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Spectral Study on Selective Encapsulation and Complexation of Chloroform by Cryptophane-E-$(OEt)_6$

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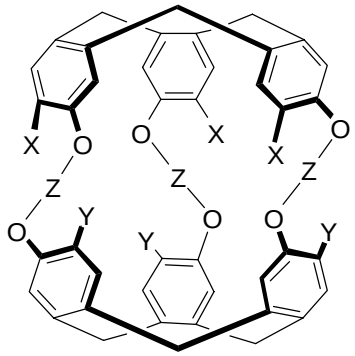
Cryptophane-E-$(OEt)_6$ was synthesized and investigated the interaction with chloroform by fluorescence spectroscopy. The results indicate that cryptophane-E-$(OEt)_6$ is able to selectively encapsulate chloroform. The variation of the fluorescence spectra in binary solvents with the increasing chloroform ratio suggests that cryptophane-E-$(OEt)_6$ and chloroform can form a 1:1 complex and the binding constant is estimated to be 235 M^{-1}, which is much smaller than the binding constant of cryptophane-E to chloroform. Without appreciable consequences on the cavity dimensions, the replacement of methoxy group in cryptophane-E by ethoxy substituents restricts the cross section of the host windows. This is mostly due to steric constraint of the larger ethoxy substituent.

Keywords: Cryptophane, Chloroform, Binding, Complex, Encapsulation, Fluorescence.

INTRODUCTION

Since the first synthesis of cryptophane-A in 1981, considerable progress has been made in design of cryptophanes that exhibit selective encapsulation properties toward organic and inorganic guests of complementary size[1-9]. Cryptophanes (Fig. 1) are globularly shaped and contain two cone-shaped cyclotriveratrylene (CTV) units attached to one another *via* three O-Z-O bridges and hence they are particularly well suited for encapsulating small neutral or charged guests with various sizes and shapes (*e.g.*, halomethanes, ammonium salts and xenon) because the characteristics of host cavities, including size, shape, polarity and chirality, can be easily tuned to achieve greater guest selectivity[10-25]. For instance, cryptophane-A with three $O(CH_2)_2O$ bridges preferentially acts as encapsulating host for dichloromethane and methane[13,14], whereas cryptophane-E with a larger cavity of three $O(CH_2)_3O$ bridges prefers to bind chloroform[15,16]. Cryptophanes can bind reversibly to a variety of guests and the complexation of halo-methanes by cryptophanes was evidenced by ^1H NMR studies[14-21]. The inclusion complexes of guests in the inner cavity of cryptophanes are generally characterized by weak but specific non-covalent interaction between the host and the guest.

The extraordinary ability of cryptophane-E to bind chloroform in lipophilic solvents has been studied by NMR spectroscopy and it is found that the binding constant K_a, is unusually strong, 470 M^{-1} at 300 K, which means that cryptophane-E can withdraw $CHCl_3$ from $(CDCl_2)_2$ at this temperature[15]. Garcia *et al.*[21] have synthesized the cryptophane-E-$(SCH_3)_6$ bearing six methylthio groups through the two-step routes and determined the binding constant K_a = 240 M^{-1} (± 10 %) for $CHCl_3$@cryptophane-E-$(SCH_3)_6$ complex. This K_a value is considerably lower than the value of 470 M^{-1}, which could be due to modification of the accessibility to the cryptophane cavity.



X=Y=OCH_3, Z=$(CH_2)_2$; cryptophane-A
X=Y=OCH_3, Z=$(CH_2)_3$; cryptophane-E
X=Y=OC_2H_5, Z=$(CH_2)_3$; cryptophane-E-$(OC_2H_5)_6$

Fig. 1. General cryptophane structure

Despite of the smaller inner windows, cryptophane-E-$(OEt)_6$, in which six larger ethoxy substituents have replaced the six methoxy groups of cryptophane-E, has much the same size of the inner cavity as cryptophane-E. These sterically-hindered OEt substituents were chosen to test the hypothesis that the measured binding constant would be smaller if the replacement of OMe by OEt substituents restricts the cross section of the host windows due to steric constraint. Our previous spectral study[23] demonstrated that chloroform could be encapsulated efficiently by cryptophane-M with a larger cavity ($O(CH_2)_4O$ bridges). In this paper, we further investigate the interaction between cryptophane-E-$(OEt)_6$ and various solvents because the results could provide useful suggestions on the development of new hosts. We report our recent endeavors to clarify if cryptophane-E-$(OEt)_6$ could encapsulate various guests with high selectivity by fluorescence spectroscopy.

