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A naphthyridine-based receptor for sensing citric acid

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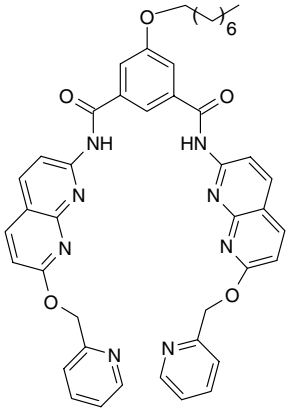
Abstract—A naphthyridine-based charge neutral receptor has been designed and synthesized. Its complexation with a series of carboxylic acids involved in the Krebs cycle has been studied by ^{1}H NMR, UV–vis and fluorescence methods. The receptor shows strong binding to citric acid ($K_a = 1.60 \times 10^5$ M^{-1}) and is also able to distinguish diastereomeric maleic acid from fumaric acid by fluorescence.

The design and synthesis of molecular receptors that can interact and sense biologically relevant carboxylic acids through an optical response is an active area of molecular recognition research. In the last decade, considerable effort has been devoted to the synthesis of various types of artificial fluorescent receptors for both mono and dicarboxylic acids and their derivatives.[1] As part of this area of research, we have recently focused on the recognition and sensing of both mono and dicarboxylic acids through hydrogen bonding interactions.[1e,2] Given the importance of carboxylic acids in biology,[3] interest in selective sensors that are able to discriminate one substrate amongst others intervening in a metabolic route is very appealing. Citric acid, in this regard, is a tricarboxylic acid that plays an important role in Krebs cycle to provide the vast majority of energy used by aerobic cells in human beings. Maleic acid is a well-known inhibitor of this cycle and its implication in different kidney diseases has been widely described.[4] Several groups have focused on various artificial receptors for recognition of citrate.[5] Many of these are based on positively charged, hydrogen bond groups or unsaturated metal centers coordinated to 1,3,5-trialkylbenzene scaffolds which adopt a 'fly-trap' conformation. Another approach that employs the indicator displacement method was elegantly demonstrated by Anslyn and co-workers.[6]

In this Letter, we report on new molecular structure **1** that shows strong binding of citric acid by exhibiting a change in the photophysical behavior of the naphthyridine units.



1

The synthesis of **1** is outlined in Scheme 1. Coupling of 2-acetylamino-7-chloro-1,8-naphthyridine, obtained by a known method,[7] with 2-hydroxymethylpyridine in dry THF in the presence of NaH and a catalytic amount of Cu_2O gave compound **2** which on amide cleavage under alkaline conditions furnished the intermediate amine **3**. In addition, 2-butyrlamino-7-chloro-1,8-naphthyridine was coupled with 2-hydroxymethylpyridine, under the same reaction conditions to give amine **3** as the sole product. Reaction of amine **3** with 5-octyloxyisophthaloyl diacid chloride gave receptor **1**[8] in 20% yield. Amine **3** was characterized by X-ray analysis (Fig. 1).[9]

Keywords: Citric acid binding; Maleic acid binding; Naphthyridine; Fluorescence sensing; Selective recognition of carboxylic acid.
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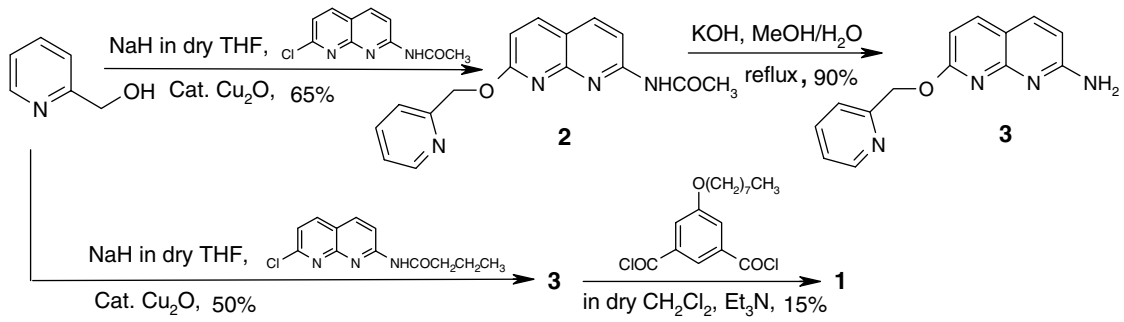

Scheme 1. Synthesis of receptor **1**.

