

Molecular association of benzene with a new cyclophane receptor

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Abstract Host/guest interactions in the cyclophane-2/benzene system have been investigated by absorption and fluorescence spectroscopy in dichloromethane. The cyclophane serves as a host and the benzene as a guest. Absorption and fluorescence titration experiments are carried out by holding either the concentration of the host or guest constant while varying the concentration of the other component. When the concentration of benzene is kept constant, an isostilbic point at 288 nm is observed in the fluorescence spectral data, suggesting that only two absorbing species are present in equilibrium. Keeping the concentration of cyclophane-2 constant while increasing the concentration of benzene results in a hypsochromic shift of the emission peaks in the range 275–360 nm. The shift is attributed to interaction of the cyclophane with benzene. The average association constant of cyclophane-2 with benzene, $K_a = 425 \pm 54 \text{ M}^{-1}$, obtains from fitting the absorption and the fluorescence spectral data to the Bourson et al. equation using non-linear regression analysis.

Keywords Aromatic compounds · Association constant · Cyclophane · Host/guest complexation

Abbreviation

DCM Dichloromethane

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Introduction

The design, synthesis [1–8], and molecular modeling [9–13] of new cyclophane molecules with selectivity for neutral guest molecules is of continuing interest to a variety of scientists. Specifically, cyclophanes that exhibit neutral molecular binding ability for aromatic compounds [3–6, 14–16] are a rapidly emerging branch of supramolecular chemistry [17]. These molecules are important because of their potential for application in biochemical [18], medicinal [19], and environmental [20] fields. They may provide insight into understanding host/guest interactions in the environment.

Few studies of the binding of benzene to cyclophane molecules exist. Studies of their complexation with benzene reported to date include works by Saigo [7], Diederich [12], and Kaifer's [21] research groups. Structures of previously studied cyclophanes (hosts) for reported cyclophane–benzene complexes are shown in Fig. 1. Novel cyclophane molecules (Fig. 2) have been synthesized from a relatively unexplored bisphenol, a π electron-rich hydrophobic unit. These molecules—a new class of cyclophanes—are able to form complexes with aromatic guests within a walled enclosure, hence are referred to as “corrals” by their finders [4]. Herein the cyclophane host molecules are referred to as corrals in compliance with the original nomenclature. The corral molecules in this class have different cavity sizes. Varying the number of methylene spacers from two to six results in varying the cavity size of the cyclophanes. The investigated corral-2 herein refers to a corral with two methylene spacers (Fig. 2), i.e., the smallest cavity size. In early studies we reported the molecular association of corral-5/anthracene and corral-5/9-fluorenone host/guest systems in dichloromethane [16]. Our results revealed that the binding of anthracene guest by

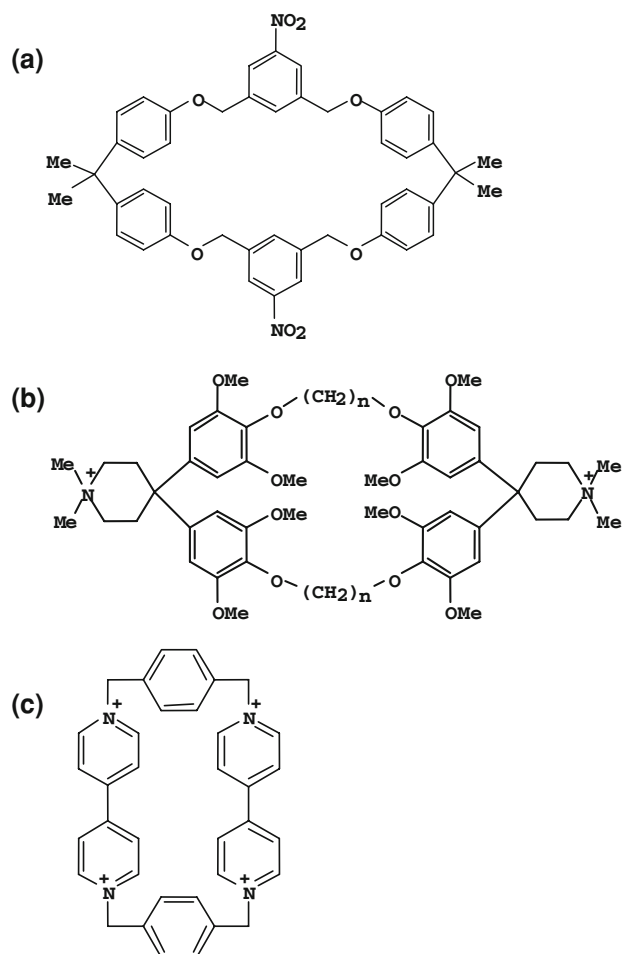


Fig. 1 (a) Saigo's novel cyclophane [7], (b) Diederich's octamethoxy tetraoxaparacyclophane, $n = 3$ [12] and (c) Kaifer's cyclobis(paraquat-*p*-phenylene), host 1^{4+} [21] having cavities capable of accommodating benzene as a guest

