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Diffusion Coefficient of Cucurbit[*n*]urils (*n* = 6 or 7) at Various Concentrations, Temperatures, and pH[†]

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The diffusion coefficient of cucurbit[6]uril (CB[6]) and cucurbit[7]uril (CB[7]) was determined using pulsed gradient spin–echo nuclear magnetic resonance spectroscopy. Both CB[6] and CB[7] diffuse faster through H₂O than D₂O with increasing temperature, consistent with the Stokes–Einstein equation where diffusion is proportional to temperature divided by viscosity. The activation energy (E_A) was also determined and is larger for CB[*n*] in 90 % H₂O/10 % D₂O v/v than in D₂O. Both compounds aggregate with increasing concentration between $(0.25 \text{ and } 2) \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$. The pH of the solution does not significantly affect the diffusion coefficient of CB[6] and CB[7], except at very low pH where protonation of the carbonyl groups induces aggregation, which slows their rate of diffusion.

Introduction

Cucurbit[*n*]urils, (CB[*n*], Figure 1) where *n* = 5, 6, 7, 8, or 10, are a family of macrocycles made from the condensation of glycoluril and formaldehyde under strongly acidic conditions.^{1,2} CB[*n*]s have an internal hydrophobic cavity which is accessible through two symmetrical ureido-carbonyl lined portals.^{3,4} The internal cavity of CB[*n*] is able to partially or fully encapsulate a range of small molecules: such binding is stabilized through hydrophobic effects within the cavity and/or ion–dipole or dipole–dipole interactions between the guest and the CB[*n*] portals.³ The host–guest interactions of CB[*n*] give rise to a range of applications including waste remediation, molecular switches, column chromatography, catalyzing charge-transfer reactions, drug delivery, nanomachine components, and self-sorting systems.^{3–5}

In many of these applications, the interactions of CB[*n*] with guests, solvent, and other solutes play a part in their recognition and binding properties.^{6–10} Such reactions play critical roles in many biophysical processes.¹¹ One aspect of CB[*n*] physical chemistry, which is particularly important in drug delivery, is the translational diffusion (or self-diffusion) of CB[*n*] and its host–guest complexes in solution. CB[*n*] host–guest diffusion is most important in drug transport and uptake and can mediate the binding of drugs to proteins and affect plasma circulation lifetimes and the drug's diffusion into and through cells. Previously, it has been shown that encapsulation by CB[7] greatly reduces the rate at which the drugs diffuse.¹² The diffusion coefficient ($D/\text{m}^2 \cdot \text{s}^{-1}$) of CB[*n*] and its host–guest complexes can be effectively measured using pulsed gradient spin–echo nuclear magnetic resonance (PGSE NMR) spectroscopy.¹³ The easiest and most commonly used technique for measuring CB[*n*] self-diffusion is diffusion nuclear magnetic resonance spectroscopy, and the most frequently used experiments are pulsed gradient spin–echo (PGSE) pulse sequences.^{14,15} In this paper, we report the diffusion coefficients of CB[6] and

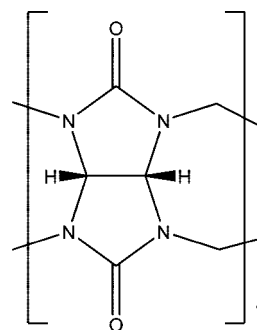


Figure 1. Chemical structure of cucurbit[*n*]uril, where *n* = 5, 6, 7, 8, or 10.

CB[7] in D₂O and 90 % H₂O/10 % D₂O that were measured using PGSE NMR at different temperatures, concentrations, and pH.

Experimental Section

Materials. CB[7] (CASRN: 259886-50-5) was purchased from Sigma-Aldrich, and CB[6] (CASRN: 80262-44-8) was made as previously described.¹ D₂O (99.9 %), DCl (99.9 %), and NaOD (99.9 %) were purchased from Cambridge Isotope Laboratories.

