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Host–Guest Systems |*Hot Paper*|

EPR Studies of the Binding Properties, Guest Dynamics, and Inner-Space Dimensions of a Water-Soluble Resorcinarene Capsule

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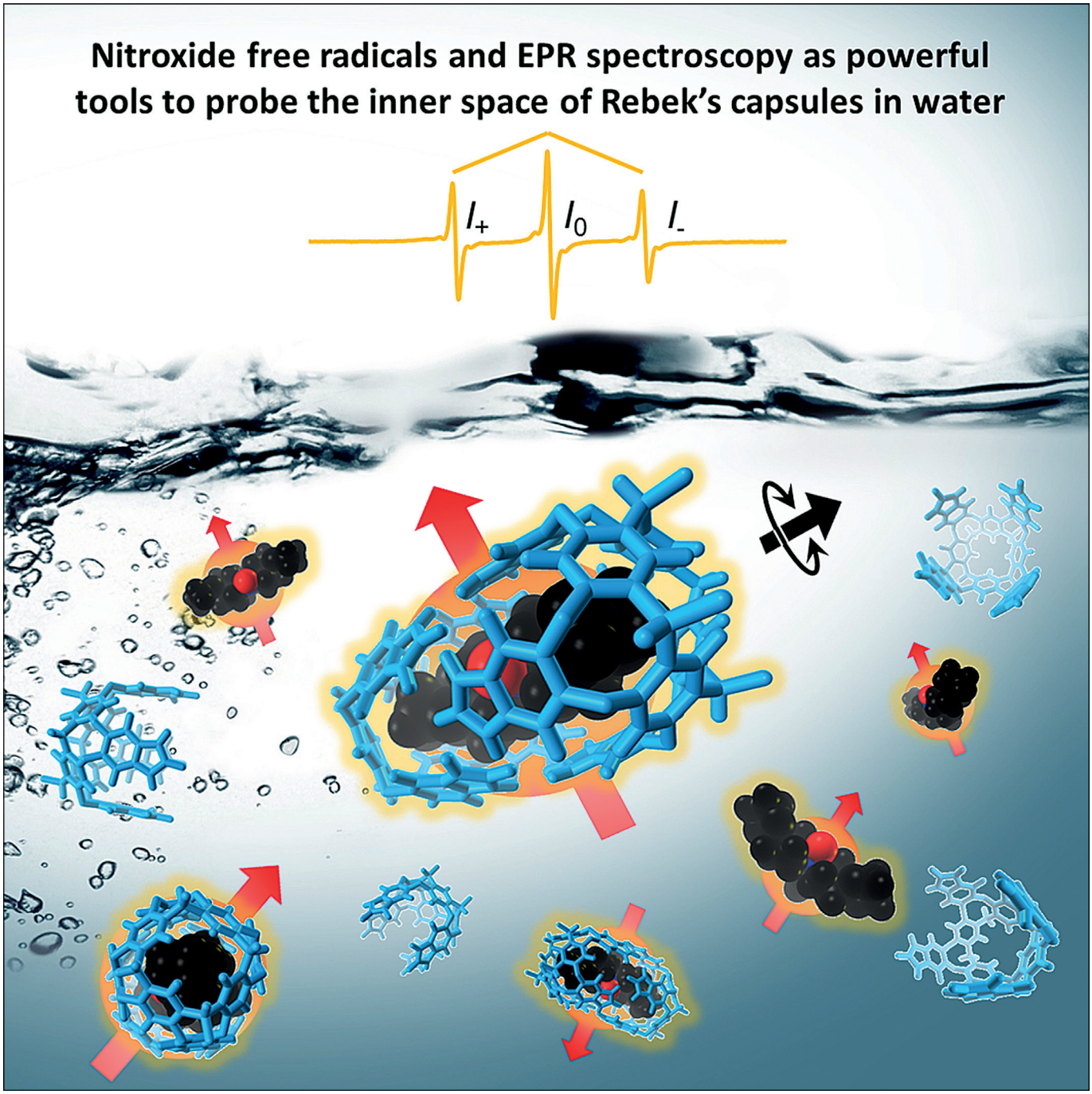
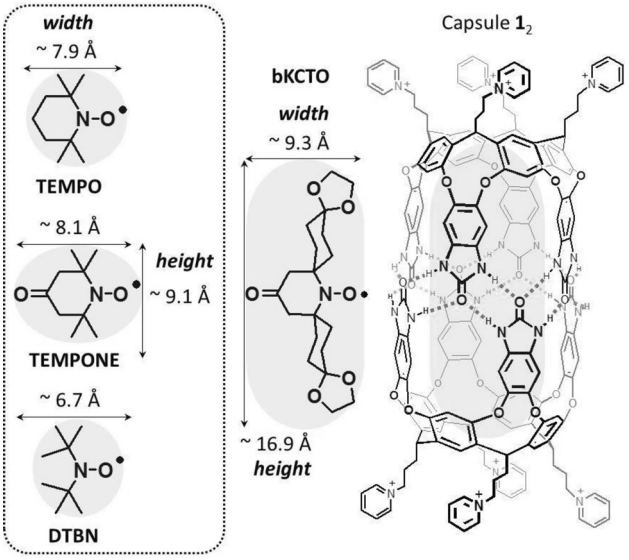


