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# A quinoline-based tripodal fluororeceptor for citric acid

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**Abstract**

The quinoline-based tripodal fluororeceptor **1** has been designed and synthesized for the detection of citric acid in less polar solvents. Receptor **1** shows monomer emission quenching followed by excimer emission upon hydrogen bond-mediated complexation of citric acid. In comparison, receptor **2**, in presence of the same acid, gives rise to a decrease in the monomer emission of the naphthyl moiety without showing any peak for the excimer. Receptor **1** is found to bind citric acid more strongly than receptor **2** in $CHCl_3$.


*Keywords:* Citric acid recognition; Quinoline; Naphthalene; Tripodal receptor

The specific detection of biologically relevant molecules is of considerable interest in molecular recognition research. In this context, the design and synthesis of fluororeceptors, which selectively interact with the substrate of choice, and report the binding events via a change in a physical signal is an area of intense interest.[1,2] As substrates, carboxylic acids are of particular importance due to their key roles in a wide range of biological processes.[3,4] Citric acid, in this regard, is a tricarboxylic acid that plays an important role in the Kreb's cycle to provide the vast majority of energy used by aerobic cells, for example, in human beings. Several groups have reported the recognition of citrate ions using various receptors.[5–10] Many of these are based on positively charged, hydrogen bonding groups or unsaturated metal centers coordinated to 1,3,5-trialkylbenzene scaffolds, which adopt a 'fly-trap' conformation. Anslyn used the indicator displacement method for the recognition of citrate. In relation to these approaches, our recent report on a naphthyridine based sensor for citric acid[11] inspired us to investigate the design of a new tripodal receptor. Tripodal receptors based on hexasubstituted arene rings are well established for anions and cations.[12] In this context, the 1,3,5-tripodal host based on 3-aminopyridinium 'arms' containing anthracenyl moieties is interesting for the selective sensing of acetate.[13] However, the use of the 1,3,5-tripodal core for recognition of carboxylic acids is unknown to the best of our knowledge and therefore a challenging theme in the area of molecular recognition. In this Letter, we, for the first time, report pyridine based tripodal fluororeceptors **1** and **2** that show significant binding ability for citric acid in the less polar solvent $CHCl_3$ (Fig. 1).

The receptors **1** and **2** were synthesized from 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene[14,15] by reaction with fluorophore labeled 2-aminopyridines **4** and **6**, respectively, in the presence of $K_2CO_3$ in a dry $CH_3CN$ and THF solvent mixture (1:1) (Scheme 1). Compounds **1** and **2** were obtained in 30% and 33% yields, respectively, and were characterized by $^1H$ NMR, $^{13}C$ and mass analyses.[16]

These tripodal receptors **1** and **2** can adopt a folded conformation with the fluorophore (naphthalene, quinoline) moieties upwards and downwards around the benzene core. Molecular modeling[17] shows that the orientation of the hydrogen bonding groups around the central benzene core is in a tripodal fashion in both **1** and **2** (Fig. 1).

The binding abilities of the tripodal receptors **1** and **2** for citric and other carboxylic acids such as *rac*-malic and D-(−)-tartaric acids were investigated using $^1H$ NMR,

