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Highly Specific Molecular Recognition by a Roughly Defined Supramolecular Nanocapsule: A Fuzzy Recognition Mechanism

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ABSTRACT: Can a supramolecular host conduct fuzzy recognition like a man? Currently, molecular recognition in supramolecular chemistry is generally promoted by specific interaction formed between a guest and a well-defined but usually costly synthesized complementary host. Here we show that a roughly defined macromolecular nanocapsule derived from hyperbranched polyethylenimine (HPEI) can act as a highly selective host for the recognition of featureless guests. The recognition is not promoted by specific molecular interaction but by a fuzzy recognition mechanism, i.e., the statistical accumulation of elementary host−guest interactions, where a guest can be regarded as a multivalent entity for supramolecular interactions. It is found that core engineering of the macromolecular nanocapsule will influence its guest affinity; the difference of the competitive guest species can be amplified, and highly specific recognition is thus possible. Because the macromolecular nanocapsule derived from HPEI is structurally featured for the dense functional groups randomly populated in the core, meticulous core engineering is conveniently available. Our results demonstrate that a roughly defined, readily available macromolecular nanocapsule can act as a highly selective host, and the fuzzy recognition is potential for the recognition of common molecules which are topologically and electronically featureless.

Introduction

Supramolecular host−guest recognition has evoked much interest in basic and applied research such as separation, catalytic chemistry, chemical and biological sensing, molecular self-assembly, and biomedical development.[1−11] Currently, the supramolecular recognition is mainly promoted by specific interaction such as H-bonding interaction, metal−ligand interaction, topological trapping, $\pi-\pi$ stack, or frequently the combination of them.[12−20] The combination of specific interaction with nonspecific interaction may also lead to high selectivity if the former plays the leading role. Such a system is also called the static molecular recognition (SMR) system because the guest has an anticipatable position and conformation upon interaction with the host. However, the SMR system is greatly limited in two aspects: (1) From the viewpoint of the availability of a host, only a few cases allow the exact control over its size, morphology, and electronic motif; thus, the synthesis of a SMR host is usually tedious and challenging. (2) From the viewpoint of the guests, most are complex and mutable in conformations and are rarely featured in electronic structure, thus defying the specific trapping by a SMR host. As a consequence, among the about 20 million molecular species now available naturally and synthetically, only a minority can be well recognized by an artificial SMR host. Such an issue poses two questions: (1) can specific recognition of a common molecule be possible, and (2) can a roughly defined and readily available host effectively recognize guests?

Covalent polymeric micelle has rarely been recommended as a highly specific host for its roughly defined structure and broad guest affinities. One type of covalent micelle, i.e., core−shell amphiphilic macromolecule derived from hyperbranched polymer (CAM),[21,22] has become readily available, and the resulting CAM can encapsulate a number of guest species,[23−34] but its guest selectivity has rarely been mentioned.[24] The uniqueness of such a CAM is the dense and randomly distributed functional groups in the core, which render convenient and meticulous core engineering possible. It was recently shown that with core engineering a CAM could highly selectively recognize a variety of ionic guest species,[35−37] indicating certain nonspecific interaction could lead to highly selective molecular recognition. However, the guests that can be well recognized by CAMs are still limited to those which are rather different in ionic nature, number of ionic charges, or size, and the recognition is mainly attributed to statistical accumulation of electrostatic interaction. Can different elementary interacting styles work synergically in molecular recognition, especially for the polar ionic interaction and the apolar hydrophobic−hydrophobic interaction? If the answer is yes, then effective recognition of very similar guests may become possible. Here we show that electrostatic interaction and hydrophobic interaction can work synergically to result in effective recognition of very similar guests, and the host is a readily available and roughly defined CAM. This methodology is here called molecular "fuzzy recognition".

Results and Discussion

General Consideration. When developing our "fuzzy recognition" methodology, the following factors need to be taken into account when a CAM is to be used as a supramolecular host since even a well-defined, dendrimer-based host shows limited guest selectivity.[38] (1) Host structure. The cavities in a CAM are irregular and flexible, and the residual functional groups randomly distribute in the core; thus, neither the geometric nor the electronic environment of the cavities in a

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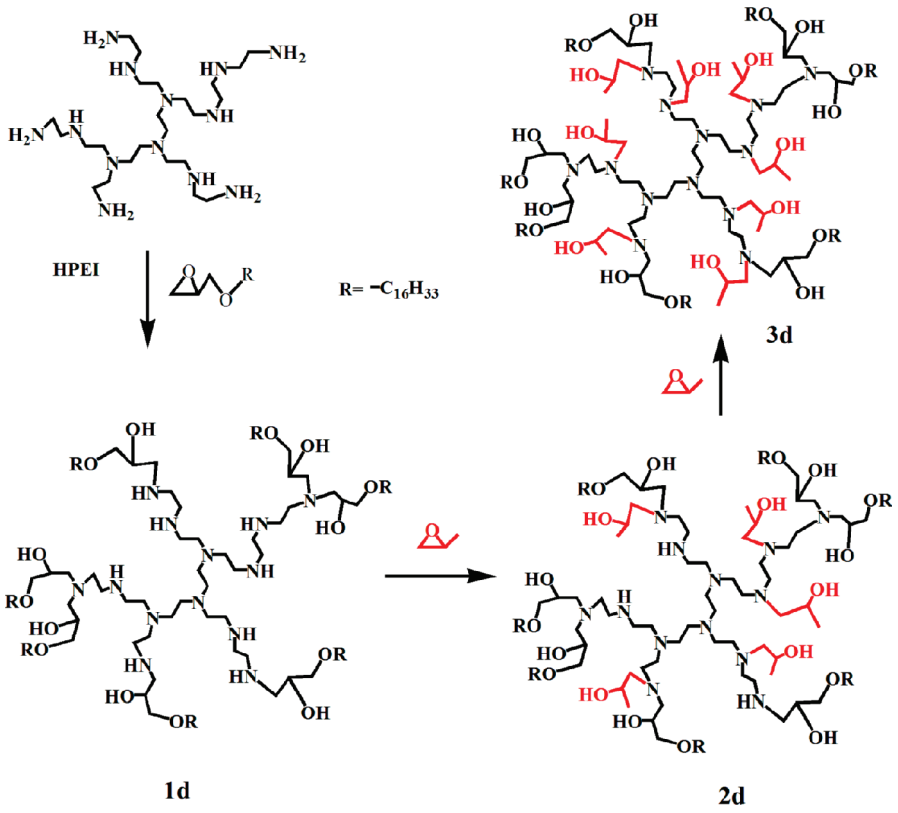
Scheme 1. Outline of the Synthesis of 1d−3d, Which Are the Same in Shell but Different in Core in Terms of the Amount of Hydroxyl and Tertiary Amine[a]