EXPERIMENTAL

Organic solvents were obtained from Chongqing Medical & Chemical Corp. Other reagents were purchased from Aldrich unless otherwise specified. The starting materials were further purified with redistillation or recrystallization before use.

Synthesis of cryptophane-E-$(OEt)_6$: According to the direct method with modified procedures, cryptophane-E-$(OEt)_6$ was synthesized from the starting material ethyl vanillin (3-ethoxy-4-hydroxybenzaldehyde, m.p. 78 °C) by the sequence presented in Fig. 2, which is similar to that used for synthesis of the cryptophane-E[9,26,27]. The key step is the double trimerization of a *bis*-benzylalcohol (**4**) in which the CH_2OH groups precursor of the benzyl cations involved in the reaction are situated para to the $O(CH_2)_3O$ spacer[21]. The first step in this synthesis is the formation of sodium phenolate (**2**) from ethyl vanillin in ethanol, which is different from previous methods[27]. Reaction of sodium salt **2** with 1,3-dibromopropane in DMF followed by reduction of the intermediate dialdehyde **3** furnished the desired diol **4** in a remarkable overall yield of 84 %. Reaction of compound **4** with formic acid afforded cryptophane-E-$(OEt)_6$ (**5**) in 5.2 % yield. ^{1}H NMR ($CDCl_3$, δ, ppm), 6.91-6.87 (s, 12H, Ar), 4.67 (d, 6H, CHa), 4.24 (s, 4H, OCH_2CH_3), 4.04 (s, 4H, OCH_2CH_2), 3.47 (d, 6H, CHe), 2.08 (m, 12H, CH_2), 1.26 (s, 18H, CH_3). Anal. Calcd. for $C_{63}H_{72}O_{12}$: C, 74.1; H, 7.11; O, 18.8. Found: C, 73.7; H, 7.1; O, 19.2%.

Instrument and spectral measurements: The melting points were measured on a Beijing Fukai melting point apparatus. Nuclear magnetic resonance (NMR) was carried out at 298 K with a Bruker 500 MHz apparatus by using tetramethylsilane (TMS) as internal standard. Element analyses were performed by CE440 elemental analysis meter from Exeter Analytical Inc. The UV-visible absorption spectra were recorded with a Cintra spectrophotometer. The emission spectra were performed with Shimadzu RF-531PC spectrofluoro-photometer. All experiments on the spectroscopic determination of the sample solutions were conducted in dark. Besides, contrast experiments were performed for the detection of encapsulation of various solvents by cryptophane-E-$(OEt)_6$. The sonicated solution was employed for the spectral detection. The fluorescence quantum yields of the samples in various solvents were determined according to the report methods[28,30].

