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Published on: 02 Jul 2008 - Supramolecular Chemistry (Taylor & Francis Group)

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Jaroslav Kriz, Jiri Dybal, Emanuel Makrlik, Jan Budka, Petr Vanura. Protonation of Tetrapropoxy-4-tert-butylcalix[4]arene: NMR Study of Interaction and Probable Structures of the Product. Supramolecular Chemistry, Taylor & Francis: STM, Behavioural Science and Public Health Titles, 2008, 20 (05), pp.487-494. 10.1080/10610270701422065 . hal-00513513

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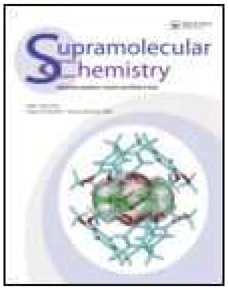

Protonation of Tetrapropoxy-4-tert-butylcalix[4]arene: NMR Study of Interaction and Probable Structures of the Product

Journal:	*Supramolecular Chemistry*
Manuscript ID:	GSCH-2007-0055.R1
Manuscript Type:	Full Paper
Date Submitted by the Author:	19-Apr-2007
Complete List of Authors:	Kriz, Jaroslav; Institute of Macromolecular Chemistry, Structure Analysis Dybal, Jiri; Institute of Macromolecular Chemistry, Structure Analysis Makrlik, Emanuel; University of West Bohemia Budka, Jan; Prague Institute of Chemical Technology Vanura, Petr; Prague Institute of Chemical Technology
Keywords:	Calixarene complex, calixarene protonation, NMR, DFT
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Protonation of Tetrapropoxy-4-*tert*-butylcalix[4]arene: NMR Study of Interaction and Probable Structures of the Product

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Using ^{1}H and ^{13}C NMR spectroscopy, the interaction of tetrapropoxy-*p-tert*-butylcalix[4]arene (1) with H_3O^+ ions produced by hydrogen bis(1,2-dicarbollyl) cobaltate (HDCC) and traces of water was studied in nitrobenzene-d_5. It was shown that 1 readily forms an equimolecular complex with H_3O^+. The equilibrium constant *K* of its formation is 2.6 at 296 K. Exchange between bound and free 1 is fast even under mild excess of HDCC, the correlation time τ_{ex} being about 0.13 ms. NMR shows that H_3O^+ is bound to the aryl-oxygen atoms and this binding forces the calixarene cup to adopt a more open and symmetrical conformation. This conclusion is in a full accord with high precision quantum DFT calculations which find one structure of the complex corresponding to a global energy minimum, in which the H_3O^+ ion is bound to three of the oxygen atoms by strong hydrogen bonds and to the remaining oxygen by two weaker hydrogen bonds. The calixarene part is forced into a C_4 symmetrical opened form.

When stored for weeks, the complex gradually transforms into other forms, most probably its hydrates, according to spectral evidence and DFT calculations.

Keywords: calixarene complex; calixarene protonation; NMR; DFT

INTRODUCTION

Calixarene-based molecules have received intense attention in the recent years [1,2]. Many studies have focused on the binding ability of calixarene derivatives with carbonyl or analogous groups at their lower rims toward metal ions [3-12]. In our recent studies [13-15], we have shown that calixarenes carrying coordinating groups, such as dimethylthioamide, ester or keto groups on their lower rim, bind a hydroxonium ion H_3O^+ in equimolecular and very stable complexes. NMR spectra and high-level quantum calculations revealed that H_3O^+ binds partly to the attached coordinating groups but also to the calixarene aryl-oxygen atoms. Quantum calculations even indicated that binding almost exclusively to the Ar-O- atoms could be even preferred in some cases. It is thus interesting to examine H_3O^+ binding to a calixarene containing only Ar-O-R groups where R is an alkyl such as *n*-propyl in our case.

Like in our previous studies [13-15, 17, 18], hydrogen bis(1,2-dicarbollyl) cobaltate (HDCC)[16] was used as a reliable source of protons, which were converted to hydroxonium ions H_3O^+ by a 3.1 mol/mol excess of water. Combining NMR spectral evidence with DFT quantum mechanical calculations, we suggest the most probable structure of the protonated calixarene.

RESULTS AND DISCUSSION

NMR measurements. Our experiments with **1** (see Scheme 1) were carried out in nitrobenzene-*d*$_5$ as one of the sufficiently polar solvents (needed for full ionization of HDCC), which do not form inclusion complexes with calixarenes. After mixing **1** with increasing amounts of HDCC, its ^{1}H NMR signals gradually shift to a various degree as illustrated in Figure 1. The signal assignment corresponds to Scheme 1, where the protons are numbered in the same way as the carbons they are attached to. The signal shifts are analogous to those observed with other calixarene derivatives [13-15] as a sign of conformation change due to binding of H_3O^+ ion at the lower rim.

As the signals shift immediately and without splitting, the protonation of **1** must be very fast. However, the persistent shift at larger excess of HDCC (cf. Figure 1) indicates that the product formation is not quantitative in the 1:1 mixture. We are thus dealing with a dynamic equilibrium, which is only moderately favorable to the complex.

Figure 1: 300.13 MHz NMR spectra of calixarene **1** (A) and its 1:2 (B) and 1:4 mol/mol (C) mixtures with HDCC (nitrobenzene-d_5, 296 K). Signal assignment in A (cf. Scheme 1), extrapolated maximal shifts $\Delta\delta_{\max}$ (in ppm) in C, correlation times of exchange τ_{ex} (in ms) in B.

Scheme 1

The equilibrium should follow the usual relation

$$K = \frac{[\mathbf{1}\cdot\mathrm{H}^+][\mathrm{A}^-]}{[\mathbf{1}][\mathrm{A}^-\mathrm{H}^+]} \quad , \qquad (1)$$

where A^-H^+ and A^- stand for HDCC or any other suitable proton donor and its anion. Under fast exchange between free and coordinated **1**, the actual chemical shift of any signal is a weighted average of the shifts corresponding to the exchanging sites. Thus the actual relative shift is $\Delta\delta = \alpha\Delta\delta_{\max}$, where $\alpha = [\mathbf{1}\cdot\mathrm{H}^+]/[\mathbf{1}]_0$ and $\Delta\delta_{\max}$, obtained by extrapolation, is the maximum relative shift corresponding to the pure complex. Using Eq.1, $\Delta\delta$ can be expressed as

$$\Delta\delta = \Delta\delta_{\max}\frac{K(1+\beta) - \sqrt{K^2(1+\beta)^2 - 4(K-1)K\beta}}{2(K-1)} \quad , \qquad (2)$$

where $\beta = [\mathrm{A}^{-}\mathrm{H}^{+}]_0 / [\mathbf{1}]_0$. Thus K can be obtained by fitting Eq.2 to the experimental values of $\Delta\delta$. Figure 2 shows $\Delta\delta$ of individual signals in the proton spectra of **1**/HDCC mixtures and the fitting curves.

Figure 2: Relative shifts Δδ of signals in ^{1}H NMR spectrum of **1** and its mixtures with HDCC in nitrobenzene-d_5 at 296 K and their fitting with Equation 2.

The value of K to which all the actual relative shifts fit is 2.61 ± 0.03. This is a much lower value than we observed in protonation of calixarenes bearing additional coordinating groups [13-15].