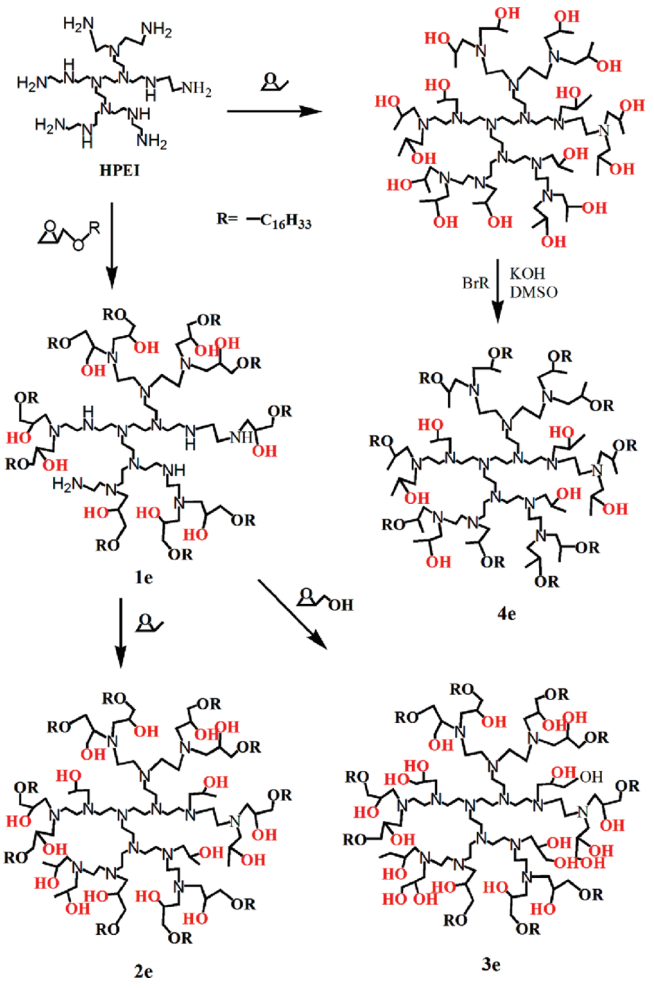
[a] HPEI has 232 repeat units, but only 13 are shown here for clarity.

CAM is uniform. (2) Guest structure. Most common guest molecules are known for their rich and time−varying conformations, which are a great challenge for a SMR host where the shape complementarity usually plays an important role. Furthermore, it is well-known that some guests can undergo partial electrolysis; thus, the host−guest interaction is pH- and solvent-dependent and probabilistic, which is unfavorable for specifically complementary recognition. (3) Host−guest interacting style. Unlike the SMR system, the host−guest interactions in a CAM-based system are of various natures, and the contribution of each elementary interaction is fuzzy, where specific interaction is absent or too weak to play a leading role. (4) The interaction between different guest species. Parallel, competitive, and synergic encapsulation of different guest species is possible in a CAM-based system,[25,37] which may render guest recognition ineffective. (5) Physical adsorption. In a SMR system, each guest is tightly complexed by the host; while in a CAM-based system, guests can be either complexed or physically adsorbed,[36] which thus poses the question whether the physical adsorption will lead to a low selectivity.

Regardless of the above factors, specific molecular recognition is theoretically possible for a CAM. As pointed out by Zadeh,[39] in a multivariable, nonlinear, time-varying system, accuracy would be against complexity; thus, fuzziness was a ubiquitous phenomenon in our world, where fuzzy mathematics was proposed to deal with such a phenomenon. According to fuzzy mathematics, in an environment with uncertainty, imprecision, and incompleteness, an approximate reasoning and judgment is still possible. We believe that this principle can be applied to the supramolecular host−guest recognition. As mentioned, in a CAM-based system, the host−guest interaction is generally complex, nonlinear, and probabilistic, but the host−guest interaction should lead to certain accumulative interacting strength, which is dependent on both the CAM structure and the guest structure. In fact, from the viewpoint of supramolecular interaction, any guest can be regarded as a multivalent entity, even for the very simple cationic sodium[13] or the anionic fluoride.[40] Stiriba et al.[28] also showed that a reverse micelle-like hyperbranched derivative can effectively entrap a guest while its linear counterpart can hardly, suggesting the former can more effectively accumulate the host−guest interactions. Furthermore, with core engineering of the CAM, the host−guest interacting strength most probably changes nonlinearly because of the interconnection of any elementary host−guest interactions such as van der Waals interaction, electrostatic interaction, H-bonding interaction, etc. Such a nonlinear effect can theoretically amplify the difference of the guest species and thus enable highly specific recognition possible.

