# STUDY OF CONFORMATION OF CRYPTAHEMISPHERANDS BY TWO-DIMENSIONAL NMR SPECTROSCOPY

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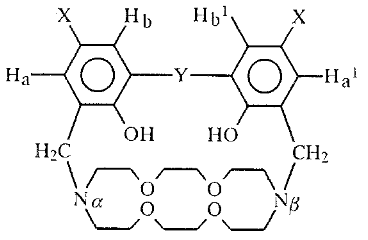
*Two-dimensional NMR spectroscopy (NOESY, COSY-DQF) has been used in a study of nitrogen-containing cryptahemispherands and their complexes with alkali metals. On the basis of experimentally established interproton distances, the preferred conformations of these molecules have been established. It has been shown that the important features of structure determining the molecular conformation are (a) the orientation of the N—$CH_2$(Ar) bond relative to the plane of the crown ether and (b) the length of the methylene bridge (spacer). The spatial and torsional angles have been determined. It has been established that as the length of the bridge is increased, the structure of these molecules approaches a betaine structure, with mutually parallel positions of the phenyl rings. Upon complexation, their orientation changes to mutually perpendicular, and this leads to enlargement of the inner cavity of the molecule and a corresponding rearrangement of its dimensions toward the ionic radius of the alkali metal.*

The selectivity of interaction of cryptands with metal ions and the stability of the resulting complexes are determined by many factors, among which one of the more important is the conformational readiness (preorganization) of the cryptand for the act of complexation. The greater the degree of matching of the conformation of the ligand in the free state to that in the complex, the smaller will be the energy loss in complexation; and as the end result, the complex will be more stable, and the selectivity of complexation higher [1, 2]. In this connection, data on the conformation of the ligand in solution and on the changes it undergoes upon complexation will convey information on the mechanism of complexation, with important ramifications in the development of methods for the directed synthesis of selective ligands.

In recent years, serious attention has been attracted to cryptands that contain anisole or phenol fragments as structural subunits (cryptahemispherands) [3]. The presence of such fragments usually results in greater conformational rigidity of the cyclic structure and higher selectivity of complexation. However, very little information is available on the conformational features of molecules of these compounds (or their complexes) in solution. A method such as two-dimensional NMR spectroscopy, which is sensitive to various kinds of conformational change, is of undoubted interest in resolving this situation.

In the work reported here, we used two-dimensional NMR spectroscopy (COSY, NOESY) to study a series of new cryptahemispherands with the general formula



I) X = Me, Y = $CH_2C_6H_2CH_3(OH)CH_2$; II) X = Me, Y = "O"; III) X = Me, Y = $CH_2OCH_2$; IV) X = $H_{C,C'}$;
Y = $(OCH_2CH_2—)_2—O—$; V) X = $H_{C,C'}$; Y = $(OCH_2CH_2—)_3—O—$

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TABLE 1. Data on Spectra of Cryptands I—VI

| Compound | Chemical shifts of protons, δ, ppm | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N—$\underline{\mathrm{CH}_2}$ (Ar) | crown ether | | | Ar | | | X | Y | |
| | | N—$\underline{\mathrm{CH}_2}$ | $\underline{\mathrm{CH}_2}$—O | $\underline{\mathrm{CH}_2}$—$\underline{\mathrm{CH}_2}$ | $H_a$ | $H_b$ | $H_c$ | | $CH_2$ | O—$\underline{\mathrm{CH}_2}$ |
| I | 3,57 | 2,55;<br>2,79 | 3,70 | 3,44 | 6,78 | 6,52 | — | 2,06;<br>2,13 | 3,76 | — |
| II | 3,51 | 2,57;<br>2,85 | 3,92 | 3,67 | 6,95 | 6,73 | — | 2,21 | — | — |
| III | 3,61 | 2,65 | 3,48 | 3,60 | 7,17 | 6,68 | — | 2,24 | — | 4,45 |
| IV | 3,75 | 2,71 | 3,61 | 3,65 | 6,74 | 6,61 | 6,55 | — | 3,81 | 4,12 |
| V | 3,73 | 2,71 | 3,55 | 3,51 | 6,77 | 6,62 | 6,60 | — | 3,97 | 4,18 |
| VI | 3,39 | 2,68;<br>2,88 | 3,82 | — | 6,81 | 6,79 | 6,72 | — | 3,83 | 4,22 |

