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ORIGINAL ARTICLE

Host–guest interactions between hemicucurbiturils and a hydroxyl-substituted Schiff base

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Abstract The host–guest interactions of hemicucurbit[6 and 12]urils with the Schiff base guest **1** has been investigated. ^{1}H NMR spectra suggest hemicucurbit[6 and 12]urils bind to guest **1** with the formation of hydrogen bondings between the phenol hydroxyl group and carbonyl groups in the host. The formation of interaction complexes are also supported by fluorescence emission spectroscopy. The moderate association constants of the interaction complexes in a ratio of 1:1 are obtained to be $(3.2 \pm 0.6) \times 10^5$ and $(5.5 \pm 0.8) \times 10^5$ L mol^{-1}, respectively, via non-linear curve fitting, which indicate that the formation of hydrogen bondings are important in the host–guest interactions.

Keywords Hemicucurbituril · Schiff base · Supramolecular chemistry · Host–guest interaction · Molecular recognition

Introduction

Macrocyclic molecules, which often serve as receptors in supramolecular chemistry, often afford useful applications in many areas [1–4]. Behrend synthesized the first cucurbituril in 1905 [5] and its structure was characterized by Mock et al., which was found to be a very rigid macrocycle made of glycoluril units linked together with a pair of methylene bridges [6]. New members of the cucurbituril family (Q[*n*], *n* = 5–8, 10 and 14) with different degrees of oligomerization and their supramolecular properties have been developed to provide a platform in supramolecular chemistry [7]. Hemicucubit[*n*]urils (HemiQ[*n*], *n* = 6 and 12) were discovered in 2004 by Miyahara et al. [8] and lead to the development of a sub-group of cucurbituril chemistry, including members such as bambusuils, cyclohexylhemicucurbiturils, biotin[6]urils and norbornahemicucurbit[6]uril [9–15], which have been applied to the molecular recognition of anions, supramolecular catalysis and the preparation of transmembranes for anion transport [10, 16–20].

The chemistry of Schiff bases has attracted the attention of scientists for many decades, which is mainly due to their desirable chemical nature [21, 22]. Due to their various structures and wide range of uses, Schiff bases have important potential applications and have been applied as magnetic [23], antibacterial [24], fluorescent [25] and catalytic compounds [26]. Hydroxyl-substituted Schiff bases have received considerable attention due to their potential anticancer activity [27]. In this work, we have designed, synthesized and characterized the Schiff base guest **1**, and investigated its interactions with HemiQ[6 and 12]uril (Scheme 1). To explore the HemiQs' influence on the Schiff base's optical properties, we have preliminary explored the regularities of the host–guest interactions between the HemiQs and guest **1**.

Results and discussion

The ^{1}H NMR resonance signals of guest **1** are assigned in Fig. 1a and one can see that the resonance signals in the chemical shift range from δ = 6.87 to 7.80 ppm are

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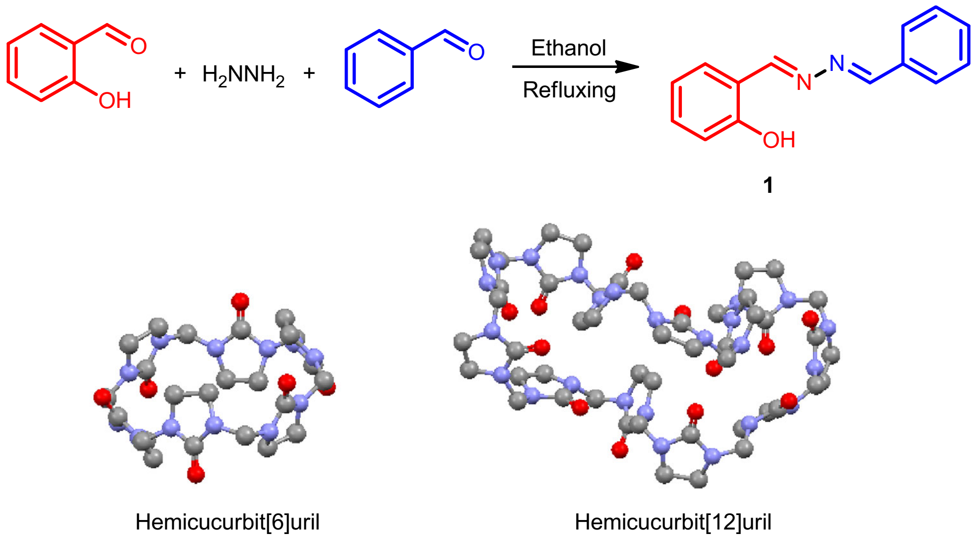
Scheme 1 Synthesis of the hydroxyl substituted dibenzylidenehydrazine guest **1** and simulated structures of hemicucurbit[6 and 12]urils with a semi-empirical method of PM6-D3H4, color codes: *grey*, carbon; *blue*, nitrogen; *red*, oxygen. (Color figure online)



