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Research Article

Host-Guest Complexations of Amine Boranes and Isoelectronic/Isostructural Quaternary Alkylammonium Cations by Cucurbit[7]uril in Aqueous Solution

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The host-guest complexation of six amine boranes (R_3NBH_3) by the macrocyclic host molecule cucurbit[7]uril (CB[7]) in aqueous solution has been investigated using ^1H and ^{11}B NMR spectroscopy. The limiting complexation-induced ^1H and ^{11}B chemical shift changes indicate that the amine boranes are included in the hydrophobic cavity of the host molecule. The host-guest stability constants for neutral {$R_3NBH_3 \cdot CB[7]$} complexes (in the range of 10^5-$10^7 M^{-1}$) have been determined by ^1H NMR competition experiments and are compared with the corresponding values for the isoelectronic/isostructural {$R_3NCH_3 \cdot CB[7]$}$^+$ complexes. Ammonia borane (H_3NBH_3) does not form a host-guest complex with CB[7]. The trends in the host-guest stability constant with the guest molar volume are examined, and the stability is ascribed to the hydrophobic effect (packing coefficient) and quadrupole-dipole interactions.

1. Introduction

Ammonia borane (H_3NBH_3) and amine boranes (R_3NBH_3) in general are of considerable current interest as hydrogen storage materials [1–4]. Catalytic hydrolysis (acid or transition-metal) of H_3NBH_3 (19.6 wt% hydrogen content) generates 3 moles of H_2 per mole of ammonia borane [5–8]. The amine boranes are also of use as reducing agents and in hydroboration reactions with alkenes [9–15]. In aqueous solution, amine boranes undergo hydrolysis with half-lives which are dependent on the B-N bond strength [11]. There have been relatively few investigations into the formation of supramolecular host-guest complexes of amine boranes and the effects on their reactivity. Stoddart and coworkers have reported complexation of ammonia borane with crown ethers, such as 18-crown-6 and chiral substituted derivatives, with the 1:1 and 1:2 host-guest complexes exhibiting N-H•••O hydrogen bonds in the solid state [16, 17]. The 18-crown-6 host has been used to catalyse the synthesis of amine boranes and deuterated derivatives [18], while host-guest complexes of amine boranes with cyclodextrins have been successfully employed in the asymmetric reductions of ketones [19].

The cucurbit[n]urils (CB[n], n = 5-8, 10, 13-15) are a family of host molecules (Figure 1) which form stable host-guest complexes with organic cations in aqueous solution [20–23]. The CB[n] hosts are oligomeric macrocycles comprised of n glycoluril units bridged by 2n methylene units. The hydrophobic cavity is accessible through two constrictive polar portals, each rimmed with n ureido carbonyl groups. With certain cationic guests, exceedingly stable host-guests complexes (up to 7 x $10^{17} M^{-1}$ with CB[7] in water) can be formed when the size of hydrophobic portion of the guest (such as with ferrocene or diamantane groups [24, 25]) matches the internal volume of the CB[n] cavity, displacing the high-energy waters within [26], and the cationic group(s) is placed adjacent to the carbonyl groups to maximize the ion-dipole interactions.