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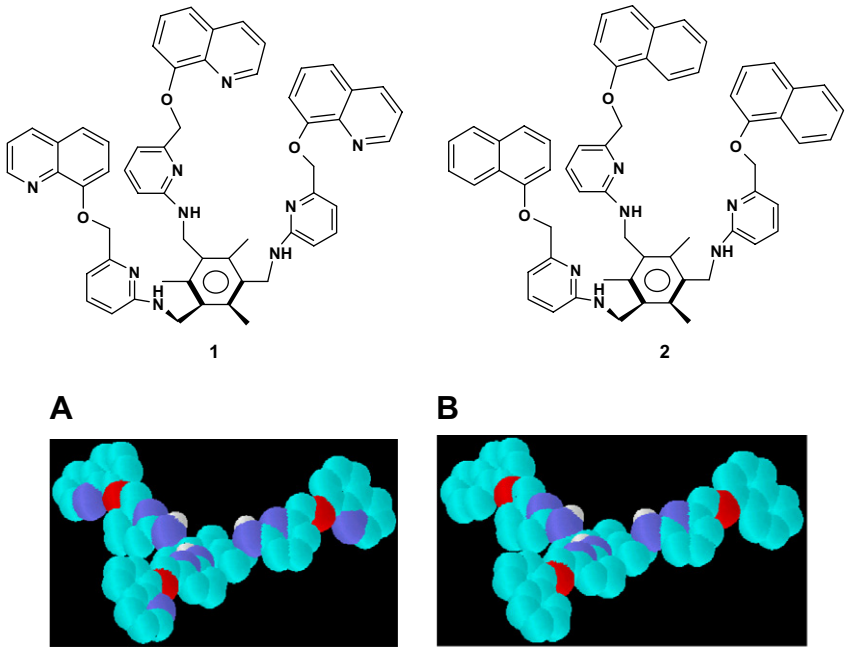
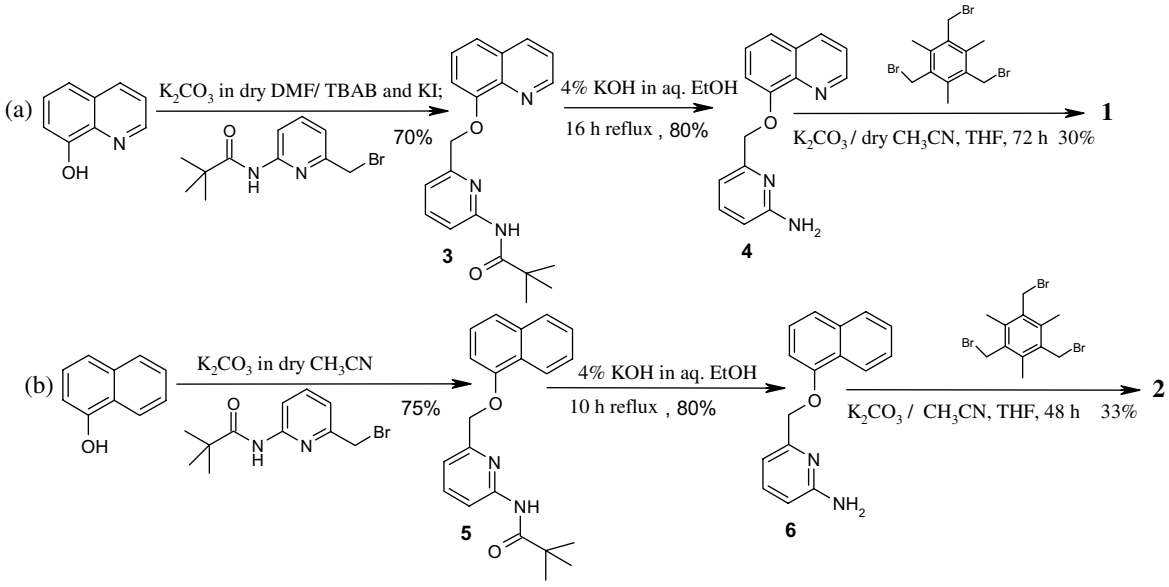



Fig. 1. Energy minimized structures of **1** ($E_{min}$ = 132.5 kcal/mol) (**A**) and **2** ($E_{min}$ = 115.0 kcal/mol) (**B**).




Scheme 1. Syntheses of receptors of **1** and **2**.