Abstract: Nitroxide free radicals have been used to study the inner space of one of Rebek's water-soluble capsules. EPR and ^{1}H NMR spectroscopy, ESI-MS, and DFT calculations showed a preference for the formation of 1:2 complexes. EPR titrations allowed us to determine binding constants (K_a) in the order of 10^7 M^{-2}. EPR spectral-shape analysis provided information on the guest rotational dynamics within the capsule. The interplay between optimum hydrogen bonding upon capsule formation and steric strain for guest accommodation highlights some degree of flexibility for guest inclusion, particularly at the center of the capsule where the hydrogen bond seam can be barely distorted or slightly disturbed.

Introduction

There is, since the early 80s, a rich tradition of work focused on the study and understanding of the chemical and physical behavior of supramolecular assemblies, with the strong desire to exploit weak noncovalent bonds to create new nano-objects and architectures.[1] One of the fascinating aspects of supramolecular chemistry is the possibility of tuning the assembly of subcomponents for the creation of advanced architectures with well-defined size and shape[2] to achieve predictable functions.[3] Belonging to these various assemblies, host–guest inclusion complexes have attracted considerable attention, with guest molecules in confined spaces providing new perspectives for nanoreactors or -containers.[4] Among pivotal families of molecules featuring macrocycles (cyclodextrins, calixarenes, cucurbiturils, …), resorcinarenes have attracted considerable attention as cavitands or dimeric capsules. Resorcinarene cavitands can give rise to self-assembled dimeric[5] or hexameric[6] capsules because of the right positioning of the self-complementary hydrogen-bonding sites along the resorcinarene skeleton in organic solvents. Several resorcin[4]arene derivatives[7] have been designed with specific recognition groups such as urea,[8] hydroxy group with pyridine,[9] amine with ketone,[10] and DNA base pairs[11] with the aim of favoring dimerization to form capsular assemblies. Among them, those containing four benzimidazolone aromatic panels form supramolecular capsules held by a seam of 16 hydrogen bonds (capsule $\mathbf{1}_2$, Scheme 1).[12] These capsules have inner spaces amenable for guest inclusion and have shown fascinating properties



Scheme 1. Structures of nitroxides and capsule $\mathbf{1}_2$.

such as host-confined guest–guest interactions,[13] catalysis,[14] or selective sequestration.[15]

However, these capsules have long been limited to organic solvents due to the inherent dimerization process that relies on multiple hydrogen-bonding interactions between two cavitands.[12,16] The main class of water-soluble resorcinarenes is Octa Acid (OA), which dimerizes upon guest binding as a result of the hydrophobic effect. Its properties have been studied in detail by NMR, EPR, and fluorescence spectroscopy since their discovery in early 2000.[17,18] In 2013, Rebek and coworkers reported the preparation of a water-soluble version of a benzimidazolone cavitand, which was able to dimerize in water due to a complementary seam of hydrogen bonds (capsule $\mathbf{1}_2$, Scheme 1).[19] Hydrophilic pyridinium "feet" grant the structure solubility in water (Scheme 1) and the self-complementarity of the hydrogen-bond donors and acceptors of the upper rims still enable dimerization even in this competitive solvent. The cylindrical self-assembled capsules have a nonspherical inner space and are able to accommodate guest molecules such as long *n*-alkanes and stilbenes. For water-soluble cavitands such as **1**, depending on the size and nature of the guest molecules, monomeric open-ended cavitands **1** or dimeric capsules $\mathbf{1}_2$ host–guest complexes are formed in water.[20] The recently reported benzimidazolone capsule[19] has

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been investigated in detail, especially by NMR spectroscopy. To provide additional insights into this capsule and its ability to accommodate guests, we reasoned that EPR spectroscopy combined with MS and NMR spectroscopy could provide valuable complementary information.