corral-5 is entropically-driven and thermodynamically favored over that for 9-fluorenone guest.

This paper reports the association constant of benzene with a newly synthesized corral molecule—corral-2—in dichloromethane (DCM) studied by absorption and fluorescence spectroscopy. The host/guest complexation of corral-2/benzene system is investigated: Corral-2 serves as the host and benzene as the guest (Fig. 2). Molecular

recognition studies of benzene by corral-2 were investigated as benchmark since benzene is the smallest and simplest aromatic hydrocarbon. Corral-2/naphthalene complexation studies were not successful due to lack of favorable spectral ranges. The absorption spectra of corral-2 and naphthalene overlap extensively. And corral-2/anthracene complexation studies did not show any significant variation of either spectral intensity or maximum wavelength for both absorption and fluorescence titrations experiments upon complexation. Thus, there was no significant data for determining the association constants of the corral-2/naphthalene and corral-2/anthracene complexes.

Experimental

Spectrophotometric grade DCM and benzene were purchased from Aldrich and used as received. Corral-2 was synthesized by the reported method [4]. Stock solutions in DCM were prepared: 5×10^{-5} M for corral-2 and 2×10^{-2} M for benzene. Absorbances of the prepared stock solution and several diluted samples were measured using a Shimadzu UV-Vis spectrophotometer (model UV-2101 PC). Several stock solutions (2.5×10^{-4} to 1×10^{-3} M) of benzene were also prepared. These solutions were then combined (1:1, by volume, that is 5 mL + 5 mL in a 10-mL volumetric flask) with a constant concentration of corral-2. The absorption spectrum was collected a few minutes following each addition. Variation of host's absorption intensity—in the region of 275–300 nm where benzene does not absorb—was monitored as a function of the benzene concentration in DCM at ambient temperature (Fig. 3). The final concentration of the host molecule was held constant (2.5×10^{-5} M) for the UV-Vis absorption experiments, while the final concentration of benzene was varied from 0 to 1×10^{-3} M.

Fluorescence spectra were measured with a Shimadzu RF-5301 PC spectrofluorometer. Two types of experiments were conducted for the fluorescence titrations. First, the concentration of benzene was held constant at 2.5×10^{-4} M while that of corral-2 was varied from

Fig. 2 Structures of (a) unbound cyclophane-2 (or corral-2) and (b) corral-2/benzene complex

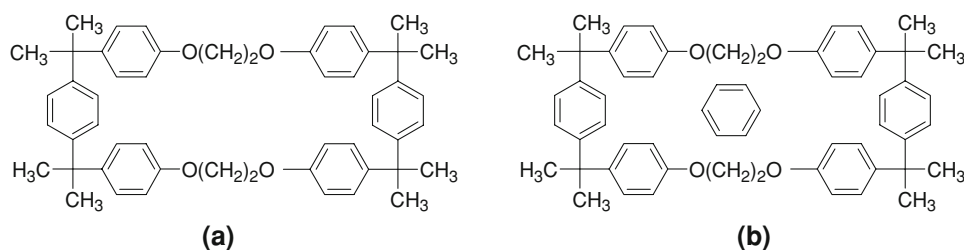


Fig. 3 Absorption spectra of corral-2 and benzene (upper panel) and UV-Vis titration experiment (lower panel) showing changes in the absorption spectrum of (a) corral-2 (2.5×10^{-5} M) upon addition of benzene, (b) 1.25×10^{-4} M, (c) 2.5×10^{-4} M, (d) 5×10^{-4} M, and (e) 1×10^{-3} M in DCM

