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8. Coumarin and benzocoumarin appended molecular receptors in the discrimination of sulphonic acids from carboxylic acids, K. Ghosh, S. Adhikari, (Communicated)

Water templated hydrogen-bonded network of pyridine amide appended carbamate in solid state

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Received 7 August 2005, received in revised form 15 September 2005, accepted 22 September 2005
Available online 8 November 2005

Abstract

The pyridine amide appended carbamates 1 and 2 have been synthesized and their hydrogen-bonded self-assemblies in solid state have been described. The self-association pattern is dependent on the nature the anchored group of the carbamate moiety and influenced by water inclusion. Inclusion of water molecule gives a ladder type hydrogen bonded assemblies with cavities.

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Keywords Carbamate, Water-assembled structure, Ladder type assembly, Hydrogen bonding selectivity

1. Introduction

The rational design of new solid-state structures is central to a wide variety of applications in crystal engineering and supramolecular chemistry [1-4]. A particular goal, therefore, involves the construction of solids with an appropriate ordered and predictable arrangement of two or more molecular components through specific noncovalent interaction, specifically hydrogen bond which has the pivotal role in molecular recognition studies by synthetic receptors as well as in the formation of supramolecular assembly due to its strength and directional nature relative to other intermolecular interactions [5-10]. Appropriate choice of molecules meeting both geometric as well as energetic interactions allow the controlled formation of different two- and three-dimensional shapes such as sheets [11], ribbons [12], spheres [13], helices [14a], tubes [14b] and zeolite-like 3D network structures with chiral channels [14c] fitted with highly ordered water molecules etc. Such organization of molecular components is controlled by proper hydrogen bonded synthons as well as sometimes by inclusion of small molecules, ions etc [15,16].

In this aspect water is an important molecule, the inclusion of which alters the molecular packing in the crystal [17a]. This is due to various types of hydrogen-bonding possibility present within the simple structure of water. It can either function as a double hydrogen bond donor and a single hydrogen bond acceptor in simple hydrate or double hydrogen bond donor and double hydrogen bond acceptor in clathrate hydrates. There are various reports on hydrogen-bonded water clusters in the form of hexamers [17b], octamers [17c], decamers [17d] and one-dimensional (1D) infinite water chains [17e] in different crystal hosts. The structures of such hydrogen bonded water clusters continue to attract attention since they play a crucial role in contributing to the stability and function of biological assemblies [17f]. In our continued research in molecular recognition and supramolecular chemistry [18-19], we report here the synthesis and solid state hydrogen bonding assembly of the pyridine amide appended carbamates 1 and 2, for the first time, with a view of establishing the hydrogen bonding nature of carbamate with the complementary pyridine amide motif.

The compounds 1 and 2 were synthesized according to the Scheme 1 and were isolated in good yield as white solids.

2. Experimental

2.1 General procedure

To a stirred solution of amine 4 [20] (1 equiv) in dry dichloromethane-triethylenglycol (1 equiv) was added. After stirring for 1 h at room temperature dry alcohol (1 equiv) was added drop wise and the mixture was left overnight stirring. The reaction was quenched with aqueous NaHCO3 (20 ml), and the organic layer was separated. The aqueous layer was extracted with
The compounds 1 and 2 were synthesized according to the scheme 1 and were isolated in good yield as white solids.

**Scheme 1**

1. 4-Nitrobenzoyl chloride + PhCH₂OH → 2)
2. 4-Nitrobenzoyl chloride + PhCH₂OH → 2)
3. 4-Nitrobenzoyl chloride + PhCH₂OH → 2)
4. 4-Nitrobenzoyl chloride + PhCH₂OH → 2)

Carbamate 1

The compound was purified by column chromatography using 2:1 (pet ether:ethyl acetate) as eluant and was obtained as white solid, m.p. 166°C, 80% yield. ¹H-NMR (300 MHz, d₆-DMSO) δ 10.49 (s, 1H), 9.97 (s, 1H), 7.99 (d, J = 9 Hz, 3H), 7.70 (t, J = 9 Hz, 1H), 7.56 (d, J = 9 Hz, 2H), 7.01 (d, J = 9 Hz, 1H), 4.16 (q, J = 6 Hz, 2H), 3.35 (bs for H2O), 2.45 (s, 3H), 1.27 (t, J = 6 Hz, 3H). FT-IR (KBr) ν₃max 3129, 1712, 1661, 1595, 1454 cm⁻¹, Mass (FAB+) [M+H₂O]+ = 316.

Carbamate 2

The compound was also purified by column chromatography using 2:1 (pet ether:ethyl acetate) and was obtained as white solid, m.p. 156°C, yield 75-80%. ¹H-NMR (300 MHz, CDCl₃) δ 8.42 (s, 1H), 8.16 (d, J = 9 Hz, 2H), 7.89 (d, J = 9 Hz, 2H), 7.63 (d, J = 10 Hz, 1H), 7.52 (d, J = 9 Hz, 2H), 7.42-7.35 (m, 5H), 6.92 (d, J = 10 Hz, 2H), 6.85 (s, 1H), 5.23 (s, 2H), 2.48 (s, 3H). FT-IR (KBr) ν₃max 3446, 3318, 1745, 1665, 1595, 1226 cm⁻¹.

Table 1

<table>
<thead>
<tr>
<th>Crystal data and structure refinement for 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Empirical formula</strong></td>
</tr>
<tr>
<td><strong>Formula weight</strong></td>
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<tr>
<td><strong>Temperature (K)</strong></td>
</tr>
<tr>
<td><strong>Wavelength (Å)</strong></td>
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<td></td>
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<tr>
<td><strong>Volume (Å³)</strong></td>
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<tr>
<td><strong>Z, calculated density (g/cm³)</strong></td>
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<tr>
<td><strong>Absorption coefficient (μ)</strong></td>
</tr>
<tr>
<td><strong>F(000)</strong></td>
</tr>
<tr>
<td><strong>Crystal size</strong></td>
</tr>
<tr>
<td><strong>Largest diff peak and hole</strong></td>
</tr>
</tbody>
</table>

**X-ray crystallography**

X-ray intensity data for a selected specimen were collected on Nonius KappaCCD diffractometer, equipped with a rotating anode generator Nonius FR591 (λ = 0.71073 Å). The following programs were used: data collection COLLECT [21], data reduction Denzo-SMN [22], absorption correction SORTAV [23], structure solution SHELXS-97 [24], structure refinement.
stereo and electrostatic reasons [27a]. These interesting features of carbamates have been considered in the design of receptors for theobromine alkaloid [27b]. The coupling of such carbamate with complementary pyridine amide in specific design is of keen interest in the context of building up of new-engineered solid in crystal engineering. In this aspect, the single crystals of 1 and 2 were grown by slow evaporation of ethyl acetate-pet ether and chloroform-pet ether combinations, respectively. The crystal data, data collection parameters and analysis statistics are listed in the Table 1 [28].

In the crystal structure of 1 one molecule of water is bonded as water of crystallization to the more basic pyridine nitrogen and crystallizes in space group $P\overline{1}$. The SCHAKAL plot with atom numbering scheme is shown in Fig. 2. The bound water molecule typically functions as a double hydrogen bond donor and a double hydrogen bond acceptor and exhibits a symmetric dimer. Each neighbouring dimers are further assembled through hydrogen bonds involving water as spacer in hydrogen bonded network and executes nice water assisted ladder type polymeric assembly (Fig 3).

It is well known that the preferred hydrogen bond coordination of the water molecule is tetrahedral or planar trigonal [29]. In the present case, the water as bridging entity forms (i) N-H O hydrogen bond [N3-H3 O 85(2), H3 O20 2.09(2), N3 O20 2.93(2) Å, N3-H3 O20 173(2)°, symmetry operation $1-x, 1-y, 1-z$] with the more favored anti form of carbamate rotamer, (ii) O-H N [O20-H20A O 80(2), H20A N14 2.17(3), O20 N14 2.95(2) Å, O20-H20A N14 169(3)°] hydrogen bond with pyridine ring nitrogen (iii) O-H O hydrogen bond [O20-H20B O 90(3), H20B O11 2.08(3), O20 O11 2.97(2) Å, O20-H20B- O11 171(2)°, symmetry operation $-x, y, z$] with pyridine amide carbonyl of the adjacent dimer and (iv) C-H O hydrogen bonds with H2AB (2.76 Å which is about 0.14 Å shorter than the sum of the van der Waals radii), where H2AB is one of the hydrogens at C2A (ethyl group) thereby giving a tetrahedral arrangement. This tetrahedral hydrogen bond co-ordination of water molecule associates 1 as cyclic dimers via the two nitrogen-water hydrogen bonds and is further connected via the oxygen-water hydrogen bond in the third direction to give a ladder type arrangement. However, in such assembly each macrocycle provides inwardly pointed two diagonal free N12-H12 hydrogen bond donors. These cavities may form inclusions of a range of guest molecules that are both functionally and dimensionally fitted into.