Moreover, the collective search for efficient cages for nitroxide radicals (cyclodextrins,[21] cucurbiturils[22,23]) has shown that capsule $\mathbf{1}_2$ is a promising supramolecular assembly for sequestering and isolating nitroxide free radicals from each other and from bulk solution. Nitroxides are stable organic free radicals that have been successfully used in various applications, such as in the site-directed spin labeling of proteins,[24] dynamic nuclear polarization,[25] the oxidation of alcohols,[26] organic magnets,[27] and living free-radical polymerization.[28]

Moreover, the use of nitroxides in combination with EPR spectroscopy has proved to be a powerful method for investigating the self-assembly of supramolecular objects and host–guest systems.[6e,22,23,29] The use of nitroxides as probes enables us to gain detailed data of various parameters, such as binding constants, the molecular dynamics of guests, polarity, and the dimensions of the inner space. Herein, we report on the formation and steric strains involved in the accommodation of guests in water-soluble capsules by combining the results obtained using nitroxides as probes by EPR, NMR, and MS characterization techniques.

Results and Discussion

TEMPO-based nitroxides are ellipsoidal molecules with dimensions that can fit into the inner space of the water-soluble capsule $\mathbf{1}_2$ (Scheme 1). Using X-band EPR spectroscopy, we performed a preliminary screening of a series of nitroxides with different sizes and hydrophilicities as molecular rulers. It is relevant to mention that the nitroxides are all soluble in water at the concentrations used in this work in the absence of the host molecules. Carboxy-PROXYL, TEMPAMINE (for the structures, see the Supporting Information), and TEMPOL (0.2 mM, Figure 1d,e) did not show any detectable variation in their EPR spectra upon addition of cavitand **1**, from 0.1 to 4 equivalents, which indicates that neither the environment of the N–O$^{\bullet}$ bond nor the rotational dynamics of the nitroxide changed on the EPR timescale (μs–ns). It seems that the presence of ionic or highly polar groups prevents the inclusion of the nitroxide in the cavitand (1:1 complex) or in the capsule (1:2 complex). Conversely, the typical three-line EPR spectra of TEMPO, TEMPONE, DTBN, and bKCTO changed after the addition of cavitand **1** (Figure 1a–c for DTBN, see the Supporting Information for the spectra of the other nitroxides; TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl, Carboxy-PROXYL = 3-carboxy-2,2,5,5-tetramethylpyrrolidin-1-oxyl, TEMPAMINE = 4-amino-2,2,6,6-tetramethylpiperidin-1-oxyl, TEMPOL = 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl, TEMPONE = 4-oxo-2,2,6,6-tetramethylpiperidin-1-oxyl, DTBN = di-*tert*-butylaminoxyl, bKCTO = 1,4,14,17-tetraoxa-9-aza-21-oxotetraspiro[4.2.1.2.4.2.3.2] tetracos-9-yl-9-oxyl.

For these four nitroxides, the formation of an inclusion complex is evidenced by 1) the broadening of the high-field line