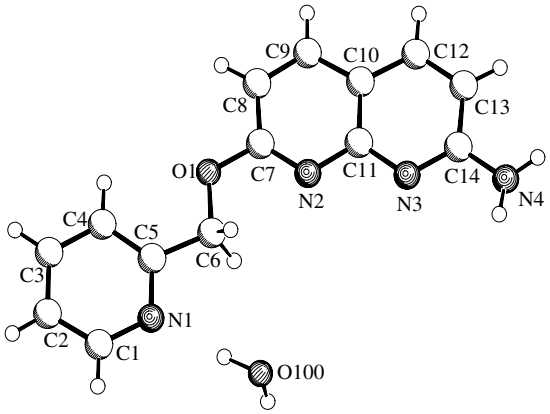

Figure 1. SCHAKAL plot of **3**.

The carboxylic acid binding properties of **1** were investigated by observing the changes in fluorescence emission, absorption spectra in $CHCl_3$ and by ^1H NMR in $CDCl_3$. Our initial experimentation to evaluate the potential of **1** as a receptor for citric acid began with a study of the ^1H NMR spectra of **1** in the presence of citric acid in dry $CDCl_3$. Upon addition of citric acid to a solution of **1** in $CDCl_3$, a complexation-induced downfield shift of the amide NH ($\Delta\delta = 1.6$ ppm) and well resolved peaks of the naphthyridine ring protons were observed. This large downfield shift indicated strong complexation. The ability of receptor **1** to provide a highly preorganized pocket-like environment in binding citric acid was further supported by molecular modeling (Fig. 2; $E_{min} = 72.62$ kcal/mol)[10] where each naphthyridine ring nitrogen is involved in bifurcated hydrogen bonds with the hydroxyl and carboxylic acid protons. One of the pendant pyridine rings in **1** binds the carboxylic acid involving a single point hydrogen bond interaction.

To ascertain the selectivity and sensitivity of **1** with citric and other acids involved in the Krebs cycle, UV–vis titration experiments were conducted in $CHCl_3$. Upon addition of the acids (citric, malic, succinic, maleic, and fumaric) the characteristic absorption peak of **1** at 343 nm gradually decreased without producing any other observable changes. Figure 2 shows the absorption spectra of **1** upon addition of citric acid. The measured absorbance $[A_0/(A_0-A)]$ at 343 nm as a function of the inverse of citric acid concentration fits with a linear relationship, indicating the 1:1 stoichiometry of the **1**/citric acid complex (Fig. 3; inset).[11] The ratio for the intercept versus slope gave the association constant K_a of 1.60×10^5 M^{-1}.

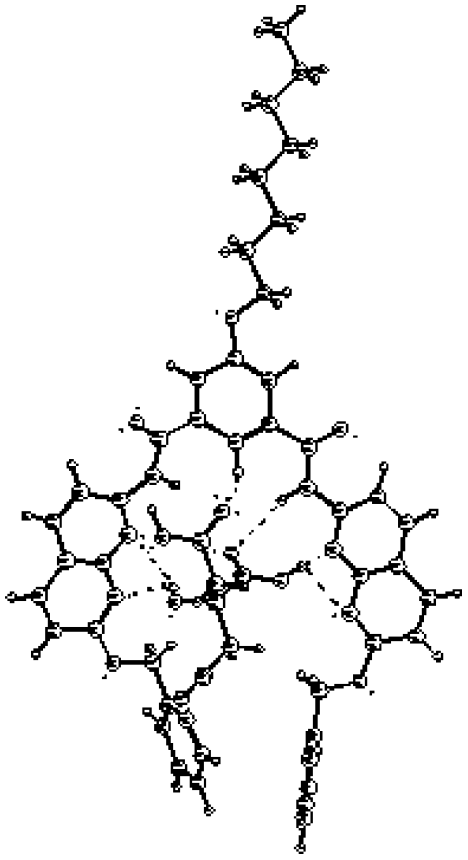

Figure 2. Energy minimized hydrogen-bonded complex of citric acid with **1**.

