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Probing interactions between hydrocarbons and auxiliary guests inside Cucurbit[8]uril using fluorinated metal-terpyridine complexes

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1. Introduction

The long-term goal of this project is to develop assays to characterize complex hydrocarbon mixtures such as crude oil batches. To that aim, we are designing a series of supramolecular hydrocarbon-binding probes from (1) a Cucurbituril macrocycle (CB[8]), and (2) an auxiliary CB[8]-binding guest bearing fluorine tags. The probe can selectively encapsulate hydrocarbons to form heteroternary complexes with the macrocycle, the auxiliary guest, and the hydrocarbon. The nature of the auxiliary unit can be changed at will, and binding is monitored by ^{19}F nuclear magnetic resonance spectroscopy (NMR) thanks to the fluorine tags.

2. Impact

So far, this grant has allowed one junior graduate student to publish his first article (*Org. Lett.* **2017**, *19*, 4303). Another junior student, as well as a post-doctoral fellow and an exchange student from the University of Upper Alsace (Mulhouse, France) are currently finalizing another manuscript, and have gathered enough data to generate two additional articles in 2019. Results gathered as part of this ACS PRF grant have been used as preliminary data for a National Science Foundation grant proposal (Macromolecular, Supramolecular and Nanochemistry program).

3. State of Research

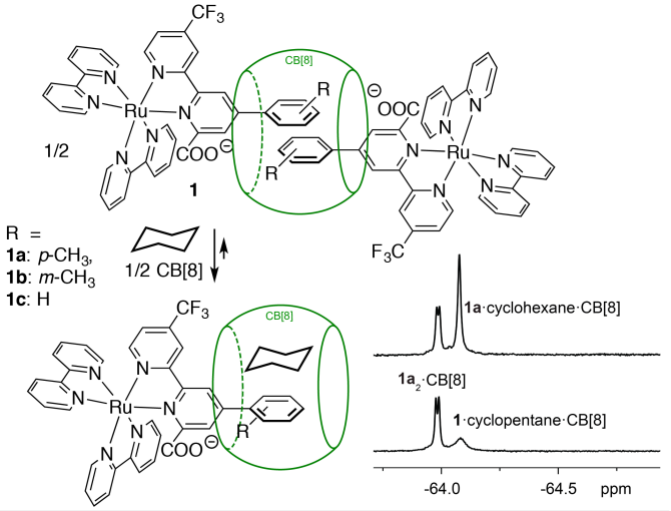

Figure 1. Equilibrium between homoternary complex **1a**$_2$·CB[8], hydrocarbons, CB[8] and hetero-ternary complex **1a**·**H**·CB[8]. Monitoring of the recognition process by ^{19}F NMR spectroscopy for the CB[8]/probe **1a** pair, cyclopentane and cyclohexane.

We are currently preparing two families of probes: Ruthenium complexes **1**, and pyridinium salts **2**. Ruthenium tris(2,2′-bipyridyl) complexes **1** bear a bipyridyl ligand that is substituted with (1) a CB[8]-binding aryl unit, and (2) a trifluoromethyl group to monitor binding by ^{19}F NMR spectroscopy. Guests **1** quantitatively form homo-ternary complexes **1**$_2$·CB[8] in the presence of 0.50 equiv CB[8] in deuterium oxide (see Figure 1). Upon addition of a hydrocarbon **H** and an excess amount of CB[8] (used at saturation), a fraction of the homoternary complexes are converted to heteroternary complexes **1**·**H**·CB[8], thereby resulting in the formation of a new ^{19}F NMR signal (see Figure 1). The equilibrium constant $K^{\mathrm{H}}_{\mathrm{aq}\rightarrow\mathrm{CB}}$ is determined using the concentration of homo- and hetero-ternary complexes, and the solubility of the hydrocarbon in the aqueous medium (see eq. 1). The binding affinity $K^{\mathrm{rel}}_{\mathrm{aq}\rightarrow\mathrm{CB}}$ (and the corresponding free energy term $\Delta G^{\mathrm{rel}}_{\mathrm{aq}\rightarrow\mathrm{CB}}$) of a hydrocarbon **H** relative to a reference hydrocarbon $\mathbf{H}_{\mathbf{ref}}$ towards the CB[8]/probe pair are obtained from equations (2) and (3).

