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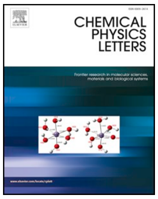

Research paper

Theoretical investigation on the binding of alkyl halides and cyclohexyl halides in water-soluble cavitands

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HIGHLIGHTS

- Encapsulated complexes in water-soluble cavitands with urea rims.
- Hexyl-halides and cyclohexyl halides in deep tetraurea and in octamethyl urea cavitands.
- Implicit-explicit inclusion of the H_2O solvent in the calculation.
- Possibility of halogen bonding in encapsulated hexyl bromide and axial cyclohexyl- bromide.

ABSTRACT

Encapsulation complexes of hexyl- and cyclohexyl-halides in water soluble cavitands with urea rims have been investigated by DFT calculations. In agreement with experiment, the most stable conformations of the different encapsulated halides have the halide at the rim of the cavity, or “up”. The possibility of halogen bonding of Br to the resorcinarenes of the cavitand is suggested by the near degeneracy of “up” and “down” conformations found in encapsulated bromides. In the calculations, in addition to the implicit inclusion of the solvent, explicit addition of water molecules at the rim of the tetra-urea cavitand is found to be necessary.

1. Introduction

Water soluble cavitands, either the deep tetraurea cavitand [1], or the recently developed [2] octamethyl urea cavitand, have been employed to encapsulate primary alkyl halides [1] as well as cycloalkyl halides [3]. The abbreviated chemical structures of the water soluble cavitands considered here are given in Fig. 1. The tetraurea cavitand was developed earlier [4,5] based on the introduction of such structures by Mendoza [6], and has been employed in different investigations of encapsulated complexes in aqueous solutions. Interest in the encapsulated halides stems from the need to respond to environmental concerns regarding the hazardous nature of halogen-containing organic compounds [7], with the possibility of cavitand II to act as a sensor for cycloalkyl halides in water [3]. Furthermore, it is of intrinsic chemical interest to examine the possibility of halogen bonding as a force in the complexation of alkyl and cycloalkyl halides [1,8]. Halogen bonding (RX…Y; X = I, Br, Cl; Y = electron donor) is a non-covalent interaction which is currently experiencing a surge of interest in supramolecular chemistry [9], even though it has been invoked as far back as 1954 in the interpretation of the crystal structure of bromine-1,4, dioxanate [10]. In the present situation, the possibility is considered of RX…π type of halogen bonding with the aromatic floor of the resorcinarene making up the cavity [1] by analogy with other such halogen bonding systems [8].

Reversible encapsulation of guest molecules in host containers allow the study of species and processes that may be difficult to observe in solution but are promoted in the confined spaces of the hosts, such as selective binding, molecular recognition and cyclization reactions. Information on encapsulated complexes and their conformations are provided by NMR spectra, where the up-field shifts may be related to the most favorable position of the nuclei of the guest molecules in the cavitand [1]. Theoretical DFT calculations may also provide insight on their structures and their energetics, as for example the relative stabilities of different hydrogen-bonded dimers [11], the effect of encapsulation on emission spectra (by Time Dependent DFT) [12], preferred conformations of different encapsulated complexes [13], enhanced halogen bonding [14] and cycloadition reactions [15]. In recent theoretical work on the water-soluble tetra-urea cavitand studied here, it has been found that in order to obtain correctly the relative energies between the complexes in the monomer cavitand and in the

