculation of a pair of neutral complexes with the V-like and axial orientations of two counterions relatively to the macrocycles and of one type of positively charged complexes with one counterion. Then calcium perchlorate molecules were removed from the complexes, and the crown ether geometry was completely optimized. The E_0 values thus obtained were used for the calculation of E_{compl}.

It is seen from the data in Table 3 that E_{compl} increases successively with an increase in the macrocycle size in azacrown ethers **1a—c** and **2a—c**. Since the size of the macrocycle cavity increases in the same series, it is evident that the deeper immersion of the calcium cation inside the cavity is energetically favorable. A comparison of E_{compl} for compounds **3** and **1b** shows that the latter is a more efficient ligand (as we believe, due to the better supramolecular pre-organization of the macrocycle). It turned out that for the 12- and 15-membered macrocycles, according to model system **5**, the V-like arrangement of two counterions is more favorable than the axial arrangement, which is completely consistent with published data.[26] On the contrary, for the 18-membered macrocycles, the axial orientation of the counterions is more energetically favorable. This is explained by the fact that the size of the macrocycle cavity in molecules **1c** and **2c** is sufficient for immersion of the whole calcium ion, due to which the O and N atoms of the macrocycle and the O atoms of the counterions can form a coordination sphere with a more uniform charge distribution than that occurred for the V-like orientation.

A comparison of E_{compl} for the complexes with two and one counterions shows that the complexation energy is higher in the latter case, because the contribution of the Coulomb interaction between the partners increases. As it should be expected, the presence of the formyl group in the aromatic ring of crown ethers decreases the efficiency of complexation. A comparison of E_{compl} for *N*-phenylaza-15-crown-5 ether and its formyl derivative **3** shows that the energy of the latter is by 4 kcal mol^{-1} worse than the energy of the unsubstituted compound. This is explained by the strong withdrawing ability of the formyl group, which decreases the electron-donating properties of the N atom linked with the benzene ring.

Correlation between complexation constants and energy. Since the calculations were carried out for isolated compounds and complexes simulating their interaction in the gas phase and the experimental complexation constants were obtained in solutions, the reliability of the theoretical E_{compl} values was estimated from the existence of a correlation between E_{compl} and $\log K_1$.

The plots of E_{compl} *vs.* $\log K_1$ for benzoazacrown ethers **1a—c** and **2a—c** are shown in Fig. 3. The nearly linear character of the plots indicates that the tendency of E_{compl} changing in these series is correctly presented by the DFT/PBE calculation. For the complexes of ligands of both types with two counterions, the correlation coefficients (R) are closer to unity than those for the complexes

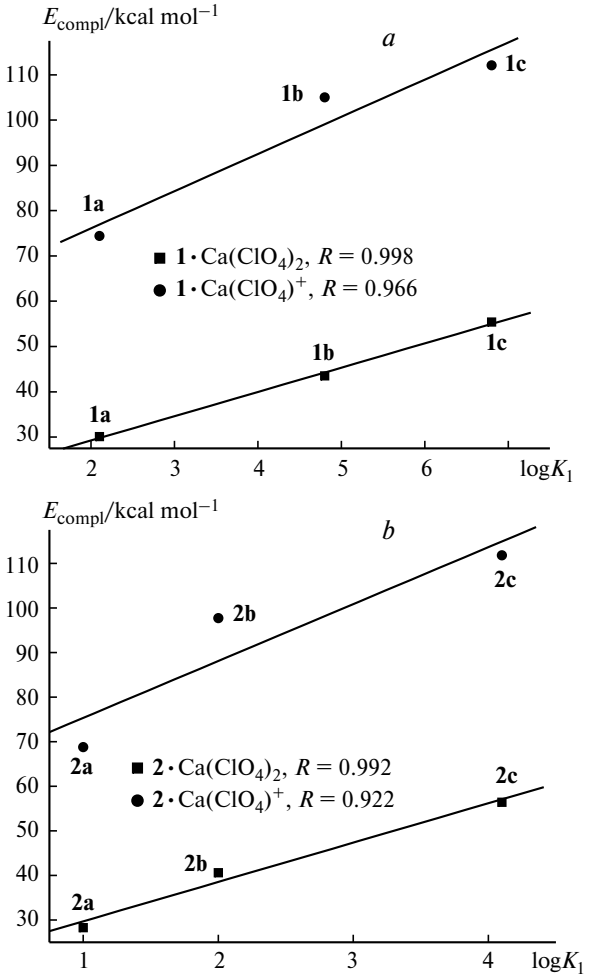


Fig. 3. Complexation energies (E_{compl}) as functions of $\log K_1$ for compounds **1a—c** (*a*) and **2a—c** (*b*).

with one counterion. Perhaps, complexes **1a—c** and **2a—c** with two counterions exist in MeCN preferentially as tight contact ion pairs, because for the complexes of the same compounds with $Ca(ClO_4)^+$, which simulate the influence of dissociation, the correlation coefficient between the theoretical E_{compl} values and $\log K_1$ values decreases noticeably. This is especially pronounced for complexes **2a—c**.