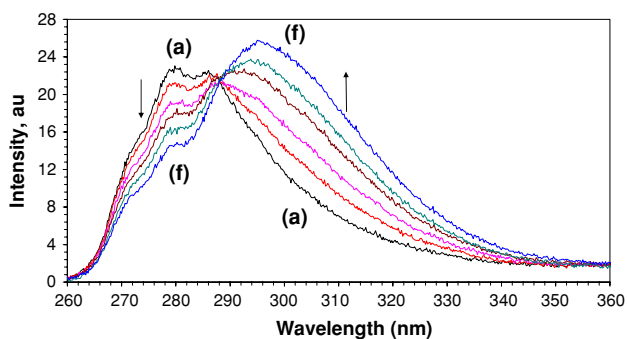
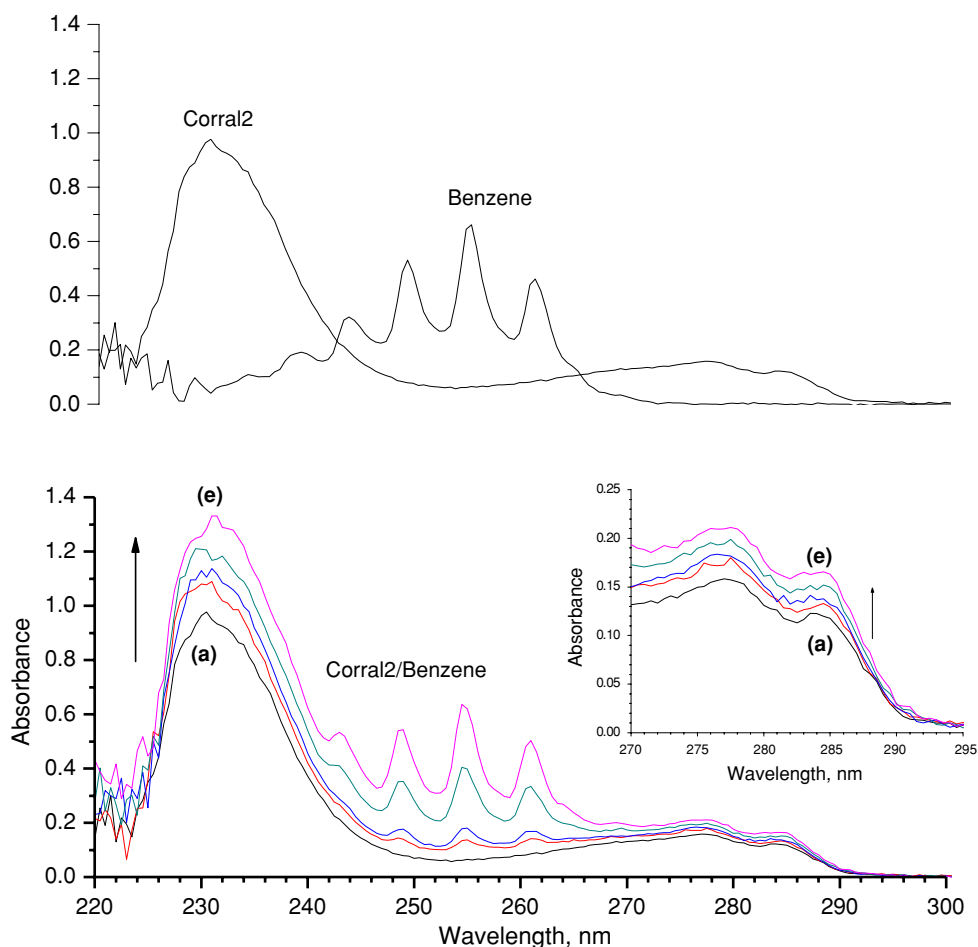


Fig. 4 Effect of increasing concentration of corral-2 on the fluorescence spectrum of benzene in DCM. (a) Benzene only, (b) 5×10^{-6} M, (c) 1.5×10^{-5} M, (d) 2×10^{-5} M, (e) 2.5×10^{-5} M, and (f) 5×10^{-5} M in DCM. Excitation wavelength is 255 nm. The isostilbic point is at 288 nm

5×10^{-6} M to 5×10^{-5} M (Fig. 4). Second, the concentration of corral-2 was held constant at 2.5×10^{-5} M and changes in the emission of corral-2 upon addition of benzene from 0 to 4×10^{-3} M were monitored (Fig. 5). All solutions were excited at 255 nm.