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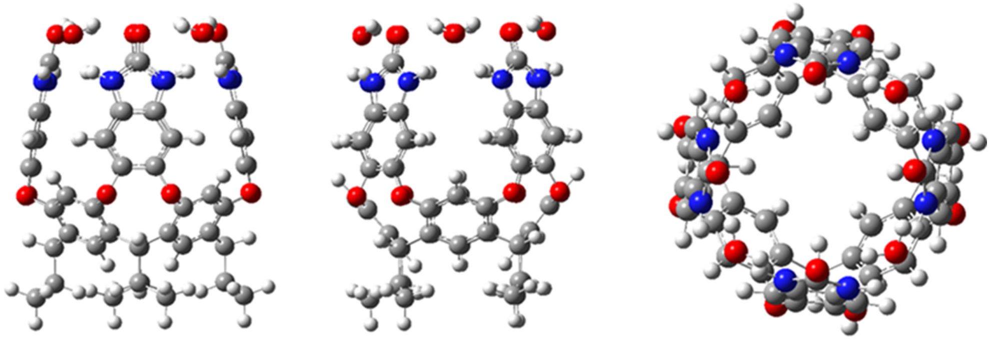
corresponding dimer cage, it was found necessary to include the effects of the solvent in the calculation not only implicitly but also explicitly with additional water molecules included in the calculations [16].

In the present work theoretical calculations are presented on encapsulated complexes of alkyl C_6-X (X = F, Cl, and Br) and cyclohexyl-X (X = F, Cl, Br) in the two cavitands mentioned above, the deep tetraurea cavitand (I) and the octamethyl urea cavitand (II), (cf. Fig. 1). Our efforts are to obtain information on the different stable conformations and their implication on the binding in these encapsulated complexes, including the interaction with the solvent and the possibility for halogen bonding. Corresponding experimental information is given in Ref. [1] for the alkyl halides and that for the cyclohexyl halides is to be published [3].

2. Calculations

The present calculations employed the DFT method [17], in conjunction with the M062X functional [18] and the 6-31G(d,p) basis in the Gaussian 16 suit of programs [19]. The two cavitands employed in the present calculations are structures I and II, for the deep tetraurea and the octamethyl urea cavitands, respectively (cf. Fig. 1). As shown in Fig. 1, the “feet” of cavitands in these models are truncated -C3H7 moieties, for computational expediency; whereas the experimental studies involved cavitands I and II with imidazolium groups at the ends of the “feet”. Cavitand I in water solvent allows interaction with water molecules stabilizing the vase-like conformation [2]. Introducing water molecules at the rim of cavitand I is very favorable with 1.05 eV calculated binding energy for each H_2O molecule added (for one and four added H_2O molecules). Structures Ia below show different views of the optimized geometry of I plus 4 water molecules at the rim, with hydrogen bonding interactions between the solvent hydrogen atoms and the oxygen atoms at the rim of the cavitand.