The apparent swiftness of exchange between free and bound **1** gives us the opportunity to examine its dynamics quantitatively. One of the possible methods is the measurement of transverse relaxation rate using the Carr-Purcell-Meiboom-Gill sequence (CPMG) [19] with a varied delay t_p between the π pulses. As shown by Luz and Meiboom [20], the actually measured relaxation rate $R_2(t_p)$ can be expressed as

$$R_2(t_p) = R_2^{\ 0} + p_1 p_2 \delta\omega^2 \tau_{ex} [1 - (\tau_{ex} / t_p) \tanh(t_p / \tau_{ex})] \tag{3}$$

where $R_2^{\ 0}$ is the part of relaxation rate independent of exchange, p_1 and p_2 are the probabilities of finding the nucleus at the sites 1 and 2, respectively, $\delta\omega$ is the relative chemical shift between the two sites in rads and τ_{ex} is the correlation time of exchange. For short τ_{ex}, Equation 3 can be approximated (slightly modifying the relations in Ref. 21) by

$$R_2(t_p) = \zeta - \xi \tau_{ex}^{\ 2} / t_p \tag{4}$$

with

$$\zeta = R_2^{\ 0} + \xi \tau_{ex} \tag{4a}$$

and

$$\xi = 4\pi^2 \alpha (1 - \alpha)(\Delta\delta_{\max})^2 \tag{4b}$$

where $\Delta\delta_{\max}$ is the relative shift (in Hz) of the given signal between free **1** and its complex. Thus the dependence of $R_2(t_p)$ on $1/t_p$ is linear with the slope $\xi\tau_{ex}^2$. As $\Delta\delta_{\max}$ is obtained by extrapolation from the spectra and α can be calculated from actual $\Delta\delta$ (see above), obtaining τ_{ex} from the slope is straightforward. Figure 3 shows dependences for three most mobile signals in the proton spectrum of the **1**/HDCC mixture 1:2 mol/mol, namely 4+8, 10 and 9e. The values of τ_{ex} obtained from the individual slopes are 1.33×10^{-4}, 1.36×10^{-4}, and 1.24×10^{-4} s, respectively. These values are sufficiently close to each other to have a physical meaning of the correlation time of exchange between free and bound forms of **1**. Evidently, the exchange is quite fast, its rate constant being about 7.6×10^{3} s^{-1}.

Figure 3: Dependence of the measured net increase in the transverse relaxation rate of the indicated most mobile signals in the 300.13 MHz ^{1}H NMR spectrum of the mixture of **1** with HDCC 1:2 (mol/mol) in nitrobenzene-d_5 at 296 K

Returning now to the shape of ^{1}H NMR spectra, the 0.323 ppm mutual approach of the signals 9a and 9e (axial and equatorial CH_2 protons) relative to free **1** is a clear sign that the aromatic part of **1** adopts a more open and symmetric conformation in the complex [12]. This conclusion is corroborated by the significant deshielding of aromatic protons 4, 8. Such a change can be forced only by a H_3O^+ binding at the lower rim of **1**, i.e. to the aryl-oxygen atoms. In agreement with this, protons 10 (O-CH_2-) are significantly deshielded, too. Assuming that H_3O^+ is bound by three strong hydrogen bonds [13-15], one would expect that one of the four O-CH_2- groups should be perceptibly different from the other three. The shape of the proton (and also carbon, see below) spectrum indicates a C_4 symmetry, however. There are two possible explanations of this behavior: either the H_3O^+ ion adopts multiple weaker bonds to the fourth oxygen atom and is thus placed near to the center of the lower rim or it rotates very fast within the molecule averaging thus its structure in the NMR time window. Deciding between these two alternatives is beyond the abilities of NMR.

Most of the just described features can also be read out from the ^{13}C NMR spectra. Figure 4 reproduces DEPT45 spectra (showing only carbons with attached protons) of **1** and its 1:4 mol/mol mixture with HDCC, the latter having been measured 6 to 18 hours after mixing. Large downfield shifts of signals 4,8 and 10 leave no doubt that a complex was formed between **1** and H_3O^+, with the ion probably bound to the aryl-oxygen atoms. In analogy to proton spectra, the signals are single (except for small accompanying signals) suggesting thus again either C_4 symmetry of the complex or fast averaging of the structure by internal motion.

Figure 4: 75.5 MHz ^{13}C NMR DEPT45 spectra of 5 mmol/L calixarene **1** (A) and its mixture with 4.0 mol/mol excess of HDCC (B) 6 – 18 h after mixing (nitrobenzene-d_5, 296 K). Assignment of signals in A (cf. Scheme 1), relative shifts (in ppm) in B.

However, measurement of long-range DEPT spectra designed to show signals of quaternary carbons shown in Figure 5 (which was more time-consuming and reflects thus a later stage of the development of the system) revealed splitting of carbon signals 5, 6 and 7 suggesting either lower symmetry of the complex or coexistence of two different structures. In addition to it, the smaller companions of each of the main signals, which already appeared in the normal DEPT45 spectra, somewhat increased in relative intensity. Evidently, a new variant of the complex is evolving very slowly from its original form and, as one can expect, the exchange between both forms is quite slow, too. Such multiple complex forms were already observed in the case of some calixarenes with attached ester and keto groups [14, 15] where the formation of the H_3O^+ complex was very slow. In contrast to it, the formation of the present original complex is very fast although its equilibrium is less favorable.

Figure 5: Parts of combined 75.5 MHz ^{13}C NMR DEPT45 and LR-DEPT45 spectra of 5 mmol/L calixarene **1** (A) and its mixture with 4.0 mol/mol excess of HDCC (B) 10 – 12 days after mixing (nitrobenzene-d_5, 296 K)

Figure 6: Parts of 300.13 MHz ^{1}H NMR (above) and 75.5 MHz ^{13}C NMR DEPT45 (below) spectra of the mixture of 5 mmol/L calixarene **1** with 4.0 mol/mol excess of HDCC measured 3 weeks after mixing (nitrobenzene-d_5, 296 K).

Inspection of the spectra of **1** – HDCC 1:4 mixture (see Figure 6, where the assignment of signals to individual forms was made using a combination of ^{1}H NOESY and ^{1}H-^{13}C HSQC spectra) after 3 weeks of storage reveals two different new forms of the complex, B and C, produced from the original form A. The same new forms can be observed in a lower relative population in systems with a lower excess of HDCC, even in the 1:1 mixture. Therefore, it is not probable that the new forms are complexes with a higher number of H_3O^+ ions. However, a 0.23 ppm downfield relative shift of the broad H_2O signal (not shown) in the long-stored 1:4 mixture indicates that water takes part in the new forms. As it can be seen in Figure 6, the more prominent form B among the new products no longer exhibits C_4 symmetry. Quite to the contrary, there is magnetic nonequivalence between at least two doubles of opposite aromatic rings (in the proton spectrum of B, even all four *tert*-butyl groups are nonequivalent). Experience with NMR spectra of calixarenes teaches us that such nonequivalence should not be overvalued: due to their strong long-range shielding effects of the aromatic rings, even subtle changes in their relative orientation can lead to remarkable shifts of the signals of adjacent nuclei. Nevertheless, the observed nonequivalence cannot be ignored for two reasons: (i) it reflects lowering of the molecular symmetry from apparent C_4 to C_2 or even lower and (ii) it shows that the residence time in the exchange between nonequivalent analogous nuclei must be larger than 0.05 s, i.e. the internal motion in the molecule B is at least two orders of magnitude slower than that in the form A. Therefore, the most plausible conclusion appears to be that the form B (and probably also C) is a hydrate of the complex A with a water molecule placed inside the calixarene cavity. The molecule has to sit near enough to the lower rim in order to interact with the bound H_3O^+ ion, which necessarily means that it interacts with at least two opposite aromatic rings (probably by a weak hydrogen bond) lowering thus the symmetry of the complex and slowing down its internal motion.