Determination of the association constants for the corral-2/benzene

Bourson et al. equation [22] (Eq. 1) was derived by assuming that the stoichiometry of the molecular recognition complex is 1:1,

$$I = I_0 + \frac{I_{\text{lim}} - I_0}{2C_0} [C_0 + C_x + 1/K_a - [(C_0 + C_x + 1/K_a)^2 - 4C_0C_x]^{1/2}] \quad (1)$$

where I = intensity of the complex, I_0 = initial intensity of the substance that is held constant (either corral-2 or benzene, in this study), C_0 = concentration of the substance that is held constant, C_x = concentration of the substance that is varied, and K_a = the association constant of the host/guest complex. The association constant was determined by plotting the intensity of the complex, I , at a selected wavelength as a function of the concentration of the substance that is varied, C_x (Figs. 6, 7). Absorption and emission spectral data were fit to equation (1) using Origin 7.5 software. Satisfactory fits were obtained ($R^2 = 0.99$) in all cases. These results support the assumption of 1:1 complexation between corral-2 and benzene.

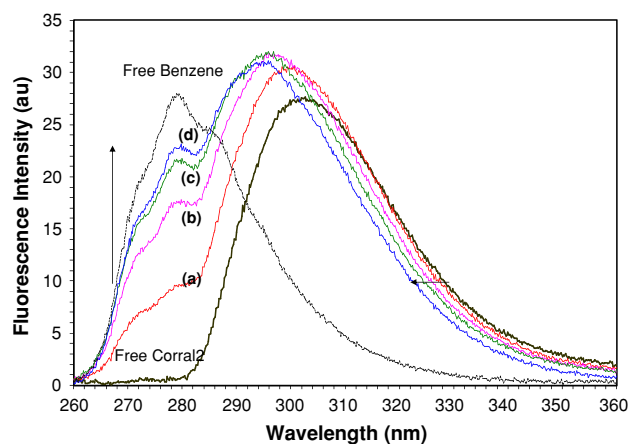


Fig. 5 Changes in the fluorescence spectrum of corral-2 in DCM, 2.5×10^{-5} M, (bold spectrum), upon addition of (a) 1×10^{-3} M, (b) 2×10^{-3} M, (c) 3×10^{-3} M, and (d) 4×10^{-3} M benzene in DCM. Excitation wavelength is 255 nm. The dotted graph is the fluorescence spectrum of benzene (1×10^{-2} M) in DCM. The horizontal arrow indicates the direction of spectral shift upon addition of benzene

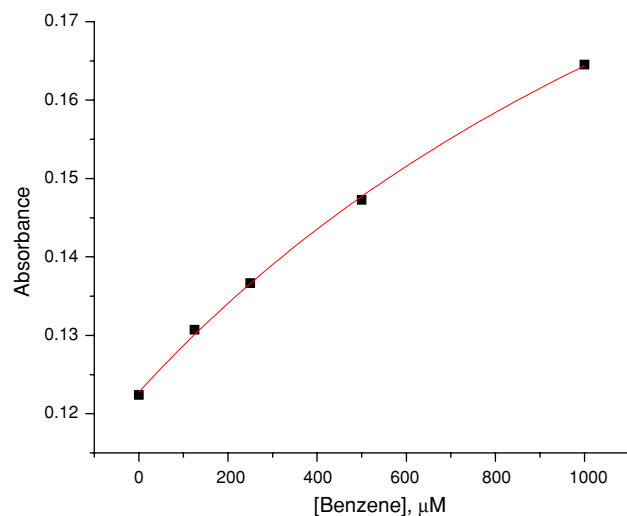


Fig. 6 Room temperature absorption spectroscopic data for the corral-2/benzene system in DCM (symbols) at 284 nm and fit to the Bourson et al. equation [22] (line)

Results and discussion

Absorption titrations

Corral-2 was held at a constant concentration of 2.5×10^{-5} M while the concentration of benzene was varied. Changes in the absorption spectrum of corral-2 were monitored in the region where free benzene does not absorb—275–300 nm. As shown in Fig. 3, the absorbance of corral-2 increased as a function of the concentration of benzene. This observation suggests that corral-2 interacts with benzene; it was used to determine the association constant.