$$K^{\mathrm{H}}_{\mathrm{aq}\rightarrow\mathrm{CB}} = \frac{\left[\mathbf{1}\cdot\mathbf{H}\cdot\mathrm{CB[8]}\right]}{\left[\mathbf{1}_2\cdot\mathrm{CB[8]}\right]^{1/2}\cdot S_{\mathrm{H}}\cdot {S_{\mathrm{CB[8]}}}^{1/2}} \quad (1) \qquad K^{\mathrm{rel}}_{\mathrm{aq}\rightarrow\mathrm{CB}} = \frac{K^{\mathrm{H}}_{\mathrm{aq}\rightarrow\mathrm{CB}}}{K^{\mathrm{H_{ref}}}_{\mathrm{aq}\rightarrow\mathrm{CB}}} \quad (2) \qquad \Delta G^{\mathrm{rel}}_{\mathrm{aq}\rightarrow\mathrm{CB}} = -RT\ln K^{\mathrm{rel}}_{\mathrm{aq}\rightarrow\mathrm{CB}} \quad (3)$$

The forces described by the $\Delta G^{\mathrm{rel}}_{\mathrm{aq}\rightarrow\mathrm{CB}}$ terms are (1) the interaction between the hydrocarbon, the probe and the inner wall of CB[8], but also (2) the desolvation energy of the hydrocarbon upon binding. In order to isolate the first term, we considered the equilibrium between hetero-ternary complexes **1**$_2$·CB[8], the hydrocarbon in the gas phase (i.e. in the headspace of the NMR tube, void of any aqueous solvation), and the homo- and heterocomplexes in solution. Equilibrium constant $K^{\mathrm{H}}_{\mathrm{gas}\rightarrow\mathrm{CB}}$ can thus be calculated using a variant of equation (1), by replacing the hydrocarbon solubility in aqueous medium with its vapor pressure (proportional to the molar gas concentration by a factor of *RT*). The new relative free energy terms $\Delta G^{\mathrm{rel}}_{\mathrm{gas}\rightarrow\mathrm{CB}}$ are calculated similarly to $\Delta G^{\mathrm{rel}}_{\mathrm{aq}\rightarrow\mathrm{CB}}$.

Remarkable selectivity was observed: (1) cyclic hydrocarbons (C_5 – C_8) undergo encapsulation by the CB[8]/probe **1a** pair, while the corresponding linear alkanes did not. (2) Adding unsaturations to the cycloalkanes reduces binding affinities, and benzene binds 160, 14 and 2.2 times weaker than cyclohexane, cyclohexene and 1,3-cyclohexadiene, respectively. Cyclohexane and cycloheptene, which display particularly strong affinities for the CB[8]/probe **1a** pair, let us to suspect that, contrary to □-□ stacking interactions, CH-□ interactions are a major contribution to the recognition event.

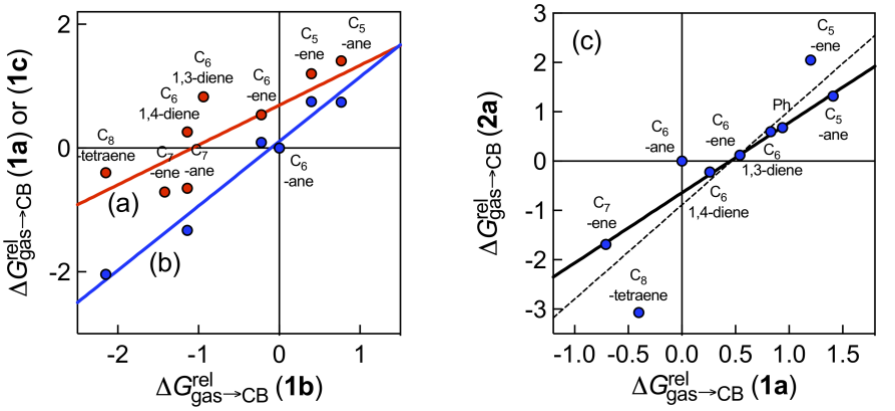

Figure 2. Relative binding affinities of hydrocarbons towards (a) CB[8]/probe **1a**, (b) CB[8]/probe **1c** as a function of the CB[8]/probe **1b** series. (c) Relative binding affinities of hydrocarbons towards CB[8]/probe **2a** as a function of the CB[8]/probe **1a** series. The reference is cyclohexane in all cases; hydrocarbons are in the gas phase and in equilibrium with the ternary CB[8] complexes in aqueous solution.