We have shown that CB[7] is selective towards the size of hydrophobic, charge-diffuse NR_4^+ cations, with the trend of R = Et > Me > n-Pr > n-Bu, and other onium cations, with PMe_4^+ > NMe_4^+ > SMe_3^+ [27]. Recently, Matsumoto et al. [28] reported that the trend in $K_{CD}NR_4^+$ reverses itself with R = n-Bu < n-hexyl < n-heptyl. The CB[7] host
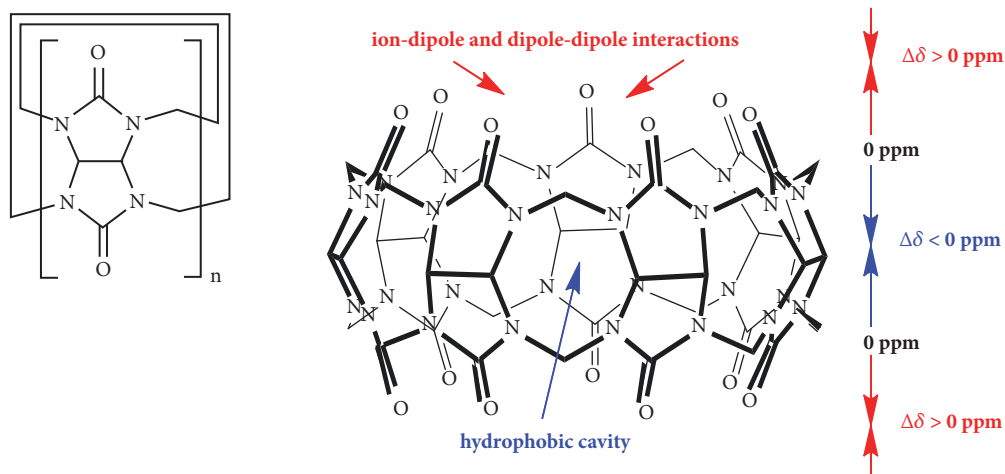
FIGURE 1: Structures of CB[n] (left) and CB[7] (right), indicating regions of CB[7] complexation-induced chemical shift changes ($\Delta\delta$) for the guest proton resonances.

is also very selective towards differing extents of the $N\varepsilon$-methylation of lysines and arginines, with a 3500-fold preference for $N\varepsilon,N\varepsilon,N\varepsilon$-trimethyllysine (a histone biomarker) over the native lysine [29]. The amine boranes with the formula R_3NBH_3 are isoelectronic and isostructural with the $R_3NCH_3^+$ cations, which exhibit host-stability constants with CB[7] in the range of 10^4-10^8 M^{-1} in aqueous solution [28]. With neutral guests, which lack the capacity for ion-dipole interactions with the CB[n] host, the stability of the resulting host-guest complexes can be related to the packing coefficient of the guest within the host internal cavity,[30] which has been correlated with the number of heavy (non-hydrogen) atoms in the encapsulated portion of the guest [31–33]. In addition, with polar neutral guests, the guest's dipole may align with the quadrupolar moment of the CB[n] cavity [31, 34].

In the present study we have investigated the formations of host-guest complexes of cucurbit[7]uril with a series amine boranes R_3NBH_3 (R = H, methyl, ethyl, t-butyl or R_3 = N-protonated or N-methylated morpholine) and the isoelectronic/isostructural $R_3NCH_3^+$ cations in aqueous solution, using ^{1}H and ^{11}B NMR spectroscopy. The host-guest stability constants ($K_{CB[7]}$) have been determined and are compared with those measured for the isoelectronic $R_3NCH_3^+$ cations in aqueous solution. The values of $K_{CB[7]}$ are correlated with the packing coefficients and the octanol-water partition coefficients.

2. Materials and Methods

The cucurbit[7]uril was prepared and characterized by the method of Day et al. [36]. The amine borane complexes, tetraalkylammonium salts, and 3-(trimethylsilyl)propionic-2,2,3,3-d$_4$ acid (TSP) were used as received (Sigma-Aldrich). The ^{1}H and ^{11}B NMR spectra were recorded on Bruker AMX-400 and AMX-500 spectrometers in D$_2$O (pD = 4.75 (50 mM NaOAc-d$_3$/25 mM DCl)). The proton resonances for the morpholine ring were assigned based on a previous study

[37]. The stability constants for the $\{R_3NBH_3\bullet CB[7]\}$ and $\{R_3NCH_3\bullet CB[7]\}^+$ complexes were determined in D$_2$O at pD = 4.75 from ^{1}H NMR competition experiments [38] using TSP ($K_{CB[7]}$ = $(1.82 \pm 0.22) \times 10^7$ M^{-1} [38]) and the NMe$_4^+$ ($K_{CB[7]}$ = $(1.2 \pm 0.4) \times 10^5$ M^{-1} [27]) and NEt$_4^+$ ($K_{CB[7]}$ = $(1.0 \pm 0.2) \times 10^6$ M^{-1} [27]) cations as competing guests. MM2 energy minimization calculations were performed using CHEM3D software (Cambridge Software), while the molar volume calculations were performed using Molinspiration Cheminformatics software [39].