Ia

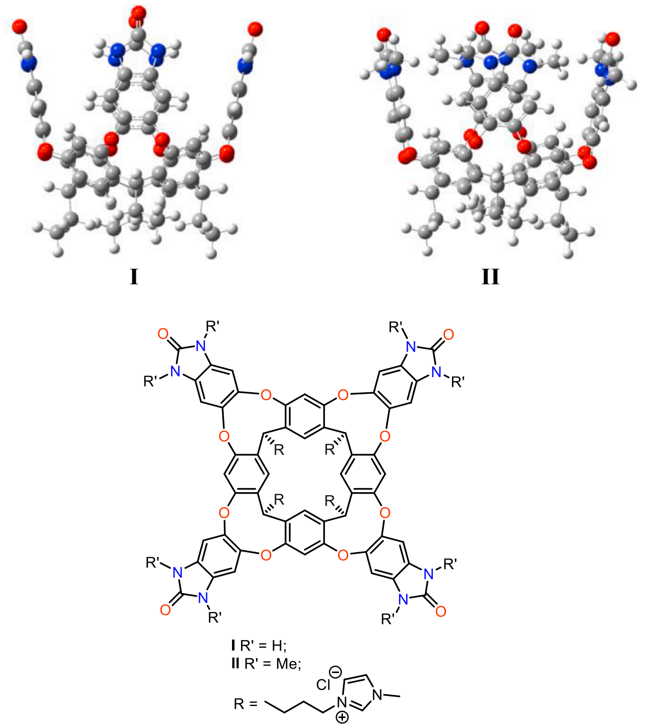


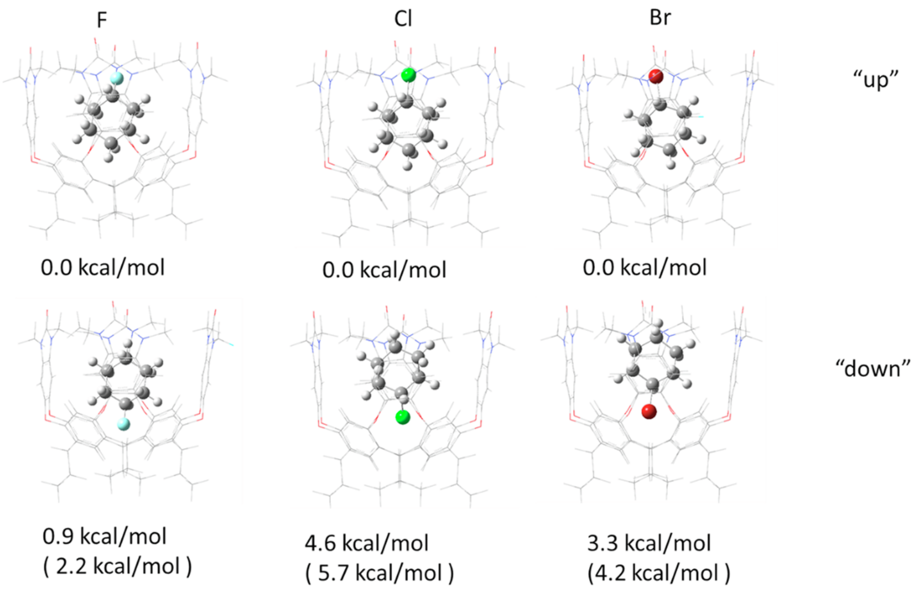
Fig. 1. Structures for tetraurea cavitand I and octamethyl urea cavitand II, theoretical models (above) and experimental (below).

A comparison of the structure of the isolated cavitand I and that of Ia shows that the rim of Ia is highly symmetrical and significantly tighter than that of I. For example, the distances between the rim oxygen atoms in I range from 7.3 to 7.6 Å while in Ia the corresponding O-O distances are all 4.9 Å.

As mentioned above, Daver et al. [16] have carried out a comprehensive study on the free energies of 1:1 and 2:1 complex formation of n-decane in cavitand I, abbreviated as C10@I versus C10@I_2, and propose a mixed explicit–implicit solvation protocol that involves a significant number of additional H_2O molecules as well as parametrization of the hydration free energy of water [16]. Such a study is beyond the scope of the present work but it might be instructive to include some details of the above study as it forms a reference study of the need to consider the effects of the solvent by including it in the calculation implicitly and also explicitly for cavities such as the deep tetraurea cavity (I). The mixed explicit-implicit solvation approach is proposed whereby for a given chemical equilibrium equation expressing the experimental process under study, different corrections are applied: first free energy corrections (for the desired temperature) are required to the calculated gas phase energy and secondly the solvent effects. Implicit inclusion of the solvent is found not to be adequate, at least for the equilibrium considered in [16], i.e. C_{10}@I versus C10@I_2 and different numbers of solvent H_2O molecules have been added explicitly in the calculation. The mixed implicit-explicit approach, subject to the criterion that formation of water clusters in water should be thermoneutral, gives very good agreement with experimental free energies for the equilibrium between the encapsulated complexes [16].