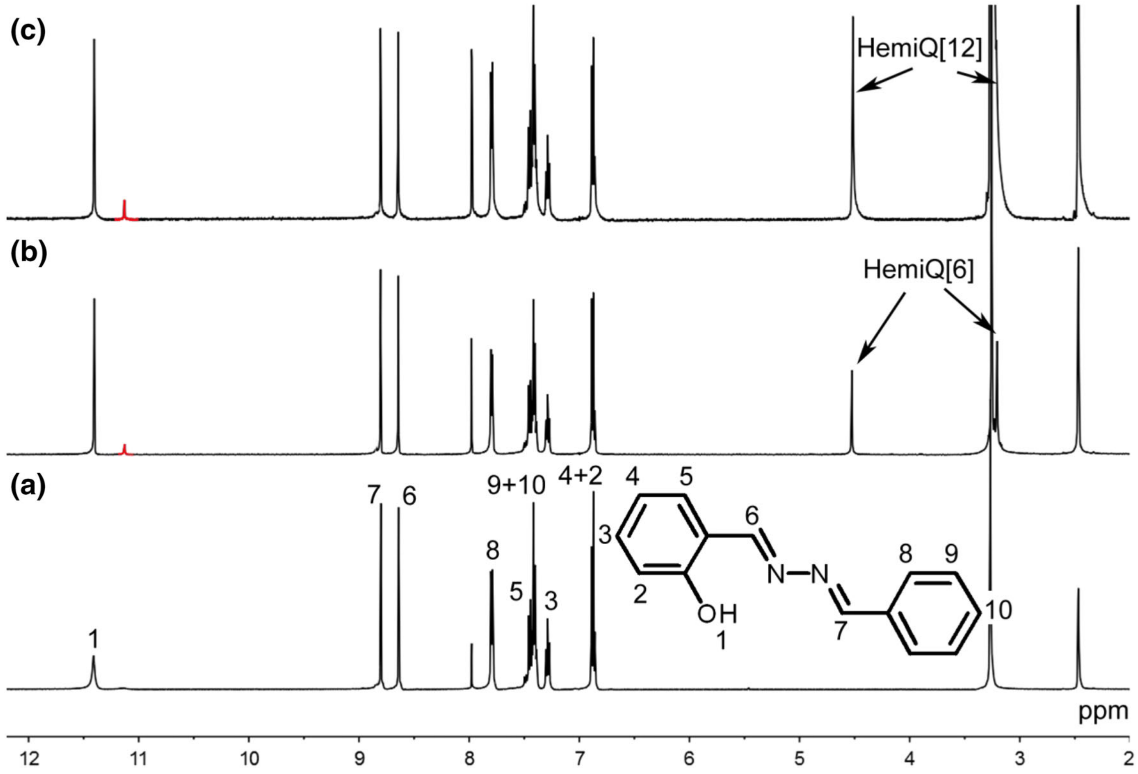


Fig. 1 The ^{1}H NMR spectra of **a** guest **1** and guest **1** in the presence of **b** hemicucurbit[6]uril and **c** hemicucurbit[12]uril

assigned to the protons on the aromatic ring of guest **1**, which show almost no change after the addition of the host HemiQ[6 or 12] (Fig. 1b, c). The resonance signals at 8.64 and 8.80 ppm are assigned to the protons on the amine groups (H6 and H8) and no significant change in the chemical shift was observed in the presence of the macrocyclic compounds. However, the proton resonance corresponding to the phenol hydroxyl group, which appears as a singlet at $\delta = 11.4$ ppm produces a new singlet at 11.1 ppm upon the addition of either HemiQ[6] or HemiQ[12], which implies the formation of stable host–guest interaction complexes between guest **1** and HemiQ[6 or 12] with the formation of hydrogen bonding between the hydroxyl group on the guest and the carbonyl groups in the hemicucurbiturils [18].