Synthesis and Aggregation of the CAM. The CAM is a reverse micelle-like covalent structure, with a hydrophobic shell which renders it soluble in a number of organic solvents and a hydrophilic core which can interact with a number of guest molecules. The syntheses of the CAMs are outlined in Schemes 1 and 2. CAM **1d**−**3d** and **1e**−**3e** are synthesized similar to a previous report.[37] One can find from Scheme 1 that the shells of **1d**−**3d** are the same, but the cores are different in both hydroxyl and tertiary amine. In contrast, from Scheme 2, one can find that the CAMs are also the same in shell but **2e**−**4e** are only different in hydroxyl group, where the density of tertiary amine is the same. The synthesis of **4e** is carried out in a two-step route. In the first step, HPEI is fully alkylated with propylene oxide.[41] In the second step, the hydroxyls of the resulting polymer are 60% O-alkylated with

Scheme 2. Outline of the Synthesis of 1e−4e, Where 2e−4e Are Different Only in Density of Hydroxyl



bromohexadecane in dimethyl sulfoxide in the presence of potassium hydroxide. Figure 1 shows the ^{1}H NMR spectra of HPEI, the intermediate, and **4e**. From the assignment in Figure 1 and the signal intensity, it can be concluded that any of the amino protons are alkylated with propylene oxide, and in the second step, 60% of the hydroxyls are O-alkylated by hexadecyls. ^{13}C NMR spectra also support the expected structure (see the data in the Experimental Section). One possible side reaction in the second step is the quaternization of the amino group by bromohexadecane. To learn if there is any such side reaction, a control experiment is carried out under similar conditions but in the absence of potassium hydroxide. After being purified by dialysis against ethanol, the product is analyzed by ^{1}H NMR (data not shown), and only trace signal due to hexadecyl moiety can be detected, indicating negligible quaternization occurs during the O-alkylation. The structure and molecular weight of the CAMs are listed in Table 1.

It was noticed previously that at 1×10^{-6} M the CAMs of **1d**, **3d**, and **1e**−**3e** existed in the form of aggregate.[37] Here **2d** and **4e** are also found to exist as aggregate and show diameters of 118 and 158 nm (in chloroform at 1×10^{-6} M), respectively, as determined by dynamic light scattering. Obviously, all the CAMs used in this article exist in the form of aggregate.

Relationship of Structure−Guest Selectivity of the CAM. *Respective Effect of Hydroxyl and Tertiary Amine in the Core on Guest Recognition.* As can be found from Scheme 1, the

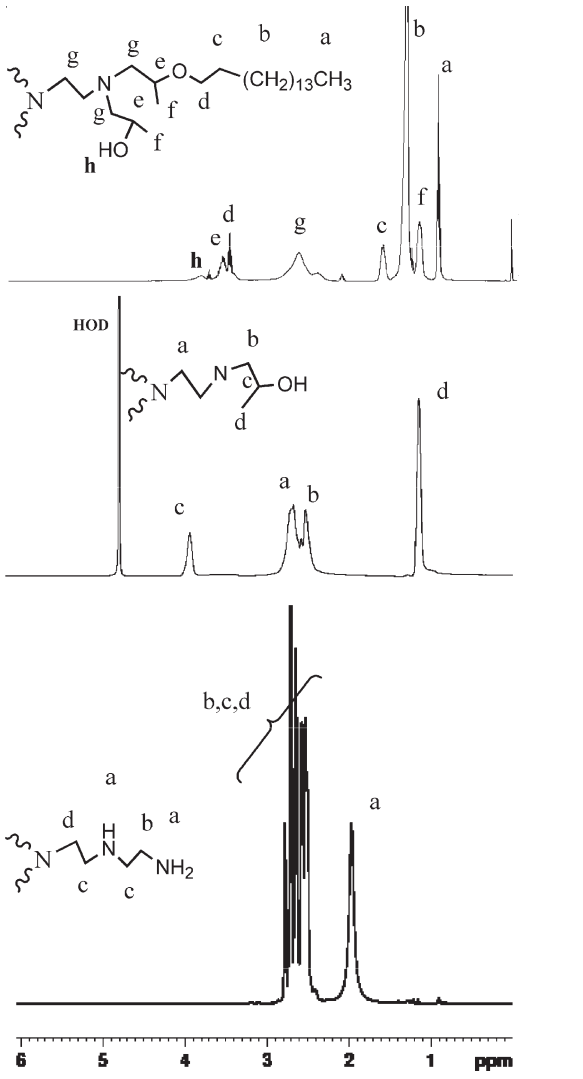


Figure 1. ^{1}H NMR of HPEI (bottom, $CDCl_3$), alkylated HPEI (middle, D_2O), and **4e** (upper, $CDCl_3$).

Table 1. Structure and Molecular Weight of CAMs 1d−3d and 2e−4e

CAMs	structure[a]	$M_n/10^3$ (calcd)[b]
1d	$HPEI(OH)_{0.3}N(H)_{0.7}R_{0.3}$	31.6
2d	$HPEI(OH)_{0.6}N(H)_{0.4}R_{0.3}$	35.6
3d	$HPEI(OH)_1N(H)_0R_{0.3}$	41.0
2e	$HPEI(OH)_1N(H)_0R_{0.6}$	58.7
3e	$HPEI(OH)_{1.4}N(H)_0R_{0.6}$	60.2
4e	$HPEI(OH)_{0.4}N(H)_0R_{0.6}$	54.6

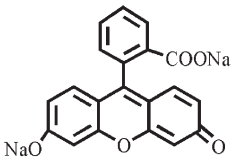
[a] Nomenclature: $HPEI(OH)_xN(H)_yR_z$ means for each repeat unit of HPEI, x fraction of OH is introduced; y fraction of amino protons resided; z fraction of R group is introduced onto the polymer. [b] The value is derived from ^{1}H NMR.

core engineering of the CAM leads to simultaneous production of tertiary amine and hydroxyl. As pointed out previously, the guest selectivity of a CAM originated from the core structure of the CAM rather than from its shell structure;[36] thus, here the CAMs with different core are prepared, and their property on guest selectivity is evaluated. The recognition of group 1 guests (Chart 1) by **1d**−**3d** is first studied, one can find that the group 1 guests are the same in ionic feature but slightly different in nonionizable moiety.