Sample Preparation. Stock solutions of $20 \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$ NaCl in D₂O and 90 % H₂O/10 % D₂O were prepared. For the temperature and concentration experiments, a minimum amount of CB[6] or CB[7] ($\approx 3 \cdot 10^{-3} \text{ g}$) was weighed into a sample vial. The required volume of $20 \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$ NaCl in D₂O or 90 % H₂O/10 % D₂O was added to yield the desired concentration. An amount of $6 \cdot 10^{-4} \text{ L}$ was transferred from the sample vial into a NMR tube. When possible (more frequently with CB[7] due to higher solubility), serial dilutions were used to make the desired concentration. This was achieved by dissolving $\approx 3 \cdot 10^{-3} \text{ g}$ in $\approx 1 \cdot 10^{-3} \text{ L}$ of $20 \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$ NaCl in D₂O. The appropriate volume was transferred into an NMR tube and made up to $6 \cdot 10^{-4} \text{ L}$ with $20 \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$ NaCl in D₂O to give the required concentration $(2 \text{ to } 20) \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$. This decreased the amount of deuterated solvent required.

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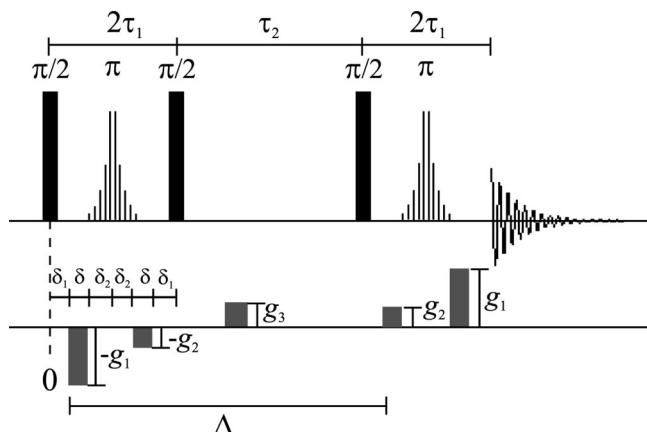


Figure 2. PGST sequence. The black columns represent $\pi/2$ RF pulses; the groupings of narrow bars represent binomial-like π pulses; and g_1 , g_2 , and g_3 are represented by rectangular gradient pulses with different amplitudes.

For the pH experiments, a minimum amount of CB[6] or CB[7] ($\approx 3 \cdot 10^{-3}$ g) was weighed in a sample vial, and the required amount of D_2O or 90 % $H_2O/10$ % D_2O (without any solubilizing NaCl) was added. Minimal amounts of DCl and NaOD were added until the required pH was achieved. An amount of $6 \cdot 10^{-4}$ L was then transferred from the sample vial into an NMR tube.

PGSE NMR. NMR spectra were recorded using a 5 mm BBO probe on a Bruker Avance 400 spectrometer at an operating frequency for 1H of 400.13 MHz. Diffusion coefficients in pure D_2O were determined using a Hahn spin-echo pulse.¹² The diffusion coefficient from each experiment was determined using nonlinear least-squares regression (NLLS) using OriginPro 8.0 (OriginLab, MA) of eq 1 on the data

$$\ln(E) = -\gamma^2 g^2 \delta^2 D \left(\Delta - \frac{\delta}{3} \right) \quad (1)$$

For samples in 90 % $H_2O/10$ % D_2O , a stimulated echo-based pulse gradient spin-echo NMR diffusion sequence (PGSTE), optimized to reduce signal loss due to spin-spin relaxation, was used to measure the diffusion coefficients (Figure 2).¹⁶ The diffusion coefficient was determined using NLLS of eq 2 on the data

$$\ln(E) = -\gamma^2 D \delta^2 \left[\left(\Delta - \frac{4}{3} \delta - 2\delta_2 \right) (g_2 + g_1)^2 + \frac{2}{3} \delta (g_2 + g_1) g_1 + \left(4\delta_2 + \frac{4}{3} \delta \right) g_1^2 \right] \quad (2)$$

where γ is the gyromagnetic ratio of the 1H nucleus and g is the gradient strength ($T \cdot m^{-1}$). Each diffusion measurement was the result of measuring the echo amplitude from at least 15 different gradient values between (0 and 0.55) $T \cdot m^{-1}$. g_1 and g_2 were set between 0.0935 and 0.165 and 0.0835 and 0.154 respectively, and the separation between the leading edges of the gradient pulses, Δ , which defines the time scale of the diffusion measurement, was set to 125 ms. The gradient pulse width, δ_1 , was set between (3.4 and 5) ms, and δ_2 was set to 2.51 ms. A recycle delay of at least $5 \cdot T_1$ was used between scans. The calculated uncertainties for the diffusion coefficients were determined from the NLLS fit of the data and in all cases are less than 1 %. However, taking into account gradient calibration errors and temperature fluctuations, the true errors are approximately 1 %.¹⁷