Quantum chemical calculations. Geometry optimizations of calixarene and its complex with H_3O^+ were performed by the quantum chemical calculations at the density functional level of theory (DFT, B3LYP functional) using the Gaussian 03 suite of programs [22]. The 6-31G(d) basis set was used and the optimization was unconstrained. The optimized structure of free calixarene is shown in Figure 7A. The most stable conformation forms a pinched cone structure with a C_2 symmetry.

The structure obtained by optimization of the calixarene - H_3O^+ complex is shown in Figure 7B, together with the lengths of hydrogen bonds (in Å). Compared to free molecule the calixarene part of the complex is distorted so that its structure is very close to the C_4 symmetry. The hydroxonium ion is placed in the cage formed by calixarene and is bound by strong hydrogen bonds to oxygen atoms of three C-O-C groups and by two somewhat weaker hydrogen bonds to the last C-O-C group. The stabilization energy of the complex calculated as the difference between the energies of the optimized complex and optimized free calixarene molecule and hydroxonium ion is -394.72 kJ/mol. Stabilization energy of the complex can be expressed also with respect to the aqueous hydroxonium ion $[H_3O^+(H_2O)_3]$ and free calixarene (**1**) according to the formula

$$[H_3O^+(H_2O)_3] + \mathbf{1} \rightarrow [H_3O^+(\mathbf{1})] + 3\ H_2O.$$

Then it is -8.20 kJ/mol. This value, corrected further for entropy change, probably corresponds to the value of *K* established above by NMR.

The gradual development of another form of the complex detected by NMR led us to explore its further possible changes or interactions. As the structure described above corresponds to the global energy minimum found by unconstrained geometry optimization, a new form could scarcely be produced by an internal rearrangement of the structure. We thus explored possible interactions of the complex with other components of the system. Nitrobenzene, which is largely prevalent in the system, does not appear do form any stable formation with the complex. However, water does. The calculated geometry of the complex hydrate is shown in Figure 8. The stabilization energy corresponding to such hydration is predicted to be – 19.75 kJ/mol, i.e. sufficiently high for the hydrate to be stable.

The interesting feature of the hydrate is that the water molecule is bound by the already bonded H_3O^+ ion by a system of three medium-strong hydrogen bonds indicated in the Figure. In order to accomplish that, the water molecule has to penetrate the rather rigid and hydrophobic calixarene cavity (no other way apparently leads to a stable product), which can be expected to lead to rather long reaction times as observed. In addition, the water molecule also interacts with the aromatic systems by two weak hydrogen bonds (some of the O-H-C$_{ar}$ distances being as short as 2.55 Å). In agreement with NMR spectra, these bonds without doubt slow down internal motions in the calixarene unit.

Figure 7: Optimized geometry of free **1** (A) and the **1**· H_3O^+ complex (B) calculated at the B3LYP/6-31G(d) level (positions of hydrogen atoms in **1** are not shown)

In contrast to NMR, however, we were not able to find any alternative stable form of the hydrate. Taking into account the fact that our calculations were done *in vacuo* (as no sufficiently reliable correction for the influence of polar medium has been found for this level of precision), we cannot be quite sure that other structural forms of the complex hydrate are excluded by theory.

Figure 8: Optimized geometry of the hydrated **1**· H_3O^+ complex calculated at the B3LYP/6-31G(d) level (positions of hydrogen atoms in **1** are not shown).

Conclusions. According to the evidence of ^1H and ^{13}C NMR spectra consistent with the predictions of high-precision DFT calculations, calixarene **1** binds the H_3O^+ ion into an equimolecular complex. The formation of the main form of the complex, similarly as the exchange between free and bound **1**, is very fast but the equilibrium is only moderately favorable to the complex. In the main form, H_3O^+ is probably bound by three strong hydrogen bonds to three aryl-oxygen atoms of **1** and by two weaker hydrogen bonds to the remaining C-O-C group. In contrast to free **1**, the complex has almost C_4 symmetry. Under prolonged storage of the complex-containing mixtures, small amounts of another form of the complex appear. It is evidently formed from the original complex and probably is the product of its hydration.

When compared with the calixarenes with strongly coordinating groups in addition to aryl-oxygen atoms at their lower rim [13-15], the present calixarene type clearly is a markedly less efficient complexing agent. From this one can conclude that the C-O-C groups, although they clearly participate in the complex H_3O^+ binding in the former types [13-15], are as such less effective than in cooperation with e.g. dimethylamide, dimethylthioamide, ester and keto-groups.

EXPERIMENTAL

Materials and samples. Nitrobenzene-d_5 was purchased by Aldrich. Tetrapropoxy-*p*-*tert*-butylcalix[4]arene **(1)** was prepared by using the procedure published elsewhere [23].

Preparation of hydrogen bis(1,2-dicarbollyl) cobaltate (HDCC) was described earlier [16]. For NMR samples, 0.5×10^{-5} mol of **1** was dissolved in a mixture of appropriate amounts of nitrobenzene-d_5 and 0.002 mol/L solution of HDCC in the same solvent. The mixing and all subsequent measurements were done at 296 K.

NMR spectra. ^{1}H and ^{13}C NMR spectra were measured in a quadrature detection mode at 300.13 and 75.45 MHz, respectively, with an upgraded Bruker Avance DPX300 spectrometer. 32 and 64 kpoints were measured for ^{1}H and ^{13}C NMR, respectively. ^{1}H NMR spectra were measured using a self-devised diffusion-filtering stimulated echo pulse sequence $–d_1\text{-}\pi/2_{\varphi}\text{-}GR\text{-}\pi/2_{\sigma}\text{-}d_2\text{-}\pi/2_{-y}\text{-}GR\text{-}REC_x$ in order to remove obscuring broad signals of water and nitrobenzene; d_1 and d_2 were 10 s and 60 ms, respectively, the z-gradient GR was 50 G/cm and phase cycling was φ = x, y, -x, -y, $\sigma = \varphi + \pi/2$. 128 scans were collected for each spectrum. ^{13}C NMR measurements were performed using either the ^{1}H-^{13}C DEPT45 sequence (collecting 8000 scans) or its combination with its long-range variant optimized for the coupling constant 6 Hz (collecting at least 20000 scans); exponential weighting (lb = 1 Hz) was used before Fourier transform. In ^{1}H – ^{13}C 2D HSQC and HMBC spectra used for signal assignment, 1028 points in F2 and 256 increments in F1 dimensions were measured using a z-gradient inverse-detection probe.

Quantum mechanical calculations. *Ab initio* molecular orbital calculations were performed using the GAUSSIAN 03 suite of programs [16]. Molecular geometry was fully optimized at the B3LYP level of density functional theory (DFT) with the 6-31G(d) basis set. The optimization was unrestrained. Several local configurations near the achieved energy minimum were examined. As the renewed optimizations converged to the same molecular geometry, we believe the achieved energy minimum to be the global one.

Acknowledgements. This work was supported by the Academy of Sciences of the Czech Republic, Project T400500402, and the Czech Ministry of Education, Youth and Sports, Projects MSM 4977751303 and MSM 6046137307.

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Protonation of Tetrapropoxy-4-*tert*-butylcalix[4]arene: NMR Study of Interaction and Probable Structures of the Product

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Using ^{1}H and ^{13}C NMR spectroscopy, the interaction of tetrapropoxy-*p-tert*-butylcalix[4]arene (1) with H_3O^+ ions produced by hydrogen bis(1,2-dicarbollyl) cobaltate (HDCC) and traces of water was studied in nitrobenzene-d_5. It was shown that 1 readily forms an equimolecular complex with H_3O^+. The equilibrium constant K of its formation is 2.6 at 296 K. Exchange between bound and free 1 is fast even under mild excess of HDCC, the correlation time τ_{ex} being about 0.13 ms. NMR shows that H_3O^+ is bound to the aryl-oxygen atoms and this binding forces the calixarene cup to adopt a more open and symmetrical conformation. This conclusion is in a full accord with high precision quantum DFT calculations which find one structure of the complex corresponding to a global energy minimum, in which the H_3O^+ ion is bound to three of the oxygen atoms by strong hydrogen bonds and to the remaining oxygen by two weaker hydrogen bonds. The calixarene part is forced into a C_4 symmetrical opened form.