3. Results and Discussion

3.1. ^{1}H and ^{11}B NMR Spectra. Nuclear magnetic resonance spectroscopy is very useful in examining both the qualitative and quantitative aspects of host-guest complex formation in solution. The magnitude and sign of the limiting complexation-induced chemical shift changes ($\Delta\delta_{lim} = \delta_{bound} - \delta_{free}$) in the guest resonances are indicative of the average positions of the proton environments with respect to the cavity and portals of the CB[7] (Figure 1). An upfield shift ($\Delta\delta_{lim} < 0$ ppm) indicates that the guest proton is located within the internal cavity, while a downfield shift ($\Delta\delta_{lim} > 0$ ppm) results when the proton is near the carbonyl groups of a portal. For all of amine borane guest molecules, the ^{1}H and ^{11}B NMR resonances shift upfield with the addition of CB[7], as did the proton resonances for the quaternary alkylammonium cations. The values of $\Delta\delta_{lim}$ for the guest ^{1}H and [11]B nuclei are given in Figure 2.

The ammonia borane (H_3NBH_3) itself does not appear to bind to CB[7] as there are no changes in the borane proton resonance with added host (Fig. S2). This is most likely due to its preference to be solvated by water, through hydrogen and dihydrogen (hydridic-to-protonic) [40] bonding, rather than residing in the CB[7] cavity. All of the other amine borane and quaternary alkylammonium guests exhibited 1:1 binding with the CB[7], based on the ^{1}H NMR titrations, with no
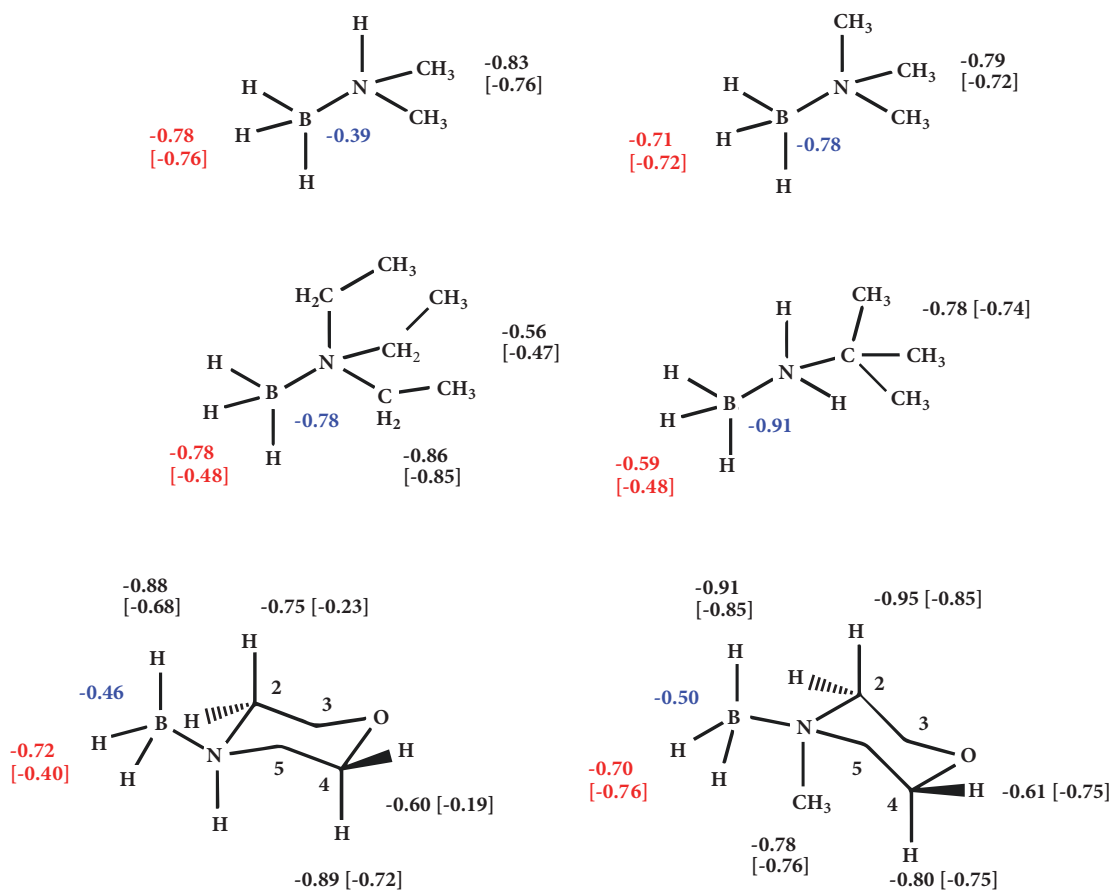
FIGURE 2: Structures of amine borane guests (R₃NBH₃) with the limiting chemical shift changes ($\Delta\delta_{lim}$, ppm) of the guest proton (C-H in black and B-H in red) and boron (blue) resonances upon complexation by CB[7]. The values in the square brackets are the $\Delta\delta_{lim}$ values for the corresponding quaternary alkylammonium cations (R₃NCH₃⁺).