The host–guest interactions between hemicucurbiturils and guest **1** were also investigated by fluorescence titrations. In Fig. 2a, the fluorescence emission of **1** appeared at

501 nm upon excitation at 397 nm. The fluorescence intensity was gradually decreased upon the addition of HemiQ[6] (Fig. 2b), while the intensity kept constant when the $C_{\mathrm{HemiQ[6]}}$:C_{guest} ratio was 1:1. An association constant (K_a) of $(3.2 \pm 0.6) \times 10^5$ L mol^{-1} for guest **1** at HemiQ[6] was obtained via non-linear fitting (Fig. S1, ESI). Moreover, the 1:1 ratio of host–guest interaction of HemiQ[6] with guest **1** was also confirmed by the Job's plots obtained from the fluorescence spectra (Fig. S2, ESI). The molecular simulation provides a hydrogen bonding of 1.84 Å between HemiQ[6] and guest **1**, and the relative small cavity of host restrains the encapsulation of guest [28], therefore, the Schiff base guest stays at the portal to form an exclusion complex in a ratio of 1:1 (Fig. 2c).

In the case of the HemiQ[12] host, the fluorescence titrations also support the formation of its host–guest interactions with guest **1** with the decreasing fluorescence intensity observed in the presence of different amounts of the host that become stable after the addition of 1 equiv of the macrocycle (Fig. 3a). The intensity decrease upon on the addition this amount of HemiQ[12] suggests a host–guest interaction ratio of 1:1 (Fig. 3b), which is similar to the interaction system between guest **1** and HemiQ[6]. Furthermore, the interaction ratio of guest **1** to hemicucurbit[12]uril was also found to be 1:1 using the Job's plots obtained from the fluorescence spectra(Fig. S3, ESI). By non-linear least square fitting using Eq. (1), the association constant (K_a) was obtained to be $(5.5 \pm 0.8) \times 10^5$ L mol^{-1} (Fig. S4, ESI), which is obvious bigger than that in the case of the interaction between guest **1** and HemiQ[6], therefore, the higher affinity of HemiQ[12] to guest **1** implies there is other driving force than the formation of hydrogen bonding. A hydrogen bonding of 2.62 Å between HemiQ[12] and guest **1** is also observed in the simulated structure (Fig. 3c), and the bigger cavity of host macrocycle allows the formation of an encapsulation complex in a ratio of 1:1, interestingly, hemicucurbit[12]uril with more flexible structure is twisted to match