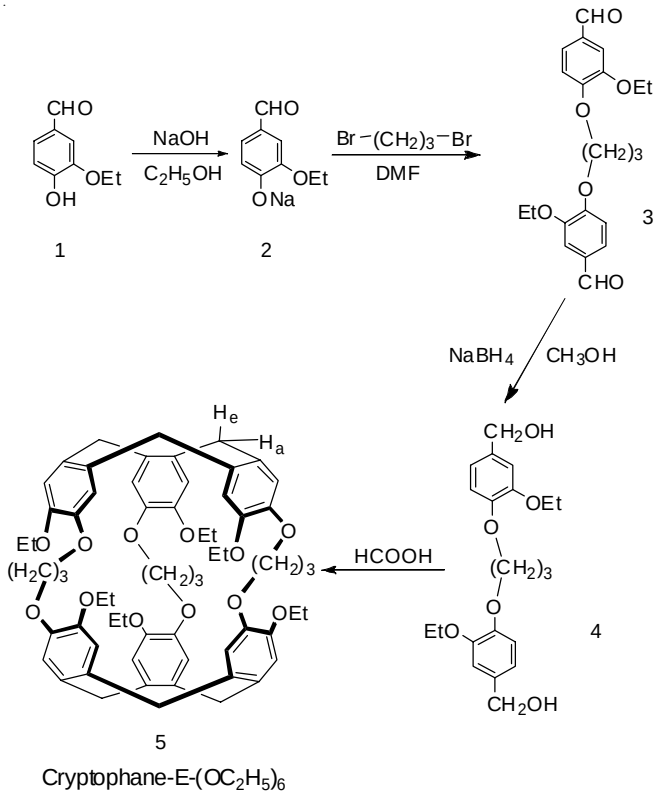


Fig. 2. Synthesis of *anti*-cryptophane-E-$(OEt)_6$

RESULTS AND DISCUSSION

Selective encapsulation toward organic solvent guests: In this work, various solvents, such as 1,4-dioxane, acetone, ethyl acetate, acetonitrile, 1,2-dichloroethane, dichloromethane and chloroform, were chosen as potential guests because they might be encapsulated by cryptophane-E-$(OEt)_6$ since they have small molecular sizes. The UV-visible absorption and fluorescence spectral data of cryptophane-E-$(OEt)_6$ in various solvents were presented in Table-1. Cryptophane-E-$(OEt)_6$ has a peak absorption at 286-289 nm when the concentration is 3.5×10^{-6} mol L^{-1}. The data suggest that the peak absorption wavelength and the molar extinction coefficients of cryptophane-E-$(OEt)_6$ are almost the same in various solvents and thus the absorption peak of cryptophane-E-$(OEt)_6$ in different solvents did not vary much with the change in the polarity of the solvents.

TABLE-1
ABSORPTION AND FLUORESCENCE SPECTRAL DATA OF CRYPTOPHANE-E-$(OEt)_6$ IN DIFFERENT SOLVENTS (298 K)

Solvent	λ_{abs} (nm)	log ε	λ_{ex}(nm)	λ_{em} (nm)	Φ_f
1,4-Dioxane	289	4.55	376	420, 432	0.335
Acetone	286	4.57	377	429	0.260
1,2-Dichloroethane	286	4.54	376	422, 434	0.233
Dichloromethane	286	4.54	376	412, 436	0.215
Ethyl acetate	287	4.53	376	420, 435	0.182
Acetonitrile	286	4.55	377	432	0.165
Chloroform	286	4.54	376	412, 433	0.041

As shown in Fig. 3, a large difference can be observed for the emission spectra of cryptophane-E-$(OEt)_6$ solution in chloroform from that in other solvents, *e.g.*, 1,4-dioxane, ethyl

acetate, 1,2-dichloroethane, *etc*. The peak emission intensity of cryptophane-E-(OEt)$_6$ is much reduced in chloroform. Table-1 shows that the fluorescence quantum yield of the cryptophane-E-(OEt)$_6$ solution in chloroform is much lower than that in other solvents. These results indicate that cryptophane-E-(OEt)$_6$ is able to selective encapsulate chloroform and the strong interaction between them makes chloroform remained inside the cavity. In other words, an inclusion complex of cryptophane-E-(OEt)$_6$ and chloroform could be formed which can affect the fluorescence yield and spectral characteristics of cryptophane-E-(OEt)$_6$. Although the other solvents could enter into the cavity, they could run out of the cavity quickly as well if the interaction between cryptophane-E-(OEt)$_6$ and the solvents are weak.

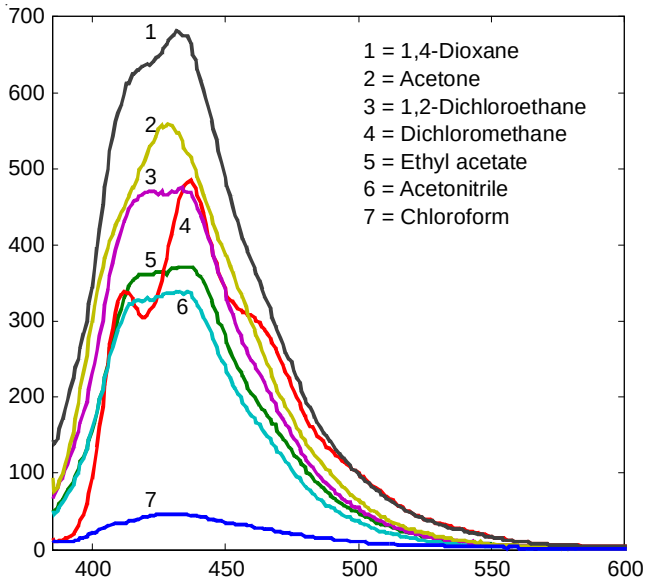


Fig. 3. Fluorescence emission spectra of cryptophane-E-(OEt)$_6$ (3.5×10^{-6} mol L^{-1}) in different solvents when excited at 376-377 nm