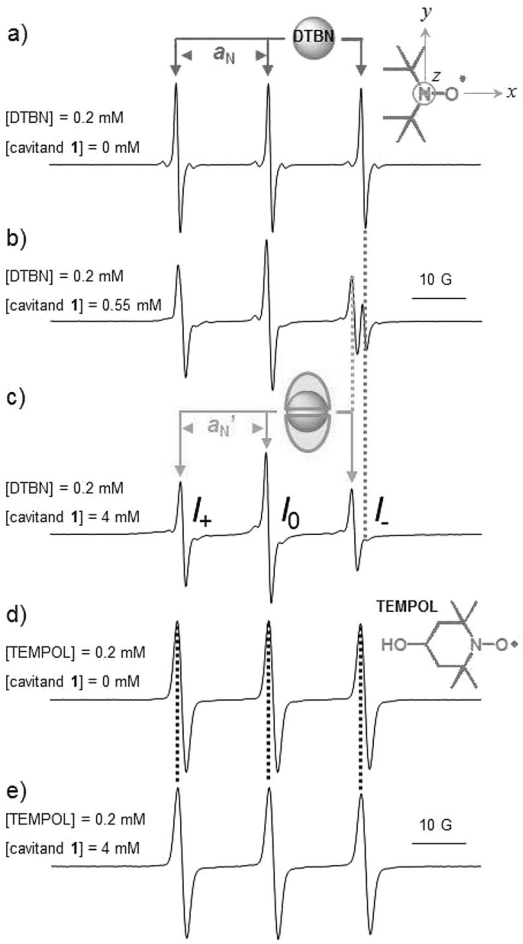

Figure 1. a–c) EPR spectra of DTBN alone (0.2 mM) and in the presence of an increasing concentration of capsule $\mathbf{1}_2$ in water showing the reduced a_N coupling constant upon inclusion. d,e) EPR spectra of TEMPOL alone (0.2 mM) and in the presence of 4 mM capsule $\mathbf{1}_2$ showing no significant changes after the addition of $\mathbf{1}_2$.

highlighting a slower rotational motion, 2) the decrease in the nitrogen hyperfine splitting constant (a_N) by around 0.1 mT (indicating a change in the environmental polarity from water to benzene), and 3) the increase in the *g* value. All these changes evidence that the nitroxide moiety has moved from the bulk water to a more hydrophobic inner space (Figure 1). Moreover, the in/out exchange of guests is relatively slow on the EPR timescale (ns), and at room temperature the spectra of the free and complexed nitroxide are superimposed. Furthermore, the formation of radical pairs was not observed by EPR spectroscopy, because no additional EPR line arising from electron–electron magnetic interactions was observed. All these results seem to indicate that inclusion complexes are formed as cavitand (1:1) or capsule (1:2) complexes.

At a concentration of 4.0 mM of cavitand **1** and 0.2 mM of DTBN (Figure 1), the concentration of free nitroxide is negligible and the EPR spectrum of DTBN@$\mathbf{1}_2$ exhibits a slightly distorted three-line signal with a triangular shape (lines of different intensity) characteristic of an anisotropic re-orientational motion of the probe, as shown in Figure 1c.

The ratios of the peak-to-peak amplitudes of the low-field (I_+), central (I_0), and high-field (I_-) lines are as follows: $I_-/I_0 = 0.55$ and $I_+/I_0 = 0.72$. For free DTBN, these ratios are $I_-/I_0 = 0.96$ and $I_+/I_0 = 1.00$. These results observed for DTBN@$\mathbf{1}_2$ indicate that the DTBN moiety undergoes faster *y*-axis rotational diffusion in the complex than around *x*- and *z*- axes,[30] in agreement with the DFT data (see below).

EPR titration experiments were performed to determine the binding constants (Table 1) and were based on the simultaneous analysis of a large number of spectra obtained with gradual increases of the cavitand concentration using the Rocky program.[31]

Table 1. Hyperfine coupling constants (a_N) of DTBN, TEMPO, TEMPONE, and bKCTO, and binding constants (K_a) for 1:1 and 1:2 inclusion complexes.

Guest	$a_{N,free}$ [mT]	$a_{N,1:1}$ [mT]	$a_{N,1:2}$ [mT]	$K_{a,1}$ [10^3 M^{-1}]	$K_{a,g}$ [10^7 M^{-2}]
DTBN	1.72	1.72	1.59	3.2	7.9
TEMPO	1.73	1.65	1.66	0.8	0.6
TEMPONE[a]	1.61	1.61	1.47	4.4	1.5
bKCTO	1.55	1.51	1.46	9.3	0.5

[a] Aggregate formation seems likely at high concentration, see the Supporting Information.