When stored for weeks, the complex gradually transforms into other forms, most probably its hydrates, according to spectral evidence and DFT calculations.

Keywords: calixarene complex; calixarene protonation; NMR; DFT

INTRODUCTION

Calixarene-based molecules have received intense attention in the recent years [1,2]. Many studies have focused on the binding ability of calixarene derivatives with carbonyl or analogous groups at their lower rims toward metal ions [3-12]. In our recent studies [13-15], we have shown that calixarenes carrying coordinating groups, such as dimethylthioamide, ester or keto groups on their lower rim, bind a hydroxonium ion H_3O^+ in equimolecular and very stable complexes. NMR spectra and high-level quantum calculations revealed that H_3O^+ binds partly to the attached coordinating groups but also to the calixarene aryl-oxygen atoms. Quantum calculations even indicated that binding almost exclusively to the Ar-O- atoms could be even preferred in some cases. It is thus interesting to examine H_3O^+ binding to a calixarene containing only Ar-O-R groups where R is an alkyl such as *n*-propyl in our case.

Like in our previous studies [13-15, 17, 18], hydrogen bis(1,2-dicarbollyl) cobaltate (HDCC)[16] was used as a reliable source of protons, which were converted to hydroxonium ions H_3O^+ by a 3.1 mol/mol excess of water. Combining NMR spectral evidence with DFT quantum mechanical calculations, we suggest the most probable structure of the protonated calixarene.

RESULTS AND DISCUSSION

NMR measurements. Our experiments with **1** (see Scheme 1) were carried out in nitrobenzene-d_5 as one of the sufficiently polar solvents (needed for full ionization of HDCC), which do not form inclusion complexes with calixarenes. After mixing **1** with increasing amounts of HDCC, its ^{1}H NMR signals gradually shift to a various degree as illustrated in Figure 1. The signal assignment corresponds to Scheme 1, where the protons are numbered in the same way as the carbons they are attached to. The signal shifts are analogous to those observed with other calixarene derivatives [13-15] as a sign of conformation change due to binding of H_3O^+ ion at the lower rim.

As the signals shift immediately and without splitting, the protonation of **1** must be very fast. However, the persistent shift at larger excess of HDCC (cf. Figure 1) indicates that the product formation is not quantitative in the 1:1 mixture. We are thus dealing with a dynamic equilibrium, which is only moderately favorable to the complex.

Figure 1: 300.13 MHz NMR spectra of calixarene **1** (A) and its 1:2 (B) and 1:4 mol/mol (C) mixtures with HDCC (nitrobenzene-d_5, 296 K). Signal assignment in A (cf. Scheme 1), extrapolated maximal shifts $\Delta\delta_{\max}$ (in ppm) in C, correlation times of exchange τ_{ex} (in ms) in B.

Scheme 1

The equilibrium should follow the usual relation

$$K = \frac{[\mathbf{1}\cdot \mathrm{H}^+][\mathrm{A}^-]}{[\mathbf{1}][\mathrm{A}^-\mathrm{H}^+]} \quad , \qquad (1)$$

where A^-H^+ and A^- stand for HDCC or any other suitable proton donor and its anion. Under fast exchange between free and coordinated **1**, the actual chemical shift of any signal is a weighted average of the shifts corresponding to the exchanging sites. Thus the actual relative shift is $\Delta\delta = \alpha\Delta\delta_{\max}$, where $\alpha = [\mathbf{1}\cdot \mathrm{H}^+]/[\mathbf{1}]_0$ and $\Delta\delta_{\max}$, obtained by extrapolation, is the maximum relative shift corresponding to the pure complex. Using Eq.1, $\Delta\delta$ can be expressed as

$$\Delta\delta = \Delta\delta_{\max}\frac{K(1+\beta) - \sqrt{K^2(1+\beta)^2 - 4(K-1)K\beta}}{2(K-1)} \quad , \qquad (2)$$

where $\beta = [\mathrm{A^-H^+}]_0/[\mathbf{1}]_0$. Thus K can be obtained by fitting Eq.2 to the experimental values of $\Delta\delta$. Figure 2 shows $\Delta\delta$ of individual signals in the proton spectra of **1**/HDCC mixtures and the fitting curves.

Figure 2: Relative shifts Δδ of signals in ^{1}H NMR spectrum of **1** and its mixtures with HDCC in nitrobenzene-d_5 at 296 K and their fitting with Equation 2.

The value of K to which all the actual relative shifts fit is 2.61 ± 0.03. This is a much lower value than we observed in protonation of calixarenes bearing additional coordinating groups [13-15].

The apparent swiftness of exchange between free and bound **1** gives us the opportunity to examine its dynamics quantitatively. One of the possible methods is the measurement of transverse relaxation rate using the Carr-Purcell-Meiboom-Gill sequence (CPMG) [19] with a varied delay t_p between the π pulses. As shown by Luz and Meiboom [20], the actually measured relaxation rate $R_2(t_p)$ can be expressed as

$$R_2(t_p) = R_2^{\,0} + p_1 p_2 \delta\omega^2 \tau_{ex}[1 - (\tau_{ex}/t_p)\tanh(t_p/\tau_{ex})] \tag{3}$$

where $R_2^{\,0}$ is the part of relaxation rate independent of exchange, p_1 and p_2 are the probabilities of finding the nucleus at the sites 1 and 2, respectively, $\delta\omega$ is the relative chemical shift between the two sites in rads and τ_{ex} is the correlation time of exchange. For short τ_{ex}, Equation 3 can be approximated (slightly modifying the relations in Ref. 21) by

$$R_2(t_p) = \zeta - \xi \tau_{ex}^{\,2}/t_p \tag{4}$$

with

$$\zeta = R_2^{\,0} + \xi\tau_{ex} \tag{4a}$$

and

$$\xi = 4\pi^2 \alpha(1-\alpha)(\Delta\delta_{\max})^2 \tag{4b}$$

where $\Delta\delta_{\max}$ is the relative shift (in Hz) of the given signal between free **1** and its complex. Thus the dependence of $R_2(t_p)$ on $1/t_p$ is linear with the slope $\xi\tau_{ex}^{\ 2}$. As $\Delta\delta_{\max}$ is obtained by extrapolation from the spectra and α can be calculated from actual $\Delta\delta$ (see above), obtaining τ_{ex} from the slope is straightforward. Figure 3 shows dependences for three most mobile signals in the proton spectrum of the **1**/HDCC mixture 1:2 mol/mol, namely 4+8, 10 and 9e. The values of τ_{ex} obtained from the individual slopes are 1.33×10^{-4}, 1.36×10^{-4}, and 1.24×10^{-4} s, respectively. These values are sufficiently close to each other to have a physical meaning of the correlation time of exchange between free and bound forms of **1**. Evidently, the exchange is quite fast, its rate constant being about 7.6×10^{3} s^{-1}.