evidence for other stoichiometries (see Fig. S4 for triethylamine borane). The exchange behaviour of the guest proton resonances (slow exchange vs. fast exchange) depended on the nature of the amine borane. The trimethylamine and triethylamine boranes exhibited slow exchange behaviour (separate resonances for the free and bound guests) in the presence of CB[7] (see Figure 3 for trimethylamine borane).

Other amine boranes exhibited intermediate to fast exchange behaviour (broadening and shifting of a resonance representing the average of the free and bound chemical shifts). In the case of morpholine borane (Figure 4) the addition of CB[7] results in a significant broadening of the guest proton resonances, maximizing at about 0.5 equivalent of the host, before sharpening again as the host-guest ratio reaches 1:1.

The CB[7] complexations of the isoelectronic/isostructural R₃NCH₃⁺ cation guests, which correspond to the amine boranes in this study, were also investigated. These guests, including the tetramethylammonium cation [27] and the protonated N-methylmorpholinium and N,N'-dimethylmorpholinium cations [41] investigated previously, also exhibit similar upfield shifts in the corresponding proton resonances (Figure 2) upon complexation by CB[7]. All of the quaternary alkylammonium guest proton resonances exhibited fast exchange behaviour.

3.2. Host-Guest Stability Constants. The host-guest stability constants ($K_{CB[7]}$) for the amine boranes and isostructural alkylammonium cations (R₃NCH₃⁺) were determined by using competitive ¹H NMR binding experiments [38] using competitor guests for whom stability constants with CB[7] have been determined previously [27, 38]. The stability constants for the corresponding R₃NCH₃⁺ guests for R = methyl (one of the competitor guests used in the present study) and for R₃N = morpholine or N-methyl morpholine have been reported previously [41]. The values for $K_{CB[7]}$, presented in Table 1, fall into the range of 10^5-10^8 M⁻¹ for both sets of guests. Good agreement was achieved for the trimethylamine borane and triethylamine borane using two different competitor guests. Table 1 also includes the molar volumes and packing coefficients for the guests along with the exchange behaviour (slow/intermediate/fast) for the guest proton resonances in the presence of the CB[7].

TABLE 1: Host-guest stability constants,[a] molar volumes[b] and packing coefficients, and the ^{1}H NMR exchange behaviour for the CB[7] complexes with the H_3BNR_3 and $H_3CNR_3^+$ guests.