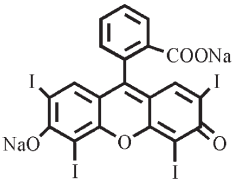
The molecular recognition is tested by biphasic water−chloroform extraction of chloroform-insoluble, aqueous binary mixture of group 1 dyes (typical at 1:1 molar ratio

Chart 1. Structure of Several Groups of Water-Soluble Dyes

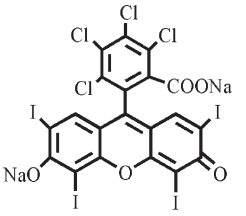
group 1:



FR

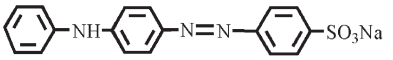


EB

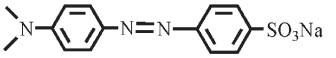


RB

group 2:

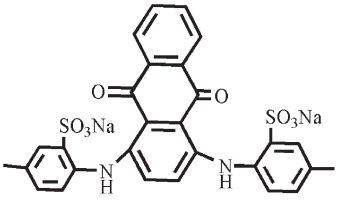


OR

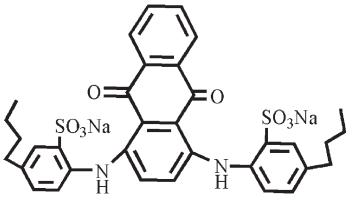


MO

group 3:



AG25



AG27

unless stated otherwise). The separation is via either of the following two methods. Typically, in the first method, **1d** in chloroform is added to a stock mixture of aqueous Fluorescein (FR)/Rose Bengal (RB) in a titration-like manner, leading to the formation of a two-layer system. The addition is continued until one of the binary dyes (RB) is completely transferred to the organic phase, which is monitored by a UV/vis spectrometer, and then the phase partition of the other dye (FR) is detected in either phase. In the second method, a stock solution of **1d** in chloroform is first saturated with aqueous RB (or FR) in excess, then the organic layer is transferred to another container and fully exposed to aqueous FR (or RB) in excess with vigorous shaking so that species−species exchanging is fully satisfied, and the exchange of guest species is detected with a UV/vis spectrometer. Experiments prove that the two methods lead to no difference in guest selectivity. It is found that although either FR or RB alone can be encapsulated by the CAM, for the mixture of FR/RB, RB can be almost exclusively encapsulated by **3d**, as shown in Figure 2, and the corresponding UV/vis spectra are shown in Figure 3c. **1d** and **2d** are tested similarly, and the results are also collected in Figure 3. It can be concluded from Figure 3 that with the increase of alkylation degree from **1d** (30% of amino protons being alkylated) to **2d** (60% of amino protons being alkylated) to **3d** (100% of amino protons being alkylated), the selectivity is improved greatly. However, in these cases, both the density of hydroxyl and tertiary amine of the CAMs are increased with the degree of alkylation; thus, it needs to be further illuminated the respective role of hydroxyl and tertiary amine.

In order to learn the role of the hydroxyl groups, **2e**, **3e**, and **4e**, which bear the same number of tertiary amines but are only different in density of hydroxyl groups, are tested on the separation efficiency of FR/RB; Figure 4 shows the result. It can be found from Figure 4 that **4e** is able to fully separate the guests (c in Figure 4), **2e** is almost as efficient as **4e** (b in Figure 4), but **3e** is less efficient (a in Figure 4), indicating the polar hydroxyl groups are unfavorable for the molecular recognition. Combining the results of both Figure 3 and Figure 4, it can be safely concluded that tertiary amine is critical for the molecular recognition, with more primary and secondary amine being transformed into tertiary

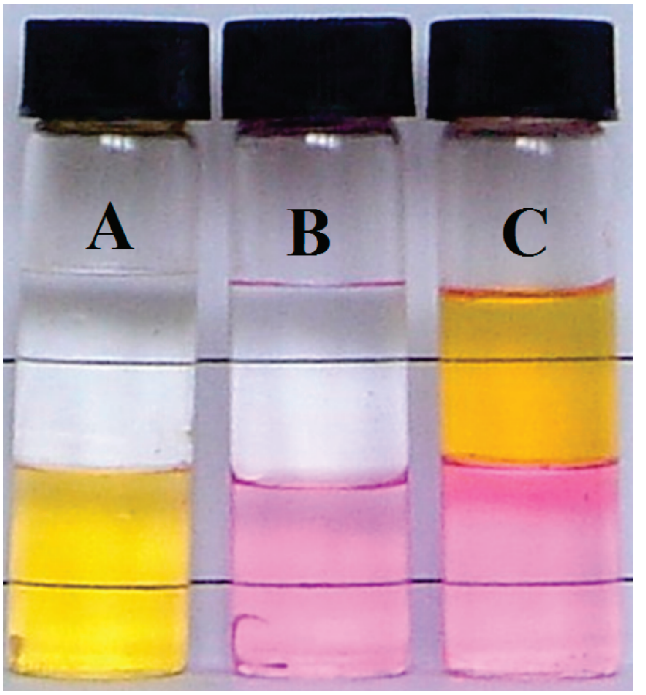


Figure 2. Either aqueous FR (A) or RB (B) alone can be completely transferred from the upper aqueous layer to the lower organic layer by **3d**, but the RB in the mixture of FR/RB is almost exclusively transferred to the lower organic layer with an appropriate amount of **3d**.