Optimized structures of the alkyl C_6-X (X = F, Cl, and Br) and cyclohexyl-X (X = F, Cl, Br) guests in cavitands I, II and also Ia have been calculated with and without implicit inclusion of water solvent following the PCM approach, which is the most commonly used model for ground electronic states [20]. Both axial and equatorial conformations of the cyclohexyl halides have been considered even though the

(a) Equatorial cyclohexyl-halides in cavitand II



(b) Hexyl-halide in cavitand II

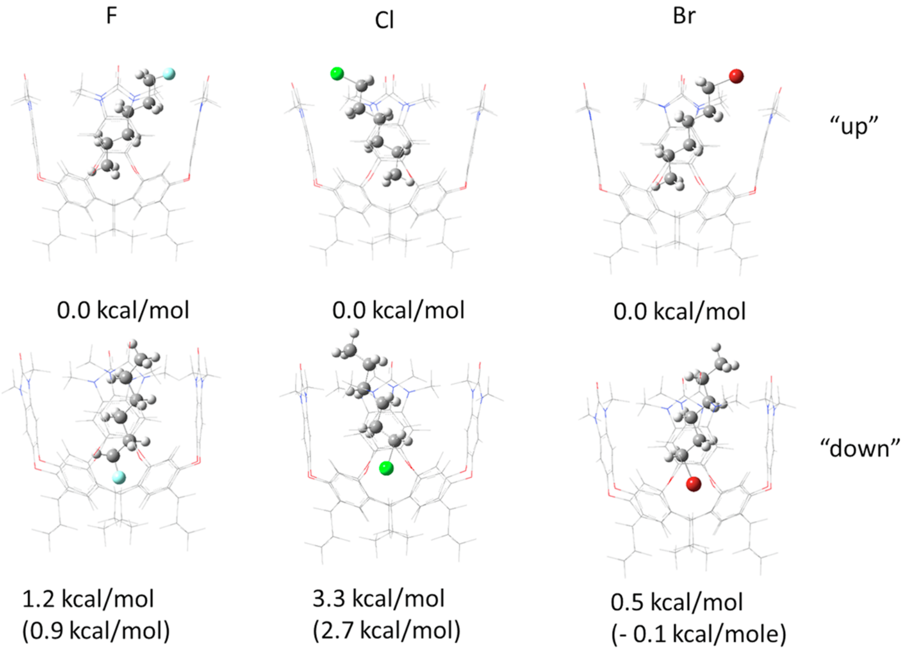


Fig. 2. Encapsulated halides in the octamethyl-urea cavitand II, (a) for equatorial cyclohexyl halide guests, (b) for hexyl halide guests: Calculated structures and relative energies in kcal/mol, solvent included. In parenthesis are given relative energy values obtained without inclusion of solvent.

equatorial correspond to the experimental data, because in the guest cyclohexyl halide molecules alone the axial and the equatorial conformations for F, Cl and Br are calculated to be close in energy (cf. Fig. S1 in the Supporting Information or SI). It is also of interest to examine whether the axial conformations fit in the cavitands better than the equatorial in the "down" conformation, thus increasing the possibility for halogen bonding.

Experimental information (NMR upfield shifts) for encapsulated cyclohexanol and bromocyclohexane indicates that both -OH and -Br favour the "up" position, in both cavitands [3]. Similarly, the "up" conformation is favoured in the encapsulated alkyl halides [1].

3. Results of the calculations

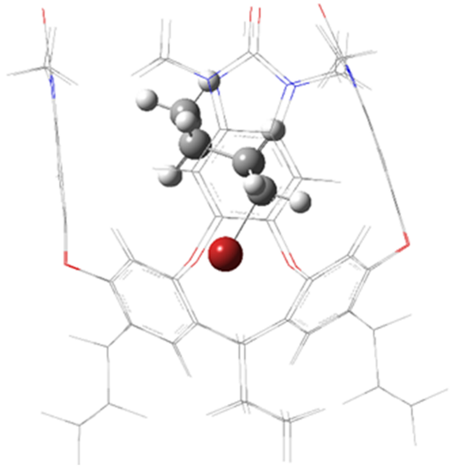
For each of the minimum energy structures calculated for the encapsulated complexes, binding energies have been calculated as the difference between the calculated energy of the encapsulated complex and the sum of the calculated energies of the empty cavitand plus that of the corresponding halide guest. These quantities have been calculated in the presence of solvent in addition to the isolated systems. The binding energies have been included in the figures of the SI, while in the figures included in the main body of the article only the relative energies are given, in kcal/mol, between the "up" and the "down" conformations for each halide.