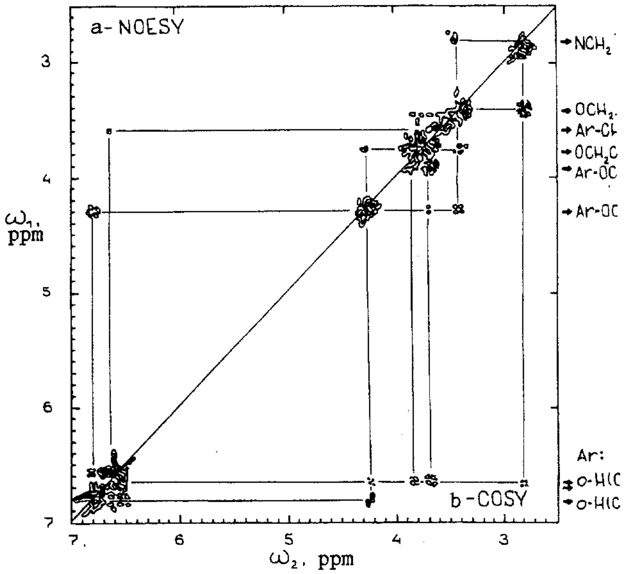

Fig. 1. Combined COSY—NOESY spectra of compound V, 0.1 M, T = 298 K. a) NOESY; b) COSY.

Distinctive features of the PMR spectra of these ligands are (a) the character of the signals of the methylene protons, which have first-order multiplicity, and (b) the absence of any signals of hydroxyl-group protons. The character of the signals of the methylene protons is evidence of free rotation around C—C, C—O, and C—N bonds in the crown ether fragment and in the spacer Y; this conclusion is supported by the values of the spin—spin coupling constant (SSCC), 5.2-5.5 Hz. The absence of signals of the hydroxyl-group protons may be a consequence of the formation of a hydrogen bond in the molecule. Here, slow proton exchange leads to very marked broadening of the signal of the methylene protons. In the spectra of compounds I-III, the protons of the outer phenyl rings are manifested in the form that is usual for an AB spin system, i.e., a quadruplet with a meta-constant equal to 1.8 Hz; but in compounds IV and V, the phenyl protons, forming an ABC spin system, are observed in the form of multiplets with ortho-constants $^3J_{ca} = {}^3J_{cb} = {}^3J_{c'a'} = {}^3J_{c'b'} = 7.1$ Hz, meta-constant $^4J_{ab} = 1.8$ Hz, and a broadened triplet with $^3J_{ac} = {}^3J_{bc} = 7.1$ Hz.

In compound I, the phenyl protons of the spacer Y prove to be chemically equivalent and have the form of a singlet at 6.87 ppm. The methylene protons of the spacer Y in compounds I and III are manifested in the form of singlets at 3.74 and 4.45 ppm, respectively. The chemical shifts of the signals of the protons in all of the compounds that were investigated are listed in Table 1. Attention is directed to the difference in chemical shifts of the methylene protons of the spacer Y and the crown ether (C), most likely reflecting the influence of magnetic anisotropy of the aromatic rings. Thus, the information extracted from such trivial spectra is extremely limited and cannot be used to judge the conformation of the ligands. Because of this situation, it became necessary to use two-dimensional NMR spectroscopy.