Figure 3: Dependence of the measured net increase in the transverse relaxation rate of the indicated most mobile signals in the 300.13 MHz ^{1}H NMR spectrum of the mixture of **1** with HDCC 1:2 (mol/mol) in nitrobenzene-d_5 at 296 K

Returning now to the shape of ^{1}H NMR spectra, the 0.323 ppm mutual approach of the signals 9a and 9e (axial and equatorial CH_2 protons) relative to free **1** is a clear sign that the aromatic part of **1** adopts a more open and symmetric conformation in the complex [12]. This conclusion is corroborated by the significant deshielding of aromatic protons 4, 8. Such a change can be forced only by a H_3O^+ binding at the lower rim of **1**, i.e. to the aryl-oxygen atoms. In agreement with this, protons 10 (O-CH_2-) are significantly deshielded, too. Assuming that H_3O^+ is bound by three strong hydrogen bonds [13-15], one would expect that one of the four O-CH_2- groups should be perceptibly different from the other three. The shape of the proton (and also carbon, see below) spectrum indicates a C_4 symmetry, however. There are two possible explanations of this behavior: either the H_3O^+ ion adopts multiple weaker bonds to the fourth oxygen atom and is thus placed near to the center of the lower rim or it rotates very fast within the molecule averaging thus its structure in the NMR time window. Deciding between these two alternatives is beyond the abilities of NMR.

Most of the just described features can also be read out from the ^{13}C NMR spectra. Figure 4 reproduces DEPT45 spectra (showing only carbons with attached protons) of **1** and its 1:4 mol/mol mixture with HDCC, the latter having been measured 6 to 18 hours after mixing. Large downfield shifts of signals 4,8 and 10 leave no doubt that a complex was formed between **1** and H_3O^+, with the ion probably bound to the aryl-oxygen atoms. In analogy to proton spectra, the signals are single (except for small accompanying signals) suggesting thus again either C_4 symmetry of the complex or fast averaging of the structure by internal motion.

Figure 4: 75.5 MHz ^{13}C NMR DEPT45 spectra of 5 mmol/L calixarene **1** (A) and its mixture with 4.0 mol/mol excess of HDCC (B) 6 – 18 h after mixing (nitrobenzene-d_5, 296 K). Assignment of signals in A (cf. Scheme 1), relative shifts (in ppm) in B.

However, measurement of long-range DEPT spectra designed to show signals of quaternary carbons shown in Figure 5 (which was more time-consuming and reflects thus a later stage of the development of the system) revealed splitting of carbon signals 5, 6 and 7 suggesting either lower symmetry of the complex or coexistence of two different structures. In addition to it, the smaller companions of each of the main signals, which already appeared in the normal DEPT45 spectra, somewhat increased in relative intensity. Evidently, a new variant of the complex is evolving very slowly from its original form and, as one can expect, the exchange between both forms is quite slow, too. Such multiple complex forms were already observed in the case of some calixarenes with attached ester and keto groups [14, 15] where the formation of the H_3O^+ complex was very slow. In contrast to it, the formation of the present original complex is very fast although its equilibrium is less favorable.

Figure 5: Parts of combined 75.5 MHz ^{13}C NMR DEPT45 and LR-DEPT45 spectra of 5 mmol/L calixarene **1** (A) and its mixture with 4.0 mol/mol excess of HDCC (B) 10 – 12 days after mixing (nitrobenzene-d_5, 296 K)

Figure 6: Parts of 300.13 MHz ^{1}H NMR (above) and 75.5 MHz ^{13}C NMR DEPT45 (below) spectra of the mixture of 5 mmol/L calixarene **1** with 4.0 mol/mol excess of HDCC measured 3 weeks after mixing (nitrobenzene-d_5, 296 K).

Inspection of the spectra of **1** – HDCC 1:4 mixture (see Figure 6, where the assignment of signals to individual forms was made using a combination of ^{1}H NOESY and ^{1}H-^{13}C HSQC spectra) after 3 weeks of storage reveals two different new forms of the complex, B and C, produced from the original form A. The same new forms can be observed in a lower relative population in systems with a lower excess of HDCC, even in the 1:1 mixture. Therefore, it is not probable that the new forms are complexes with a higher number of H_3O^+ ions. However, a 0.23 ppm downfield relative shift of the broad H_2O signal (not shown) in the long-stored 1:4 mixture indicates that water takes part in the new forms. As it can be seen in Figure 6, the more prominent form B among the new products no longer exhibits C_4 symmetry. Quite to the contrary, there is magnetic nonequivalence between at least two doubles of opposite aromatic rings (in the proton spectrum of B, even all four *tert*-butyl groups are nonequivalent). Experience with NMR spectra of calixarenes teaches us that such nonequivalence should not be overvalued: due to their strong long-range shielding effects of the aromatic rings, even subtle changes in their relative orientation can lead to remarkable shifts of the signals of adjacent nuclei. Nevertheless, the observed nonequivalence cannot be ignored for two reasons: (i) it reflects lowering of the molecular symmetry from apparent C_4 to C_2 or even lower and (ii) it shows that the residence time in the exchange between nonequivalent analogous nuclei must be larger than 0.05 s, i.e. the internal motion in the molecule B is at least two orders of magnitude slower than that in the form A. Therefore, the most plausible conclusion appears to be that the form B (and probably also C) is a hydrate of the complex A with a water molecule placed inside the calixarene cavity. The molecule has to sit near enough to the lower rim in order to interact with the bound H_3O^+ ion, which necessarily means that it interacts with at least two opposite aromatic rings (probably by a weak hydrogen bond) lowering thus the symmetry of the complex and slowing down its internal motion.

Quantum chemical calculations. Geometry optimizations of calixarene and its complex with H_3O^+ were performed by the quantum chemical calculations at the density functional level of theory (DFT, B3LYP functional) using the Gaussian 03 suite of programs [22]. The 6-31G(d) basis set was used and the optimization was unconstrained. The optimized structure of free calixarene is shown in Figure 7A. The most stable conformation forms a pinched cone structure with a C_2 symmetry.

The structure obtained by optimization of the calixarene - H_3O^+ complex is shown in Figure 7B, together with the lengths of hydrogen bonds (in Å). Compared to free molecule the calixarene part of the complex is distorted so that its structure is very close to the C_4 symmetry. The hydroxonium ion is placed in the cage formed by calixarene and is bound by strong hydrogen bonds to oxygen atoms of three C-O-C groups and by two somewhat weaker hydrogen bonds to the last C-O-C group. The stabilization energy of the complex calculated as the difference between the energies of the optimized complex and optimized free calixarene molecule and hydroxonium ion is -394.72 kJ/mol. Stabilization energy of the complex can be expressed also with respect to the aqueous hydroxonium ion $[H_3O^+(H_2O)_3]$ and free calixarene (**1**) according to the formula

$$[H_3O^+(H_2O)_3] + \mathbf{1} \rightarrow [H_3O^+(\mathbf{1})] + 3\ H_2O.$$

Then it is -8.20 kJ/mol. This value, corrected further for entropy change, probably corresponds to the value of *K* established above by NMR.

The gradual development of another form of the complex detected by NMR led us to explore its further possible changes or interactions. As the structure described above corresponds to the global energy minimum found by unconstrained geometry optimization, a new form could scarcely be produced by an internal rearrangement of the structure. We thus explored possible interactions of the complex with other components of the system. Nitrobenzene, which is largely prevalent in the system, does not appear do form any stable formation with the complex. However, water does. The calculated geometry of the complex hydrate is shown in Figure 8. The stabilization energy corresponding to such hydration is predicted to be – 19.75 kJ/mol, i.e. sufficiently high for the hydrate to be stable.

The interesting feature of the hydrate is that the water molecule is bound by the already bonded H_3O^+ ion by a system of three medium-strong hydrogen bonds indicated in the Figure. In order to accomplish that, the water molecule has to penetrate the rather rigid and hydrophobic calixarene cavity (no other way apparently leads to a stable product), which can be expected to lead to rather long reaction times as observed. In addition, the water molecule also interacts with the aromatic systems by two weak hydrogen bonds (some of the O-H-C$_{ar}$ distances being as short as 2.55 Å). In agreement with NMR spectra, these bonds without doubt slow down internal motions in the calixarene unit.