A closer look on the geometrical parameters shows a distance of 3.72 Å between the centers of neighboring pyridine rings (symmetry operation $-x, -y, -z$). indicating the influence of π-π interactions. In contrast, there is no indication for C-H π interactions (closest distance from H2AA to the center of the benzene ring is 3.10 Å, symmetry operation $2-x, 2-y, 1-z$).

The presence of anchored water was also supported by the appearance of the peak at 316 [(M++H2O)+1] in mass spectrum. The thermal stability of the water molecule in 1 H2O was studied by thermogravimetric analysis (TGA) (Fig 4). The weight loss for water is 5.7% that takes place in the temperature region 25-140 °C and second weight loss occurs after 212 °C.
DSC experiment showed two endothermic peaks at 137° and 171 °C. The first endotherm is, therefore, due to dehydration and second one due to melting.

Such water-assisted hydrogen bonded architecture of 1 is absent in 2 when benzyl group replaces the ethyl group of the carbamate part. The SCHAKAL plot of 2, which crystallizes in chiral space group P1, is presented in Fig. 5. The packing mode (Fig. 6) indicates a parallel arrangement of the molecules with parallel hydrogen bonds keeping all the pyridines at one end and phenyls on the other end and surprisingly the achiral compound 2 crystallizes in an enantiomorphic space group.

In summary, we have thus established that the inclusion of water is dependent on the nature of the group anchored in the carbamate moiety in our examples 1 and 2. Pyridine appended carbamate having normal aliphatic group instead of aliphatic chain containing pendant aromatic group, prefers water inclusion that alters the molecular packing of carbamates.

The compound 1 H2O is stable hydrate above the boiling point of water and exhibits a unique hydrogen bonding architecture with cavities. Further exploration in this direction is in progress in our laboratory.

Acknowledgements

Financial support from CSIR, New Delhi, India [Project No 01(1922)/04/EMR-II] is gratefully acknowledged.

References

(b) M.R. Ghadim, JR Grana, RA Milligan, D E McRae, N Kusiovich, Nature 366 (1993) 324,


[28] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-255451 and 274439. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336-033, email deposit@ccdc.cam.ac.uk)

Fluorescence sensing of tartaric acid: a case of excimer emission caused by hydrogen bond-mediated complexation

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Received 10 December 2005, revised 3 March 2006, accepted 9 March 2006
Available online 5 April 2006

Abstract—A novel quinoline based receptor that shows monomer emission quenching followed by intramolecular excimer emission upon hydrogen bond mediated complexation of tartaric acid has been designed and synthesized. The excimer emission has been used to confirm the selective recognition of tartaric acid over its nonhydroxy analogue, succinic acid. Binding ability was studied by NMR, UV-vis and fluorescence spectroscopic methods.

Due to many applications in analytical chemistry and biomedical research, the development of receptors which have the ability selectively to bind and sense neutral molecules, anions and cations through an optical response has attracted much attention in recent years. In this regard, one of the recent approaches to the design of fluorescent signalling systems relies on guest-induced folding of flexible receptors, which brings the fluorophores close enough as to function as an excimer. This excimer emission formation is sometimes used to 'read out' the molecular recognition process more conveniently.

Given the importance of dicarboxylic acids due to their biological relevance, the need for fluorescent receptors as sensors for carboxylic acids in different contexts of molecular recognition research has recently been of paramount interest. In this respect, tartaric acid, a common natural product in wines and other grape derived beverages, has received attention due to its structural features possessing several hydrogen bond donors and acceptors. Many hydrogen bonding receptors for the binding of tartaric acid and its derivatives have been reported.

A naphthol-based amopyridyl group for enantioselective recognition of diacetyl tartaric acid derivatives, a unique trench type binding on a porphyrin for tartaric acid derivatives, a colorimetric chemosensing ensemble for tartrate/malate in beverages developed by Anslyn and co-workers, are notable. Tryptophan-based chiral sensors for dibenzoyl tartarate and anthracene labelled fluorescent chiral sensors for enantiomeric discrimination of tartaric acid are also interesting. As a result of our research on molecular recognition, we herein report the design and synthesis of a quinoline-based sensor which shows selective recognition of tartaric acid from its nonhydroxy analogue succinic acid by exhibiting selective excimer emission.

The receptor 1 was synthesized according to Scheme I and was isolated in 55% yield. The lumophore, 8-hydroxyquinoline was first coupled with 2-A-pivaloylamino-6-methylpyridine (obtained from 2-N-pivaloylamino-6-methylpyridine by reaction with NBS in dry CCl4) to give compound 2. Amide hydrolysis of 2 then afforded compound 3 in 80% yield. On coupling 3 with 5-octyloxy-1,3-benzenedicarbonyl chloride (prepared by etherification of diethyl 5-hydroxyisophthalate with octyl bromide in dry acetone using K2CO3 and hydrolysis of the esters followed by reaction with oxalyl chloride) yielded the desired receptor 1.
Scheme 1. The synthesis of receptor 1

with a separation of distance of 4.01 Å and the open biding cleft assumes a nonplanar shape (Fig 1). The hydrogen bonding groups in the cavity are well arranged for complexation of hydroxydecarboxylic acids.

The synthesis and the selectivity of receptor 1 were evaluated by observing the change in H NMR, UV-Visible and fluorescence emission in CHCl3.

1H NMR of the receptor 1 in CDCl3 (5.83 x 10^-3 M) revealed the position of the amide protons at 8.96 ppm. The addition of powdered d(-)-tartaric acid to this solution showed clear dissolution after sonication. This was evident from the downfield shift of the amide protons (8.86-9.90 ppm = 0.94 ppm) of 1 as well as from the appearance of a new peak at 8.47 ppm due to methine protons in the 11 complex (Fig 2). The integration ratio of tartaric acid methine protons to the receptor amide protons in the NMR spectrum of the complex (Fig 2, top) clearly revealed the formation of a 11 complex. On dilution of the 11 complex, there was practically no shift of the receptor amide protons. This suggests strong complexation of tartaric acid into the open cleft of the receptor 1 as in the mode shown in complex A (Fig 1).

Determination of the association constants was, however, impossible because of the negligible change in the position of the amide protons after forming the 11 complex.

The absorption spectra of 1 and its 11 complexes with d(-)-tartaric, rac-malic, and succinic acids in CHCl3 were recorded to investigate the interactions in the ground state. Chloroform solutions of the 11 complexes were diluted gradually with chloroform and the change in intensity, as a function of the concentration was linear in each case. Figure 3 shows the effect of dilution on the UV spectra of the tartaric acid 11 complex with 1. This change in the UV-Visible spectra was used conveniently to study the binding since the lower concentration used led to a more accurate determination of the values of the association constants11 for the acids (Table 1). The hydroxy analogues of succinic acid show higher binding constants due to the greater number of hydrogen bonds. Interestingly, the binding values were reduced 10-fold as the number of OH groups decreases. The binding constant values in our case, however, are greater in magnitude than the previously reported naphthyridine-based receptors10b.

The fluorescence spectra of the receptor 1 were simultaneously recorded in CHCl3 both in the presence and
a. Receptor 1 in CHCl3 (1 x 10^3 M) complex with succinic acid
b. 1-1 complex with rac-malic acid
c. 1-1 complex with tartaric acid
d. 1-1 complex with tartaric acid

Table 1 Association constants determined by UV (CHCl3)

<table>
<thead>
<tr>
<th>Guest</th>
<th>Association constant K_a (M⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(—)-Tartaric acid</td>
<td>9.81 x 10⁴</td>
</tr>
<tr>
<td>rac-Malic acid</td>
<td>4.96 x 10⁸</td>
</tr>
<tr>
<td>Succinic acid</td>
<td>9.38 x 10⁷</td>
</tr>
</tbody>
</table>

absence of dicarboxylic acid guests. Figure 4 shows the fluorescence spectra of 1 and its 1:1 complexes with D(-)-tartaric, rac-malic and succinic acids in CHCl3. On complexation with these acids significant fluorescence quenching takes place.