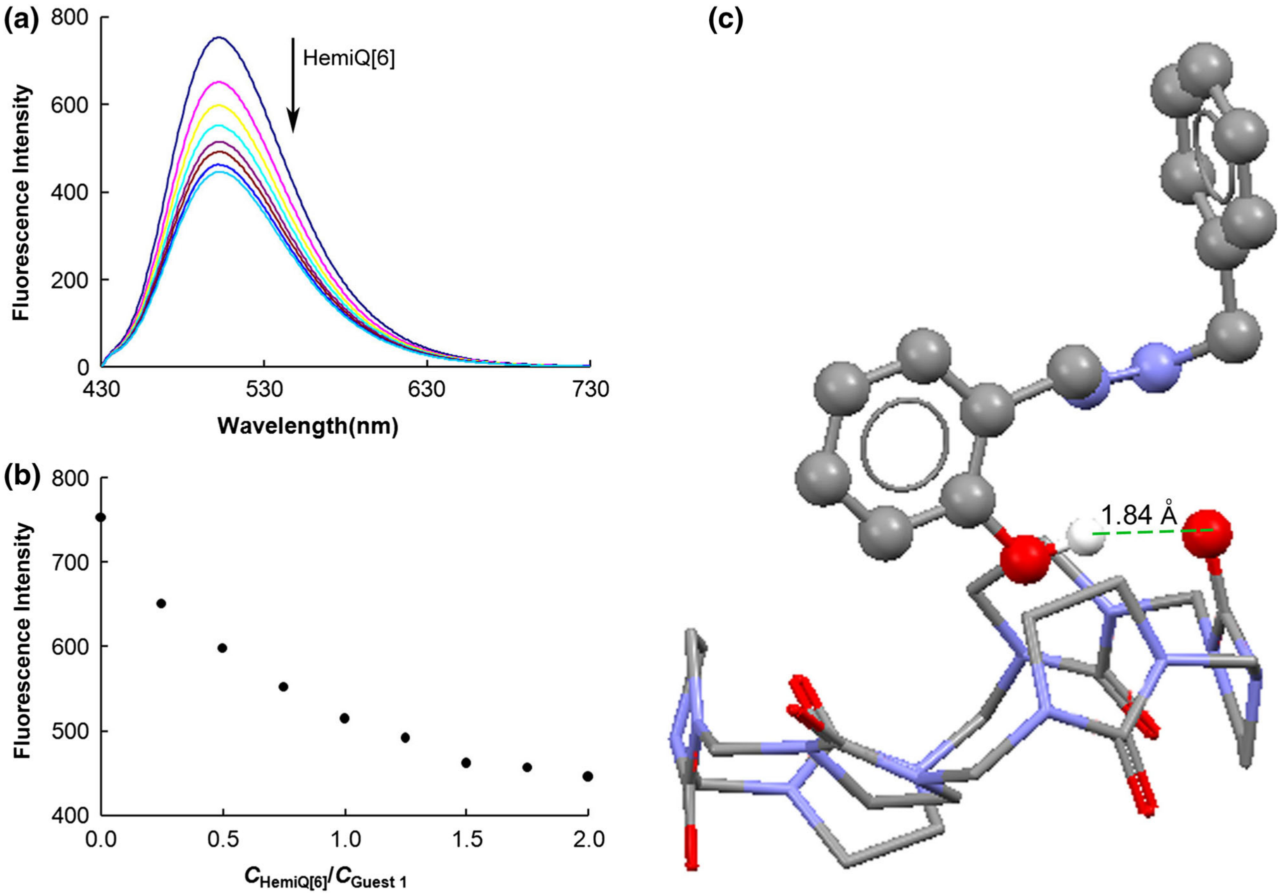


Fig. 2 **a** The emission spectra ($\lambda_{em} = 501$ nm excited at $\lambda_{ex} = 397$ nm) of guest **1** (2.5×10^{-5} mol L^{-1} upon the addition of an increasing amount of HemiQ[6] from 0 to 2 equiv. in $CHCl_3/CH_3OH$ (1:1); **b** The fluorescent intensity at 501 nm of guest **1** (2.5×10^{-5} mol L^{-1} upon the addition of an increasing amount of HemiQ[6] from 0 to 2 equiv. in $CHCl_3/CH_3OH$ (1:1); **c** The energy minimized structure of interaction complex of HemiQ[6] with guest **1** with a semi-empirical method of PM6-D3H4, color code: *grey*, carbon; *blue*, nitrogen and *red*, oxygen; *white*, hydrogen. (Color figure online)