Figure 7: **O**ptimized geometry of free **1** (A) and the **1**· H_3O^+ complex (B) calculated at the B3LYP/6-31G(d) level (positions of hydrogen atoms in **1** are not shown)

In contrast to NMR, however, we were not able to find any alternative stable form of the hydrate. Taking into account the fact that our calculations were done *in vacuo* (as no sufficiently reliable correction for the influence of polar medium has been found for this level of precision), we cannot be quite sure that other structural forms of the complex hydrate are excluded by theory.

Figure 8: Optimized geometry of the hydrated **1**·H_3O^+ complex calculated at the B3LYP/6-31G(d) level (positions of hydrogen atoms in **1** are not shown).

Conclusions. According to the evidence of ^{1}H and ^{13}C NMR spectra consistent with the predictions of high-precision DFT calculations, calixarene **1** binds the H_3O^+ ion into an equimolecular complex. The formation of the main form of the complex, similarly as the exchange between free and bound **1**, is very fast but the equilibrium is only moderately favorable to the complex. In the main form, H_3O^+ is probably bound by three strong hydrogen bonds to three aryl-oxygen atoms of **1** and by two weaker hydrogen bonds to the remaining C-O-C group. In contrast to free **1**, the complex has almost C_4 symmetry. Under prolonged storage of the complex-containing mixtures, small amounts of another form of the complex appear. It is evidently formed from the original complex and probably is the product of its hydration.

When compared with the calixarenes with strongly coordinating groups in addition to aryl-oxygen atoms at their lower rim [13-15], the present calixarene type clearly is a markedly less efficient complexing agent. From this one can conclude that the C-O-C groups, although they clearly participate in the complex H_3O^+ binding in the former types [13-15], are as such less effective than in cooperation with e.g. dimethylamide, dimethylthioamide, ester and keto-groups.

EXPERIMENTAL

Materials and samples. Nitrobenzene-*d*$_5$ was purchased by Aldrich. Tetrapropoxy-*p*-*tert*-butylcalix[4]arene **(1)** was prepared by using the procedure published elsewhere [23].

Preparation of hydrogen bis(1,2-dicarbollyl) cobaltate (HDCC) was described earlier [16]. For NMR samples, 0.5×10^{-5} mol of **1** was dissolved in a mixture of appropriate amounts of nitrobenzene-d_5 and 0.002 mol/L solution of HDCC in the same solvent. The mixing and all subsequent measurements were done at 296 K.

NMR spectra. ^{1}H and ^{13}C NMR spectra were measured in a quadrature detection mode at 300.13 and 75.45 MHz, respectively, with an upgraded Bruker Avance DPX300 spectrometer. 32 and 64 kpoints were measured for ^{1}H and ^{13}C NMR, respectively. ^{1}H NMR spectra were measured using a self-devised diffusion-filtering stimulated echo pulse sequence $–d_1-\pi/2_\varphi-GR-\pi/2_\sigma-d_2-\pi/2_{-y}-GR-REC_x$ in order to remove obscuring broad signals of water and nitrobenzene; d_1 and d_2 were 10 s and 60 ms, respectively, the z-gradient GR was 50 G/cm and phase cycling was $\varphi = x, y, -x, -y$, $\sigma = \varphi + \pi/2$. 128 scans were collected for each spectrum. ^{13}C NMR measurements were performed using either the ^{1}H-^{13}C DEPT45 sequence (collecting 8000 scans) or its combination with its long-range variant optimized for the coupling constant 6 Hz (collecting at least 20000 scans); exponential weighting (lb = 1 Hz) was used before Fourier transform. In ^{1}H – ^{13}C 2D HSQC and HMBC spectra used for signal assignment, 1028 points in F2 and 256 increments in F1 dimensions were measured using a z-gradient inverse-detection probe.

Quantum mechanical calculations. *Ab initio* molecular orbital calculations were performed using the GAUSSIAN 03 suite of programs [16]. Molecular geometry was fully optimized at the B3LYP level of density functional theory (DFT) with the 6-31G(d) basis set. The optimization was unrestrained. Several local configurations near the achieved energy minimum were examined. As the renewed optimizations converged to the same molecular geometry, we believe the achieved energy minimum to be the global one.

Acknowledgements. This work was supported by the Academy of Sciences of the Czech Republic, Project T400500402, and the Czech Ministry of Education, Youth and Sports, Projects MSM 4977751303 and MSM 6046137307.