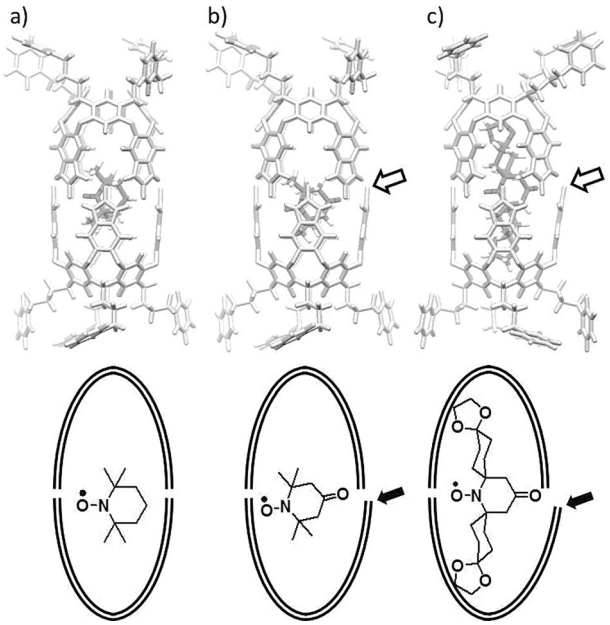

Figure 2. Most stable 1:2 inclusion complexes of a) TEMPO, b) TEMPONE, and c) bKCTO in Rebek capsule $\mathbf{1}_2$, as determined by DFT calculations.

After simulation of the entire set of spectra, a major 1:2 binding model was found with a binding constant of $K_a = 7.91 \times 10^7$ M^{-2} for the inclusion complexation of DTBN in capsule $\mathbf{1}_2$, together with a small amount of the 1:1 complex (< 10%, Table 1 and Figure S8 in the Supporting Information). Furthermore, high-resolution ESI mass spectrometry experiments confirmed the formation of 1:2 DTBN complexes (DTBN@$\mathbf{1}_2$): Peaks at $m/z = 450.8834$ (theoretical 450.8832) corresponding to the formula $C_{184}H_{162}N_{25}O_{25}Cl^{7+\cdot}$ and at $m/z = 531.8591$ (theoretical 531.8586) to $C_{184}H_{162}N_{25}O_{25}Cl_2^{6+\cdot}$, in good agreement with a composition of DTBN@$\mathbf{1}_2$ with one and two chloride ions, respectively (see the Supporting Information).

Based on the EPR data and titration fitting, the ESI-MS data, and the size of the nitroxide, notably for bKCTO, the 1:2 capsular complexes seem to be preferred. This hypothesis is further supported by the NMR data (see below). To gain a more detailed picture of the inclusion complex, molecular mechanics and DFT calculations of the capsular complexes were carried out (Figure 2). The results revealed two favored orientational isomers separated by only 0.3 kcal mol^{-1} that differ only in a slightly different position near the center of the capsule (see the Supporting Information).

TEMPO and DTBN gave similar results: The DFT calculations of the 1:1 complex of TEMPO with cavitand **1** show that it is not stable and that the guest is rapidly expelled from the cavity. The two isomers exhibit an N–O$^\bullet$ bond (*x* axis, Figure 1) perpendicular to the capsule C_4 axis, pointing towards the seam of the capsule for possible hydrogen bonding with the donors of the polar seam, as reported for dicyclohexylurea.[32]

Similar results were observed for the complexation of TEMPO and TEMPONE, with binding constants of the same order of magnitude as for DTBN (Table 1), and the same triangular shape of the EPR spectra (see Figures S5, S9, and S11 in the Supporting Information).

The results observed with TEMPONE can seem surprising, because of a width (8.1 Å, Scheme 1) that is similar to the diameter of the capsule. In a preliminary study, DFT calculations were performed by using a water polarizable continuum model (PCM) and showed that for TEMPONE@$\mathbf{1}_2$, the ketone group of the guest pushes one of the eight walls of capsule $\mathbf{1}_2$ slightly out of the ideal shape (Figure 2). The two orientational isomers are within 0.5 kcal mol^{-1} and even if deformed, the hydrogen-bonding network of the capsule is nearly optimum (Figure 2b).[20a]

^{1}H NMR experiments were also performed to confirm the capsule formation as hypothesized by EPR spectroscopy and ESI-MS. In agreement with the formation of inclusion complexes, diamagnetic analogues of TEMPONE and bKCTO (amine derivatives) showed all of the ^{1}H signals shifted upfield (Figure 3c,f) due to the magnetic shielding provided by the surrounding aromatic walls.[16,18]

For example, for 2,2,6,6-tetramethyl-4-oxopiperidine (TEMPONE diamagnetic analogue), the upfield signals of the methyl and methylene protons appear at $\delta = -0.21$ and -1.62 ppm, respectively ($|\Delta\delta| \geq 2.56$ ppm), and these shifts reflect the positioning of these groups in front of the aromatic walls of the capsule. As reported previously by Rebek and co-workers,[19a] the ^{1}H NMR spectrum of cavitand **1** alone in D_2O exhibits multiple signals arising from at least two "conformations" (C_{4v} "vase" and D_{2d} "kite" shapes, Figure 3a). However, after the addition of the diamagnetic analogue of TEMPONE (Figure 3c) or bKCTO (Figure 3f), the ^{1}H NMR spectrum features one sole conformation on the NMR timescale due to the formation of an inclusion complex. The diamagnetic analogues of TEMPO and