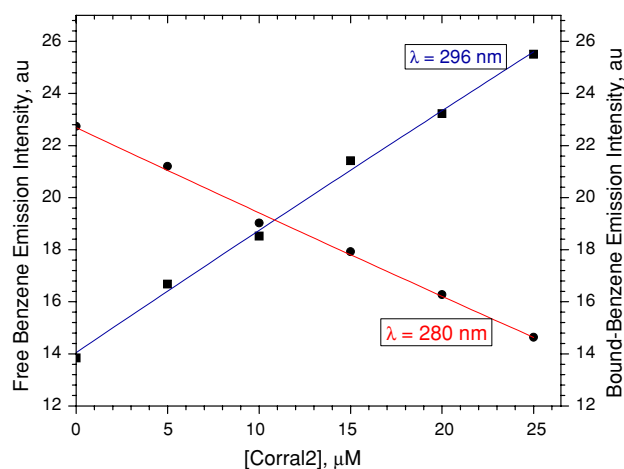


Fig. 7 Non-linear regression analysis of the fluorescence spectral data for benzene (●) and corral-2/benzene complex (■) in DCM at 280 and 296 nm, respectively, using the Bourson equation [22]. Emission intensities obtained from Fig. 4

For data analysis, wavelengths were chosen where corral-2 absorbs but benzene does not, and where the variations of the absorbance of the complex as a function of the concentration of benzene were largest. The association of corral-2 with benzene in DCM was assessed by non-linear curve fitting of the absorption spectral data using Origin 7.5. A fit to the Bourson et al. equation [22] of absorption spectral data at 284 nm (Fig. 6) yields an association constant of $506 \pm 10 \text{ M}^{-1}$.

Fluorescence titrations

When the concentration of benzene was held constant, the emission intensity of free benzene at the wavelength maximum of 280 nm decreased as corral-2 was added and the signal attributed to complexed benzene at $\lambda_{\text{max}} = 296$ nm increased (Fig. 4). Observation of an isostilbic point at 288 nm suggests the presence of only two absorbing species in equilibrium, in agreement with 1:1 complexation between the corral-2 and benzene.

Alternatively, when the concentration of corral-2 was held constant the emission intensity of corral-2 increased as more and more benzene was added, and the maximum intensity peak was blue shifted, a hypsochromic shift. The emission spectrum due to free corral-2 has a λ_{max} at 304 nm (Fig. 5). The blue shift to higher energy or lower wavelength suggests a direct relationship between the concentration of benzene and its capability to donate π -electrons to the corral-2 upon complexation.

Fitting of the fluorescence spectral data at 280 nm for the constant benzene concentration to the Bourson et al. equation produced a negative slope, whereas the fit at 296 nm resulted in a positive slope (Fig. 7). The negative slope fit corresponds to the decreasing fluorescence

Table 1 Association constant, K_a , of corral-2/benzene complex obtained by titration experiments and free energy of complexation, ΔG°

| Corral2–benzene | Constant | λ (nm) | K_a (M^{-1}) | ΔG° (kcal/mol) |
|-----------------|------------|----------------|--------------------|-----------------------------|
| Absorption | [corral-2] | 284 | 506 ± 10 | -3.62 |
| Fluorescence | [corral-2] | 340 | 395 ± 20 | -3.48 |
| Fluorescence | [Benzene] | 280 | 400 ± 30 | -3.49 |
| Fluorescence | [Benzene] | 296 | 400 ± 30 | -3.49 |

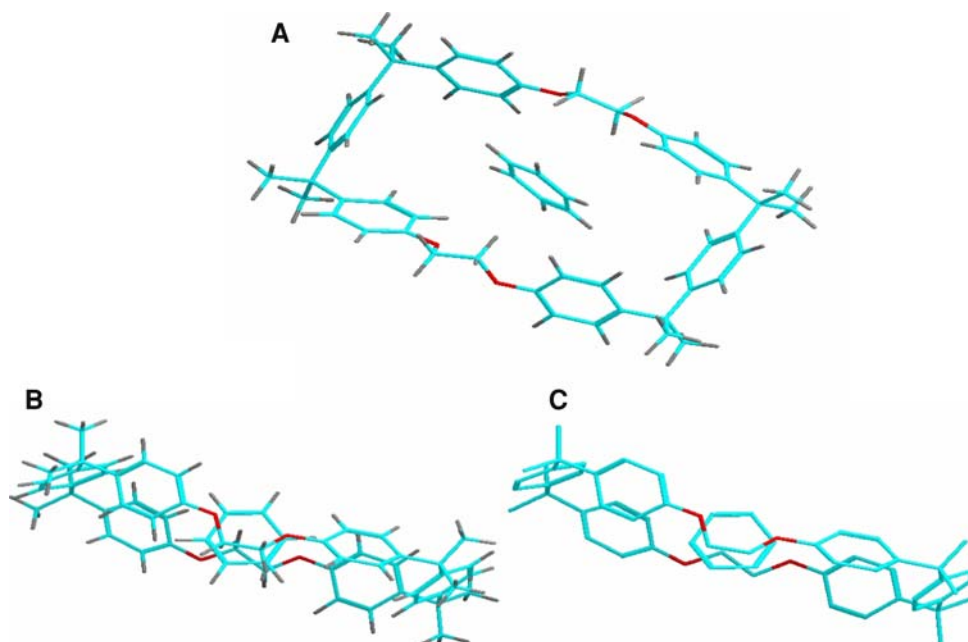
$T = 293$ K, average $K_a = 425 \pm 54$ and $\Delta G^\circ = -3.52$ kcal/mol