Chloroform complexation by cryptophane-E-(OEt)$_6$: In order to shed light on the deep reason for the large changes of the emission spectra of the cryptophane-E-(OEt)$_6$ solution in chloroform, we detected the emission spectra of the cryptophane-E-(OEt)$_6$ solution in various chloroform/1,4-dioxane binary solvents. Fig. 4 shows the typical variation of emission spectra of cryptophane-E-(OEt)$_6$ solution in chloroform/1,4-dioxane binary solvents. It can be seen from Fig. 4, the fluorescence intensity decreases dramatically while chloroform ratio rising from 0 to 10 % (vol.) and then reduces gradually with the increase of chloroform ratio (10-80 %); meanwhile, the emission spectrum was also slightly hypsochromic shifted. This demonstrates that chloroform has a stronger interaction with cryptophane-E-(OEt)$_6$ than other solvents. This also indicates that an inclusion complex between cryptophane-(OEt)$_6$ and chloroform could be formed and explains well why the emission intensity of the cryptophane-E-(OEt)$_6$ solution is much reduced in chloroform.

The emission quenching effect of chloroform on cryptophane-E-(OEt)$_6$ in 1,4-dioxane is displayed in Fig. 5. Cryptophane-E-(OEt)$_6$ shows strong fluorescence-emission when excited by UV at 370 nm. The fluorescence was efficiently quenched upon the addition of chloroform. This indicates

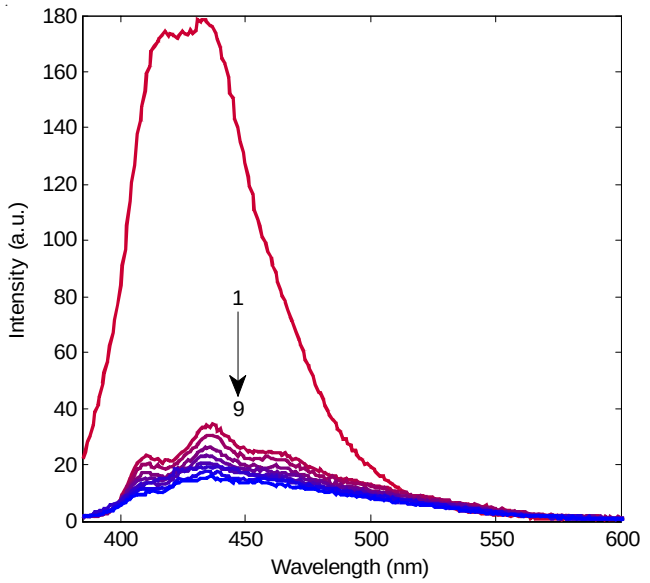


Fig. 4. Fluorescence spectra of cryptophane-E-(OEt)$_6$ (1×10^{-6} mol L^{-1}) in 1,4-dioxane/chloroform binary solvents (v/v): (1) 100:0; (2) 90:10; (3) 80:20; (4) 70:30; (5) 60:40; (6) 50:50; (7) 40:60; (8) 30:70; and (9) 20:80 (excited at 376 nm)

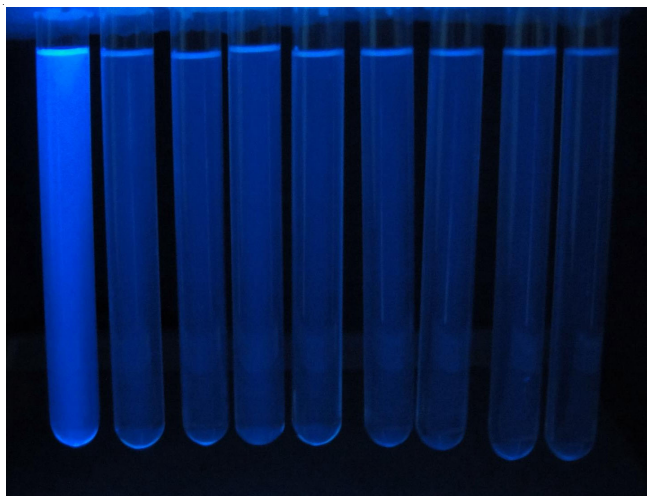


Fig. 5. Emission photographs of solutions of cryptophane-E-(OEt)$_6$ (1×10^{-6} mol L^{-1}) in 1,4-dioxane/chloroform binary solvents directly taken in ultraviolet lamp with excitation at 370 nm. From left to right: 0, 10, 20, 30, 40, 50, 60, 70 and 80 % (v/v) chloroform