UV–vis and fluorescence methods. To gain an insight on the binding interactions with citric acid, $^1$H NMR spectra of **1** and **2** were taken in $CDCl_3$ ($c = 3.08 \times 10^{-3}$ M and $3.31 \times 10^{-3}$ M, respectively). The amine NHs in **1** and **2** appeared at $\delta$ 4.32 and 4.43 ppm, respectively and were too broad to detect accurately upon addition of citric acid (dissolved in $CDCl_3$ containing 4% DMSO-$d_6$). Even the amine NHs in **1**, which appeared at $\delta$ 4.32 ppm, were also broadened after addition of powdered citric acid to a dry $CDCl_3$ solution of **1** followed by sonication. The clear dissolution of citric acid was evident from the appearance of new resonances at $\delta$ 2.85 and 2.66 ppm for the –$CH_2$– groups of citric acid. All the signals in the aromatic region of **1** were resolved and no other new signals were noticed. When dry HCl was passed into the chloroform solution of **1**, immediate precipitation occurred to give an insoluble product. The $^1$H NMR of this insoluble product was recorded in DMSO-$d_6$. All the signals were broad and new resonances in the regions $\delta$ 9.29, 7.90, and 7.27 ppm, presumably for the protonated quinoline, pyridine, and ammonium cations, respectively, were observed. The absence of such new resonances at $\delta$ 9.29, 7.90, and 7.27 ppm during the complexation of citric, *rac*-malic, and D-(−)-tartaric acids with both **1** and **2** thus confirmed

that the tripodal receptors **1** and **2** were involved in complexation with the carboxylic acid guests in $CDCl_3$ mainly through H-bonding instead of ion pair binding via proton transfer.

Once the nature of the interactions had been established, both **1** and **2** were studied by UV–vis and fluorescence to establish their selectivities and sensitivities toward citric, *rac*-malic, and D-(−)-tartaric acids. Initially, the photophysical properties of **1** were determined in solvents of different polarities to gain an insight into its solvatochromic behavior. The absorption spectra of **1** in dry $CHCl_3$ exhibited a structureless absorption band at 310 nm, characteristic of quinoline. The position of this peak was unaltered in dry THF, $CH_3OH$, and $CH_3CN$. A slight red shift in dry DMSO was observed. In the presence of citric acid, the absorption peak at 310 nm for the quinoline in **1** showed a large red shift ($\Delta\lambda = 21$ nm) in $CHCl_3$ only, which illustrated a strong hydrogen bond interaction between citric acid and receptor **1**. A chloroform solution of the 1:1 complexes of citric, *rac*-malic, and D-(−)-tartaric acids with receptor **1** was diluted gradually with chloroform and the change in intensity, as a function of concentration was linear in each case. Figure 2, for example, shows the effect of dilution on the UV–vis spectra of the 1:1 complex of **1**·citric acid. This change in the UV–vis spectra was used conveniently to study the binding since the lower concentration led to a more accurate determination of the association constants for the acids (Table 1).[18] Citric acid, having more hydrogen bonding groups, shows a higher binding constant in comparison to the other acids tested. Similar control experiments on **2** gave lower binding constant values with the other acids (Table 2). This underlines the fact that the quinoline ring nitrogen in **1** plays a key role in hydrogen bonding to increase the binding of the carboxylic acids.

The chemosensor behavior was also investigated by steady state fluorescence. As shown in Figure 3a, the fluorescence emission of the quinoline in **1** varied with the polarity of the solvents when excited at 290 nm. Compound **1** displayed a structureless monomer emission at 382 nm when irradiated at 290 nm in $CHCl_3$. The addition of citric, *rac*-malic, and D-(−)-tartaric acids to a $CHCl_3$ solution of **1** in 1:1 stoichiometry resulted in a decrease in the fluorescence emission of the quinoline moiety along with a simultaneous generation of the excimer bands at 456, 444, and 464 nm, respectively (Fig. 4a). As shown in Figure 4a, the intensity of the excimer band varies with the nature of the carboxylic acid and is found to be significant in case of citric acid. This excimer emission of **1** in the presence of citric acid showed a sensitive dependence on the polarity of the solvent, being much less important in more polar solvents such as $CH_3OH$, THF, and DMSO except for $CH_3CN$ where a weak excimer band at 475 nm was observed (Fig. 3b). We suggest that this excimer emission results from the guest-induced hydrogen bond-mediated upward folding of the quinoline moieties that occurs with

Table 1
Binding constant values of **1** by UV–vis titration

| Guest acid | $K_a$ ($M^{-1}$)[a] | $K_a$ ($M^{-1}$)[b] |
|---|---|---|
| Citric | $6.36 \times 10^5$ | $5.75 \times 10^4$ |
| *rac*-Malic | $7.25 \times 10^4$ | $7.49 \times 10^3$ |
| D-(−)-Tartaric | $7.62 \times 10^4$ | $2.90 \times 10^4$ |

[a] Determined in pure dry $CHCl_3$.
[b] Determined in dry $CHCl_3$ containing 0.7% DMSO.