TABLE 2. Nuclear Overhauser Effect (NOE) and Interproton Distances in Molecules of Compounds I and III-VI

| Compound | d-Bond | Magnitude of NOE | r, Å |
|---|---|---|---|
| I | $N(CH_2)_2 \rightarrow H(Ar)$ | 0,072 | 3,45 |
| | $N(CH_2)_2 \rightarrow N{-}CH_2(Ar)$ | 0,060 | 3,56 |
| | $O{-}\underline{CH_2}{-}\underline{CH_2}{-}O(C)^* \rightarrow H(Ar)$ | 0,027 | 4,06 |
| | $O{-}\underline{CH_2}{-}CH_2(Y) \rightarrow H(Ar)$ | 0,016 | 4,41 |
| III | $N(CH_2)_2 \rightarrow H(X)$ | 0,004 | 4,09 |
| | $N{-}CH_2(Ar) \rightarrow H(X)$ | 0,002 | 4,40 |
| | $H(Ar) \rightarrow CH_2(Y)$ | 0,021 | 3,10 |
| IV | $N{-}CH_2(Ar) \rightarrow N(CH_2)_2$ | 0,085 | 2,86 |
| | $N(CH_2)_2 \rightarrow H(Ar)$ | 0,053 | 3,09 |
| | $H(Ar) \rightarrow O\underline{CH_2}{-}CH_2(Y)$ | 0,061 | 3,02 |
| | $CH_2{-}\underline{CH_2}{-}O(C) \rightarrow N{-}CH_2(Ar)$ | 0,028 | 3,44 |
| V | $CH_2{-}\underline{CH_2}{-}O(C) \rightarrow N{-}CH_2(Ar)$ | 0,020 | 3,64 |
| | $N{-}CH_2(Ar) \rightarrow N(CH_2)_2$ | 0,073 | 2,95 |
| | $N(CH_2)_2 \rightarrow H(Ar)$ | 0,026 | 3,51 |
| | $O{-}CH_2{-}\underline{CH_2}(Y) \rightarrow CH_2{-}O(C)$ | 0,002 | 5,16 |
| | $H(Ar) \rightarrow O{-}\underline{CH_2}{-}CH_2(Y)$ | 0,028 | 4,46 |
| VI | $N{-}CH_2(Ar) \rightarrow CH_2{-}\underline{CH_2}{-}O(C)$ | 0,008 | 3,30 |
| | $CH_2{-}\underline{CH_2}{-}O(C) \rightarrow H(Ar)$ | 0,001 | 4,19 |
| | $H(Ar) \rightarrow N{-}CH_2(Ar)$ | 0,007 | 3,35 |
| | $H(Ar) \rightarrow CH_2{-}\underline{CH_2}{-}O(Y)$ | 0,004 | 3,71 |

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*Methylene protons of crown ether.

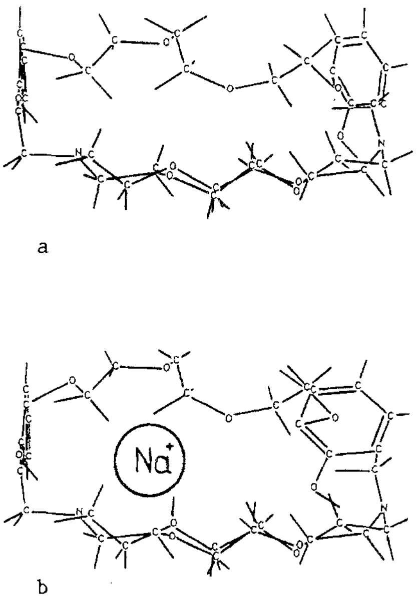

Fig. 2. Preferred conformations of molecules: a) free ligands (compound V); b) complex with sodium ion (compound VI).

Exact assignments of the signals of all protons in these molecules were made by means of J-correlation phase-sensitive two-dimensional NMR spectroscopy with a double quantum filter (COSY-DQF). With this method, we were also able to refine the values of the scalar SSCCs of the methylene protons and to confirm the conclusions that had been drawn on the basis of the PMR spectra. A combined COSY—NOESY spectrum of compound V is shown in Fig. 1.