However, the degree of quenching is dependent on the nature of the acid. The magnitude of the quenching...
efficiency ($\phi_h$) follows the order of d-(−)-tartaric acid (0.92) > rac-malic acid (0.87) > succinic acid (0.53), reflecting the stabilities of the complexes (see the binding constant values in Table 1). In the case of d-(−)-tartaric acid, an additional peak at 453 nm along with monomer emission at 377 nm was noticed due to excimer formation. The excimer emission resulted from the intramolecular excimer, rather than intermolecularly, as indicated by the dilution experiments at different concentrations in which the intensities of the ratio of excimer to monomer emission changed gradually (Fig. 5). The formation of this excimer in the presence of d-(−)-tartaric acid could be attributed to the tartaric acid templated hydrogen bond induced organization of the quinoline moieties. Such excimer formation was not observed in the case of succinic acid due to the lack of –OH groups which are necessary to bring closer together the pendant quinoline groups of the binding arms via hydrogen bond formation. This was confirmed using rac-malic acid where the excimer emission was observed (Fig. 4) due to the possibility of hydrogen bonding structure 4 which may remain in equilibrium with 5 and 6 (Fig. 6). It is, therefore, worth noting that the conformation of 1 was changed substantially only on binding with hydroxydicarboxylic acids rather than with a dicarboxylic acid of the same chain length.

In pursuit of a fluorescent sensor we have demonstrated that hydrogen bond-mediated complexation of tartaric acid with 1 results in monomer emission quenching followed by intramolecular excimer emission. This excimer emission is moderate and convenient for practical use to distinguish tartaric acid from its nonhydroxy analogue succinic acid. Further study on this subject is underway in our laboratory.

Acknowledgements

We thank CSIR [01(1922)/04/EMR-II], New Delhi, India, for financial support and DST-FIST, for providing the facilities in the Department.

References and notes


9. Receptor 1 Mp 110-111 °C, 1H NMR (CDCl3, 400 MHz) δ 8.95 (s, 2H, –NHCO–), 8.95 (d, 2H, J = 8 Hz), 8.26 (d, 2H, J = 8 Hz), 8.19 (a, 1H), 8.12 (d, 2H, J = 8 Hz), 7.71 (t, 4H, J = 8 Hz), 7.42 (m, 2H), 7.37-7.33 (m, 6H),
6.95 (d, 2H, J = 8 Hz), 5.32 (s, 4H), 4.08 (t, 2H, J = 8 Hz), 1.85–1.80 (m, 2H), 1.46 (m, 2H), 1.33–1.15 (m, 8H), 0.86 (t, 3H, J = 6 Hz). \( ^{13}C \) (CDCl\(_3\), 125 MHz) \( \delta \): 165.2, 154.3, 151.6, 149.7, 140.7, 139.5, 136.4, 136.1, 129.8, 126.9, 122.1, 120.5, 118.1, 118.6, 117.9, 113.7, 109.5, 71.1, 69.1, 52.2, 29.7, 29.6, 28.5, 28.3, 23.4, 14.5. HRMS: calcd for C\(_{24}\)H\(_{44}\)N\(_6\)O\(_5\) 760.3363; Found 760.3382. FTIR (KBr) \( \nu_{\text{max}} \): 3300, 2924, 2853, 1674, 1597, 1577, 1457, 1109 cm\(^{-1}\).

10. MM2 calculations were performed using CS Chem 3D version 6.0.


12. The quenching efficiency was determined using the equation: \( \phi_s = (\phi_{\text{host}} - \phi_{\text{complex}}) / \phi_{\text{host}} \), where \( \phi_{\text{host}} \) and \( \phi_{\text{complex}} \) are the fluorescence intensities (377 nm) of 1 and its complex, respectively.
Colorimetric and fluorescence sensing of anions using thiourea based coumarin receptors

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Available online 4 October 2006

Abstract—Thiourea-containing coumarins 1, 2 have been designed and synthesized via reaction of 6-aminomethylcoumarin and the corresponding isothiocyanates. Their anion-binding ability has been examined using UV-vis, fluorescence and $^1$H NMR. The anion recognition takes place through charge neutral thiourea receptor sites with concomitant fluorescence quenching of the coumarin moiety with 1 showing a strong binding to $\text{C}_6\text{H}_5\text{COO}^-$ over $F^-$ with a distinct change in color.

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The design of host molecules that can recognize and sense anions selectively through visible, electrochemical and optical responses has received considerable interest in recent years because of the important roles played by the anions in biological, industrial, and environmental processes. Molecules that possess functional groups such as amides, ureas/thioureas, guanidinum and ammonium derivatives have proven to be particularly effective in this regard as they are able to bind anions using directional hydrogen bonding interactions. The attachment of such functional groups with a suitable chromophoric part either covalently or intermolecularly provides a complete receptor that can intimate binding information either by a color change, fluorescence or both. Several reviews on such functionalized systems have appeared. Despite the significant development in this domain, the search for new luminescent sensors with structural simplicity and easy synthesis has recently been of keen interest in molecular recognition research.

In pursuit of developing anion receptors during the course of our work on molecular recognition, we present coumarin-based chemosensors 1 and 2 for the selective recognition of anions employing the criteria of PET sensing using the "fluorophore-spacer-receptor" model developed by de Silva for the detection of cations. Although several PET sensors for anions are known, no such thiourea-linked coumarin systems, employing neutral anion receptors, have been reported that exhibit an ideal PET behavior and color changes as signaling events, detectable by the naked eye, upon binding of anions.

Chemosensors 1 and 2 were easily synthesized in good yields from readily available starting materials, following Scheme 1. 6-Aminomethylcoumarin 7, was synthesized via a series of reactions on 4-hydroxybenzaldehyde as indicated in Scheme 1, was reacted in dry THF (containing few drops of dry DMF due to insolubility) at room temperature under an inert atmosphere with an equimolar amount of sodium cyanate to afford 1 or 2 at pale...
yellow and white solids, respectively. The crude products were purified by column chromatography and were analyzed by conventional methods. It is also worth noting that the amide derivative was successfully synthesized in 68% yield under solvent-free conditions using microwave irradiation.

The anion-binding properties of 1 and 2 were investigated by observing the changes in their fluorescence emission, absorption spectra in CH$_3$CN and by $^1$H NMR in CDCl$_3$. The UV-vis experiments were carried out in CH$_3$CN containing 0.08% DMSO for homogeneity of the solution. The titration of 1 (c = 5.63 × 10$^{-3}$ M), which exhibits a broad strong absorption band at 330 nm due to the coumarin moiety, was carried out with anions such as tetrabutylammonium fluoride, bromide, iodide, hydrogen sulfate and benzoate. Upon the addition of fluoride, the intensity of the absorption peak at 330 nm was remarkably reduced with a simultaneous growth of a new peak at 455 nm (Fig. 1) and the almost colorless solution turned yellow brown (Fig. 4c). In the case of benzoate, the absorption peak at 330 nm was shifted to 348 nm (Δλ = 18 nm) with a concomitant decrease in the intensity of the absorption (Fig. 2) and the solution turned light green in color (Fig. 4b). The presence of isobestic points during titration with both F$^-$ and C$_6$H$_5$COO$^-$ revealed the formation of 1:1 complexes. No significant change in absorption or a noticeable color change was observed for other anions such as Br$^-$, I$^-$ and HSO$_4^-$.

The analogous thiourea receptor was evaluated to establish the role of the acidity of the thiourea protons in binding with the putative anions. The addition of F$^-$, C$_6$H$_5$COO$^-$, Br$^-$, I$^-$ and HSO$_4^-$ as tetrabutylammonium salts to a solution of 2 in CH$_3$CN (containing 0.08% DMSO) resulted in a minor change in the UV-vis spectrum of receptor 2 and did not result in any new peaks at higher wavelengths or color changes of the solution. The fluorescence changes of 2 upon addition of F$^-$ and C$_6$H$_5$COO$^-$ were significant, but smaller compared to 1. The fluorescence emissions at 369 nm (λ$_{ex}$ = 320 nm) were ca 12% and 19% 'switched...
The smaller quenching of emission here was ascribed to a weak hydrogen bonding interaction between the less acidic thiourea protons and anions. This is reflected in their binding constant values (Table 1), which were measured by following the change in absorbance as a function of the concentration of the anions. As shown in Table 1, it is clear that the association constants of both the receptors for benzene is greater than for fluoride. This is solely due to strong hydrogen bonding interactions instead of deprotonation as observed in the case of fluoride.

To understand the binding events further, $^1$H NMR experiments were carried out in CDCl₃. The large down...