(i) Results of the calculations on cyclohexyl halides and hexyl halides in the octamethyl urea cavitand II.

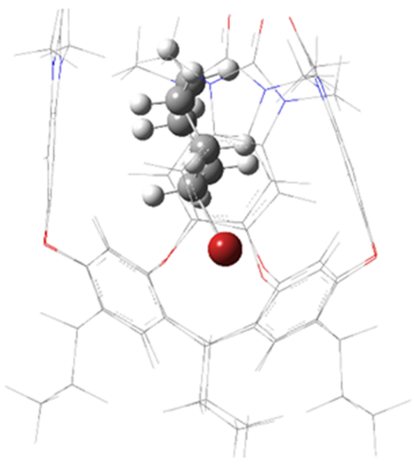
Cavitand II (cf. Fig. 1) has been recently proposed as a sensor for cycloalkyl halides in water [3]. It has a wide rim due to the steric interactions between the methyl groups on adjacent walls at the rim, yielding a wider cavitand than the deep tetraurea cavitand.

The results of the calculations on the encapsulated cyclohexyl halides in II are summarized in Fig. 2a for the equatorial halogen positions and Fig. S2 (in the SI) for both the equatorial and the axial. As shown, the “up” conformation is preferred for equatorial cyclohexyl halides (cf. Fig. 2a), in good agreement with experiment: Experimental data for equatorial cyclohexyl halides with X = Cl, Br and I, indicate that the conformations of the encapsulated complexes with the halogen atoms pointing “up” or towards the rim of the cavitands are preferred [3].

The present calculations show that in the case of the encapsulated complexes with the halogens in the axial position, (cf. Fig. S2b in SI) the “up” conformation is again preferred, but for the cyclohexyl bromide the “up” and “down” conformations are nearly degenerate, with the “down” conformation lower by only 0.8 kcal/mole in the absence of solvent and the “up” obtained lower in energy by only 0.4 kcal/mol when the solvent is included in the calculation. What we may conclude regarding the small magnitude of these calculated relative energies is that the “up” and “down” conformations in the case of the axial encapsulated bromocyclohexane are very close in energy, whereas in the equatorial complexes the preferences for the “up” conformations are clear (cf. Fig. 2a and S2a). This might indicate the possibility of a halogen-bonding type of interaction in the case of the axial bromocyclohexane in the “down” conformation. The axial and equatorial “down” conformations of encapsulated bromocyclohexane are illustrated below in III and IV, respectively, viewed from a different angle than in Fig. 2a and S2b for comparison in view of the increased stability for this conformation in the case of the axial halide. However this increased stability is not easily related to the structures III versus IV below.



III



IV

In Fig. 2b, the results on the encapsulated alkyl C6-X (X = F, Cl, and Br) in cavitand II are summarized, showing a clear preference for the “up” conformation in the chloride and near degeneracies between the up and down in the fluoride and the bromide. In particular for the bromide, inclusion of the solvent implicitly leads to increased relative stability for the “up” conformation. These results are similar to those obtained for the cyclic halides in the axial position (cf. Fig. S2), showing that in the case of bromide, the down conformation gains stability and one reason for this may be the formation of halogen bonding, which however does not completely cancel the preference for the “up” conformation.