In order to establish the preferred conformation of these ligands, we used phase-sensitive homonuclear dipole-correlation two-dimensional NMR spectroscopy (NOESY-PH). The mixing times of the pulses were determined on the bases

TABLE 3. Torsion Angles in Molecules*

| Compound | Torsion angle | Magnitude of torsion angle, deg | |
|---|---|---|---|
| | | crown ether | spacer Y |
| I | HCN$_\alpha$C | 21,1; 10,0 | — |
| | CN$_\alpha$CC | -41,7; 79,8 | |
| | N$_\alpha$CCO | 20,9; 87,2 | |
| | HCN$_\beta$C | -16,4; 23,3 | |
| | CN$_\beta$CC | -6,7; -70,7 | |
| | N$_\beta$CCO | 21,7; 41,2 | |
| III | HCN$_\alpha$C | -87,9; 55,3 | — |
| | CN$_\alpha$CC | -68,5; 41,1 | |
| | N$_a$CCO | -41,3; 16,5 | |
| | HCN$_\beta$C | -30,2; 60,9 | |
| | CN$_\beta$CC | -53,6; -88,8 | |
| | N$_\beta$CCO | 13,3; -86,1 | |
| | CCOC | -18,4; 24,3 | 32,8; -80,4 |
| | OCCO | -2,0; 35,5 | |
| V | HCN$_\alpha$C | 31,6; -8,5 | — |
| | CN$_\alpha$CC | -16,7; -30,8 | |
| | N$_\alpha$CCO | -77,1; -54,9 | |
| | HCN$_\beta$C | 3,9; 80,0 | |
| | CN$_\beta$CC | -56,4; 31,8 | |
| | N$_\beta$CCO | 23,2; 78,0 | |
| | CCOC | -17,6; 63,5 | 77,7; 39,6 |
| | OCCO | 53,1; -7,1 | 54,5; -84,9 |
| VI | HCN$_\alpha$C | 31,6; -8,5 | — |
| | CN$_\alpha$CC | -16,7; -67,4 | |
| | N$_\alpha$CCO | 38,5; 54,9 | |
| | HCN$_\beta$C | -62,8; 80,0 | |
| | CN$_\beta$CC | -56,4; 29,0 | |
| | N$_\beta$CCO | -78,0; -32,1 | |
| | CCOC | -38,6; -42,0 | 62,1; 77,7 |
| | OCCO | 22,3; -12,6 | -84,9; -59,8 |

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*Confidence interval ±10°.

of the spin—lattice relaxation times of the protons of all groups of atoms in the molecule, which were found by the inversion—recovery method.

According to [4], the interproton distance between adjacent protons (d-bond) is determined by the following equation:

$$\mathrm{NOE} = A \cdot r^{6}$$

Using values of the nuclear Overhauser effect (NOE) found from the NOESYPH spectra and the relationship [4]

$$(\mathrm{NOE})_{ij}^{-1} r_{ab}^{6} = (\mathrm{NOE})_{ab}^{-1} r_{ij}^{6},$$

we determined the distances $r_{ij}$ between adjacent protons in the molecules of the compounds. As the basis distances $r_{ab}$ we used the distances between ortho-protons ($r_{ab}$ = 2.48 Å, compounds IV and V) and meta-protons ($r_{ab}$ = 4.29 Å, compounds I and III) of the aromatic rings. The magnitudes of the nontrivial d-contacts determining the preferred conformation of these molecules are shown in Table 2. It will be seen that interactions of aromatic ring protons with methylene protons of N—$CH_2$ of the crown and O—$CH_2$ of the spacer Y do represent such d-contacts in the molecule. Using the computer modeling technique and the set of distances that had been found, we modeled the structure of the preferred molecular conformation of each of the compounds. We found that the common significant elements determining the structures that are obtained are the orientation of the N—$CH_2$(Ar) bond and the length of the spacer Y, as these factors govern the mutual spatial positions of the aromatic rings and the crown ether fragment. Thus, for the preferred molecular conformation of II, a parallel position is characteristic for the phenyl rings of the spacer and the plane of the crown ether. In the preferred conformations of compound I, the calculated values of the spatial angles between the planes of the phenyl rings are 30° and 90°, respectively, in compound III 25°, and in compounds IV and V 45° and 70°, respectively.