Amine in H_3BNR_3	$K_{CB[7]}$, M^{-1} (R_3NBH_3)	Molar Volume, Å^3 (Packing Coefficient)	^{1}H NMR exchange behaviour (R_3NBH_3)	$K_{CB[7]}$, M^{-1} ($R_3NCH_3^+$)	Molar Volume, Å^3 (Packing Coefficient)	^{1}H NMR exchange behaviour ($R_3NCH_3^+$)
dimethylamine	1.6×10^5 [c]	99 (41%)	intermediate	3.5×10^4 [c]	78 (32%)	fast
trimethylamine	4.1×10^6 [c] 5.6×10^6 [d]	116 (48%)	slow	1.2×10^5 [e]	95 (39%)	fast
triethylamine	3.3×10^6 [c] 3.1×10^6 [d]	166 (69%)	slow	6.5×10^7 [e]	146 (60%)	fast
t-butylamine	4.3×10^5 [c]	129 (53%)	intermediate/fast	3.7×10^5 [c]	109 (45%)	fast
morpholine	1.4×10^5 [c]	131 (54%)	intermediate	2.3×10^6 [f]	110 (45%)	fast
N-methyl-morpholine	3.3×10^7 [g] 3.8×10^7 [d]	148 (61%)	slow	5.1×10^6 [g]	127 (52%)	fast

[a] Error limits of ±15 %. [b] Calculated using Molinspiration software [39]. [c] Calculated using NMe$_4^+$ as the competitor. [d] Calculated using NEt$_4^+$ as the competitor. [e] From [27]. [f] From [40]. [g] Calculated using TSP as the competitor.
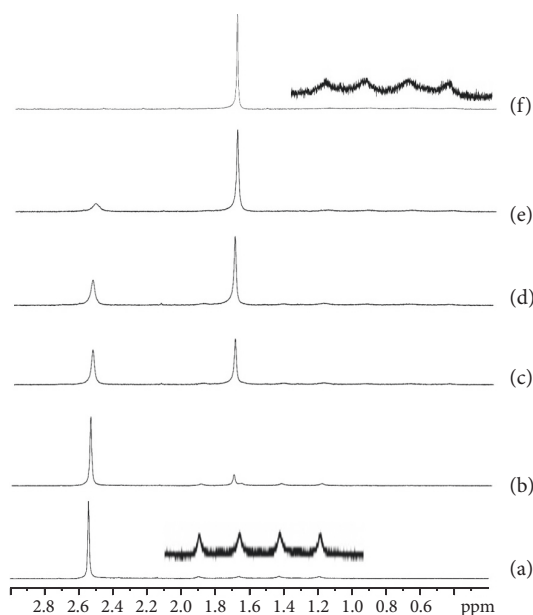

FIGURE 3: ^{1}H NMR titration of trimethylamine borane (1.0 mM) with (a) 0.00, (b) 0.17, (c) 0.50, (d) 0.67, (e) 0.83, and (f) 1.25 equivalents of CB[7] in D$_2$O. B-H proton resonance shown expanded.

With neutral guests, such as the amine boranes, the reasonably high stability observed for CB[n] host-guest complexes may be achieved by maximizing the hydrophobic effect through an effective filling of the internal cavity, displacing some or all of the estimated eight "high-energy" water molecules in the process. Nau and coworkers [31–33, 35, 42–44] have used Mecozzi and Rebek's empirical determination [30] that a packing coefficient (PC) of 55 ± 9 % provides for optimal binding, to propose that the internal cavity of the CB[7] host (242 Å^3 [31]) can encapsulate up to 12 heavy atoms (note that the aforementioned guest has heavy atoms in the diamantane core).