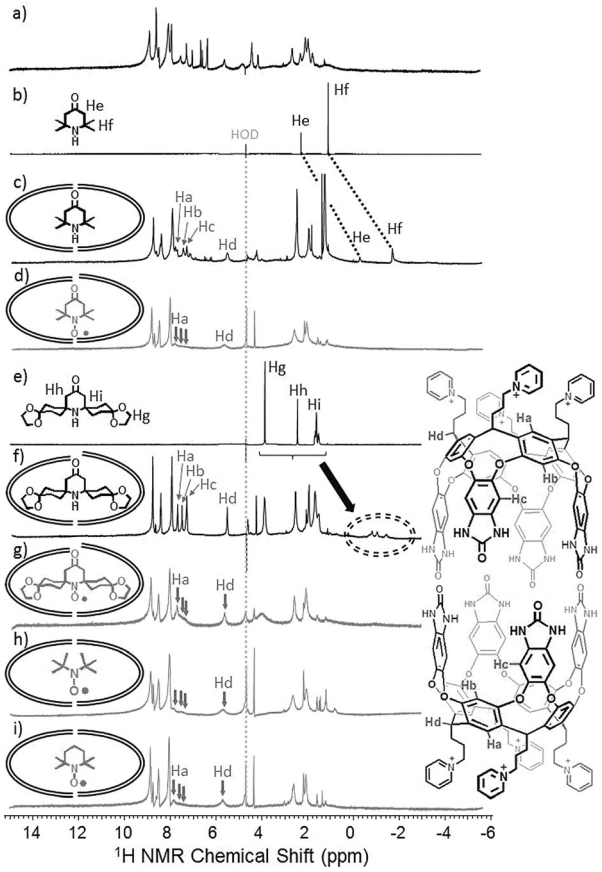

Figure 3. ^{1}H NMR (400 MHz) spectra of cavitand **1** (a), diamagnetic amine guests (b and e) and corresponding nitroxides highlighting the occurrence of highly shielded signals upon capsule inclusion and the disappearance of protons H_b and H_c from capsule $\mathbf{1}_2$ with protons H_a and H_d less affected. Note that tail protons of the capsule ($\delta = 1$–3 ppm) experience much less line-broadening than H_b and H_c. Guest and Host concentrations were 1 and 4mM in D_2O, respectively.

bKCTO in the presence of **1** (Figure 3c,f) exhibit very similar ^{1}H NMR patterns, which indicates a similar orientation of the guest inside the host (cavitand or capsule), that is, with the N–O$^\bullet$ bond perpendicular to the capsule C_4 axis. Based on the size and shape of bKCTO, and on the ^{1}H NMR spectrum of the diamagnetic analogue of TEMPO, additional indications are gained in support of the formation of a 1:2 complex (capsule). When the paramagnetic nitroxide guests are included, considerable broadening occurs of the signals corresponding to the H_b and H_c protons of the capsule $\mathbf{1}_2$, which are presumably close to the paramagnetic center (Figure 3d,g,h,i). Conversely, the tail protons of the capsule are slightly broadened and are still clearly visible (pyridinium and alkyl regions: $\delta = 8$–9 and 2–3 ppm, respectively). The situation is intermediate for capsule protons H_a and H_d, for which the nitroxide moiety is close enough to modify their signal in the spectra (Figure 3d,g,h,i). These results show that the nitroxide moiety tends to stay close to the central polar dimerizing region and not to the floor of the capsule. These results are in good agreement with the EPR data and DFT calculations.

With the goal of estimating the maximum height (Scheme 1) of a guest, bKCTO was assessed with cavitand **1** by using the same procedure. The EPR and NMR data indicate the formation of inclusion complexes (Table 1 and Figure 3f,g). Also, ESI-MS shows peaks in agreement with capsule formation (see Figure S13 in the Supporting Information) and a monoisotopic peak at $m/z = 568.8681$ corresponding to $[bKCTO+\mathbf{1}_2+2Cl^-]^{6+}$ ($m/z = 568.8674$ calculated for composition $C_{195}H_{172}N_{25}O_{30}Cl_2^{6+\cdot}$) was observed.