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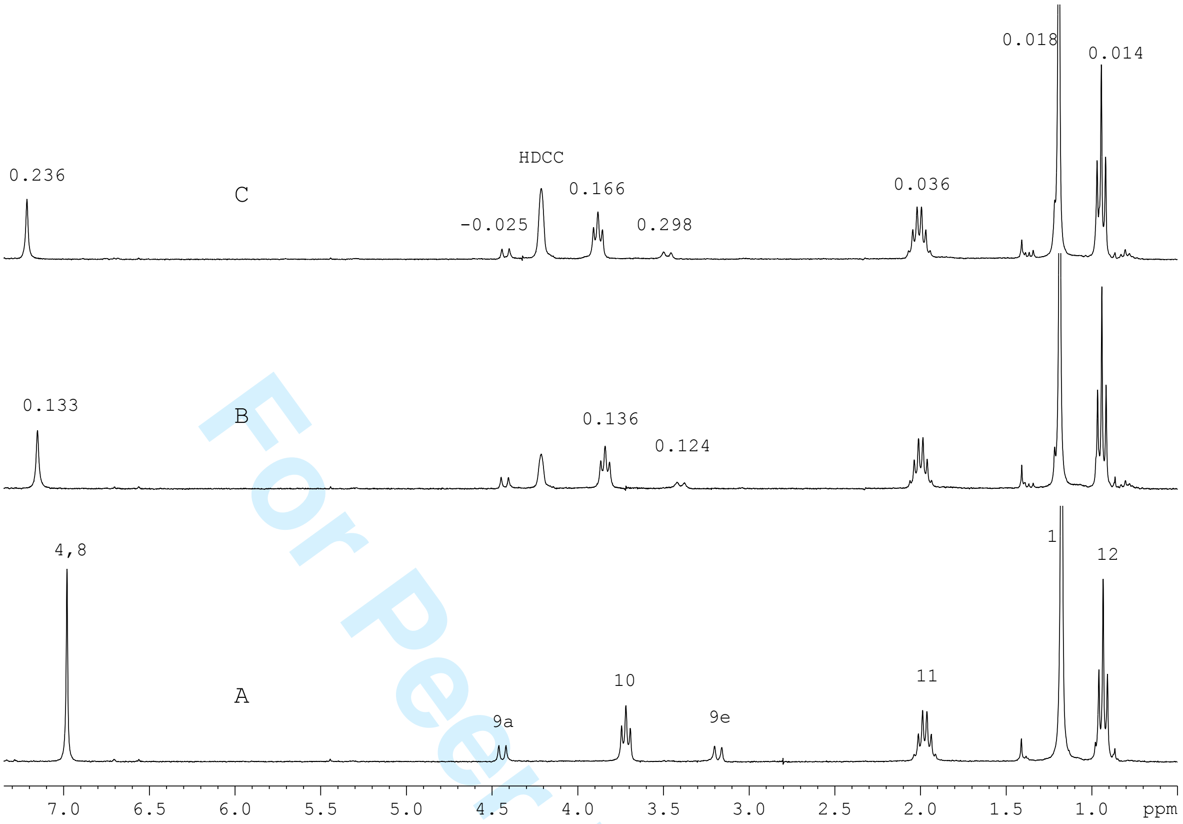
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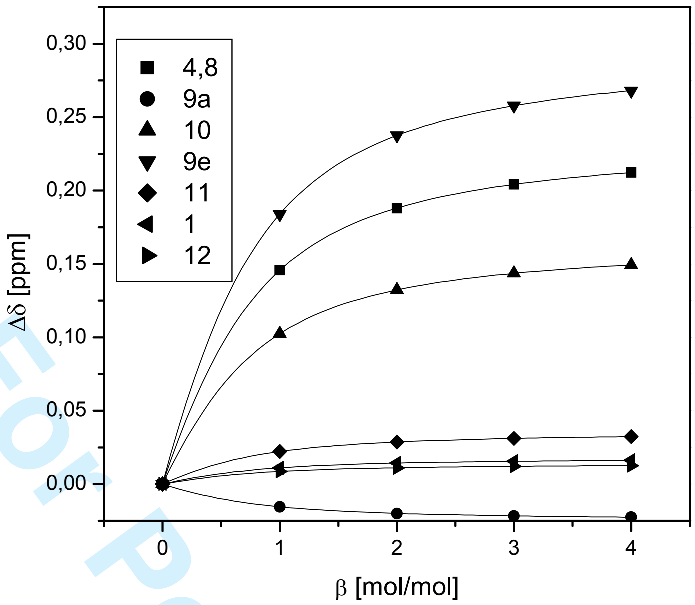
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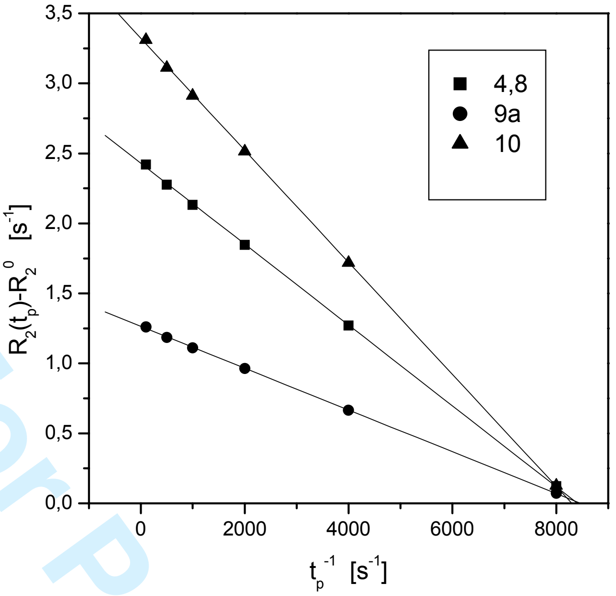
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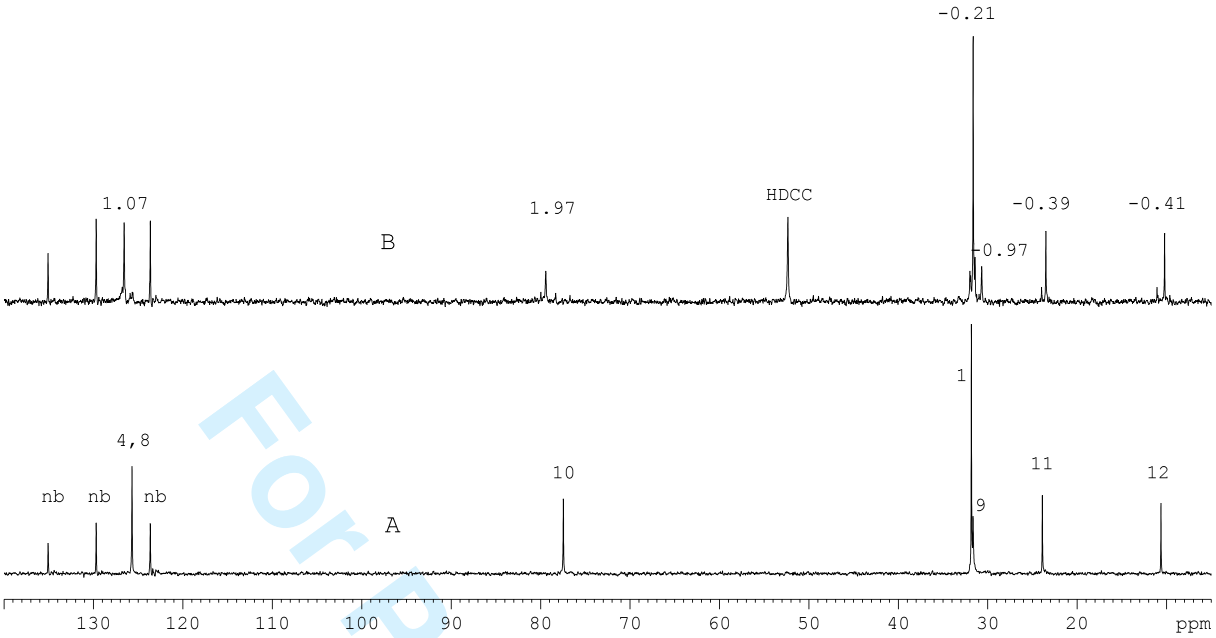
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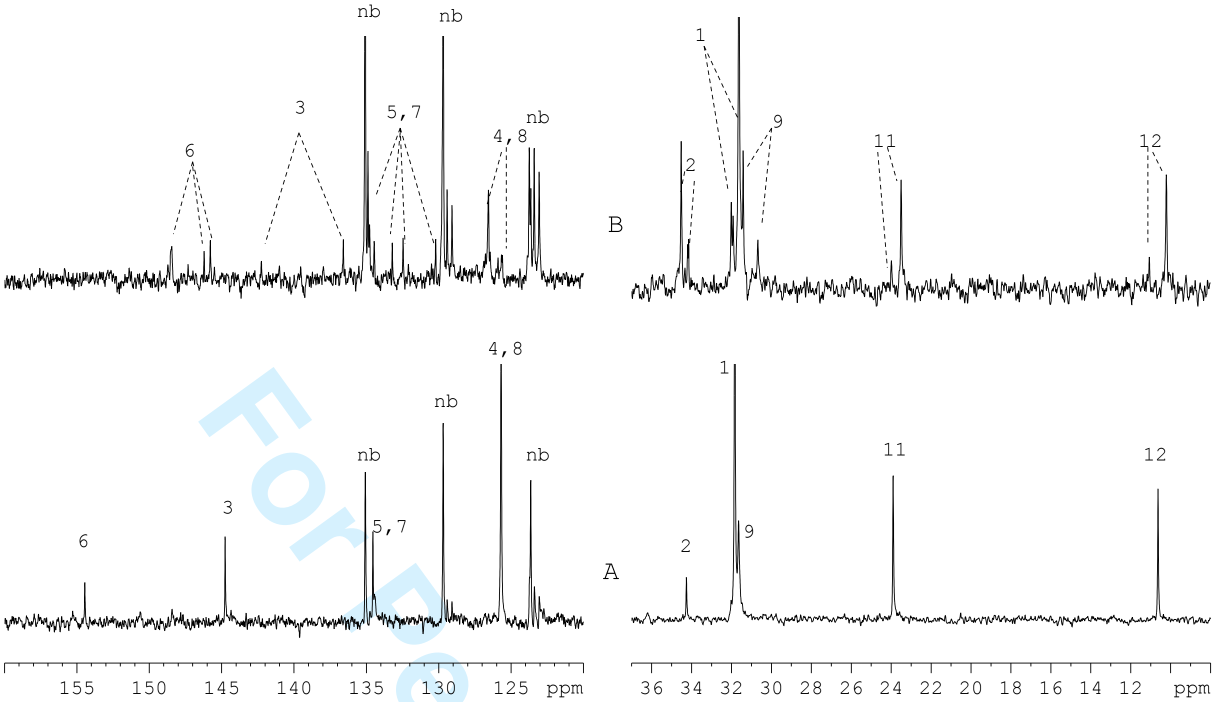
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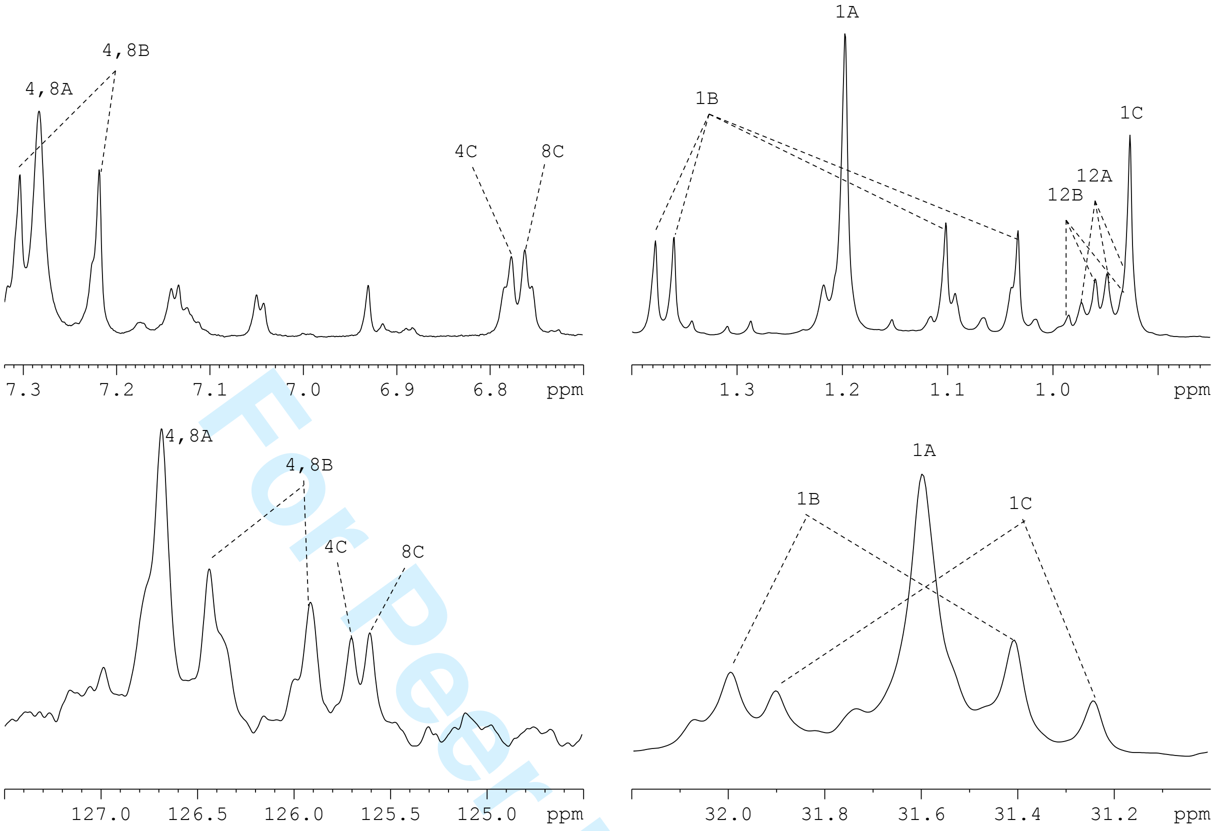
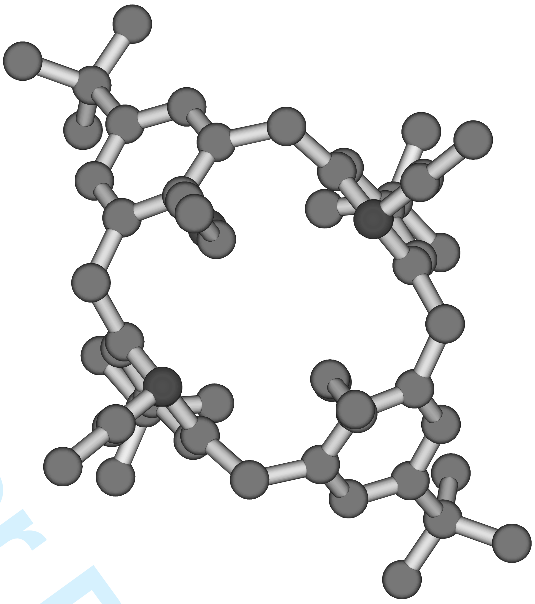
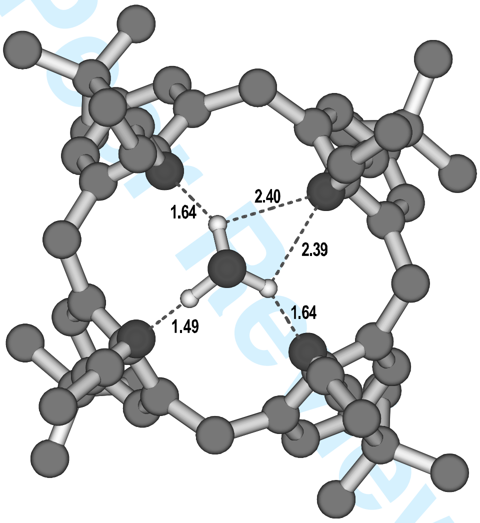
12
B
4,8
nb
nb
nb
6
3
5,7
1
11
12
2
9
A
155 150 145 140 135 130 125 ppm
36 34 32 30 28 26 24 22 20 18 16 14 12 ppm