Correlation between the complexation energy and chemical shifts in ^{15}N NMR spectra. To prove that the N atom plays an important role in complexation, we examined the dependences of the chemical shifts (δ_N) in the ^{15}N NMR spectra of complexes **1a—c** with $Ca(ClO_4)_2$ [27] and complexation-induced changes in the chemical shifts ($\Delta\delta_N$) on the theoretical energy of complexation (Fig. 4).

When the cycle size and complexation energy increase, the δ_N value decreases and $\Delta\delta_N$ increases on going from the free ligand to the complex. Linear correlations between E_{compl} and $-\delta_N$ and between E_{compl} and $-\Delta\delta_N$ indicate that the N atom is really involved in complex formation, donating the LEP to the metal cation. At the same time, a decrease in $\Delta\delta$ indicates, evidently, a decrease in the contribution of the N atom to complexation with cycle expansion, because the total number of donor atoms increases and the degree of macroheterocycle pre-organization to complexation enhances.

Pre-organization of macrocycles to complexation. In this work, we attempted to quantitatively estimate the degree of pre-organization of the macrocycle to complexation. As mentioned above, the ligand in which minimum structural transformations occur during coordination with the metal ion is considered pre-organized.[28] We used two methods for quantitative estimation of the macrocycle pre-organization: geometric and energetic methods.

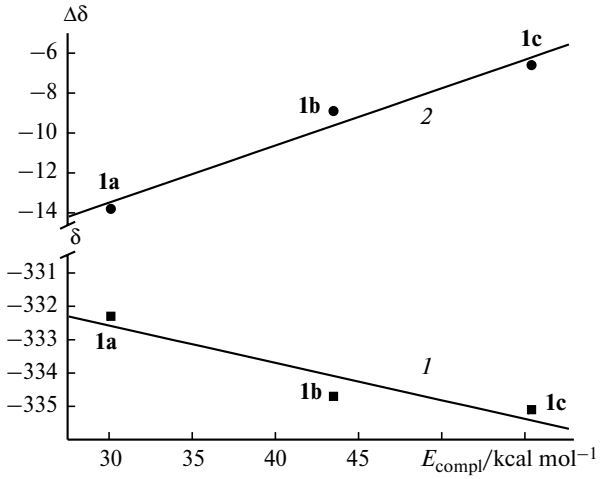


Fig. 4. Chemical shifts (δ) (*1*, $R = 0.937$) and their changes (Δδ) (*2*, $R = 0.985$) in the ^{15}N NMR spectra of complexes **1a—c** · $Ca(ClO_4)_2$ as functions of the theoretical energy of complexation ($\Delta\delta_N = \delta_{compl} - \delta_{ligand}$).

Table 4. Differences of torsion angles ($\Delta\tau_{av}$) in the complexes of compounds **1a—c**, **2a—c**, and **3** with $Ca(ClO_4)^+$ and $Ca(ClO_4)_2$ *

Compound	$\Delta\tau_{av}$	
	complex with $Ca(ClO_4)_2$	complex with $Ca(ClO_4)^+$
1a	82.9	113.5
1b	61.3	64.3
1c	10.4	36.2
2a	102.3	112.3
2b	77.0	76.6
2c	22.7	40.4
3	90.2	72.5

* $\Delta\tau_{av} = \Sigma|\Delta\tau_n|/n$, where n is the number of independent torsion angles in macrocycles **1a—c**, **2a—c**, and **3** (n = 11, 14, 17, and 15, respectively); $\Delta\tau_n = \tau_{n,compl} - \tau_{n,ligand}$.

In the geometric method, we compared the averaged differences of torsion angles of the macrocycle ($\Delta\tau_{av}$) before and after the formation of complexes with calcium perchlorate with one and two counterions (Table 4).

It is seen that $\Delta\tau_{av}$ decreases, on the whole, with an increase in the macrocycle size, indicating that the matching-up of the smaller cycles to the metal cation size should be stronger than that of the larger cycles. A comparison of the complexes with one and two counterions exhibits a lower degree of pre-organization of the former complexes (higher $\Delta\tau_{av}$ values).