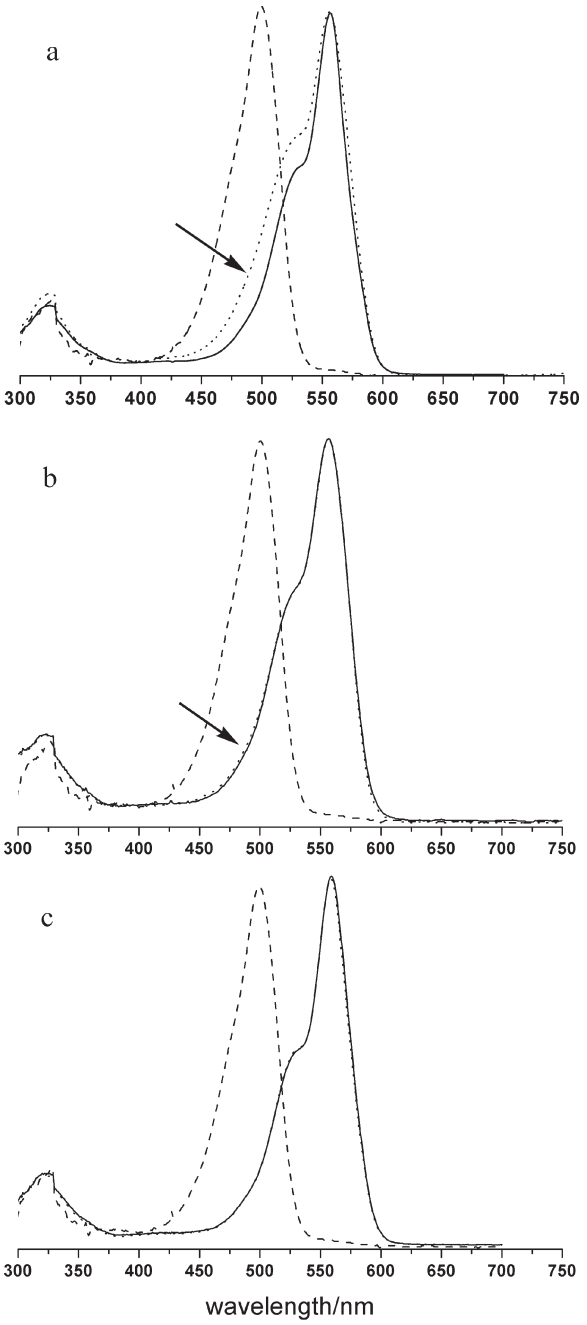


Figure 3. Recognition of FR/RB by **1d**−**3d** as detected by UV/vis spectrometer. (a) The stock chloroform solution of **1d** is exposed to aqueous FR alone (dash line), to aqueous RB alone (solid line), and to aqueous FR/RB (dot line); (b) the same case when **2d** is used in place of **1d**; (c) the same case when **3d** is used in place of **1d**. Conditions: [**1d**] = [**2d**] = [**3d**] = 1×10^{-6} M, [FR] = [RB] = 1×10^{-4} M; the pH is 7.4 (in buffer of PBS). The absorbance is normalized at the maximum absorbance. The arrow marks absorbance due to minor amount of FR.

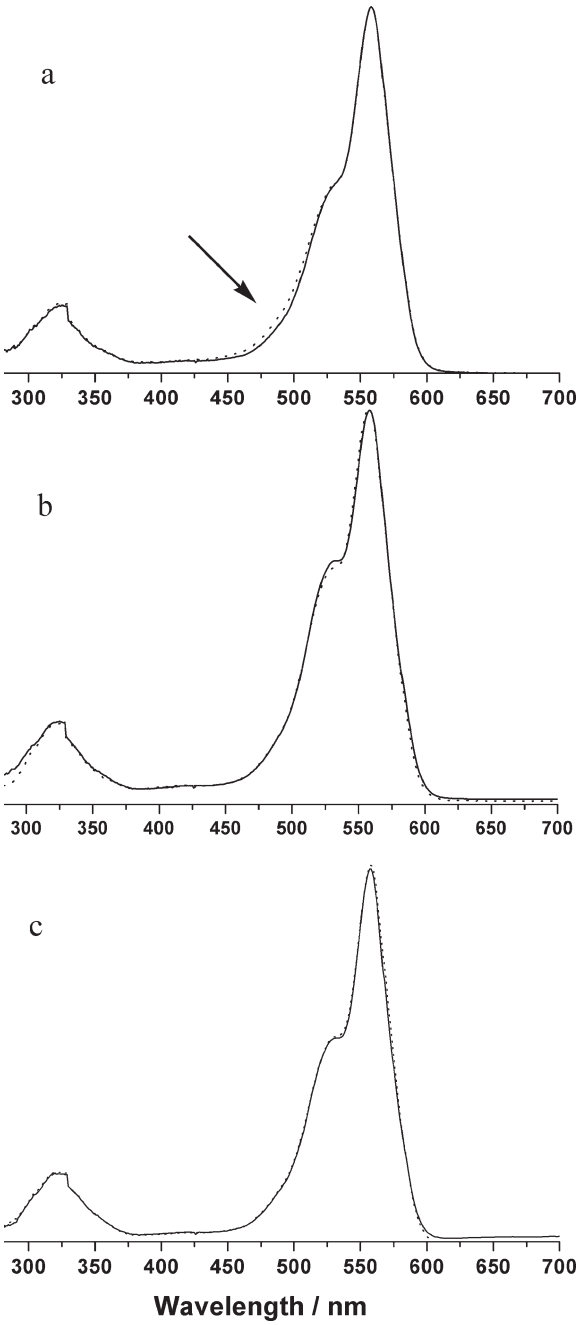


Figure 4. Recognition of FR/RB by **2e**−**4e** as detected by UV/vis spectrometer. (a) The stock chloroform solution of **3e** is exposed to aqueous RB alone (solid line) and to the mixture of aqueous FR/RB (dot line); (b) the same case when **2e** is used in place of **3e**; (c) the same case when **4e** is used in place of **3e**. Conditions: [**2e**] = [**3e**] = [**4e**] = 1×10^{-6} M, [FR] = [RB] = 1×10^{-4} M; the system is unbuffered. The arrow marks absorbance due to minor amount of FR.

amine; guest selectivity is dramatically improved. With these results, it can be proposed that **4e** is the best CAMs for the recognition of group 1 guests. In further experiments in a buffered environment, little difference from that of Figure 4 is detected. Furthermore, for a mixture of RB:FR = 1:1000 (molar ratio, [RB] = 10^{-5} M, [FR] = 10^{-2} M), RB can still be exclusively extracted out from FR if an appropriate amount of **4e** (10^{-6} M) is used, indicating the molecular recognition by **4e** is highly efficient. And in group 1, Erythrosin B (EB) is more similar to FR than RB is, but **4e** can still fully separate EB from FR (Figure 5), indicating that core engineering can greatly amplify the difference of guest species during molecular recognition.

The structure-encapsulating capacity of the CAM can also provide some information on guest selectivity; Table 2 shows the result. It can be noticed that the encapsulating capacity of the CAMs is related to their substitution degree, as previously noticed.[29] Meanwhile, it is obvious that the guest affinity is tightly related to the core structure of the CAM. For example, one **4e** can encapsulate only 0.3 FRs but can encapsulate 15 RBs, while one **2e** can encapsulate up to 1.6 FRs but 10.3 RBs; moreover, with high density of hydroxyl in the core, **3e** can only encapsulate 0.7 RBs or 0.8 FRs.