The torsion angles in the molecules of these compounds are listed in Table 3. With increasing length of the spacer Y (compound V), the molecular structure becomes betaine-like, with the phenyl rings diaxial relative to the plane of the crown ether and practically parallel to each other (Fig. 2a). In this case the Ar—OH bond becomes exo- and endo-directional relative to the plane of the ligand but is oriented toward the nitrogen atom of the crown ether, favoring the formation of an intramolecular hydrogen bond.

In the context of these studies, it appeared advisable to attempt to determine the conformational changes taking place upon complexation, using the same methods of investigation. Such an attempt was made in the example of the complex of V with sodium perchlorate with a 1:1 stoichiometric composition, in deuteriochloroform (compound VI; see Table 1). By means of the NOESYPH method and computer modeling (see Table 2), as described above, we established that in the preferred molecular conformation of this compound, a number of distinctive features are observed. Upon complexation, the orientation of the aromatic rings changes to mutually perpendicular, and there is a related change in the character of bending of the spacer Y. All this leads to enlargement of the inner cavity of the cryptand (Fig. 2b). Modeling of this structure in the presence of a sodium ion has shown that the volume of the resulting cavity is suitable for "capture" of this metal ion. In this case, the metal ion is placed in the "basket" formed by the cryptand molecule.

Thus, the results obtained in this work have provided evidence of the high informational value of two-dimensional NMR spectroscopy in studying complexation processes and in registering conformational changes in the structure of ligands.

## EXPERIMENTAL

**PMR spectra** and two-dimensional $^1H$ NMR COSY-DQF and NOESY-PH spectra were obtained on 0.1 M solutions of the test compounds in a Bruker AM-250 NMR spectrometer with a working frequency of 250 MHz, equipped with an Aspect 3000 computer.

**COSY-DQF spectra** were obtained by means of a pulse sequence $[D_1-90°-t_1-90°-t_2]\cdot NS$ [5], where $t_1$ is the length of the period of evolution; $t_2$ is the time of listening for the response [detection]; NS = 64 is the number of accumulations. The width of the spectrum was 1600-2000 Hz with a length of 1024 data points (1.5-1.9 Hz per point). The evolution period was varied from 3 μsec with a step of 370 μsec (a total of 512 increments). The data matrix $t_2 \cdot t_1 = 1024 \cdot 512$ points.

**NOESY-PH spectra** were obtained by means of a pulse sequence $[D_1-90°-t_1-\tau_m-90°-t_2]\cdot NS$ [5], where NS = 64 accumulations. The length of the relaxation lag $D_1 = 3.0$ sec, pulse mixing time $\tau_m = 0.3$-1.1 sec. During the evolution period, 256 increments were accomplished. The width of the spectrum was 1600-2000 Hz with a length of 1024 data points (1.5-1.9 Hz per point). The data matrix $t_2 \cdot t_1 = 256 \cdot 1024$ points.

The data matrix before the Fourier transform was multiplied in the COSY-DQF and NOESY-PH experiments by a sine-squared function with a shift $\pi/2 - \pi/4$, and then zero-filled to $1024 \cdot 1024$ points. The pulse mixing time was determined from values of $T_1$.

The spin—lattice relaxation time $T_1$ of the $^1H$ nuclei was measured by the inversion—recovery method, using a sequence of frequency pulses [180°—$\tau$—90°—T]. The value of $\tau$ was varied from T to 0.08 sec, and T was selected greater than 5 $T_1$ (for complete relaxation of the nuclei).

The compounds used in this study were obtained by methods described in [6].

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