The energetic method for estimation of pre-organization is a comparison of the energies of two conformations of free macrocycles: idealized and real conformations. The method includes three steps.

(1) At first we calculated molecules of simplest crown ethers, *viz.*, 12-crown-4 ether (C_4 and D_4 symmetry, respectively) and 15-crown-5 ether (C_5 and D_5 symmetry), and three conformations of 18-crown-6 ether (D_{3d}, S_6, and C_i symmetry) in two symmetric conformations conventionally named "crown" and "star." The "crown" conformation is maximally suitable for the formation of complexes with metal ions, because the O atoms are spatially close to the assumed coordination center (Fig. 5, *b*, *d*). On the contrary, the "star" conformation is minimally suitable for complexation, because its O atoms are at the periphery of the macrocycle and, thus, most remote from each other and from the center of the molecule, where (or outside it) the metal ion is localized in the complex (see Fig. 5, *a*, *c*).

The calculation showed that the "crown" conformation for 12-crown-4 and 15-crown-5 ethers are energetically more favorable than the "star" conformation with the D_4 and D_5 symmetry by 12.6 and 10.6 kcal mol^{-1}, respectively. For 18-crown-6 ether, on the contrary, the

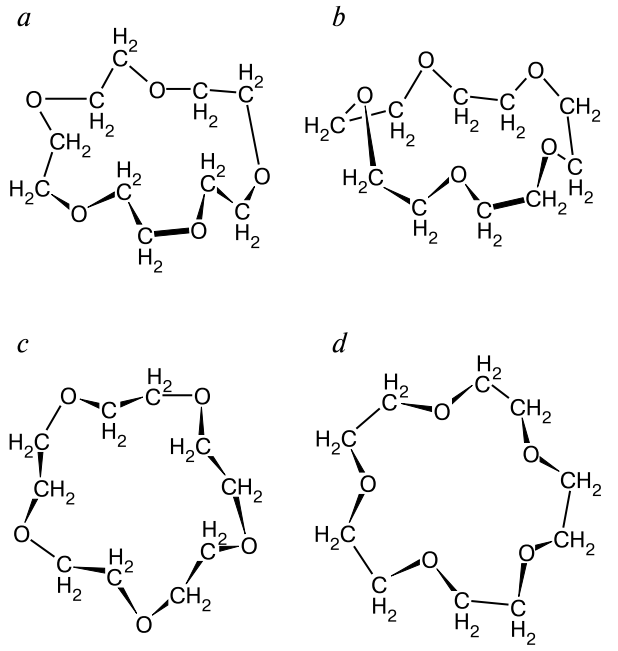


Fig. 5. Conformations of the 15-crown-5 ether molecule: "star" (*a*, *c*) and "crown" (*b*, *d*).

conformer with the D_{3d} symmetry is more favorable (by 12.2 kcal mol^{-1}) than the conformer of the S_6 symmetry, while the conformer of the C_i symmetry found in crystal[29] is only by 0.1 kcal mol^{-1} less favorable than the conformer with the D_{3d} symmetry. Other DFT calculations predict the higher (by 1.6 kcal mol^{-1}) stability of the conformers of the D_{3d} symmetry compared to C_i.[30]

(2) Then the optimized structures of conformers of simplest crown ethers were used for building and subsequent optimization of the geometry of molecules **1a—c**, **2a—c**, and **3**. We expected that idealized conformers of benzoazacrown ethers suitable for metal ion binding can thus be obtained.

(3) Finally, we compared the energies of free ligands **1a—c**, **2a—c**, and **3** (E_0), obtained by the optimization of the geometry after $Ca(ClO_4)_2$ was removed from the complexes, with E_0 of the same ligands formed of simplest crown ethers. First, it was of interest to find out which of the structures is more energetically favorable. Second, it was significant to elucidate how the difference in energies of two conformers (ΔE_0) changes with an increase in the cycle size and replacement of substituents at the N atom. Since the E_0 values in Eq. (3) are negative, the positive ΔE_0 value corresponds to the energetically less favorable conformation of the free ligand and *vice versa*. Correspondingly, the lower E_{compl} value corresponds to the less favorable conformation of the free ligand. Thus, if the real conformation is more favorable than the idealized one, then the pre-organization exists in fact, and the lower the difference in energies of two conformations (idealized and real), the lower the extent to which the macrocycle