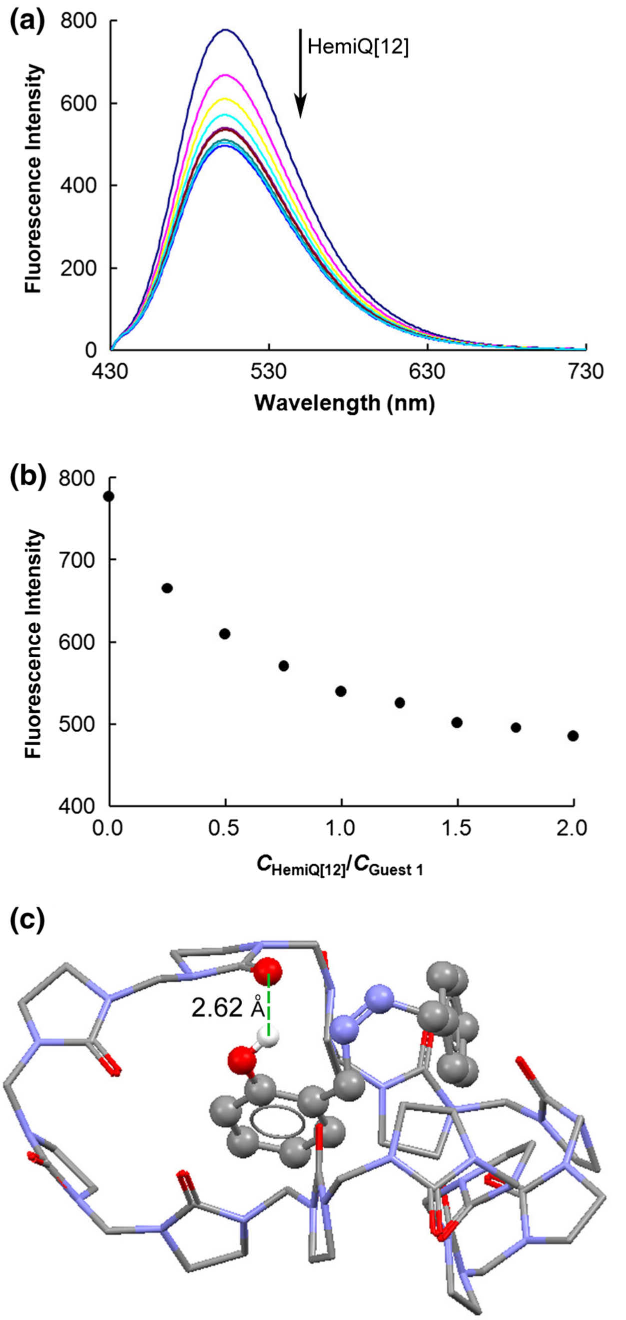


Fig. 3 **a** The emission spectra ($\lambda_{em} = 501$ nm excited at $\lambda_{ex} = 397$ nm) of guest **1** (2.5×10^{-5} mol L^{-1} upon the addition of an increasing amount of HemiQ[12] from 0 to 2 equiv. in $CHCl_3/CH_3OH$ (1:1); **b** The fluorescent intensity at 501 nm of guest **1** (2.5×10^{-5} mol L^{-1} upon the addition of an increasing amount of HemiQ[12] from 0 to 2 equiv. in $CHCl_3/CH_3OH$ (1:1); **c** The energy minimized structure of interaction complex of HemiQ[12] with guest **1** with a semi-empirical method of PM6-D3H4, color code: *grey*, carbon; *blue*, nitrogen and *red*, oxygen; *white*, hydrogen. (Color figure online)

the guest geometrically, which could offer the extra stability in the host–guest interaction.

The host–guest interactions of guest **1** with HemiQ[6 and 12] have been supported by the decrease in the fluorescence intensity, which should be the result of the formation of hydrogen bonding as found in the analysis of the interactions using ^{1}H NMR spectroscopy. It is well known that intramolecular proton transfer from the hydroxyl group to the imino nitrogen atom occurs in *ortho*-hydroxyl substituted Schiff base compounds [29–31] and in the presence of hemicucurbiturils, the intramolecular proton transfer of guest **1** should be restrained due to the formation of hydrogen bonding between the hydroxyl group in the guest molecule and the carbonyl groups in the hosts, which then leads photo-induced electron transfer from the nitrogen atom in the imino group to the aromatic ring and results in the decrease in fluorescence intensity.

To understand the important role of the hydroxyl group in the host–guest interactions, another Schiff base, 1,2-dibenzylidenehydrazine, was subjected to the host–guest interactions with hemicucurbit[6 and 12]urils, and as expected, the results obtained from both ^{1}H NMR spectroscopy and fluorescence spectroscopy show no interactions between the HemiQs and the 1,2-dibenzylidenehydrazine substrate (Figs. S4, S5, ESI). Therefore, it was proposed that the formation of the interactions in complexes of guest **1** with HemiQ[6 and 12] was through hydrogen bonding between the phenol hydroxyl group to the macrocyclic hosts.

Conclusions

In summary, the host–guest interactions of hemicucurbit[6 and 12]urils with a Schiff base guest **1** have been investigated using ^{1}H NMR spectroscopy and fluorescence emission spectroscopy. The results obtained from the ^{1}H NMR spectra suggest guest **1**, the *ortho*-hydroxyl substituted Schiff base, interacts with HemiQ[6 and 12] via the formation of hydrogen bonding between the phenol hydroxyl group and carbonyl groups in the host. Fluorescence emission spectroscopy revealed that the formation of the interaction complexes of guest **1** with hemicucurbit[6 and 12]uril were in a ratio of 1:1 with moderate association constants of $(3.2 \pm 0.6) \times 10^5$ L mol^{-1} (for the HemiQ[6] host) and $(5.5 \pm 0.8) \times 10^5$ L mol^{-1} (for the HemiQ[12] host), respectively. The simulated structures of the interaction complexes suggest two different interaction models, that is, exclusion complex forms between HemiQ[6] and guest 1, and the guest could be encapsulated by hemicucurbit[12]uril. Another synthetic guest, 1,2-dibenzylidenehydrazine, was also subjected to the host–guest system and the lack of observed interactions indicate that the phenol hydroxyl group was important in the binding of guest **1** to the hemicucurbiturils.