The molar volumes [39] and packing coefficients for the amine boranes and isostructural alkylammonium cations are presented in Table 1. With both sets of guests, there is a general increase in the host-guest stability constant with an increase in the packing coefficient, as depicted in Figure 5. It is interesting to note that with the amine boranes, the trimethylamine borane forms a slightly more stable complex than the triethylamine borane, whereas with the corresponding alkylammonium cations, the methyltriethylammonium complex with CB[7] is significantly more stable than that of the tetramethylammonium cation. The binding constants for the dimethylamine borane and trimethylamine borane are also comparable in magnitude to those for the isoelectronic/isostructural isobutane (2.7×10^5 M^{-1}, PC = 33%) and neopentane (1.0×10^6 M^{-1}, PC = 40%) [35]. The similarities in binding constants between cationic $R_3NCH_3^+$, dipolar R_3NBH_3, and neutral R_3CCH_3 guests suggest that there may be offsetting differences in the desolvation and dispersion energies for the guests [35, 43]. The packing coefficient calculated for the triethylamine borane is 69%, outside the ideal range of 55 ± 9% for optimum binding. This is consistent with the smaller limiting chemical shift changes for the B-H and methyl protons on this guest, suggesting that these portions of the guest are located towards the portals of the host. We previously observed, for the NR$_4^+$ cation complexes with CB[7], that the trend in the stability constants was R = Et > Me > n-Pr > n-Bu, reflecting suboptimal packing coefficients for the larger substituents, as fewer of the alkyl groups of the guest are included in the cavity. With R = n-hexyl and n-heptyl, the increasing size of the included arm(s) of NR$_4^+$ reversed the trend [28]. The value of $K_{CB[7]}$ for NMeEt$_3^+$ (Table 1) is higher than NEt$_4^+$, reflecting a slightly more compatible packing coefficient of 60% compared with 67% for the NEt$_4^+$ cation [39].

Figure 5 also contains data for peralkylated onium cations, as well as other neutral guests, such as n-alkanes [35], ketones [34], bicyclic azoalkanes [31], and perfluorinated alkanes and alcohols [32]. We have previously shown that small polar neutral guests, such as ketones, can form reasonably stable ($K_{CB[7]}$ up to 10^4 M^{-1}) host-guest complexes with CB[7] in aqueous solution [27]. We have also observed that,
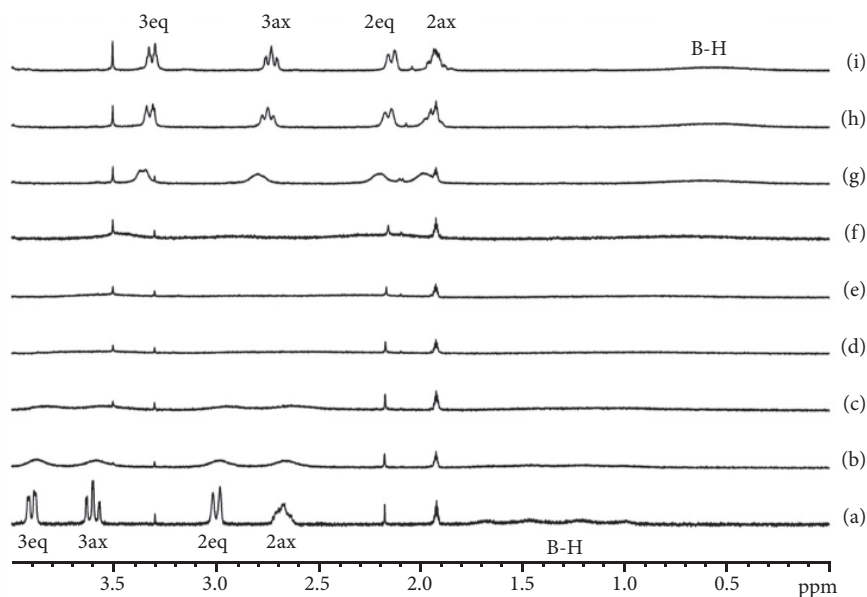
FIGURE 4: ^{1}H NMR titration of morpholine borane (1.0 mM) with (a) 0.00, (b) 0.16, (c) 0.30, (d) 0.44, (e) 0.62, (f) 0.83, (g) 1.17, (h) 2.24, and (i) 3.13 equivalents of CB[7] in D_2O (pD = 4.75).
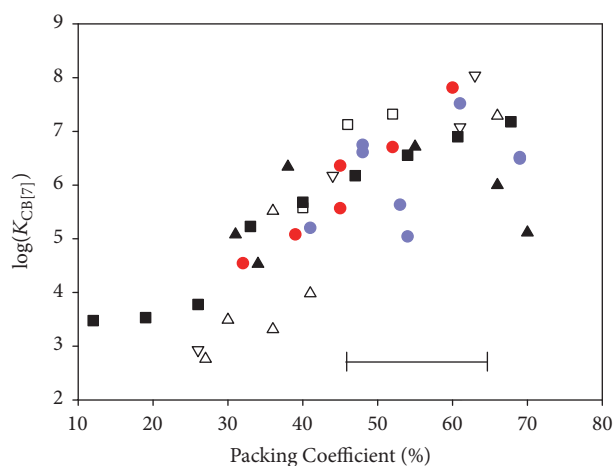