Table 2
Binding constant values of **2** by UV–vis titration

| Guest acid | $K_a$ ($M^{-1}$)[a] | $K_a$ ($M^{-1}$)[b] |
|---|---|---|
| Citric | $8.82 \times 10^4$ | $2.28 \times 10^4$ |
| *rac*-Malic | $1.02 \times 10^4$ | $1.62 \times 10^4$ |
| D-(−)-Tartaric | $1.81 \times 10^4$ | $1.30 \times 10^4$ |

[a] Determined in pure dry $CHCl_3$.
[b] Determined in dry $CHCl_3$ containing 0.7% DMSO.

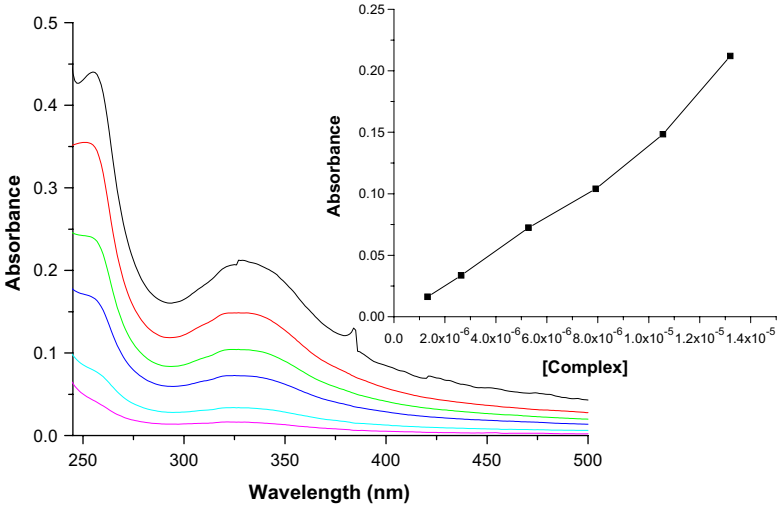



Fig. 2. UV spectra of a 1:1 complex of **1** with citric acid and the change of absorbance on dilution; (inset) plot of absorbance vs. concentration of the complex of citric acid with **1**.

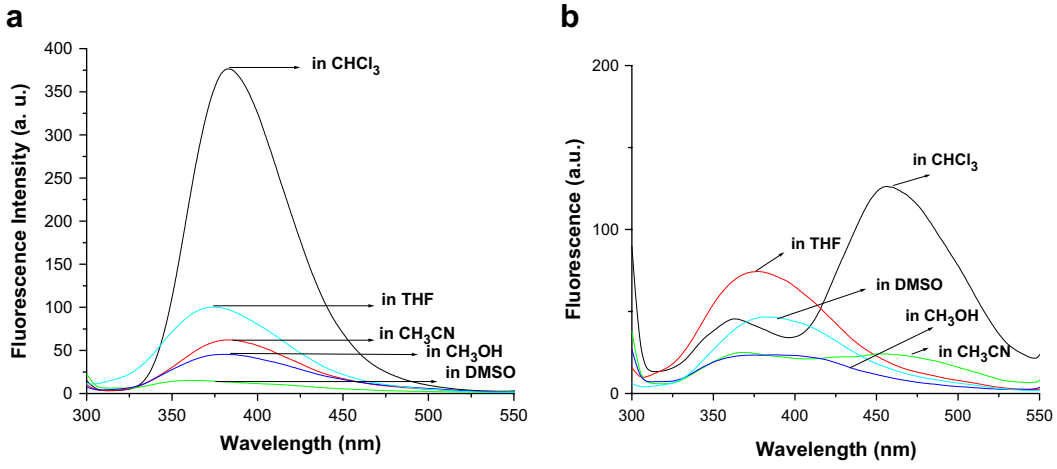



Fig. 3. (a) Fluorescence spectra of **1** ($c = 1.32 \times 10^{-5}$ M ); (b) in the presence of citric acid (1:1) in different solvents.