Table 5. Pre-organization energy of the macrocycles (ΔE_0)*

Crown ether	ΔE_0 /kcal mol^{-1}	Crown ether	ΔE_0 /kcal mol^{-1}
1a	0.0	**2a**	0.0
1a (C_4)	2.2	**2a** (C_4)	0.8
1a (D_4)	11.5	**2a** (D_4)	9.1
1b	0.0	**2b**	0.0
1b (C_5)	4.7	**2b** (C_5)	3.0
1b (D_5)	16.8	**2b** (D_5)	18.8
1c	0.0	**2c**	0.0
1c (D_{3d})	0.3	**2c** (D_{3d})	−1.9
1c (S_6)	6.0	**2c** (S_6)	12.0
1c (^1C_i)	3.4	**2c** (^1C_i)	−1.0
1c (^2C_i)	−0.3	**2c** (^2C_i)	−1.7
3	0.0	**3** (C_5)	6.4
3 (D_5)	13.5		

* ΔE_0 is determined by the difference between E_0 of the azacrown ether formed of the corresponding simplest crown ether and E_0 of this azacrown ether optimized after $Ca(ClO_4)_2$ was removed from its complex. The symmetry types of simplest crown ethers used for the optimization of structures **1a—c** and **2a—c** are indicated in parentheses.

should match its conformation to capture the metal ion for the formation of the most thermodynamically favorable complex and, hence, the higher the degree of the initial macrocycle pre-organization, and *vice versa*. The differences in energies of two conformations of crown ethers are presented in Table 5.

The calculations showed that the real conformations **1a—c**, **2a—c**, and **3** formed after calcium perchlorate removal from their complexes and the subsequent optimization of their geometry are thermodynamically more favorable than the idealized conformations based on the most favorable conformations of simplest crown ethers of the "crown" type. Therefore, they correspond to higher complexation energies and, hence, yet before the complex formation the azacrown ethers exist in solutions in conformations better prepared for metal ion capturing to the coordination sphere of the O and N donor atoms and we can speak, in fact, about the initial pre-organization of these macrocycles. Then we compared ΔE_0 for 15-membered macrocycles **1b**, **2b**, and **3**. In **1b** and **2b**, the benzene ring is condensed with the crown ether cycle. In **3**, the Ph group is the substituent at the N atom of the macrocycle. It can be seen that for benzoazacrown ethers **1b** and **2b** ΔE_0 is by 4.7 and 3.0 kcal mol^{-1}, respectively, lower than ΔE_0 for phenylazacrown **3** (6.4 kcal mol^{-1}). Therefore, during complexation macrocycles **1b** and **2b** have to match their conformations to a less extent and, hence, they are more pre-organized than macrocycle **3**. This conclusion agrees with the higher complexation constants (see Table 1) and energies (see Table 3). When these differences are considered from the viewpoint of the energetics of equilibria between the conformations ob-

tained after $Ca(ClO_4)_2$ removal and the structures formed of simplest crown ethers, it should be expected that the concentrations of the first conformations would predominate considerably over the second structures and, hence, the latter would be first involved in complexation. Therefore, the pre-organization facilitates, in fact, the complexation, and the annelation of the benzene ring with the crown ether cycle favors the pre-organization leading to energetically more favorable complexes.

Compared to smaller cycles, more flexible 18-membered cycles **1c** seem to be most pre-organized, because their ΔE_0 are low. However, the role of the rigid aromatic ring in this process is also insignificant. For example, structure **1c** formed after calcium perchlorate removal is energetically more favorable than the structure obtained from 18-crown-6 ether with the D_{3d} symmetry. However, the difference in energies (0.3 kcal mol^{-1}) is too low to speak about the energetically significant rearrangement of the geometry of compound **1c** (D_{3d}) into **1c**. Similarly, structure **1c** with the ^2C_i symmetry obtained from 18-crown-6 ether with the C_i symmetry is only by 0.3 kcal mol^{-1} more favorable than structure **1c** after calcium perchlorate was removed.

Structures **2c** are least pre-organized. Since ΔE_0 are negative, all conformations **2c** obtained from symmetric species of 18-crown-6 ether, except for the least favorable conformation **2c** (S_6), are more energetically preferential than the structure obtained after calcium perchlorate was removed. However, since the differences in energies for conformations **2c** do not exceed 2 kcal mol^{-1}, all conformations discussed can be considered to be thermodynamically equilibrated with each other, although conformation **2c** (D_{3d}) is still preferable. Thus, 18-membered cycles in **2c**, being rather flexible, are not prone to pre-organization, despite the rigid benzene ring was introduced into their structures.