The 1:1 stoichiometry was also determined from the break of the titration curve at [G]/[H] = 1 in Figure 4. In a similar way, malic acid (having an additional OH group) was shown to interact only moderately. The association constant values are collected in Table 1. From Table 1, we can see that receptor **1** has strong affinity and good selectivity for citric acid. This is due to the location of the naphthyridine rings with respect to the isophthaloyl spacer which converges all the hydrogen bonding groups to citric acid in a cooperative fashion as shown in Figure 2. These secondary hydrogen bonding interactions in naphthyridine-based receptors are well documented.[12] In this context, it is important

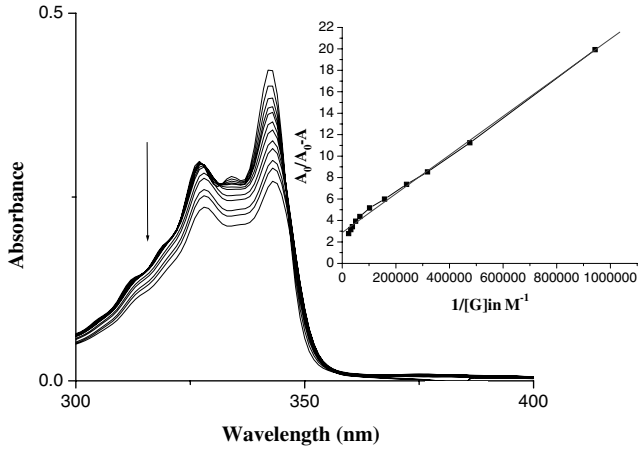

Figure 3. Absorption spectra of **1** ($c = 0.42 \times 10^{-5}$ M) in $CHCl_3$ upon addition of citric acid. Inset: The plot of $[A_0/(A_0-A)]$ versus 1/[G].

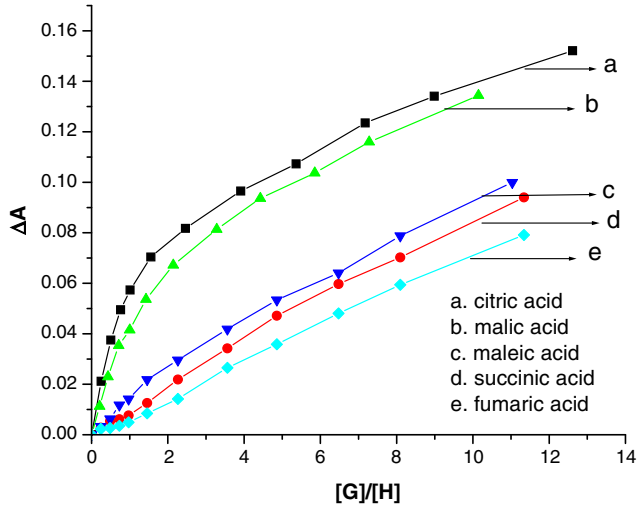

Figure 4. UV–vis titration curves ([Guest]/[Host] vs change in absorbance) for **1** (measured at 343 nm) with various acids.

Table 1. Association constants (K_a) in M^{-1} for **1** with the acid guests

Guest acids	K_a by UV–vis method	K_a by fluorescence method
Citric	1.60×10^5	9.31×10^4
rac-Malic	7.93×10^4	5.31×10^4
Succinic	2.77×10^4	1.45×10^4
Maleic	1.97×10^4	8.50×10^3
Fumaric	1.69×10^4	2.60×10^3

to mention that receptor **1**, in the present case, binds D-(−)-tartaric acid ($K_a = 1.26 \times 10^5$ M^{-1}) more strongly than the previously reported value.[13] Other guest acids with the exception of citric acid (Table 1), show relatively weak binding, possibly due to formation of fewer hydrogen bonds with the naphthyridine ring nitrogens.

Figure 5 explains the hydrogen bond induced fluorescence changes of receptor **1** in $CHCl_3$ upon addition of citric acid (dissolved in $CHCl_3$ containing 0.6% DMSO). Upon addition of the acid, the characteristic emission spectrum of monomeric naphthyridine gradually increased to different extents. During the course of titration there was no other spectral change in the emission spectra. In this context, the negligible change in fluorescence emission with fumaric acid (Fig. 6) is worth mentioning in the discrimination between diastereomeric maleic and fumaric acids although in the ground state their binding selectivity is poor. The association constants (Table 1) determined by fluorescence titrations[11] indicated similar trends in selectivity as shown by the UV–vis method.

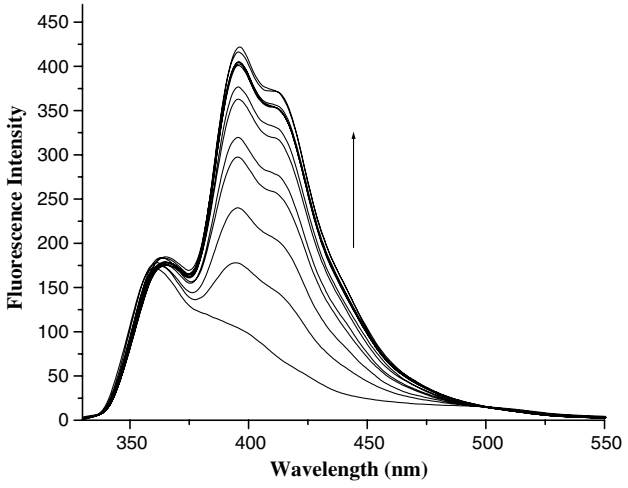

Figure 5. Fluorescence spectra of **1** ($c = 2.10 \times 10^{-5}$ M) in $CHCl_3$ upon addition of citric acid ($\lambda_{ex} = 320$ nm).