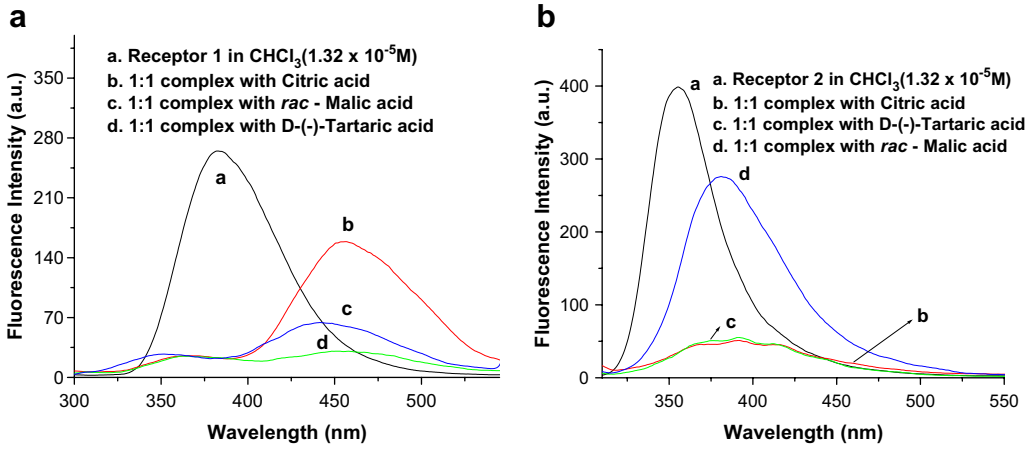



Fig. 4. (a) Fluorescence change of **1** in $CHCl_3$ in the presence of citric, *rac*-malic and D-(−)-tartaric acids ($\lambda_{ex} = 290$ nm); (b) fluorescence change of **2** in $CHCl_3$ in the presence of citric, *rac*-malic and D-(−)-tartaric acids ($\lambda_{ex} = 300$ nm).

citric acid due to its larger size and strong hydrogen bonding interaction. This was proved by performing similar control experiments using **2** with the same carboxylic acids in $CHCl_3$. Interestingly, **2** in presence of the same acids, gave rise to a decrease in the monomer emission of the naphthyl moiety to different extents without showing any peak at 456 nm for excimer formation (Fig. 4b). Even upon addition of the tetrabutylammonium salt of citric acid to the chloroform solution of **1**, no measurable change in the fluorescence was observed (see Supplementary data). These observations support the conclusion that the nitrogen of the quinoline ring is indeed an important factor in the guest induced, hydrogen bond-mediated, substantial conformational change of **1**, which brings the quinoline moieties close enough for the formation of the excimer. The excimer emission resulted from the intramolecular excimer, rather than intermolecularly, as indicated by dilution experiments at different concentrations in which the intensities of the ratio of excimer to monomer emission

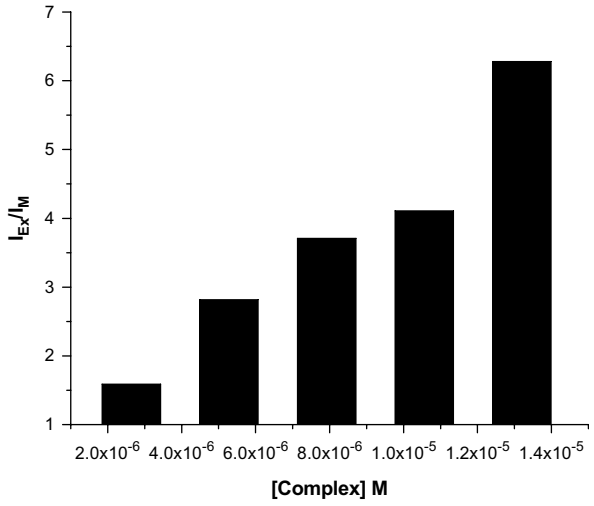



Fig. 5. Plot of the ratio of excimer to monomer emission versus concentration of the complex of **1** with citric acid.