Table 1: Association constants of receptors 1 and 2 with anions in CH₃CN

<table>
<thead>
<tr>
<th>Anion</th>
<th>Receptor 1 ($K_a$ in M$^{-1}$)</th>
<th>Receptor 2 ($K_a$ in M$^{-1}$)</th>
</tr>
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<tbody>
<tr>
<td>$F^-$</td>
<td>$5.78 \times 10^3$</td>
<td>$2.26 \times 10^2$</td>
</tr>
<tr>
<td>$C_{6}H_{5}COO^-$</td>
<td>$2.02 \times 10^5$</td>
<td>$1.04 \times 10^4$</td>
</tr>
<tr>
<td>$Br^-$</td>
<td>$b$</td>
<td>$b$</td>
</tr>
<tr>
<td>$I^-$</td>
<td>$b$</td>
<td>$b$</td>
</tr>
<tr>
<td>$HSO_4^-$</td>
<td>$b$</td>
<td>$b$</td>
</tr>
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</table>

*Anions were used as their tetrabutylammonium salts

*The changes in the spectra were too small to calculate the association constants precisely
field chemical shift of the thiourea protons (Δδ H1 3 21, H2 3 37 ppm) of I in the 1 1 complex with benzene indicated a strong hydrogen bonding interaction. In the case of the 1 1 complex of fluoride with I, both the thiourea protons (H2 and Hs) underwent downfield shifts (Δδ H1 196, H2 1 44 ppm) and became broad and then disappeared in the presence of excess fluoride, suggesting either deprotonation or strong hydrogen bonding. The relatively smaller downfield shifting of the thiourea protons in 2 upon addition of benzene and fluoride indicated a weaker binding. The electron donating resonance effect of the phenyl group increases the charge density on the carboxylate group allowing it to form strong hydrogen bonds with the acidic thiourea protons of I. Fluoride, on the other hand, due to its small size and high charge density, initially forms a hydrogen-bonded complex (see Fig 8b) and then, in the presence of excess F−, causes deprotonation (shown in Fig 8c) to form the L2− species (L = coumarin receptor).

However, these non-covalent interactions altogether enhance the efficiency of the PET process. The high degree of fluorescence quenching is believed to result from the increase in the reduction potential of the thiourea receptor moieties after anion recognition. This increases the rate of electron transfer from the HOMO of the thiourea-anion complex to the coumarin-excitated state and encourages the PET process. It appears that the deprotonated species LH /L2−, being more electron rich compared to the hydrogen-bonded complex with benzene, activates the PET process more efficiently and shows a greater quenching. The origin of the color change in the host solution of I is ascribed to the charge-transfer interactions between the electron-rich thiourea-anion complex donor unit and the electron-deficient p-nitrophenyl moiety.

In conclusion, 'fluorophore-spacer-receptor' model based thiourea linked coumarin receptors 1 and 2 have been presented. The receptor 1 shows a strong binding to benzene over fluoride ions and can report the molecular recognition events both by changes in fluorescence and color. Further research in this direction is underway in our laboratory.

Acknowledgments

We thank the CSIR [01(2122)/04/EMR-II], New Delhi, India, for financial support and DST-FIST for providing the facilities in the Department.

References and notes


Receptor 1 mp 170-172 °C, yield = 50%, $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 10.31 (s, 1H, urea NH), 8.77 (dt, 1H, urea NH), 8.19 (d, 2H, $J = 8$ Hz), 8.10 (d, 1H, $J = 8$ Hz), 7.84 (d, 2H, $J = 8$ Hz), 7.68 (s, 1H), 7.61 (d, 1H, $J = 8$ Hz), 7.46 (d, 1H, $J = 8$ Hz), 6.45 (d, 1H, $J = 8$ Hz), 4.85 (s, 2H, $J = 4$ Hz), $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 181.2, 160.9, 153.4, 147.5, 142.1, 142.8, 137.5, 132.2, 127.9, 125.3, 121.4, 119.3, 117.1, 117.2, 47.1, FTIR (KBr pellet, cm$^{-1}$) 3345, 3191, 3015, 2917, 1731, 1608, 1591, 1230, 1514, HRMS (ESI, m/z) calcd for C$_{17}$H$_{13}$N$_3$O$_4$S 355.0620 Found 356.0653 (M+1)

Receptor 2 mp 140-142 °C, yield = 65%. $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 9.66 (s, 1H, urea NH), 8.24 (dt, 1H, urea NH), 8.05 (d, 1H, $J = 8$ Hz), 7.63 (s, 1H), 7.57 (dd, 1H, $J_1 = 4$ Hz, $J_2 = 8$ Hz), 7.59-7.33 (m, 3H), 7.70 (t, 2H, $J = 8$ Hz), 7.47 (t, 1H, $J = 8$ Hz), 6.46 (d, 1H, $J = 8$ Hz), 4.47 (d, 2H, $J = 4$ Hz), $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 181.1, 160.8, 153.3, 143.9, 135.5, 131.6, 129.2, 127.3, 125.6, 124.4, 118.9, 116.9, 115.8, 47.4, FTIR (KBr pellet, cm$^{-1}$) 3450, 3337, 3181, 2919, 1764, 1619, 1537, Mass (ESI, m/z) 311.1 [M+H$^+$], 309.1, 292.8, 252.2 139.1

A quinoline-based tripodal fluororeceptor for citric acid

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Received 31 August 2007, revised 14 November 2007, accepted 22 November 2007

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 CHCl₃.

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. As substrates, carboxylic acids are of particular importance due to their key roles in a wide range of biological processes. Citric acid, in this regard, is a tri-carboxylic 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. Many of these are based on positively charged, hydrogen bonding groups or unsaturated metal centers coordinated to 1,3,5-trisubstituted benzene 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 naphthylmine based sensor for citric acid 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. In this context, the 1,3,5-tripodal host based on 3-amminopyridinium 'arms' containing anthracenyl moieties is interesting for the sensitive sensing of acetate. 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 CHCl₃ (Fig. 1).

The receptors 1 and 2 were synthesized from 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene by reaction with fluorophore labeled 2-amminopyridines and K₂CO₃ in a dry CH₃CN and THF solvent mixture (Scheme 1). Compounds 1 and 2 were obtained in 30% and 33% yields, respectively, and were characterized by ¹H NMR, ¹³C and mass analyses.

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 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 acid and other carboxylic acids such as rac-malic and DL(-)-tartaric acids were investigated using ¹H NMR,
UV-vis and fluorescence methods To gain an insight on the binding interactions with citric acid, 1H NMR spectra of 1 and 2 were taken in CDCl₃ (c = 3.08 × 10⁻³ M and 3.31 × 10⁻³ M, respectively) The amine NHs in 1 and 2 appeared at δ 4.32 and 4.43 ppm, respectively and were too broad to detect accurately upon addition of citric acid (dissolved in CDCl₃ containing 4% DMSO-d₆) Even the amine NHs in 1, which appeared at δ 3.32 ppm, were also broadened after addition of powdered citric acid to a dry CDCl₃ solution of 1 followed by sonication The clear dissolution of citric acid was evident from the appearance of new resonances at δ 2.85 and 2.66 ppm for the -CH₂- 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 1H NMR of this insoluble product was recorded in DMSO-d₆ All the signals were broad and new resonances in the regions δ 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 δ 9.29, 7.90, and 7.27 ppm during the complexation of citric, rac-malic, and o-(-)-tartaric acids with both 1 and 2 thus confirmed
that the tripod receptors 1 and 2 were involved in complexation with the carboxylic acid guests in 
CDC13 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 CHCl3 exhibited a structureless absorption band at 310 nm, characteristic of quinoline. The position of this peak was unaltered in dry THF, CH3OH, and CH3CN. 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 CHCl3 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 and citric acid. The 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). 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 4a, 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 CHCl3. The addition of citric, rac-malic, and d(-)-tartaric acids to a CHCl3 solution of 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 CH3OH, THF, and DMSO except for CH3CN where a weak excimer band at 475 nm was observed (Fig 4b). We suggest that this excimer emission results from the guest-induced hydrogen bond-mediated upward folding of the quinoline moieties that occurs with

![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](image-url)
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 CHCl₃. 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

![Fluorescence spectra of 1 in CHCl₃](image1)

![Fluorescence spectra of 2 in CHCl₃](image2)

**Fig. 3** (a) Fluorescence spectra of 1 (c = 1.32 x 10⁻⁵ M) in the presence of citric acid (1:1) in different solvents. (b) Fluorescence spectra of 2 (c = 1.32 x 10⁻⁵ M) in the presence of citric acid (1:1) in different solvents.

**Fig. 4** (a) Fluorescence change of 1 in CHCl₃ in the presence of citric, rac-malic and d-(-)-tartaric acids (λₓ = 290 nm), (b) fluorescence change of 2 in CHCl₃ in the presence of citric, rac-malic and d-(-)-tartaric acids (λₓ = 380 nm).