In conclusion, we have developed a new fluorescent chemosensor **1**, which is simple in design, shows strong binding and good selectivity for citric acid and is also able to distinguish diastereomeric maleic versus fumaric acids by fluorescence. The selectivity arises from participation of the naphthyridine motifs in the formation of cooperative hydrogen bonds with the guest acids. Further studies along this direction are under progress in our laboratory.

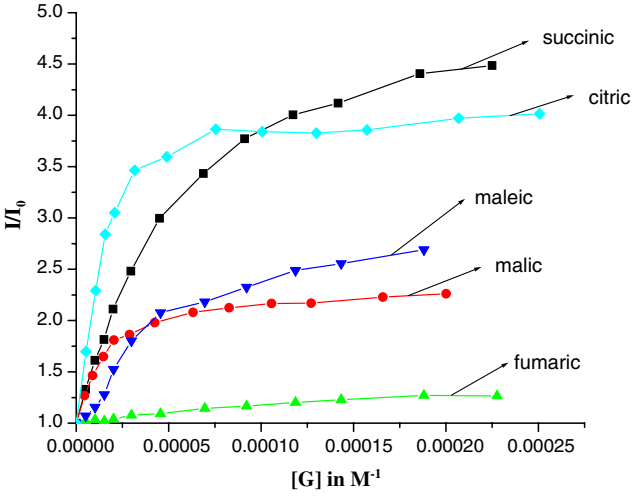

Figure 6. Relative change in fluorescence of **1** ($c = 2.10 \times 10^{-5}$ M) in $CHCl_3$ upon addition of guest acids.

Acknowledgments

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8. Compound **1**: mp = 124 °C, ^{1}H NMR (500 MHz, $CDCl_3$, δ in ppm) 9.17 (2H, s, –NHCO–), 8.64 (2H, d, $J = 5$ Hz), 8.58 (2H, d, $J = 10$ Hz), 8.19 (3H, d, $J = 10$ Hz), 8.04 (2H, d, $J = 10$ Hz), 7.72 (2H, t, $J = 10$ Hz), 7.68 (2H, s), 7.52 (2H, d, $J = 10$ Hz), 7.25–7.23 (2H, m), 7.07 (2H, d, $J = 10$ Hz), 5.74 (4H, s), 4.11 (2H, t, $J = 5$ Hz), 1.89–1.82 (m, 2H), 1.53–1.50 (m, 2H), 1.40–1.30 (m, 8H), 0.90 (t, 3H, $J = 5$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) 165.1, 160.4, 156.8, 154.4, 149.8, 139.5, 139.3, 137.1, 136.2, 123.2, 122.6, 118.7, 118.2, 117.8, 117.6, 113.4, 113.3, 112.9, 69.3, 69.0, 32.2, 29.7, 29.6, 29.5, 26.3, 23.1, 14.5. FTIR (ν cm^{-1}, KBr): 3363, 3062, 2922, 2851, 1682, 1612, 1458, 1187, 1133; Mass (ESI): 763.2 $(M+H)^+$, 556.3, 425.2, 382.3, 362.2.
9. Crystal data of **3**: $C_{14}H_{12}N_4O{\cdot}H_2O$, monoclinic, $P2_1/n$ (No. 14), $a = 6.596(1)$, $b = 14.676(1)$, $c = 13.796(1)$ Å, $\alpha = 90$, $\beta = 99.66$ (1), $\gamma = 90^0$, $V = 1316.6(2)$ Å^3, $T = 293$ K, $Z = 4$, $\rho_{cacd} = 1.364$ mg m^{-3}, graphite monochromator, 7809 total reflections of which 2673 were independent, 1602 observed $[I > 2\sigma(I)]$. Structure solution and refinement with SHELXS-97 and SHELXL-97, final refinement against F^2 with 194 parameters, R_1 $[I > 2\sigma(I)] = 0.046$, $wR^2 = 0.103$. CCDC No. 631313.
10. Energy minimization: MMX (PC Model Serena Software 1993) using standard constants and dielectric constant of 1.5.
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