intensity signal of the free benzene at 280 nm and the positive slope fit is attributed to the increasing bound-benzene emission intensity at 296 nm as a function of the increasing concentration of corral-2. As expected, both fits yielded an identical association constant, K_a , of $400 \pm 30 M^{-1}$ as shown in Table 1. The fit of the fluorescence titration data at constant concentration of corral-2 yielded $K_a = 395 \pm 20 M^{-1}$, which is in agreement with the value determined at the constant concentration of benzene. The fluorescence spectral data analysis at 340 nm was selected for the constant concentration of corral-2 titrations because free benzene does not fluoresce at 340 nm, and spectral changes in emission intensity as a function of benzene are largest (Fig. 5).

Table 2 Association constant, K_a , and relative free energy of binding (ΔG_{bind}) of cyclophane/benzene complexes

^a Charge-transfer band and $\Delta G_{\text{bind}} = -RT \ln K$ at $T = 293$ K

| Complex | Solvent | K_a (M^{-1}) | ΔG_{bind} (kcal mol ⁻¹) | Experimental technique | Ref. |
|--------------------------------------|---------------------------------|--------------------|--|------------------------------------|-----------|
| Host 1 ⁴⁺ /benzene | CH ₃ CN | 18 | -1.68 | Absorption ^a | [21] |
| Cyclophane 1 /benzene | D ₂ O | 102 | -2.69 | ¹ H NMR titrations | [12] |
| Corral-2/benzene | CH ₂ Cl ₂ | 425 | -3.52 | Absorption and emission titrations | This work |

Fig. 8 Corral-2/benzene complex PCModel 9.1 autodock structure (a) top view, (b) side view, and (c) side view without hydrogens

Summary of the association studies of cyclophane/benzene system

Absorption and fluorescence titration experiments were conducted for measuring the association constant of benzene with corral-2. The obtained average association constant for the corral-2/benzene complex is $425 \pm 54 M^{-1}$ in DCM. Reported association constants for other cyclophane/benzene complexes are 18 and $102 M^{-1}$, for the host **1**⁴⁺/benzene [21] and cyclophane **1**/benzene [12], respectively. The association constant of Saigo et al. [7] cyclophane/benzene complex was not reported. Thus it appears that the corral-2/benzene complex has the strongest host/guest interaction. However, direct comparison of the association constants is not possible because the measurements were taken in different solvents (Table 2) and the host molecules have different charges—corral-2 is neutral, cyclophane **1** has a net charge of +2 and host-1⁴⁺ has a net charge of +4 (Fig. 1).

Molecular modeling

Molecular modeling was performed with PCModel 9.1 [23]. Molecular mechanics geometry optimization of the corral-2, benzene, and corral-2/benzene complex were

carried out using the MMX force field. The docking option (auto dock) in PCModel was employed to find the best interaction geometry between corral-2 and benzene. The lowest energy conformation of the complex obtained from docking computations is shown in Fig. 8. Complexation of the guest molecule within the π -electron rich cavity of the host species is clearly evident.

Conclusion

We have measured an average association constant for the corral-2/benzene complex of $425 \pm 54 \text{ M}^{-1}$ in DCM at room temperature from absorption and fluorescence titration experiments. Observation of an isostilbic point at 288 nm in the emission spectral data reveals that a 1:1 complex between corral-2 and benzene has been formed. Molecular modeling suggests that the benzene molecule is intercalated in the cavity of corral-2. We are currently attempting to grow crystals of the corral-2/benzene complex for structural analysis by X-ray diffraction. Corral-2 may potentially serve as a sensor for benzene. Future studies of the selective binding of benzene to corral-2 in a mixture of benzene with toluene and xylenes may yield further useful results for the development of chemical sensors.

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