that there are enough chloroform molecules in the cavity of cryptophane-E-(OEt)$_6$ that the complex could be formed. However, due to weak interaction between cryptophane-E-(OEt)$_6$ and other solvents, the amount of the guest molecules in the cavity of cryptophane-E-(OEt)$_6$ could be too few to interact with the host.

Binding constant: The formation constant (K_a) of complex of cryptophane-E-(OEt)$_6$ and chloroform could be determined by direct measurement of the fluorescence intensity and the appropriate equilibrium concentrations. We assume the complex formation between a host and a guest can be analyzed in terms of conventional host-guest equilibrium and described by a chemical reaction as:

$$\text{Host} + n\text{Guest} \xleftrightarrow{K_a} \text{Host} \cdot \text{Guest}_n \quad (1)$$

The formation constant (K_a) and the ratio of the complex at a given temperature (298 K) were calculated from the

spectral data obtained using the modified Benesi-Hildebrand equation[30]:

$$\log\left(\frac{F_0}{F}-1\right)=\log K_a + n\log[\text{Guest}] \quad (2)$$

wherein F and F_0 represent the fluorescence intensity of cryptophane-E-$(OEt)_6$ in the presence and absence of chloroform, respectively; K_a represents the binding constant and n is the number of binding sites and [Guest] is the concentration of chloroform. A plot of log (F_0/F-1) *versus* log [Guest] will give a straight line with a slope of n and a y-axis intercept log K_a.

The fluorescence emission spectra of cryptophane-E-$(OEt)_6$ at *various* chloroform concentrations are shown in Fig. 6 and the inset of which shows the plot of log (F_0/F-1) *versus* log [Guest] exhibits excellent linearity at chloroform concentration range of 0.0-0.00600 mol L^{-1}. The fluorescence data are well fitted to eqn. 3 and can be used to determine the binding constant (K_a) and the binding stoichiometry (n) for the complex formation of cryptophane-E-$(OEt)_6$ with chloroform. The fitting parameters for the Benesi-Hildebrand model are given in Table-2, which implies that the inclusion complex has a stoichiometry of 1:1 and the binding constant K_a = 235 M^{-1}. The result indicates that the cryptophane-E-$(OEt)_6$ can form a stable 1:1 complex with chloroform.

TABLE-2
FITTING PARAMETERS FOR
QUENCHING OF CRYPTOPHANE-E-$(OEt)_6$

$CHCl_3$ concentration range (M or mol L^{-1})	n	log K_a	Binding constant K_a (M^{-1})	R^2	Number of data points
0.0-0.00600	0.998	5.46	235	0.996	10

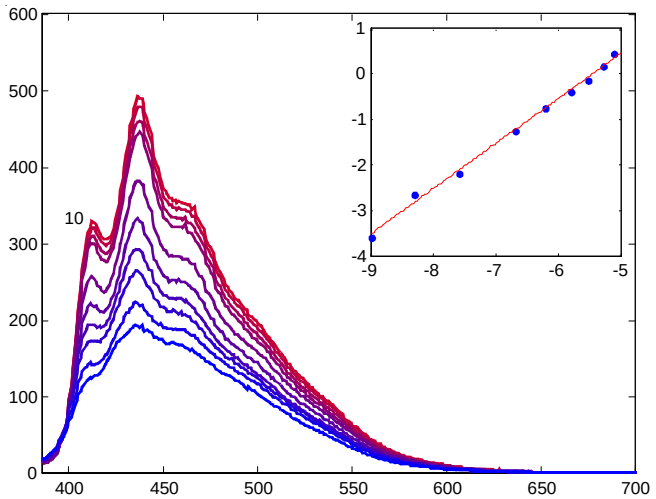


Fig. 6. Fluorescence quenching effect of chloroform on the emission of cryptophane-E-$(OEt)_6$ (2.5×10^{-6} mol L^{-1}) in 1,4-dioxane (excited at 376 nm; (1) 0.0; (2) 0.000125; (3) 0.00025 (4) 0.00050; (5) 0.00125; (6) 0.00200; (7) 0.00300; (8) 0.00400; (9) 0.00500; and (10) 0.00600 mol L^{-1} of chloroform. The inset diagram shows Benesi-Hildebrand plot of log (F_0/F-1) *versus* log [Guest]