4,8B
4,8A
4C
8C
7.3
7.2
7.1
7.0
6.9
6.8
ppm
1A
1B
1C
12A
12B
1.3
1.2
1.1
1.0
ppm
4,8A
4,8B
4C
8C
127.0
126.5
126.0
125.5
125.0
ppm
1A
1B
1C
32.0
31.8
31.6
31.4
31.2
ppm

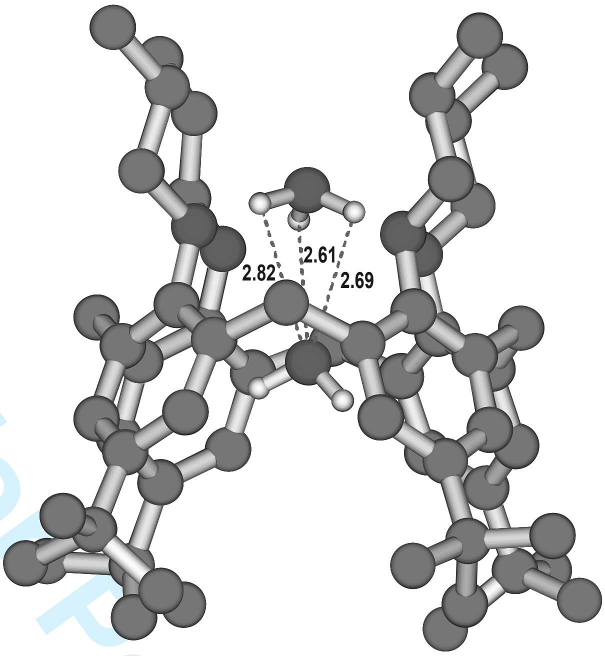


A



1.64
2.40
2.39
1.64
1.49

B


2.82
2.61
2.69