The activation energies (E_A) for the translational motion of CB[6] and CB[7] in 90 % $H_2O/10$ % D_2O v/v and D_2O were

Table 1. Diffusion Coefficient of CB[6] and CB[7] ($0.5 \cdot 10^{-3}$ mol \cdot L $^{-1}$) in 99.9 % D_2O and 90 % $H_2O/10$ % D_2O v/v as a Function of Temperature

<i>T</i> /K	<i>D</i> /($\cdot 10^{-10}$ m $^2 \cdot$ s $^{-1}$) ^b			
	CB[6]		CB[7]	
	D_2O	H_2O^a	D_2O	H_2O^b
298.15	3.45 \pm 0.02	3.91 \pm 0.02	3.23 \pm 0.02	3.59 \pm 0.01
303.15	4.07 \pm 0.01	4.52 \pm 0.02	3.75 \pm 0.02	4.19 \pm 0.02
308.15	5.15 \pm 0.01	5.80 \pm 0.02	4.43 \pm 0.02	4.98 \pm 0.01
310.15	5.84 \pm 0.01	6.12 \pm 0.02	5.04 \pm 0.01	5.66 \pm 0.02
313.15	7.11 \pm 0.02	7.64 \pm 0.03	5.98 \pm 0.05	6.88 \pm 0.02
318.15	10.33 \pm 0.03	10.99 \pm 0.05	8.28 \pm 0.10	9.44 \pm 0.09

^a 90 % $H_2O/10$ % D_2O v/v. ^b Are derived from the exponential fitting curve determined in OriginPro 8.0.

determined by fitting data (in Arrhenius form) using OriginPro 8.0 (OriginLab, MA).

Convection effects were assessed by determining diffusion at different Δ values [(30 and 125) ms], while all other experimental conditions remained constant.

pH Measurements. The pH of the NMR samples was determined using a Radiometer analytical pH electrode, calibrated using buffered solutions at pH 4 and 7. The pH values of the CB[6] and CB[7] samples were varied by the addition of DCl or NaOD and are uncorrected for isotope effects.

Results and Discussion

The diffusion coefficients of CB[6] and CB[7] were examined using PGSE NMR. The low water solubility of CB[6] necessitated the use of $20 \cdot 10^{-3}$ mol \cdot L $^{-1}$ NaCl in 99.9 % D_2O and 90 % $H_2O/10$ % D_2O . For consistency, CB[7] was dissolved in the same solvent. The diffusion coefficient of CB[8] was not determined due to the poor solubility of this compound in all saline solutions up to concentrations of $200 \cdot 10^{-3}$ mol \cdot L $^{-1}$. Previously, we have shown that the addition of alkali earth metal salts does not affect the diffusion coefficient of CB[7].¹²

The diffusion coefficient of CB[6] and CB[7] at varying temperatures is given in Table 1. For both compounds, their diffusion coefficient increased with increasing temperature. Hardy and Cottingham have shown that the viscosity of D_2O decreases exponentially with increasing temperature.¹⁸ The change in diffusion coefficient of CB[6] and CB[7] demonstrates a similar relationship between D , temperature, and viscosity indicating that the change in the rate of diffusion of CB[6] and CB[7] is consistent with the Stokes-Einstein equation where $D \propto T/\eta$. The data are presented in Arrhenius form in Figure 3. The diffusion of CB[6] and CB[7] in solutions of 90 % $H_2O/10$ % D_2O v/v also increases proportionally with increasing temperature and change in viscosity. The diffusion coefficients of CB[6] and CB[7] are larger in H_2O than in D_2O at the same temperature, consistent with the decreased density and viscosity of H_2O compared with D_2O .¹⁸ The E_A for the translational motion of CB[6] and CB[7] were determined by fitting the data using Origin 8.0 (OriginLab, MA) and are given in Table 2. In D_2O , they were calculated to be [(55.4 \pm 4.0) and (49.8 \pm 2.3)] kJ \cdot mol $^{-1}$ in the temperature range of (310.15 to 318.15) K and [(29.3 \pm 5.9) and (24.3 \pm 1.1)] kJ \cdot mol $^{-1}$ in the temperature range of (298.15 to 308.15) K, respectively. The E_A for the translational motion of CB[6] and CB[7] in H_2O were determined to be [(57.2 \pm 3.2) and (52.5 \pm 0.1)] kJ \cdot mol $^{-1}$ in the temperature range of (310.15 to 318.15) K and [(31.3 \pm 5.9) and (25.0 \pm 0.6)] kJ \cdot mol $^{-1}$ in the temperature range of (298.15 to 308.15) K, respectively. Overall, the E_A for the translational motion of CB[*n*] in D_2O was smaller than the E_A for CB[*n*] in