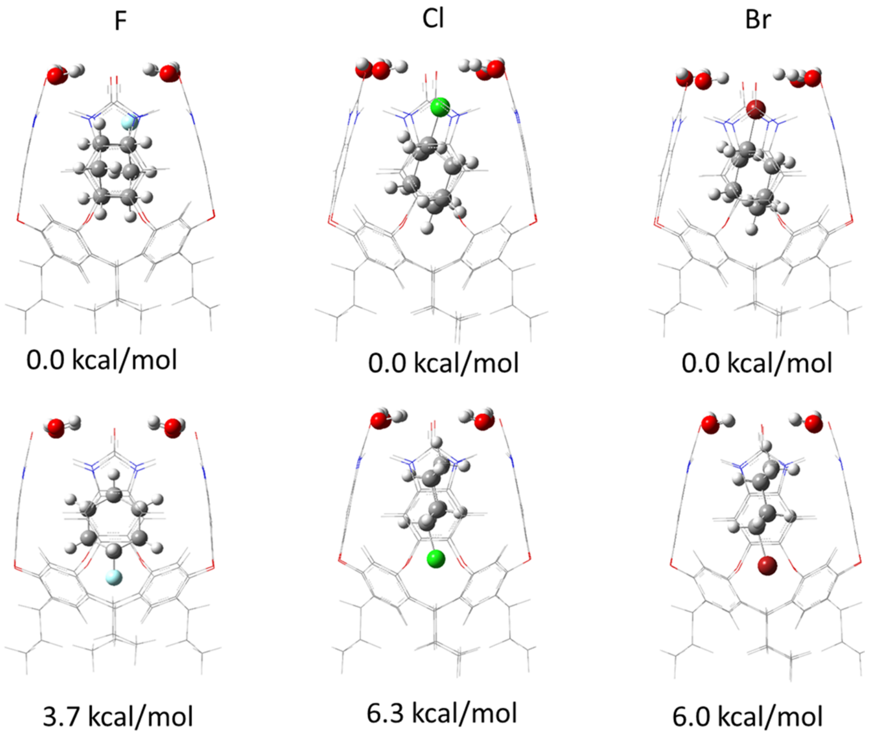
(ii) Results of the calculations on cyclohexyl and hexyl halides in the deep tetraurea cavitand I and Ia.

We consider here different approaches for the encapsulated axial halide complexes, including isolated molecule calculations, implicit inclusion of water solvent, explicit addition of one H_2O molecule at the rim of the cavitand only, explicit inclusion of 4 H_2O solvent molecules at the rim of the cavitand (cf. Ia above) and finally including the solvent both and explicitly with 4 water molecules added at the rim of cavitand I. For the equatorial halides the final treatment was employed only, i.e. implicit inclusion of the H_2O solvent plus four H_2O molecules added explicitly at the rim of I. In Fig. 3, the results of the calculations on the encapsulated cyclohexyl halides, including solvent and 4 additional H2O molecules are summarized, for the equatorial (Fig. 3a) and the axial (Fig. 3b) cyclohexyl halides. As shown, the “up” conformation is preferred, in agreement with experiment, where greater stabilization is obtained for all the complexes of equatorial halides (compared to the axial) and especially so for the “up” conformations.

It is instructive to consider the results of the different types of calculation approaches on the axial encapsulated halides: In the absence of any solvent, the calculations on the encapsulated axial bromide show a preference for the “down” conformation, but not for the chloride or the fluoride (cf. Fig. S3 in SI). Focusing on the axial cyclohexyl bromide, a calculation again without solvent but adding a single H_2O molecule at the rim of I, reverses the calculated relative stability of the “up” and “down” conformations from 3.8 kcal/mol for the “down” (cf. Fig. S3) to 0.09 kcal/mole for the “up”. Adding 4 H_2O molecules leads to increased stability for the “up” to 2.4 kcal/mole, (cf. Fig. S4), while inclusion of the solvent implicitly does not have any further significant effect on the relative stability, cf. Fig. 3 and S4. These results indicate that in the tetraurea cavitand there may be stabilization of the “down” conformation by halogen bonding in the case of the Br, but it is compensated by the interaction with the solvent molecules in the “up” conformation (cf. Fig. 3b), which turns out to be the most stable.