The degree of charge transfer from the donor atoms of crown ether to the calcium atom due to complexation is presented in Table 6.

The simple calculation shows that the transferred charge value (calculated per donor atom) changes from ~0.02 to ~0.03 e and, as a whole, increases with an increase in the cycle size. This means that the more uniform the surrounding of the calcium cation by the donor O and N atoms, the higher the degree of charge transfer.

As for the role of the N atom in complexation, the calculation shows that the complexation leads to an increase in both the negative charge itself (q) and its change (Δq) with an increase in the cycle size from 12- to 15-membered cycles, and then they decrease on going to the 18-membered cycle (Table 7).

In our opinion, this situation is related to the change in the conditions of hybridization of the N atom from the sp^2- to sp^3-type due to complexation. The negative charge value can also be considered as a measure of hybridization: the higher the charge, the closer the real hybridization to sp^3 and, hence, the lower the degree of conjugation of the LEP of the N atom with the benzene ring. In the case of sp^3-hybridization of the N atom, its LEP is maximally involved in the coordination sphere of the Ca^{2+} cation, *i.e.*, the forced sp^3-hybridization of the N atom due to complexation can be discussed.

In the 12-membered cycles, the hybridization of atoms cannot change strongly because of the strain in the cycle. Therefore, the hybridization of the N atoms in these cycles remains closer to the sp^2-type. This is indicated by the very low negative charge (−0.008 e) in compound **1a**. In the 18-membered cycles, the hybridization of the N atom is also closer to sp^2 compared to those in compounds **1b** and **2b**, because the flexibility of the macrocycle is sufficient to retain the conjugation of the N atom with the benzene ring. Thus, in the case of 15-membered benzoazacrown ethers, the hybridization of the N atom is closest to sp^3.

Table 6. Total charge (q) on the atoms of the $Ca(ClO_4)_n$ species ($n = 1, 2$) in the complexes of compounds **1a—c**, **2a—c**, and **3**

Compound	q/e	
	$Ca(ClO_4)_2$	$Ca(ClO_4)^+$
1a	−0.066	0.910 (−0.090)
1b	−0.084	0.904 (−0.096)
1c	−0.168	0.842 (−0.159)
2a	−0.056	0.907 (−0.093)
2b	−0.057	0.936 (−0.064)
2c	−0.149	0.842 (−0.158)
3	−0.110	—

Note. For comparison of the degree of charge transfer in the complexes with one and two counterions, −1 was added to the charges of the first complexes (values in parentheses).

Table 7. Charges on the N atoms in azacrown ethers **1a—c**, **2a—c**, and **3** and their complexes with $Ca(ClO_4)_2$

Compound	q/e		Δq*/e
	crown ether	complex	
1a	0.006	−0.008	−0.014
1b	0.025	−0.274	−0.299
1c	−0.008	−0.169	−0.162
2a	−0.182	−0.460	−0.278
2b	−0.257	−0.512	−0.255
2c	−0.263	−0.493	−0.231
3	0.181	0.108	−0.072

* The difference of charges on the N atom in the free ligand and its complex.

The complexation constants of the series of azacrown ethers with $Ca(ClO_4)_2$ increase with an increase in the macrocycle size. In the complexes of aza-12(15)-crown-4(5) ethers with $Ca(ClO_4)_2$, the metal cation is localized outside the averaged plane of heteroatoms of the macroheterocycle, and the coordination of both counterions is V-like. In the complexes of aza-18-crown-6 ethers, both counterions are in the axial position relatively to the macrocycle in the center of which the Ca^{2+} ion is localized. According to the calculations, the complexation energies increase with an increase in the size of the azacrown ether macrocycle. An almost linear dependence between the $\log K_1$ and E_{compl} indicates that the DFT calculation is valid for the tendency in changing the complexation energy of the compounds studied. The linear dependence between E_{compl} and the change in chemical shifts of the N atom in the ^{15}N NMR spectra due to complexation indicates a decrease in the participation of the N atom in Ca^{2+} ion binding with the macrocycle expansion. Two methods were proposed for the quantitative estimation of the ligand pre-organization to complexation: the geometric method based on a comparison of average changes in torsion angles after complexation and the energetic method based on a comparison of differences in energies of the ligand conformations obtained by the geometry optimization after $Ca(ClO_4)_2$ removal and energies of the conformations formed of simple crown ethers in the "crown" conformations, which are maximally suitable for metal ion capturing. It is established that benzoaza-15-crown-5 ether is a ligand more pre-organized to complexation than *N*-phenylaza-15-crown-5 ether.

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