![Plot of the ratio of excimer to monomer emission versus concentration of the complex of 1 with citric acid](image3)

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

Wavelength (nm) Wavelength (nm)

Fig 6 Change in fluorescence of 1 (c = 1.32 \times 10^{-5} M) in CHCl₃ upon addition of citric acid, dissolved in CHCl₃ containing 0.7% DMSO. (b) Change in absorbance of 1 in CHCl₃ (c = 1.32 \times 10^{-5} M) upon addition of citric acid dissolved in CHCl₃ containing 0.7% DMSO.

In conclusion, a simple modular approach has been described to a quinoline-based tripod 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

We thank CSIR [01(1922)/04/EMR-II], New Delhi, India, for financial support and DST-FIST for providing the facilities in the Department.

Supplementary data

1H NMR, 13C NMR and mass spectra of compounds 1 and 2, fluorescence spectra of 1 on addition of the tetra-n-butylammonium 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

References and notes

16. Receptor 1 mp = 100°C (decompr.), \( ^1H \) NMR (500 MHz, CDCl₃, \( \delta \) in ppm) 8.98 (dd, \( J = 2.5 \) Hz, 2 Hz, 3H), 8.55-7.94 (m, 6H), 7.98 (dd, \( J = 4.5 \) Hz, 6H), 7.70 (t, \( J = 1.5 \) Hz, 3H), 6.19 (d, \( J = 7.5 \) Hz, 2H), 6.31 (d, \( J = 8 \) Hz, 3H), 5.41 (s, 6H), 5.41 (s, 6H), 4.22 (t, \( J = 4 \) Hz, 3H), 2.49 (s, 3H), \( ^{13}C \) NMR (125 MHz, CDCl₃) 133.0, 130.3, 149.3, 144.3, 133.4, 133.2, 131.8, 130.9, 128.4, 124.4, 121.6, 116.6, 114.8, 105.3, 104.9, 104.7, 100.7, 66.6, 56.6, 27.6, FTIR (v cm⁻¹, KBr) 3386, 2922, 2852, 1602, 1571, 1465, 1397, 1377, HRMS (TOF MS EI⁺) calcd for C₅₁H₇₁N₉O₃ 910.4181 Found 910.4181 (M+1), 932.4004 (M+Na)
17. Receptor 2 mp = 80°C, \( ^1H \) NMR (400 MHz, CDCl₃, \( \delta \) in ppm) 8.20 (dd, \( J = 8 \) Hz, 2 Hz, 3H), 7.80 (d, \( J = 8 \) Hz, 2H), 7.52-7.47 (m, 9H), 7.42 (d, \( J = 8.8 \) Hz, 3H), 7.34 (t, \( J = 8.1 \) Hz, 3H), 6.96 (d, \( J = 8.8 \) Hz, 3H), 6.80 (dd, \( J = 8 \) Hz, 3H), 6.00 (d, \( J = 8 \) Hz, 3H), 5.92 (s, 6H), 4.13 (br s, 3H), 2.47 (t, \( J = 9 \) Hz, \( ^{13}C \) NMR (100 MHz, CDCl₃) 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, 105.3, 105.4, 70.8, 41.6, 36.5, 29.0, FTIR (v cm⁻¹, KBr) 3412, 2922, 1598, 1574, 1463, 1306, 1357, Mass (ESI⁺) 907.0 (M+H), 791.1, 454.2
18. 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.
Quinoline based receptor in fluorometric discrimination of carboxylic acids

Kumares Ghosh1,1, Suman Adhikan1, Asoke P. Chattopadhyay1 and Purnendu Roy Chowdhury2

Abstract
Quinoline and naphthalene-based fluororeceptors 1 and 2 have been designed and synthesized for detection of hydroxy carboxylic acids in less polar solvents. The receptor 1 shows monomer emission quenching followed by excimer emission upon hydrogen bond-mediated complexation of carboxylic acids. The excimer emission distinguishes aromatic dicarboxylic acids from aliphatic dicarboxylic acids and even long chain aliphatic dicarboxylic acids from short chain aliphatic dicarboxylic acids. The receptor 1 is found to be selective for citric acid with a strong excimer emission in CHCl3. On the contrary, the receptor 2 exhibited less binding constant value and did not form any excimer upon complexation with the same acids under similar conditions. This established the role of quinoline ring nitrogen in binding with the acids.

Introduction
The sensing and monitoring of ions and molecules by designed synthetic receptors is currently of major interest in the area of molecular recognition [1-3]. Among various sensing techniques available for clinical, biological and environmental analyses, fluorescence sensing is unique because of high sensitivity and compatibility for online and real-time analyses [4]. A large number of examples of fluorescent sensors capable of sensing ions and molecules have appeared over the past few years [5-7]. In this context, fluorescent sensors, which rely on guest-induced folding of flexible receptors bringing the fluorophore probes close enough to function as an excimer, are proved to be useful to read out the molecular recognition process more conveniently [8,9].

The recognition and sensing of carboxylic acids has attracted considerable attention owing to their important role in biology [10]. The recognition of both mono- and dicarboxylic acids by a large number of receptors of different architectures is known [11-14]. We have also reported a series of synthetic receptors for carboxylic acids of various types [15-18]. In continuation,
we report here a new quinoline based sensor 1 (Figure 1) which is able to bind citric, gluconic and tartaric acids strongly in the less polar solvent CHCl₃. The guests can be clearly distinguished by observing the strong excimer emission formed by the pendant quinoline probes upon complexation. To establish the role of quinoline ring nitrogen in complexation we also report here an alternative naphthalene-based receptor 2 (Figure 1), where quinoline has been replaced by naphthalene keeping all the other hydrogen bonding groups fixed. The key in all the designs is the appropriate flexible ether linkage to hold the fluorophore probes viz. quinoline and naphthalene in such a manner as to create open clefts of different topologies.

Results and Discussion

Synthesis

The receptors 1 and 2 were synthesized according to Scheme 1. The alcohols 3 and 6, obtained from 8-hydroxyquinoline and 1-naphthol, were coupled with 2-(pivaloylamino)-6-bromomethylpyridine (obtained from 2-(pivaloylamino)-6-methylpyridine by reaction with NBS in dry CCl₄) to give compounds 4 and 7, respectively. Amide hydrolysis of 4 and 7 afforded the corresponding amines 5 and 8 in good yields. Coupling of these amines with isophthaloyl chloride yielded the desired receptors 1 and 2. All the compounds were characterized using ¹H NMR, ¹³C, mass, IR and UV spectroscopic methods.

Interaction studies

UV-vis study

The sensitivity and selectivity of the receptors 1 and 2 were evaluated by observing the changes in ¹H NMR, UV-vis and...
fluorescence emission in CHCl₃. Initially, the photophysical behaviors of the receptors 1 and 2 were noticed in solvents of different polarities. In the ground state, the absorption peak at 289 nm for quinoline of 1 and at 290 nm for naphthalene of 2 in CHCl₃ are considerably affected in intensities as well as positions (red shift, ~18 nm) as the solvent polarity is varied (see Figure 2 and Figure 3).

The absorption spectra of 1 and its 1:1 complexes with citric, D(-)-tartaric, D(-)-gluconic, succinic and terephthalic acids in CHCl₃ were recorded to investigate the interactions in the ground state. Chloroform solutions of the 1:1 complexes were diluted gradually with chloroform and the change in intensity, as a function of the complex concentration, was linear in each case. Figure 4, for example, shows the effect of dilution on the UV spectra of the 1:1 complex of citric acid with 1. In the 1:1 complex of 1, the absorption at 290 nm is significantly reduced. The change in absorbance with complex concentration is found to be linear (Figure 4, right side). Figure 5 indicates the case of 1 with D(-)-tartaric acid where a similar nature of interaction is attributed. These changes in the UV-vis spectra were used conveniently to study the binding since lower concentrations led to a more accurate determination of the values of the association constants for the acids (Table 1) [19]. Citric acid, a tricarboxylic acid with more hydrogen bonding groups, shows a higher binding constant than D(-)-gluconic and D(-)-tartaric acids. D(-)-Gluconic acid with more -OH groups in the backbone, exhibits a value of 1.55 x 10⁵ M⁻¹ which is slightly less than tartaric and citric acids. The non-hydroxy dicarboxylic acids such as succinic, glutaric, terephthalic acids bind weakly.
UV titrations of the receptor 2 in presence of the same guests were carried out in CHCl₃. The change in absorbance of the complexes of 2 with the acid guests on dilution with CHCl₃ was linear in each case. Figure 6 and Figure 7, for example, demonstrate the changes in absorbance of the 1:1 complexes of citric acid and D-(-)-tartaric acid respectively with receptor 2. The binding constant values are collected in Table 2.