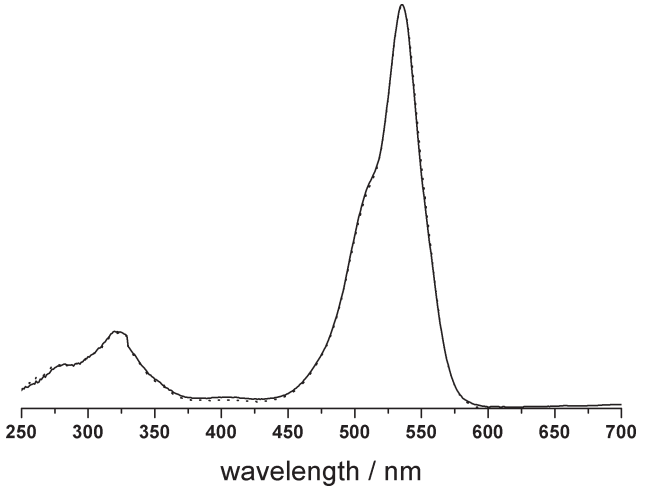


Figure 5. Recognition of FR/EB by **4e** as detected by UV/vis spectrometer. The stock chloroform solution of **4e** is exposed to aqueous EB alone (dotted line) and to the mixture of aqueous FR/EB (solid line). Conditions: [**4e**] = 1×10^{-6} M, [FR] = [EB] = 1×10^{-4} M; the system is unbuffered.

Table 2. Guest Molecules Encapsulated per CAM[a]

CAMs	FR[b]	RB[b]
1d	6.0	14.0
2d	2.6	13.8
3d	2.2	12.0
2e	1.6	10.3
3e	0.8	0.7
4e	0.3	15.0

[a] Conditions: [CAM] = 10^{-6} M, [FR] = [RB] = 10^{-4} M; water−chloroform biphasic extraction under unbuffered condition; the data are obtained from UV/vis spectra. [b] The error is 5−10%.

These results indicate that the guest affinity of the CAM is partly determined by the chemical structure in the core.

Role of pH and Mechanism of Guest Selectivity. It was shown that HPEI could be partly protonated at pH up to around 11.5;[42] thus, the core of our CAM is partly charged in a degree depending on pH value. On the other hand, like most ionic molecules, the guests in groups 1 can undergo partial electrolysis[43] and exist in time-varying, solvent- and pH-dependent states; thus, pH is an important parameter for the recognition. The protonation of the core of the CAMs can be regarded as one means of core engineering; thus, the molecular recognition is carried out at different pH. It is found that when the pH is below 7, the guest recognition becomes less and less efficient with the decrease of pH, but at high pH, the recognition is very efficient. For example, at pH > 10, any CAM of **1d**−**3d**, **1e**−**4e** can completely separate RB from FR or EB from FR, though the encapsulating capacity is much lower than that around pH 7. It was noticed previously that precise recognition of the these guests was possible if a perfect dendritic poly(propylenimine) derivative was employed as the host and if the pH was within certain range (at least larger than 8).[44] Our experiment, however, proves that the roughly defined and readily available CAM can also fully recognize these guests, even when the pH is slightly smaller than 8. The efficient molecular recognition should be attributed to the synergic effect of various elementary interactions, as concluded from the following facts. (1) It is found that at pH higher than 12, where the core would completely deprotonated,[42] still some RB molecules can be encapsulated. Thus, the encapsulation of RB at this pH does not originate from electrostatic interaction, but from other interaction including hydrophobic−hydrophobic interaction. (2) RB is insoluble in apolar solvents, and the apolar shell of the CAM cannot encapsulate any RB;[36] thus, the molecular recognition should not solely stem from hydrophobic−hydrophobic interaction, but also from ion−dipole, dipole−dipole interaction, and so on, maybe H-bonding interaction as well. (3) With the decrease of pH from 12 to around 7, much more RB molecules can be encapsulated by the CAM, indicating electrostatic interaction contribute greatly to the host−guest interacting strength. With these observations, it can be concluded that the molecular recognition is due to the synergic effect of various elementary interactions, where statistical accumulation of these interactions lead to enhanced host−guest interacting strength, and core engineering of the host CAM can amplify the guest species' difference.

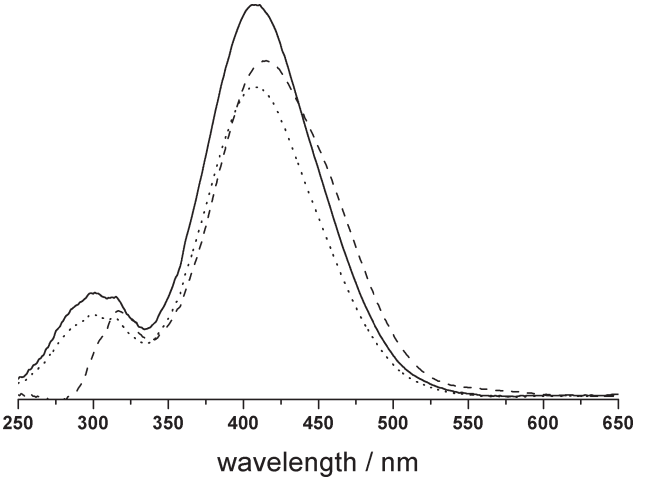


Figure 6. UV/vis spectra of dyes transferred to organic layer by **2d**. The stock chloroform solution of **2d** is exposed to aqueous OR alone (solid line, at pH 11), to aqueous MO alone (dashed line, at pH 7), and to the mixture of aqueous OR/MO (dotted line, at pH 11). The intensity is arbitrary, but the amplified dotted line can completely superpose on the solid line, indicating OR is exclusively extracted by **2d**.

Further tests with group 2 dyes (Chart 1) are carried out. It can be found from Chart 1 that the ionic feature of the guests is very similar. Orange IV (OR) is more hydrophobic than methyl orange (MO), and OR can be exclusively extracted from the mixture of MO/OR with any of the CAMs (Figure 6 shows the result in case of **2d**) if the pH is high enough (for example, 10), indicating that the recognition is mainly promoted by van der Waals force. This result shows that these CAMs are versatile in molecular recognition, and topological feature of the guest is not critical for the guest recognition.