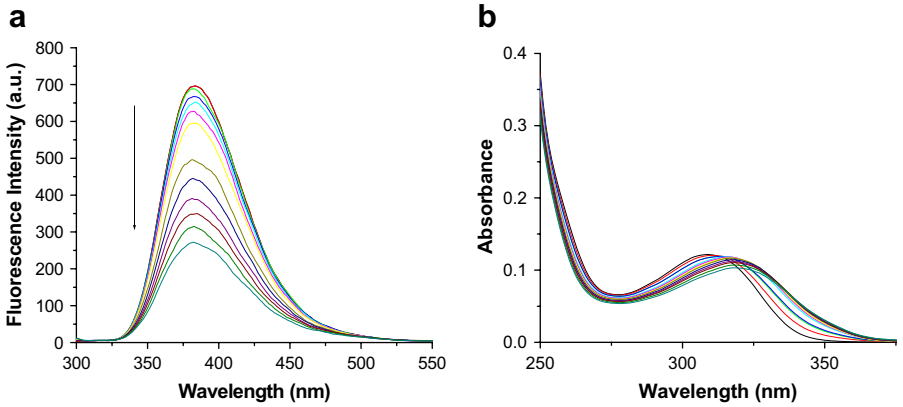



Fig. 6. Change in fluorescence of **1** ($c = 1.32 \times 10^{-5}$ M) in $CHCl_3$ upon addition of citric acid, dissolved in $CHCl_3$ containing 0.7% DMSO; (b) Change in absorbance of **1** in $CHCl_3$ ($c = 1.32 \times 10^{-5}$ M) upon addition of citric acid dissolved in $CHCl_3$ containing 0.7% DMSO.

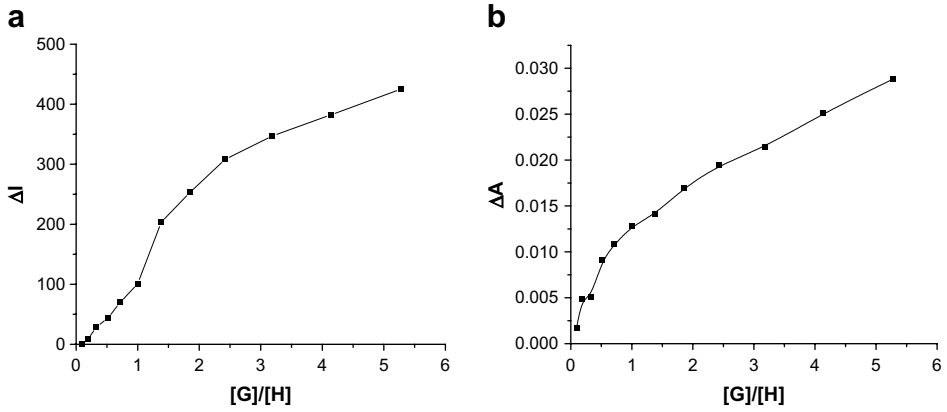



Fig. 7. (a) Fluorescence titration and (b) UV–vis titration curves for **1** with citric acid, dissolved in $CHCl_3$ containing 0.7% DMSO.

changed gradually (Fig. 5). In order to find out the influence of the polar solvent on the binding of citric and other acids, fluorescence titrations on both **1** and **2** were conducted by taking the guest acids in $CHCl_3$ containing 0.7% DMSO. It is of note that the excimer was absent when the guest acids, dissolved in $CHCl_3$ containing 0.7% DMSO, were gradually added to the $CHCl_3$ solution of **1** ($c = 1.32 \times 10^{-5}$ M). In this regard, Figure 6a shows the change in fluorescence of **1** upon addition of citric acid. The corresponding change in absorption in $CHCl_3$ on gradual addition of citric acid dissolved in $CHCl_3$ containing 0.7% DMSO is also worth noting (Fig. 6b).