Fluorescence study

To ascertain their excited state properties, fluorescence spectra of the receptor 1 were recorded in CHCl₃ both in the presence and absence of the guest acids. Figure 8 shows the fluorescence spectra of receptor 1 and its 1:1 complexes with citric, D-(-)-tartaric, D-(-)-gluconic, succinic, glutamic, adipic, sebacic and terephthalic acids. On complexation, fluorescence quenching of the monomer emission occurs significantly with simultaneous generation of a new peak at longer wavelength, presumably due to hydrogen bonding.

### Table 1: Association constants of 1 by UV method

<table>
<thead>
<tr>
<th>Guest acid</th>
<th>$K_a^\text{v} [\text{M}^{-1}]$</th>
<th>$K_a^\text{v} [\text{M}^{-1}]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citric acid</td>
<td>$3.01 \times 10^5$</td>
<td>$2.98 \times 10^4$</td>
</tr>
<tr>
<td>D(-)-Tartaric acid</td>
<td>$2.76 \times 10^5$</td>
<td>$2.12 \times 10^4$</td>
</tr>
<tr>
<td>D(-)-Gluconic acid</td>
<td>$1.55 \times 10^5$</td>
<td>$1.67 \times 10^4$</td>
</tr>
<tr>
<td>Succinic acid</td>
<td>$4.45 \times 10^4$</td>
<td>$3.29 \times 10^3$</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>$7.34 \times 10^3$</td>
<td>$5.04 \times 10^2$</td>
</tr>
<tr>
<td>Adipic acid</td>
<td>$7.26 \times 10^3$</td>
<td>$9.23 \times 10^2$</td>
</tr>
<tr>
<td>Sebacic acid</td>
<td>$2.96 \times 10^3$</td>
<td>$1.95 \times 10^2$</td>
</tr>
<tr>
<td>Terephthalic acid</td>
<td>$2.00 \times 10^3$</td>
<td>$4.33 \times 10^2$</td>
</tr>
</tbody>
</table>

* Determined in dry CHCl₃ by dilution method (at wavelength 290 nm)
* Determined in dry CHCl₃ by adding guests dissolved in CHCl₃ containing 0.8% DMSO (at wavelength 290 nm)

Compared to the hydroxy acids, besides the dilution method we also followed a continuous variation method where the absorbance of receptor 1 was measured as a function of guest concentrations [20]. In order to do so, the receptor was dissolved in CHCl₃ and the carboxylic acid guest, dissolved in CHCl₃ containing 0.8% DMSO, was gradually added to the receptor solution. The corresponding change in absorption of the receptor was noted after each addition. The binding constant values determined by this method are found to be less (Table 1) due to the presence of DMSO, a competitive hydrogen-bonding partner which reduces the binding affinity.

Interestingly, as we move from receptor 1 to receptor 2, the binding constant value is also reduced due to fewer hydrogen bonds being formed during complexation owing to the replacement of quinoline moiety in 1 by naphthalene, which does not take part in complexation. To ascertain the binding potencies, UV titrations of the receptor 2 in presence of the same guests were carried out in CHCl₃. The change in absorbance of the complexes of 2 with the acid guests on dilution with CHCl₃ was linear in each case. Figure 6 and Figure 7, for example, demonstrate the changes in absorbance of the 1:1 complexes of citric acid and D-(-)-tartaric acid respectively with receptor 2. The binding constant values are collected in Table 2.
The degree of quenching and the appearance of excimer are dependent on the nature of the acids. The nonhydroxy dicarboxylic acids of different chain lengths are less efficient in forming strong excimers than hydroxy dicarboxylic acids. Terephthalic acid, an example of aromatic dicarboxylic acid, on the contrary, did not produce any excimer upon complexation. This is attributed to the rigidity and steric features of the aromatic diacid that fail to bring the pendant quinolines close enough for excimer formation. We also tested the possibility of excimer formation in the presence of different aliphatic dicarboxylic acids of different chain lengths. It was interesting that the excimer was noticed only in the presence of succinic, glutaric, and adipic diacids. In the presence of diacids of higher chain length such as sebacic and the peak for the excimer at higher wavelength did not appear. This observation is thus interesting and useful in distinguishing aliphatic from aromatic dicarboxylic acids and also aliphatic dicarboxylic acids of specific chain lengths.

The excimer emission resulted from the intramolecular excimer, rather than intermolecularly, as indicated by the dilution experiments at different concentrations in which the intensities of the ratio of excimer to monomer emission changed gradually (Figure 9). The formation of strong excimers in the presence of hydroxy dicarboxylic acids could be attributed to the guest acid templated hydrogen bond induced organization of the pendant...
Interestingly, under similar conditions, the receptor 2 showed weak interaction with the same guests and did not produce a strong excimer upon complexation. As shown in Figure 12, the initially present less intense peak at higher wavelength (~500 nm) for weak excimer in 2 is marginally perturbed in the 1:1 complexes with the respective guests. Figure 13 indicates the change in fluorescence of 2 in CHCl₃ upon gradual addition of citric acid, dissolved in CHCl₃ containing 0.6% DMSO. It is of note that the change is insignificant compared to the case of the receptor 1 (see Figure 11). These observations prove the key role of quinoline in strong complexation of carboxylic acids, especially hydroxy acids.
Figure 12 Fluorescence change of 2 in CHC\(_3\) in the presence of carboxylic acids (3 = 290 nm) 

Figure 13 Fluorescence change of 2 in CHC\(_3\) in the presence of carboxylic acids (3 = 290 nm) 

**1H NMR study** 

To identify the possible hydrogen bonding sites and also to realize the conformational behavior of both 1 and 2, 1H NMR spectra were recorded in CDCl\(_3\). To the receptor solutions in CDCl\(_3\), diacids were added in excess and the solutions were thoroughly sonicated for 10 mm. Insoluble particles were removed by filtration and clear solutions were used to record the 1H NMR spectra. In all cases the complexes were of 1:1 stoichiometries, confirmed from the integration ratio of the receptor to the guest signals in 1H NMR. The receptor 1, in CDCl3, showed a sharp peak at 6 9 45 ppm for the amide protons, which underwent a considerable downfield shift (\(\Delta \delta = 0.21-1.08\) ppm) upon addition of 1 molar equiv of the diacids studied, suggesting that ammopyridyl moieties serve as potential binding sites for carboxylic acids. The CH2 protons of the ethers, perfectly aligned into the cavity, also moved significantly downfield upon complexation. Among the three types of CH2 protons (a, b and c, see the structure 1), types a and c moved more downfield (\(\Delta \delta = 0.07-0.20\) ppm) indicating a clear-cut case of H-bonding. This significant downfield shift of the CH2 protons (types a, c) of the ethers in the presence of the guest carboxylic acids (except terephthalic acid) in Table 1, led us to suggest that the lower rim of the receptor 1 is actively involved in complexation for which there is a substantial conformational change of the receptor 1. As can be seen from Figure 14, a and c type protons of the ether chains undergo downfield shift upon complexation with carboxylic acid. This subtle change via H-bonding presumably influences the quinoline groups to be close enough for formation of exciplex. This is also evidenced by a change in the chemical shift values of the quinoline ring protons (Figure 14) during complexation with carboxylic acid. The quinoline ring protons (marked with asterisks in Figure 14) suffer a downfield shift upon complexation and led us to presume a weak \(\pi\) edge to face \(\pi\)-stacking interaction between the pendant quinolines.

**Theoretical calculations on receptors and selected complexes**

In order to understand the flexible nature as well as modes of binding of the receptors 1 and 2 with the guest molecules studied in the present case, electronic structure calculations were carried out. Geometries of all compounds involved were subject to optimization at the AM1 level [21].

It is evident from the optimized geometry of the complex of 1 with citric acid (Figure 15a) that citric acid is strongly complexed in the cleft involving a large number of hydrogen bonding interactions. Both the amides as well as the isophthaloyl amide proton form hydrogen bonds with one of the carboxylic acid groups. The other terminal carboxylic acid forms bifurcated hydrogen bonds at the lower rim with the quinoline ring nitrogens and this is further stabilized by the adjacent three hydrogen bonds, formed from the participation of the ether oxygen of one arm, -OCH2- of another arm and one pendant quinoline ring hydrogen. The -CO2H group, attached to the carbon with an -OH group, remains uncomplexed. The -OH at the middle carbon forms a single hydrogen bond with the ether oxygen of one arm. Surprisingly, the methylene hydrogens of citric acid also form two hydrogen bonds. Such strong interaction brings the pendant quinolines close to exhibit a weak \(\pi\)-edge to face \(\pi\)-stacking interacation showing the shortest possible distance of 3.48 Å. The hydrogen bond distances are listed in Figure 15a.