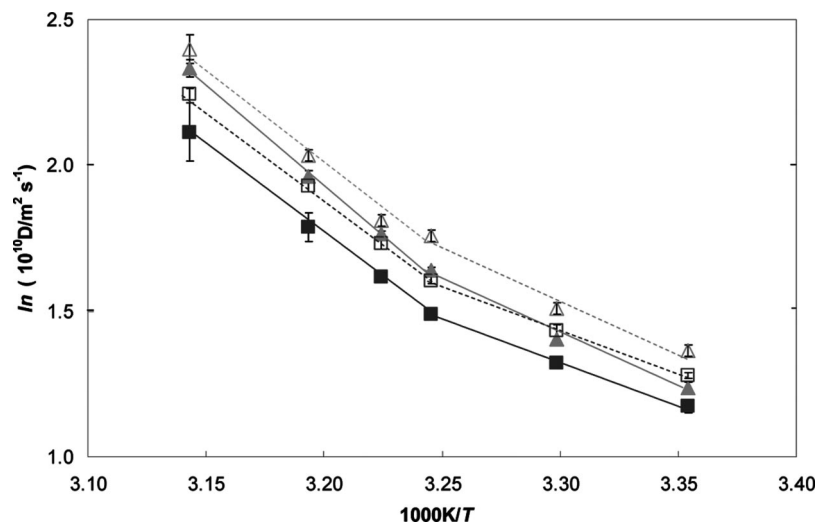


Figure 3. Arrhenius plot of the diffusion coefficient of CB[6] (\blacktriangle , in D_2O ; \triangle , in 90 % H_2O /10 % D_2O) and CB[7] (\blacksquare , in D_2O ; \square , in 90 % H_2O /10 % D_2O) with increasing temperature. E_A was determined from the exponential plot of D vs T . The data are plotted in linear form to illustrate the change in E_A . The two linear sections of the graph demonstrate that a change in E_A occurs around 325 K.

Table 2. E_A of CB[6] and CB[7] ($0.5 \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$) in 99.9 % D_2O and 90 % H_2O /10 % D_2O v/v as a Function of Temperature

T/K	$E_A/(\text{kJ} \cdot \text{mol}^{-1})^b$			
	CB[6]		CB[7]	
	D_2O	H_2O^a	D_2O	H_2O^a
298.15 to 308.15	29.3 ± 5.9	31.3 ± 5.9	24.3 ± 1.1	25.0 ± 0.6
310.15 to 318.15	55.4 ± 4.0	57.2 ± 3.2	49.8 ± 2.3	52.5 ± 0.1

^a 90 % H_2O /10 % D_2O v/v. ^b Are derived from the exponential fitting curve determined in OriginPro 8.0.

90 % H_2O /10 % D_2O . This is in contrast to the E_A determined for the translational motion of H_2O and D_2O , alone, at 25 °C being (16.6 and 18.8) $\text{kJ} \cdot \text{mol}^{-1}$, respectively.^{19,20} The difference in E_A between CB[6] and CB[7] in 90 % H_2O /10 % D_2O v/v and H_2O (alone) is (14.7 and 8.4) $\text{kJ} \cdot \text{mol}^{-1}$, while in D_2O the difference is less, (10.6 and 5.6) $\text{kJ} \cdot \text{mol}^{-1}$, respectively, which was not expected. It is acknowledged that the viscosity of 90 % H_2O /10 % D_2O v/v is not identical to water, but this would not be expected to induce a change in E_A of this magnitude. The E_A value of CB[6] and CB[7] increases with temperature, suggesting that the increased frequency of interactions between molecules and/or aggregation may be a contributing factor. Convection effects were assessed by measuring the diffusion at different Δ values [(30 and 125) ms] and were found to not contribute to the apparent diffusion coefficients determined in these experiments.