We then repeated the assays with probes **1b** and **1c**, to test how small variations in the geometry of the probe would affect hydrocarbon binding selectivity. As shown in Figure 2, series a, switching the methyl group of probe **1a** from the *para* to the *meta* position of the aryl unit does result in variations in selectivity, but overall trends are similar: good binders to the CB[8]/probe **1a** pair also bind well to the CB[8]/probe **1b** pair. An even better linear correlation is observed between relative free energy terms obtained with probes **1b** and **1c** (see Figure 2, ser. b).

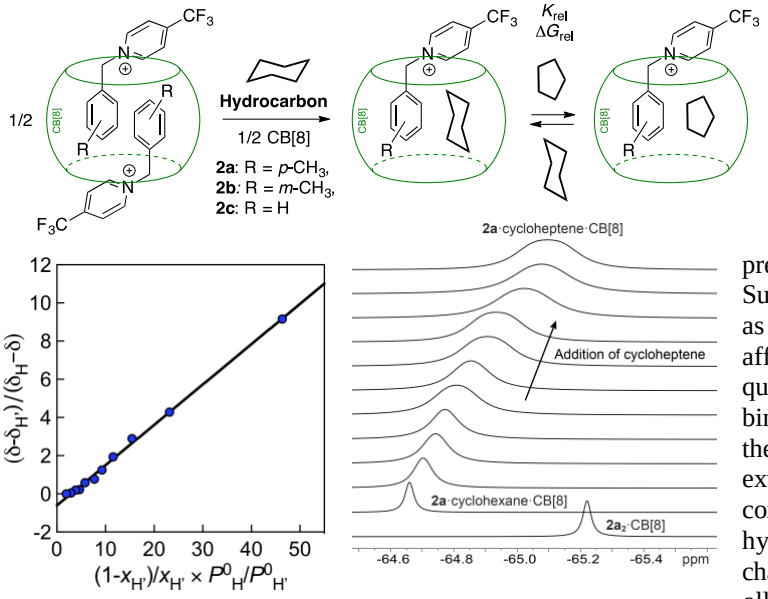

Figure 3. Changes in ^{19}F NMR chemical shifts measured upon addition of aliquots of cycloheptene to a solution of complex **2a**·cyclohexane·CB[8].

A limitation of the ruthenium series of probes **1** is the difficulty to rationalize the subtle variations in hydrocarbon binding affinities by density functional theory calculations. This led us to consider the minimalist design of probes **2**, which form homoternary complexes **2**$_2$·CB[8] in the presence of CB[8] (at least 0.50 equiv.). Subsequent addition of cyclic hydrocarbons **H**, as well as benzene, to complex **2a**$_2$·CB[8] affords heteroternary complex **2a**·**H**·CB[8] quantitatively, and linear hydrocarbons do not bind; this unfortunately prevents us from using the method described above for series **1** to extract binding affinities. However, titrating complex **2a**·**H**·CB[8] with a competitive hydrocarbon **H'**, and monitoring the subtle changes in ^{19}F NMR chemical shifts of probe **2a**, allows an accurate determination of the binding affinity of hydrocarbon **H'** to the CB[8]/probe **2a** pair, relative to hydrocarbon **H** (see Figure 3; $x_{H'}$ is the molar fraction of hydrocarbon **H'**, and P^0_H ($P^0_{H'}$) their respective vapor pressures; δ is the ^{19}F NMR chemical shift measured with mixtures of hydrocarbons, and δ_H ($\delta_{H'}$) in the presence of only one of the hydrocarbons). Binding affinities relative to cyclohexane are presented in Figure 2c and plotted as a function of the affinities measured with probe **1a**, which also bears a CB[8]-binding tolyl unit. The correlation between both probes is remarkably linear despite their different nature, thereby raising confidence in both types of assays.