In comparison, this weak \(\pi\)-stacking interaction between the quinolines is no longer found in the complex of 1 with terephthalic acid (Figure 15). In the complex, the pendant quinolines are separated enough to form a cleft in which the carboxylic acid is complexed with the pyridine amide. The other
carboxylic acid is singly bonded to one of the pendant quinolines via a ring hydrogen. One of the phenyl hydrogens of the guest terephthalic acid is bonded to the quinoline ring nitrogen. The hydrogen bond distances associated with this complex are listed in Figure 15b.

We also did the same calculations on the complex of receptor 2 with citric acid. As can be seen from Figure 16, citric acid is complexed into the cleft with a number of hydrogen bonds and the pendant naphthalenes are separated by a large distance with no π-stacking interaction between them. This is in accordance...
with the experimental results, shown in the fluorescence experiment.

Conclusion
We have discussed the synthesis and sensing behaviors of receptors 1 and 2 in the less polar solvent CHCl₃. The conformationally flexible receptor 1 is able to distinguish hydroxy dicarboxylic acids from their non-hydroxy analogues and also aliphatic dicarboxylic acids from aromatic diacids by showing characteristic excimer emission, which is moderate and convenient for practical use. The findings have been explained by theoretical results. In the design 1, quinoline ring nitrogen played a key role in the binding process and was established by doing the control experiments on the receptor 2. The receptor 2 was found less effective than 1 in the binding and selection of the guest carboxylic acids.

Experimental

General details All reactions were carried out under a nitrogen atmosphere. Solvents were dried before use. Solvents for spectroscopic measurements were of spectroscopic or HPLC grade. THF was freshly distilled from sodium benzenephone ketyl and stored over KOH pellets under a nitrogen atmosphere. Melting points were determined in open capillaries and are uncorrected. ¹H NMR spectra were recorded on a Bruker 400 MHz spectrometer. UV-vis absorption and fluorescence spectra were recorded on a PerkinElmer Lambda 25 spectrophotometer and a PerkinElmer LS-50B spectrofluorimeter, respectively. FTIR spectra were obtained from a PerkinElmer L120-000A model.

2-(Qunolin-8-yl)ethanol (3)
To a mixture of 8-hydroxyquinoline (1 g, 6.80 mmol) and potassium carbonate (0.95 g, 6.80 mmol) in dry CH₂CN, 2-chloroethanol (1.11 g, 13.7 mmol) in 5 mL CH₂CN was added dropwise and the reaction mixture was refluxed for 24 h. The reaction mixture was concentrated under vacuum and 30 mL water was added to the mixture. The aqueous layer was extracted with 3 × 100 mL CHCl₃ and the combined organic extracts were dried over anhydrous Na₂SO₄. After evaporation of the solvents under vacuum, the crude product was purified by column chromatography using 23% ethyl acetate in petroleum ether as eluent to give a brownish crystalline product 3 (685 mg, yield 50%).

Melting point = 72 °C. ¹H NMR (400 MHz, CDCl₃, δ in ppm) 8.94 (1H, d, J = 2.40 Hz), 8.29 (1H, d, J = 8.00 Hz), 7.47–7.40 (3H, m), 7.11 (1H, d, J = 8.00 Hz), 5.54 (1H, br s, OH), 4.28 (2H, t, J = 4.00 Hz), 4.08 (2H, t, J = 4.00 Hz) ESI (positive ionisation) mass 212.1 (M + Na)+, 190.1 (M + H)+. FTIR (v cm⁻¹, KBr) 3400, 3157, 2922, 1577, 1380, 1116.

N-Nitro-[2-(Qunolin-8-yl)ethoxy)methyl]-pyridin-2-yl)pyvalamide (4)
To a solution of 3 (500 mg, 2.60 mmol) in dry THF, NaH (63 mg, 2.60 mmol) was added and stirred under a nitrogen atmosphere for 2 h. Then a solution of 2-(pyvaloylamino)-6-bromo-methylpyridine (0.72 g, 2.60 mmol) dissolved in 10 mL of THF was added and stirring was continued overnight. After completion of the reaction, the reaction mixture was concentrated under vacuum and water (30 mL) was added to the reaction mixture. The aqueous layer was extracted with 3 × 100 mL CHCl₃ and the combined organic extracts were dried over anhydrous Na₂SO₄. The solvent was evaporated and the crude product was purified by column chromatography using 20% ethyl acetate in petroleum ether as eluent to give compound 4 (702 mg, yield 70%) as a brownish gummy product.

¹H NMR (400 MHz, CDCl₃, δ in ppm) 8.93 (1H, dd, J₁ = 1.60 Hz, J₂ = 1.60 Hz), 8.29 (1H, s, -CONH-), 8.15–8.11 (2H, m), 7.65 (1H, t, J = 8.00 Hz), 7.47–7.40 (3H, m), 7.16 (1H, d, J = 8.00 Hz), 7.10 (1H, d, J = 7.60 Hz), 4.66 (2H, s), 4.46 (2H, t, J = 4.00 Hz), 1.32 (9H, s) ESI (positive ionisation) mass 402.3 (M + Na)+, 380.2 (M + H)+. FTIR (v cm⁻¹, KBr) 3411, 1689, 1452, 1107.
Receptor 1

To a solution of amide 4 (0.3 g, 0.79 mmol) in 20 mL ethanol, 10 mL of a 4 N KOH solution was added and the reaction mixture was refluxed for 12 h. After completion of the reaction (monitored by TLC) ethanol was evaporated and water (20 mL) was further added to the reaction mixture. The aqueous layer was extracted with 3 × 100 mL CHCl₃ and the combined organic extracts were dried over anhydrous Na₂SO₄. The solvent was evaporated and the crude product was purified by column chromatography using 4% methanol in petroleum ether as eluent to give the corresponding amine 5 (175 mg, yield 75%). Without characterization, the amine 5 was directly used in the next step.

Compound 5 (0.1 g, 0.30 mmol) was dissolved in dry CH₂Cl₂ and 0.15 mL of Et₃N was added to it. Then this solution was added dropwise to a solution of isophthaloyl dichloride (0.034 g, 0.16 mmol) in dry CH₂Cl₂ and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated and a saturated Na₂CO₃ solution (30 mL) was added to the reaction mixture. The aqueous layer was extracted with CHCl₃ and the combined organic extracts were dried over anhydrous Na₂SO₄. The solvent was evaporated and the crude product was purified by column chromatography using ethyl acetate as eluent to give 1 (146 mg, yield 60%).

N-(6-[[2-(Naphthalen-1-yloxy)ethoxy]methyl]-pyridin-2-yl]pivalamido (7)

To a mixture of 1-naphthol (1 g, 6.90 mmol) and potassium carbonate (0.96 g, 6.90 mmol) in dry CH₂CN, 2-chloroethanol (1.12 g, 13.9 mmol) in CH₂CN (5 mL) was added and the reaction mixture was refluxed for 7 h. After completion of the reaction mixture was concentrated under vacuum and water (30 mL) was added to the reaction mixture. The aqueous layer was extracted with CHCl₃ and the combined organic extracts were dried over Na₂SO₄. The solvent was evaporated and the crude product was purified by column chromatography using 10% ethyl acetate in petroleum ether as eluent to give compound 7 as deep brown gummy product (744 mg, yield 74%).

Receptor 2

To a solution of amide 7 (0.4 g, 1.05 mmol) in dry THF, NaH (63 mg, 2.6 mmol) was added and the reaction mixture was stirred under nitrogen atmosphere for 2 h. Then the solution of 2-(pivaloylamino)-6-bromomethylpyridine (0.72 g, 2.6 mmol) dissolved in 10 mL of THF was added and stirring was continued overnight. After completion of the reaction, the reaction mixture was concentrated under vacuum and water (10 mL) was added to the reaction mixture. The aqueous layer was extracted with CHCl₃ and the combined organic extracts were dried over Na₂SO₄. The solvent was evaporated and the crude product was purified by column chromatography using 10% ethyl acetate in petroleum ether as eluent to give compound 8 (243 mg, yield 78%).