The diffusion coefficients of CB[6] and CB[7] at varying concentrations are given in Table 3. The diffusion of both CB[6] ($3.45 \cdot 10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$) and CB[7] ($3.23 \cdot 10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$) at $0.5 \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$ is similar to other macrocycles of roughly the same size and determined under similar conditions, particularly *p*-sulfonatocalix[4]arene, which we previously determined to be $3.21 \cdot 10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$.²¹

CB[6] diffuses slower with increasing concentration between (0.25 and $2 \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$), whereas CB[7] shows only an initial change between (0.25 and $0.75 \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$). Within experimental error, the diffusion coefficient of CB[7] does not change between (0.75 and $2 \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$), although previously we have demonstrated that at saturation and with no solubilizing NaCl CB[7] diffuses significantly slower at $2.8 \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$.¹² For both CB[6] and CB[7], the decrease in the diffusion coefficient with increasing concentration is due

Table 3. Diffusion Coefficient of CB[6] and CB[7] (298.15 K) in 99.9 % D_2O as a Function of Concentration

$c/10^{-3} \text{ mol} \cdot \text{L}^{-1}$	$D/(\cdot 10^{-10} \text{ m}^2 \cdot \text{s}^{-1})^a$	
	CB[6]	CB[7]
0.25	3.47 ± 0.02	3.23 ± 0.04
0.50	3.45 ± 0.02	3.23 ± 0.02
0.75	3.42 ± 0.01	3.16 ± 0.02
1.00	3.41 ± 0.01	3.12 ± 0.01
1.25	3.35 ± 0.01	3.14 ± 0.01
1.50	3.34 ± 0.03	3.13 ± 0.02
1.75	3.38 ± 0.01	3.13 ± 0.01
2.00	3.37 ± 0.01	3.15 ± 0.01

^a Are derived from the exponential fitting curve determined in OriginPro 8.0.

Table 4. Diffusion Coefficient of CB[6] and CB[7] (298.15 K, $0.5 \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$) in 99.9 % D_2O as a Function of pH

pH	$D/(\cdot 10^{-10} \text{ m}^2 \cdot \text{s}^{-1})^a$	
	CB[6]	CB[7]
1	3.26 ± 0.03	2.88 ± 0.04
4	3.55 ± 0.03	3.20 ± 0.02
7	3.57 ± 0.04	3.08 ± 0.02
10	3.50 ± 0.02	3.19 ± 0.02
13	3.35 ± 0.02	3.13 ± 0.02

^a Are derived from the exponential fitting curve determined in OriginPro 8.0.

to the formation of small pockets of aggregation, rather than a change in viscosity of the D_2O . For solutions of CB[6] at different concentrations, the diffusion coefficient of the HDO resonance is unchanged ($2.00 \pm 0.03 \cdot 10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$, at $(0.25$ and $2.0) \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$).

The diffusion coefficient of CB[6] and CB[7] at varying pH is given in Table 4. Between pH 4 and 13, there is relatively little change in the diffusion coefficient of either molecule. When the pH is decreased to 1, both CB[6] and CB[7] diffuse significantly slower. The pK_a of the conjugate acid of CB[6] and CB[7] is 3.0 and 2.2, respectively.^{3,22} Therefore, the large decrease in the diffusion coefficient of CB[6] and CB[7] at pH 1 is due to the protonation of the carbonyl portals. Hwang et al. have previously shown that at low pH (between 0 and 2) and under specific temperature and concentration conditions CB[7] forms hydrogels.²² Our result demonstrates that while hydrogels are not formed by CB[6] or CB[7] under our conditions (the use

of DCl instead of H_2SO_4 and a substantially lower acid concentration $0.5 \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$ compared with $\approx 26 \cdot 10^{-3} \text{ mol} \cdot \text{L}^{-1}$ used by Hwang et al.²² there is still aggregation effects at very low pH from protonation of the carbonyl portals.

The diffusion results for CB[6] and CB[7] at pH 13 indicate repulsion of the negative charge on the carbonyl portals. Added salts (cations) affect the diffusion coefficient at pH 13 by facilitating aggregation by forming a connective network of cations to balance the negative charge on the carbonyl portals.

Conclusions

Using PGSE and PGSTE NMR, we have determined the diffusion coefficients of CB[6] and CB[7] under a variety of conditions in D_2O and 90 % $\text{H}_2\text{O}/10$ % D_2O . E_A is larger for CB[n] in 90 % $\text{H}_2\text{O}/10$ % D_2O v/v than in D_2O . The E_A increase for the translational motion of CB[n] with temperature suggests that aggregation formation may be a contributing factor. These results provide a baseline for further work into the applications of CB[n] host–guest chemistry, particularly in the field of drug delivery.

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