To get structural information, the sizes of the guest and host are calculated[31] by Hyper Chem 8 and shown in Fig. 7. It is obvious that considering the molecular sizes, all solvents could enter into cryptophane-E-$(OEt)_6$ with the opening size of 4.77 × 6.95 Å. While, the strong non-covalent interaction (could be dipole-dipole interaction) could stabilize the association between cryptophane-E-$(OEt)_6$ and chloroform[23,32,33]. For cryptophane-E-$(OEt)_6$, the internal cavity size is similar to that of cryptophane-E but where the six methoxy groups have been replaced by ethoxy groups. This significantly decreases the size of the portals used by the guest molecule to access and escape from the cavity. According to the results of complexation experiments with chloroform, a drastic change of the binding constant to chloroform was observed with host with respect to cryptophane-E in $(CDCl_2)_2$. The stability of the chloroform@cryptophane-E-$(OEt)_6$ complex is characterized by a quite remarkable binding constant (K_a) of 235 M^{-1} at 298 K, which is much smaller than the binding constant of cryptophane-E to chloroform, for which value of K_a = 470, or 600, or 542.2 M^{-1} had been measured before[15,21,22]. Therefore, the changes in peripheral substituents are of great importance for guest encapsulation, as they modulate the size of the different openings that allow guests to enter and leave the molecular cavity.

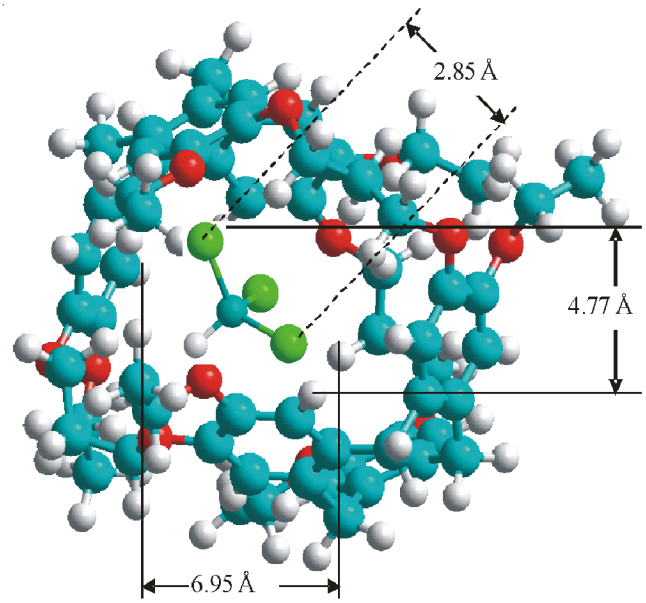


Fig. 7. Molecular model of the $CHCl_3$@cryptophane-E-$(OEt)_6$ complex. The size of the portals in cryptophane-E-$(OEt)_6$ is 4.77 Å × 6.95 Å

Conclusion

This work presents the synthesis of cryptophane-E derivative **5** bearing six OEt groups instead of OMe groups, whose internal cavity size is similar to that of cryptophane-E. The spectral investigation on the interaction of cryptophane-E-$(OEt)_6$ with chloroform, demonstrates that chloroform could be encapsulated selectively by cryptophane-E-$(OEt)_6$. The structural modifications came only from the larger ethoxy groups, which significantly decreases the size of the portals used by the guest molecule to enter and leave the molecular cavity. When performing complexation experiments with chloroform, a drastic change of the binding constant of complex was observed with respect to cryptophane-E in $(CDCl_2)_2$. The binding constant of complex reaches 235 M^{-1}, which is much smaller than that of complex of chloroform by cryptophane-E.

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