FIGURE 5: Plot of $\log(K_{CB[7]})$ against the packing coefficient for the CB[7] complexes of the (blue circle) amine boranes and (red circle) isostructural alkylammonium cations from this study, (black triangle) peralkylated onium cations [27, 28], (black square) n-alkanes [35], (empty triangle) ketones [34], (empty square) bicyclic azoalkanes [31], and (empty down triangle) perfluorinated alkanes and alcohols [32]. The horizontal line represents Mecozzi and Rebek's optimal packing coefficient of 55 ± 9 % [30].

FIGURE 6: Energy-minimized (MM2, gas-phase) structure of the CB[7] host-guest complex of morpholine borane.

for the antiseptic agent benzethonium chloride, while the more stable CB[7] binding ($K_{CB[7]} = (8.7 \pm 1.3) \times 10^7 \, M^{-1}$) is to the cationic benzyltrimethylammonium moiety, a second binding of CB[7] occurs over the neutral hydrophobic 2-(2,4,4-trimethylpentyl) tail with $K_{CB[7]} = (4.0 \pm 1.9) \times 10^3 \, M^{-1}$ [45]. With eight heavy atoms in this group, a packing coefficient of 61% was calculated, accounting for the reasonable strength in binding.
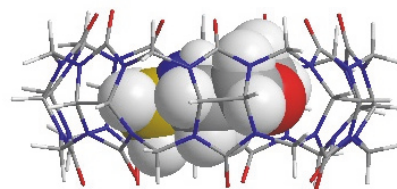
In addition to the hydrophobicity of its cavity, the CB[n] molecule has a quadrupole moment aligned with the n-fold principal axis of symmetry, such that neutral polar solvent molecules will form host-guest complexes with CB[7] in which the guests may align their dipole with the host quadrupole [31, 34]. We have previously reported that neutral ketones and other polar solvent molecules, based on ^{1}H NMR $\Delta\delta_{lim}$ values and energy minimization calculations, orient themselves such that the dipole moment of the guest is aligned perpendicularly to the quadrupole moment of the CB[7] host [31]. With the dipolar nature of the amine boranes, a similar guest orientation might be expected and would allow for all of the guest protons to be residing within the internal cavity of the host molecule, as observed. This additional interaction may account for the slower guest exchange behaviour observed in the ^{1}H NMR spectra. The structure of the morpholine borane complex with CB[7] has been calculated using a gas-phase MM2 energy minimization, and two views of the complex are shown in Figure 6. This dipole-quadrupole alignment with this guest may be further assisted by the presence of the oxygen atom in the morpholine ring.

4. Conclusions

Amine boranes (R_3NBH_3) form relatively stable host-guest complexes with cucurbit[7]uril in aqueous solution, with stability constants in the range of $K_{CB[7]} = 10^4$-10^7 M^{-1}. The trend in the host-guest stability constants and those of the isoelectronic/isostructural alkylammonium cations can be related to their abilities to fill the host internal cavity and displace some or all high-energy waters, as reflected in their packing coefficients. The slower guest exchange behaviour for the amine boranes, compared to the alkylammonium cations, as exhibited in the ^{1}H NMR spectra, may result from additional quadrupole-dipole interactions available.

Data Availability

The NMR spectral data and binding plots used to support the findings of this study are included within the article and the supplementary materials or are available upon request from the corresponding author.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

Supplementary Materials

The Supplementary Materials contain additional ^{1}H and ^{11}B NMR host-guest titration spectra and chemical shift titration plots (Figures S1 to S7) for the amine borane guests. *(Supplementary Materials)*

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