However, for DTBN, TEMPO, and TEMPONE, detection of the 1:1 complex was only marginal (see the Supporting Information), whereas for bKCTO, the 1:2 complex (bKCTO@$\mathbf{1}_2$) prevails only at higher concentrations of the host (>2.5 mM vs. 0.2 mM guest).

The higher proportion of the 1:1 complex for this banana-shaped guest bKCTO at low concentration (Figure S12) is probably the price paid for host–guest contortions, because geometrical considerations indicate that full inclusion with full recognition between the eight arms of the capsule (16 hydrogen bonds) is not possible (Figure 2c).

Indeed, whereas the maximum height of the available space inside the capsule is estimated to be 16–17 Å (subtracting the van der Waals radii of carbon atoms near the end of the cylindrical inner space), the height of bKCTO is close to 17 Å. For comparison, 1,2-bis-4-picoliniumethane dichloride (height ca. 15.9 Å) is reported to be included in $\mathbf{1}_2$ whereas bis-*N*-ethylpyridinium-4,4′-ethylene dichloride (ca. 18.6 Å) is not included.[19a] DFT calculations support this result, but show a significant variation of the "ideal" capsule shape with enlargement of the central part in agreement with a non-ideal hydrogen-bonding pattern between the two cavitands. It is estimated that 12 hydrogen bonds remain instead of the ideal 16 hydrogen-bond pattern, that is, one of the eight walls has shifted. Cavitand dimerization seems to compete with guest steric hindrance to maximize the number and lengths of the hydrogen bonds between each benzimidazolone during capsule formation, as already reported for alkanes and other guests. These results highlight that flexibility is allowed and small deformations of either the capsule[33] and/or the guest can occur, as was observed by Rebek[34] for alkanes in this family of capsular cavitands.

Conclusion

Several nitroxide spin probes, TEMPO, TEMPONE, DTBN, and bKCTO, have been used to investigate the formation and inner space of a water-soluble capsular assembly. The use of the EPR/spin-probing technique to monitor the binding process has allowed us to 1) evaluate the inner cylindrical space metrics providing maximum guest width and height, 2) quantitatively determine the strength of molecular recognition, and 3) show the ability of the capsule to widen in the central part by bending one of the aromatic panels. Furthermore, the banana shape of bKCTO has allowed us to redefine the limits of guests that can be included, highlighting the subtle interplay between guest accommodation and capsule flexibility to support non-ideal full self-closure.

Experimental Section

All the experimental procedures and details of instrumentation used are reported in the Supporting Information.

Cavitand **1** was synthesized according to a literature procedure.[19a] The synthesis of bKCTO is described in the Supporting Information.

EPR spectroscopy: A 10 mM aqueous stock solution of the host (cavitand **1**) and a 2 mM stock solution of guest (radical) in water were prepared. The required amounts of host and guest aqueous solutions were added to a vial and the final volume was made up to 100 μL with additional water. The above solution was sonicated in an ultrasonic bath (Bandelin sonorex, 35 kHz, 215/860 W) for 15 min at 50 °C to ensure host–guest complexation. A longer sonication time may cause decomplexation. After sonication, EPR measurements were performed at room temperature.

DFT calculations: After a preliminary exploration of guest inclusion in capsular assemblies by using Chem3D, the most stable conformers were further investigated by DFT. Eight minimized structures, the energies and atomic coordinates of which are given in Supporting Information. DFT calculations were performed with the Gaussian 09 software package.[35] All the structures were fully optimized at the B3LYP/6-31G(d) level of theory taking into account solvation effects with a water continuum model (conductor polarized continuum model, CPCM[36] because explicit account of water molecules in such large assembled systems by quantum methods is not possible.

NMR spectroscopy: A 2 mM stock solution of the guest (radical) in D_2O was prepared. Then the required amounts of guest solution and host as a solid (cavitand **1**) were added to an NMR tube and the final volume was made up to 500 μL with additional D_2O. The NMR tube was sonicated in an ultrasonic bath (Bandelin sonorex, 35 kHz, 215/860 W) for 15 min at 50 °C to ensure host–guest complexation. After sonication, NMR measurements were performed at room temperature over 1–2 h.

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Keywords: capsules · EPR spectroscopy · host–guest systems · nitroxides · supramolecular chemistry

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