More evidence is found from the recognition of the pair of acid green 25 (AG25)/acid green 27 (AG27) (Chart 1) that van der Waals force promoted the molecular recognition. One can find that AG25 and AG27 are of little difference except the aliphatic group, where the former bears a methyl group but the latter bears a butyl group. Figure 7 shows that in case when **1d** is used as the host AG25/AG27 can hardly be recognized (one can compare the absorbance of each spectrum around 410 and 460 nm in Figure 7), while in case when **4e** is used as the host, though sufficient separation is still impossible, mainly AG27 is preferred (quantitative analysis is impossible yet). This experiment strongly suggests that hydrophobic interaction, along with electrostatic interaction, contributes to the molecular recognition and once again supports that core engineering can amplify the difference of guest molecules. It is also noticed that with pH as high as 14, where the CAM can be regarded as neutral in core, neither

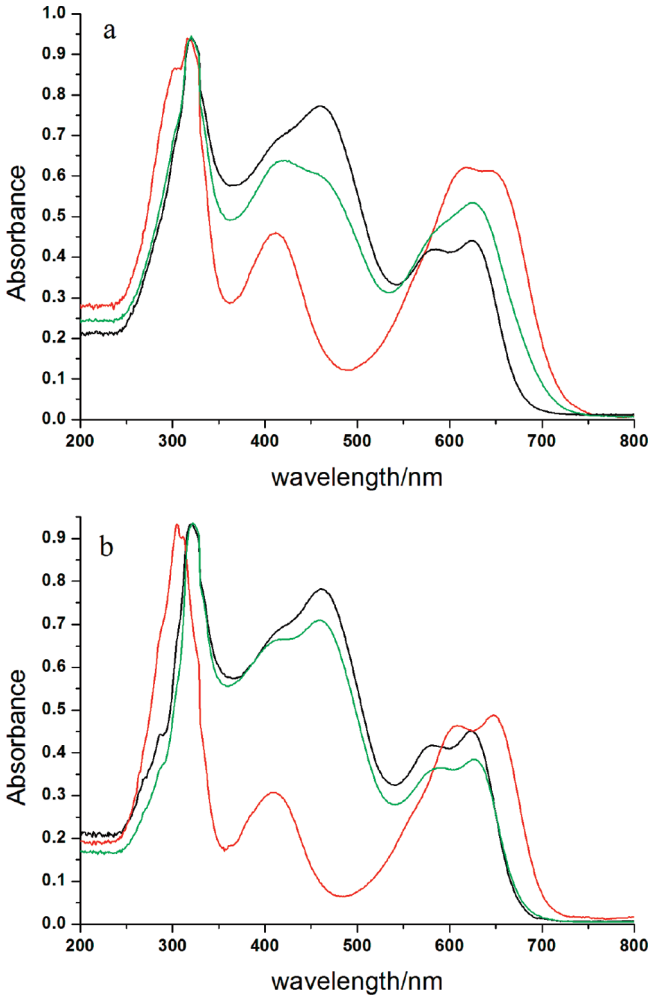


Figure 7. UV/vis spectra of AG25 (red line), AG27 (black line), or their mixture (green line) transferred to organic phase by **1d** (a) or **4e** (b). Conditions: [AG25] = [AG27] = 1×10^{-4} M in water, [**1d**] = [**4e**] = 1×10^{-6} M in chloroform. The spectra are obtained unbuferred and normalized at the maximum absorbance around 300 nm.

AG25 nor AG27 can be completely released by the CAMs, indicating that both AG25 and AG27 are rather hydrophobic that current CAMs cannot fully distinguish them.

Aggregation of the CAMs was found to exert little influence on guest recognition;[36] however, our final concern is why physical adsorption of the guest,[37] electrolysis of the guest, and conformation transition of the guest do not lead to a failed molecular recognition. That the physical adsorption of guest, known to generally occur in a CAM-based system, does not lead to a failed molecular recognition may be due to the fast exchanging equilibration formed between the complexed and the adsorbed guests; as a consequence, the species adsorbed by the host is mainly determined by the host−guest interacting strength. Similarly, owing to the rapid interconversion, electrolysis and conformational transition of the guest can somewhat influence the host−guest interacting strength, but this influence is limited.

Conclusion

A roughly defined, readily available macromolecular nanocapsule can act as a highly selective host in supramolecular recognition. Core engineering of the host can exert a nonlinear influence on the host−guest interacting strength and therefore amplify the difference of the guests, thus ensuring highly selective guest recognition feasible. The macromolecular nanocapsule derived from HPEI is uniquely featured for the dense functional groups randomly distributed in the core, which render various core engineering convenient and in turn leads to versatile molecular recognizing hosts. The molecular recognition is not promoted by specific host−guest complementary interaction but by the statistical accumulation of elementary host−guest interactions where specific interaction is absent or too weak to play a leading role. This methodology called molecular fuzzy recognition can hopefully be anticipated to recognize common molecules that are topologically and electronically featureless since no specific interaction is necessary for the specific recognition and since exact size, morphology, and electronic motif of the host are no longer essential for the host; even a roughly defined macromolecule can act as a highly selective host if its core is chemically adjustable.

Although the recognition is generally pH dependent, it can be an advantage, especially for the recycle of the CAM.[35,45]

Experimental Section

Materials. HPEI ($M_n = 1 \times 10^4$, $M_w/M_n = 2.5$, degree of branch (DB) = 60%) was purchased from Aldrich. Methyl orange (MO), Rose Bengal (RB), propylene oxide, KOH, and bromohexadecane were purchased from SCRC (China) with the highest purity available and are used directly unless stated otherwise.