The isosbestic point at 315 nm infers 1:1 stoichiometry of the complex. The stoichiometry was further ascertained from the break of both the fluorescence and UV titration curves at [G]/[H] = 1 (Fig. 7a and 7b, respectively). However, the presence of DMSO, a competitive hydrogen bonding partner, reduces the binding affinity of **1** with the guest acids (Table 1; the binding is approximately 10 times less than the values in pure $CHCl_3$)[19] so that upward folding of the quinoline moieties is presumably less efficient than in pure $CHCl_3$. The binding constant values as presented in Table 1, indicate that receptor **1** is an efficient binder of citric acid in $CHCl_3$, even more so than receptor **2**.

In conclusion, a simple modular approach has been described to a quinoline-based tripodal receptor displaying marked citric acid binding in the less polar solvent chloroform. This binding relies solely on weak non-covalent interactions. The hydrogen bond-mediated complexation of citric acid by the quinoline-based sensor has been followed by excimer emission. This excimer emission is moderate and convenient as a practical method to detect and distinguish citric acid from tartaric and malic acids. Further studies on this subject are underway in our laboratory.

## Acknowledgments

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## Supplementary data

$^1$H NMR, $^{13}$C NMR and mass spectra of compounds **1** and **2**, fluorescence spectra of **1** on addition of the tetrabutylammonium salt of citric acid and the binding constant determination curve for citric acid are available.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.139.

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16. Receptor **1**: mp = 100 °C (decomposition), $^{1}$H NMR (500 MHz, $CDCl_3$, $\delta$ in ppm) 8.98 (dd, $J = 2.5$ Hz, 2 Hz, 3H), 8.13 (dd, $J = 6.5$ Hz, 2 Hz, 3H), 7.45–7.41 (m, 6H), 7.37 (d, $J = 4.5$ Hz, 6H), 7.10 (t, $J = 4.5$ Hz, 3H), 6.91 (d, $J = 7$ Hz, 3H), 6.37 (d, $J = 8$ Hz, 3H), 5.41 (s, 6H), 4.51 (d, $J = 4$ Hz, 6H), 4.32 (br t, $J = 4$ Hz, 3H), 2.49 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) 153.0, 150.5, 149.3, 144.3, 135.4, 133.2, 131.9, 130.9, 128.8, 124.4, 121.6, 116.6, 114.8, 105.3, 104.9, 100.7, 66.6, 36.6, 24.7; FTIR ($\nu$ cm$^{-1}$, KBr): 3386, 2922, 2852, 1602, 1571, 1499, 1465, 1377, 1317; HRMS (TOF MS ES$^{+}$) calcd for $C_{57}H_{51}N_9O_3$: 909.4115. Found: 910.4181 (M+1), 932.4004 (M+Na). Receptor **2**: mp = 80 °C, $^{1}$H NMR (400 MHz, $CDCl_3$, $\delta$ in ppm)8.40 (dd, $J = 8$ Hz, 2 Hz, 3H), 7.80 (dd, $J = 8$ Hz, 2 Hz, 3H), 7.52–7.47 (m, 9H), 7.42 (d, $J = 8$ Hz, 3H), 7.34 (t, $J = 8$ Hz, 3H), 6.96 (d, $J = 8$ Hz, 3H), 6.88 (d, $J = 8$ Hz, 3H), 6.40 (d, $J = 8$ Hz, 3H), 5.24 (s, 6H), 4.51 (s, 6H), 4.43 (br s, 3H), 2.47 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) 157.9, 155.8, 154.3, 138.2, 136.9, 135.1, 134.5, 133.8, 127.4, 126.3, 125.8, 125.2, 122.1, 120.4, 110.0, 105.6, 105.4, 70.8, 41.6, 26.3; FTIR ($\nu$ cm$^{-1}$, KBr): 3412, 2922, 1598, 1574, 1508, 1462, 1396, 1357; Mass (ESI$^{+}$) 907.0 (M+H), 761.1, 454.2.
17. Energy minimization was carried out using MMX (PC Model Serena Software 1993). Molecular modeling was performed using standard constants, and the dielectric constant was maintained at 1.5.
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