The results on the encapsulated hexyl halides in cavitand I and Ia, are summarized in Figs. S5, S6 and 4. For these systems corresponding experimental data have been reported (for X = Cl and Br) for comparison [1]. The experimental observations find the chloride mostly in

(a) Equatorial cyclohexyl halide in cavitand I, implicit and explicit inclusion of solvent.



(b) Axial cyclohexyl halide in cavitand I, implicit and explicit inclusion of solvent.

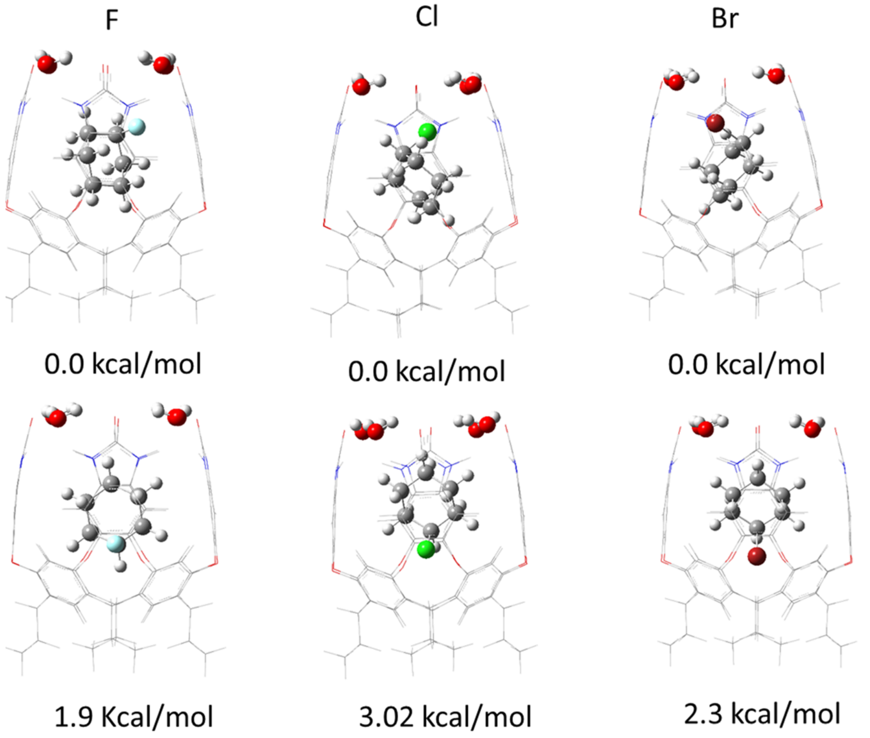


Fig. 3. Encapsulated halides in the tetraurea cavitand, I, (a) for equatorial cyclohexyl halide guests, (b) for axial cyclohexyl halide guests. Calculated structures, and relative energies in kcal/mol. The calculations include the solvent implicitly and explicitly, by 4 additional H_2O molecules at the rim of I.