Measurement. UV/vis spectra were recorded on a 760 CRT UV/vis spectrometer (Shanghai Analytical Instrument Factory). ^{1}H NMR spectra were recorded on Bruker (600 MHz), with TMS as reference. Dynamic light scattering (DLS) was recorded on a commercial laser light scattering (LLS) spectrometer (Malvern Autosizer 4700) equipped with a solid-state laser (ILT 5500QSL, output power 100 mW at $\lambda_0 = 532$ nm) as the light source. All the DLS measurements were performed at 25 ± 0.1 °C in chloroform. Size and polydispersity index ($\mu^2/\langle\Gamma\rangle^2$) were obtained by a CONTIN analysis mode. All the solutions at different concentrations were clarified using a 0.45 μm Millipore filter (hydrophobic PVDF) before the measurements.

Synthesis. 1d, **3d**, and **1e**−**3e** were synthesized similar to a previous report.[36,37]

Synthesis of ***2d***. **1d** (0.316 g, 1.62 mmol NH) in ethanol (10 mL) was mixed with propylene oxide (0.045 g, 0.71 mmol) and stirred at room temperature for 3 days. The volatile was removed on a rotary evaporator at reduced pressure to yield a colorless viscous liquid (0.36 g, 100% yield). ^{1}H NMR ($CDCl_3$, δ/ppm): 0.90 (t, 3H, CH_3), 1.15 (t, 3H, CH_3), 1.28 (s, 18H, CH_2), 1.57 (t, 2H, OCH_2), 2.00−3.00 (m, 17.3H, $CH_2CH_2NCH_2$), 3.20−3.60 (m, 4H, CH-OH, and CH_2OH), 3.70−4.00 (br, 2H, OH). ^{13}C NMR ($CDCl_3$), δ/ppm: 14.08 ($CH_3(CH_2)_{15}O-$), 22.66 ($CH_3(CH)O-$), 25.74 ($CH_3CH_2(CH_2)_{14}O-$), 26.14 ($-OCH_2CH_2CH_2$), 29.34−29.70 ($H(CH_2)_3(CH_2)_9(CH_2)_2O-$), 31.91 ($-OCH_2CH_2$), 32.82 ($CH_3$-$CH_2CH_2$), 47.40−52.90 ($-NCH_2CH_2N-$), 63.00 ($-NCH_2$-$CHO-$), 70.56 ($-OCH_2(CH_2)_{15}H$), 71.68 ($-OCH_2CHOH$), 74.54 ($-NCH_2CHO-$). FTIR (KBr), ν/cm^{-1}: 3100−3300 (OH, NH), 2960 (CH_3), 2930 (CH_2).

Synthesis of ***4e***. A mixture of HPEI intermediate (fully alkylated with propylene oxide[41]) (3.03 g, 30 mmol OH), KOH (5.6 g, 100 mmol), and bromohexadecane (9.15 g, 30 mmol) in dimethyl sulfoxide (30 mL) was stirred at 50 °C for 2 days. The mixture was poured into a large amount of water/chloroform with vigorous stirring. The oil layer was separated, washed twice with fresh water, and subjected to dialysis against a large amount of chloroform for 2 days (Spectro/Por, WMCO 2000). The chloroform solution was dried on sodium sulfate. Removal of the salt (by filtration) and solvent (by evaporation) yielded a light red solid, 7.08 g. ^{1}H NMR ($CDCl_3$): δ/ppm: 0.89 (t, 1.8H, CH_3 of hexadecyl), 1.13 (d, 3H, CH_3 of propylol), 1.26 (s, 15.6H, OCH_2CH_2-$(CH_2)_{13}CH_3$), 1.55 (m, 1.2H, $OCH_2CH_2(CH_2)_{13}CH_3$), 2.36 (s, 1.2H, $NCH_2CH(O-)CH_3$), 2.40−2.90 (br, 4H, NCH_2-CH_2), 3.40−4.5 (m, 3.4H, $CHOHCH_3$, $CHOCH_2$). ^{13}C NMR

($CDCl_3$), δ/ppm: 14.10 ($CH_3(CH_2)_{15}O$), 22.69 ($CH_3(CH)O$), 14.10 ($CH_3(CH_2)_{15}O$), 26.20 ($CH_3CH_2(CH_2)_{14}O$), 14.10 (CH_3-$(CH_2)_{15}O$), 29.60−29.70 ($H(CH_2)_2(CH_2)_{11}(CH_2)_2O$), 31.93 ($OCH_2CH_2$), 70.96 ($OCH_2CH_2$), 74.23 (CHOH), 63.01 ($NCH_2$-CHO), 51.0−52.0 and 61.4−61.6 (NCH_2CH_2N).

To learn if any of the amino group was quaternized during the above reaction, a control experiment was carried out similarly but in the absence of KOH. The resulting mixture was dialyzed against ethanol for 2 days (Spectro/Por, WMCO 2000). After removal of the solvent, the product was analyzed with ^1H NMR.

General Procedure for Mixture Separation. In case the FR/RB/EB is used as the guest, the amount of the CAMs is essential for the separation efficiency. Typically, **4e** in chloroform (10^{-6} M) is added in a titration-like manner to an aqueous binary mixture of FR/RB (FR:RB = 1:1 molar ratio, [FR] + [RB] = 10^{-4} M) with vigorous shaking, and following equilibration (0.5−24 h), the titration is continued until RB is completely transferred to the organic phase; the partition of FR is detected in either phase with UV/vis spectrometer. Alternatively, a stock solution of **4e** (10^{-6} M, 4 mL) in chloroform is first fully saturated with FR in water (10^{-4} M, 4 mL); the organic layer is then separated and exposed to RB in water (10^{-4} M, 4 mL) for equilibration. The organic layer is separated and subjected to UV/vis measurement to show any FR−RB exchange. If any precipitate is observed, the aqueous phase is removed and the residual is diluted until complete dissolution of the precipitate; the resulting solution is detected with UV/vis spectrometer, and the absorbance is amplified to an equivalent concentration of the original one.

When OR/MO is used as the guest and when the pH is high enough, the amount of CAM is no longer essential for the separation efficiency.

When pH adjustment is needed, 0.1 N HCl or NaOH is used. In the case of buffered condition, PBS (phosphate-buffered saline, Na_2HPO_4, 10 mM; KH_2PO_4, 2 mM) is prepared, and the pH is adjusted to 7.4 with aqueous HCl; 137 mM NaCl and 2.7 mM KCl are used to maintain the ionic strength.

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