Experimental

Materials and apparatus

The HemiQ[n] (n = 6 or 12) samples were prepared and purified according to a literature method [8] and were characterized by ^{1}H NMR spectroscopy. HemiQ[6] ($CDCl_3$, δ): 3.38 (s, 24 H), 4.68 (s, 12 H) ppm; HemiQ[12] ($CDCl_3$, δ): 3.40 (s, 48 H), 4.68 (s, 24 H) ppm. Salicylaldehyde, benzaldehyde and hydrazine hydrate were obtained commercially and used without further purification. ^{1}H NMR spectra were recorded at 22 °C on a VARIAN INOVA-400 spectrometer using $SiMe_4$ as an internal reference in a mixture of $CDCl_3$/CD_3OD (1:1, v/v). UV–Vis absorption spectra were recorded on a Unico UV-2102 instrument. Fluorescence absorption spectra of the guest molecule and the host–guest complexes were recorded on a Varian RF-540 fluorescence spectrophotometer at 25 °C. All calculations have been processed with MOPAC 2016 software package. The semi-empirical method of PM6-D3H4, PM6 with corrected dispersion and hydrogen bond terms using the D3H4 method, was used for full geometry optimization.

Preparation of the guest molecules

Guest **1**: **1** was synthesized according to a literature method [32]. To a stirred solution of salicylaldehyde (1.5 g, 12 mmol) and benzaldehyde (1.3 g, 12 mmol) in ethanol (25 mL), a solution of hydrazine hydrate (0.75 mL, 12 mmol) in ethanol (5 mL) was added dropwise. The solution was refluxed for 5 h, cooled to room temperature, the solvent distilled under reduced pressure and the resulting residue purified by column chromatography (silica gel; eluent: ethyl acetate/normal hexane 5:1) to afford a yellow solid. The yellow solid was dried under vacuum to give compound **1** (0.83 g) in 31 % yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.98(t, 1 H, $J = 8.0$ Hz), 6.99(d, 1 H, $J = 8.0$ Hz), 7.40(t, 1 H, $J = 8.0$ Hz), 7.52(t, 1 H, $J = 8.0$ Hz), 7.54(t, 2 H, $J = 8.0$ Hz), 7.70(d, 1 H, $J = 8.0$ Hz), 7.89(d, 2 H, $J = 4.0$ Hz), 8.82(s, 1 H), 8.97(s, 1 H), 11.3(s, 1 H) ppm. ^{13}C NMR (400 MHz, DMSO-d_6) δ 116.94, 118.64, 120.00, 128.94, 129.43, 131.69, 132.06, 133.53, 134.02, 159.19, 162.80, 163.64 ppm. ESI–MS (m/z), [$M+H^+$]: calc. 225.1; found 225.1.

1,2-Dibenzylidenehydrazine: A solution of benzaldehyde (2.6 g, 24 mmol)and hydrazine hydrate(0.75 mL, 12 mmol)in ethanol (25 mL)was heated at reflux for 5 h and then cooled to room temperature to provide a yellow crystal precipitate that was collected by filtration to give the desired product(2.45 g) in 98 % yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53(d, 2 H, $J = 8.0$ Hz), 7.55(m, 4 H, $J = 8.0$ Hz), 7.92(d, 4 H, $J = 8.0$ Hz), 8.75(s, 2 H) ppm [33].

Fluorescence measurements of the host–guest interactions

Fluorescence titrations were carried in a mixed solution of $CHCl_3$ and CH_3OH (1:1, v/v) and the guest was prepared at a fixed concentration of 2.5×10^{-5} mol L^{-1}. The solution was combined with HemiQ[n] (n = 6 or 12) in C_{host}:$C_{\mathbf{1}}$ ratios of 0, 0.25:1, 0.5:1, 0.75:1, 1:1, etc. For the Job plots, the total concentration of ($C_{\text{host}} + C_{\mathbf{1}}$) was 2.5×10^{-5} mol L^{-1}. All fluorescence measurements were carried out with an emission wavelength at $\lambda = 502$ nm and an excitation wavelength at $\lambda = 397$ nm. The association constants of the host–guest interactions were obtained via non-linear fitting using Eq. (1):

$$\Delta I = \frac{\Delta a([\mathrm{H}]_0 + [\mathrm{G}]_0 + 1/K_a) \pm \sqrt{\Delta a^2([\mathrm{H}]_0 + [\mathrm{G}]_0 + 1/K_a)^2 - 4\Delta a^2[\mathrm{H}]_0[\mathrm{G}]_0}}{2} \tag{1}$$

where ΔI is the change in the fluorescence intensity of guest **1** upon the gradual addition of HemiQ[6 or 12] and Δa refers to the difference in the proportionality constant between the free guest and the interaction complex. The total concentration of the host and guest are denoted by $[\mathrm{H}]_0$ and $[\mathrm{G}]_0$, respectively [34].

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