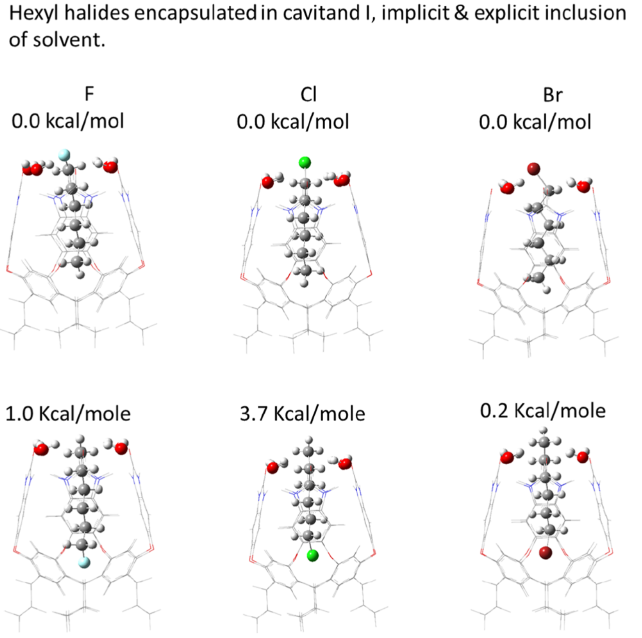


Fig. 4. Calculated structures and relative energies in kcal/mol, for hexyl halide guests in the tetraurea cavitand including the solvent implicitly and explicitly by 4 additional H_2O molecules at the rim of the cavity.

the “up” conformation with only about 20% of the time in the “down”, while for the bromide the proportion of time in the down conformation increases to 30% [1]. The theoretical results (cf. Fig. 4) are in good qualitative agreement with the experimental, indicating an increased propensity for the “up” conformation in the chloride, with the “up” conformation calculated at 3.7 kcal/mol more stable than the “down”. For the bromide, the calculated ΔE favoring “up” is only 0.2 kcal/mol, at the level of calculation of the present work. Although this result is in qualitative agreement with the experimental in that the “up” conformation is favored, and in that sense it might be gratifying, it must be kept in mind that such small calculated energy differences serve only as an indication of a near degeneracy in the calculated stabilities of the “up” and the “down” conformations. Considering the approaches without inclusion of solvent in any way (cf. Fig. S5) leads to results with the “down” lower in energy for all three halides in disagreement with experiment. Explicit addition of 4 H_2O molecules but without implicit inclusion of the solvent leads to results in qualitative agreement with experimental results (available for Cl and Br).

The above results show that the most significant correction to the theoretical results on the encapsulated complexes in cavitand I, is obtained by the explicit addition of 4 H_2O molecules both for the hexyl halide guests and for the axial cyclohexyl halide guests, leading to qualitative agreement with experimental observations, available for the alkyl halides. As mentioned above the addition of H_2O molecules at the rim of cavity I is calculated to be very favorable leading to a more symmetric and stable cavity, Ia. The structures of the encapsulation complexes of axial cyclohexyl bromide in I and in Ia are similar without any evidence for direct interaction of Br with solvent H_2O molecules of Ia in the “up” conformation. Thus, the stabilization of the “up” conformation in Ia may be attributed to the tighter rim of the cage leading to slightly smaller distances and increased interaction between Br and the cage atoms.

4. Conclusion

Theoretical calculations have been carried out on different conformations of encapsulated complexes of cyclohexyl- halides and hexyl-halides in two water soluble cavitands. The results on the equatorial cyclohexyl halides are in qualitative agreement with available experimental data, i.e., they show clear preference for conformations with the halide pointing towards the rim of the cavitands, in both cavitand I and II. For the axial halides in the octamethyl urea cavitand, the “up” conformation is calculated to be more stable but for the case of Br, there is very small energy difference between the “up” and the “down” conformations and inclusion of the solvent in the calculation reverses the stability between the “up” and “down”. Similar results are obtained for the complexes of hexyl chloride in the octamethyl urea cavitand, showing preference for the “up” conformations, with those of hexyl-bromide showing a less pronounced preference for the “up” conformation, requiring the implicit inclusion of the solvent in the calculation in order to obtain agreement with the experimental result. The calculations on the complexes of cyclohexyl halides and of hexyl halides in the deep tetraurea cavitand show that it is required to include the effects of the solvent explicitly, by the addition of four H_2O molecules at the rim of the deep tetraurea cavitand. Finally, the present results indicate that while halogen bonding may occur in the case of the bromides, it is not the dominant factor for the preferred conformation of the encapsulated complexes.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cplett.2019.05.007.

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