2-(Naphthalen-1-yloxy)ethanol (6)

To a mixture of 1-naphthal (1 g, 6.90 mmol) and potassium carbonate (0.96 g, 6.90 mmol) in dry CH₂CN, 2-chloroethanol (1.12 g, 13.9 mmol) in CH₂CN (5 mL) was added and the reaction mixture was refluxed for 60 h. After completion the reaction mixture was concentrated under vacuum and 30 mL water was added to the mixture. The aqueous layer was extracted with 3 × 100 mL CHCl₃ and the combined organic extracts were dried over Na₂SO₄. After evaporation of the solvent the crude product was purified by column chromatography using 3% ethyl acetate in petroleum ether as eluent to give 6 as a deep brown gummy product (587 mg, yield 45%).
combined organic extracts were dried over anhydrous Na2SO4. The solvent was evaporated and the crude product was purified by column chromatography using ethyl acetate as eluent to give 2 (190 mg, yield 52%).

Methods for the determination of binding constant (Kr) values by UV titration

**a) Binding constant determination by dilution method**

The receptor was dissolved in 50 mL dry UV grade CHCl3. From this solution 25 mL was taken in a stopped volumetric flask and to this the carboxylic acid guest was added and sonicated for 10 min. The mixture was filtered to remove any insoluble particle. Different solutions of varied compositions of receptor-carboxylic acid complex solution were prepared from this 25 mL stock solution of receptor-carboxylic acid complex and solution containing 0.8% DMSO in dry CHCl3. From this solution 25 mL was taken in a cuvette and carboxylic acid guests, dissolved in dry CHCl3 containing 0.8% DMSO, were individually added in different amounts to the receptor solution. The corresponding absorbance values during titration were noted and used for the determination of binding constant values. Binding constants were determined by using the expression

\[
A = A_0 - A = \left[A_0 \left(\frac{1}{q} - 1\right) + 1\right] - 1
\]

where \(A_0\) and \(A\) refer to the concentration, absorbance, molar extinction coefficient for the receptor and the hydrogen-bonding complex, respectively at selected wavelength, \(q\) denotes the absorbance of the free receptor at the specific wavelength and \(C_{rs}\) is the concentration of the carboxylic acid guest. The measured absorbance \(A_0 - A\) as a function of the inverse of the carboxylic acid guest concentration fits a linear relationship, indicating a 1:1 stoichiometry of the receptor-carboxylic acid complex. The ratio of the intercept to the slope was used to determine the binding constant \(K_r\).

**Acknowledgments**

We thank DST, New Delhi for FIST program for providing facilities in the department. SA thanks CSIR, New Delhi for a fellowship during the course of work.

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doi 10.1021/cr010421e
doi 10.1039/b009041g
doi 10.1021/ol051735h
doi 10.1021/ol020162v
doi 10.1021/ol605175h
doi 10.1021/ol049628v
doi 10.1021/ja9623121
doi 10.1021/ja0769234

Acid references therein

doi 10.1021/ja010201g
doi 10.1039/b000041g
doi 10.1016/j.tet.2005.03.064
Geometry optimization of all conformations of receptors 1 and their complexes at the AM1 level were carried out using the GAMESS-US software suite. See [22]. We have refrained from citing calculated total energy values (and binding energy estimates based on their differences) as being not very meaningful, the calculations being for molecules only in the gas-phase. For example, the difference in binding energies of receptor 1 with citric and terephthalic acids comes out to be only about 0.15 kcal/mol, the value estimated from the difference in $K_{\text{ass}}$ is much more than this.


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The definitive version of this article is the electronic one which can be found at doi:10.3762/bjoc.4.52
A pyridine-based macrocyclic host for urea and acetone
Kumares Ghosh a,b, Suman Adhikana,b, Roland Frohlich b

A pyridine-based macrocycle with a polyester chain has been designed and synthesized. The macrocycle shows strong binding for acetone involving both conventional and unconventional hydrogen bonds. The acetone in the cavity is exchangeable in CHCl₃ by urea. This has been studied thoroughly by ¹H NMR, ¹³C NMR, mass and X-ray analyses.

The application of hydrogen bonding as a design principle in the construction of host molecules for selective complexation of guest molecules is very important in biology, chemistry and material science. Despite the relative weakness of hydrogen bonding interactions, both conventional and unconventional hydrogen bonds have been used extensively to control the supramolecular structure of solids, giving rise, for example, to linear ribbons, planar networks or helical structures. In this respect, C-H—O and C-H—N unconventional hydrogen bonds play an important role in determining the supramolecular structures. Although short C-H—O contacts have been reported regularly in the crystallographic literature, it is only recently, notwithstanding Sutor's study, that their importance in organic structures has been accepted and their recognition as hydrogen bonds has been reached without scepticism. According to Taylor and Kennard, C-H—O contacts are not static effects but distinct electrostatic phenomena and the frequency with which they occur suggests that they play a significant role in determining the packing arrangements of some organic crystal structures. It has also been suggested that these weak forces have an impact on the selectivity/reactivity of chemical transformations.

As a part of our work in the area of molecular recognition, we report here the design, synthesis and hydrogen bonding properties of simple pyridine-based macrocycle 1. The macrocycle 1 exhibits the unique property of inclusion of both acetone and urea.

Urea, the end product of nitrogen metabolism, is a toxic pollutant that causes serious biological disorders. Various groups have addressed the recognition of urea using designed synthetic receptors. Crown ether-based receptors developed by Pedersen and the carbonyl acid-containing macrocyclic receptor of Renhoudt are known to bind urea. Renhoudt et al. have also explored the concept of using an electrophilic centre to bind urea in the cavity of a crown ether. Bell et al. reported the synthesis of naphthyndine fused polyaza heterocycles for urea recognition. A recent report has shown that benzimidazole-containing cleft is able to form a complex with urea. Coswami et al. reported the recognition of urea using a macrocyclic fluorescent receptor in chloroform based on their previous approach to a naphthyndine receptor for urea.

In this study, our pyridine amide-based macrocyclic receptor 1 shows a strong propensity to form hydrogen-bonded complexes with carbonyl guests, especially with less polar acetone and more polar urea molecules. This is due to correct alignment of all the hydrogen bond donors and acceptors of 1 in the cavity as well as size/shape complementarity. The AM1 optimized geometry of 1 in Figure 1a demonstrates that the cavity has enough room to accommodate small molecules with correct hydrogen bonding information. Figures 1b and 1c, in this connection, indicate the AM1 optimized geometries of complexes of 1 with acetone and urea, respectively.

The synthesis of macrocyclic receptor 1 is outlined in Scheme 1. Initially, the coupling of digol with 2-(N-pivaloyl)-6-bromopyridine afforded pyridine amide appended polyester 2, which on alkaline hydrolysis gave the diamine 3 in 80% yield. High dilution coupling of diamine 3 with naphthyndiyi diacid chloride in dry THF produced the macrocycle 1 in 18% yield.

Characterization of the macrocycle 1 by ¹H NMR indicated all the expected signals but with an extra signal at δ 2.26 ppm in the FTIR, a peak at 1673 cm⁻¹ was observed along with the amide
carbonyl stretch at 1682 cm\(^{-1}\). These findings led us to suspect the presence of a carbonyl compound with a -COCH\(_3\) group in the cavity. In the \(^{13}\)C NMR spectrum, signals at 178.7 ppm and 21.7 ppm further supported the presence of a carbonyl carbon and methyl carbon, respectively. In the ESI mass spectra, the ion peak at 449.3 confirmed the (M+H)* ion and HRMS analysis showed the same result indicating no inclusion of any molecule in the cavity.

To solve this problem, single crystals of 1 were obtained by slow evaporation from a chloroform/methanol mixture (2:1). The crystallographic information is listed in Table 1. The macrocycle 1 yields all inclusion complexes with acetone (melting point = 226 °C), which crystallizes in the orthorhombic space group, Pnma (No 62). As can be seen from Figure 2, the macrocycle 1 shows strong inclusion of acetone involving

**Table 1**

Crystalllographic and structure refinement data for the inclusion compounds of 1

<table>
<thead>
<tr>
<th>Empirical formula</th>
<th>C(<em>{20})H(</em>{24})N(_4)O(_6)Cl(_2)</th>
<th>C(<em>{20})H(</em>{24})N(_4)O(_6)Cl(_2)</th>
<th>C(<em>{20})H(</em>{24})N(_4)O(_6)Cl(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula weight</td>
<td>506.55</td>
<td>506.55</td>
<td>506.55</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>198(2)</td>
<td>223(2)</td>
<td>223(2)</td>
</tr>
<tr>
<td>Wavelength (Å)</td>
<td>0.71073</td>
<td>1.54178</td>
<td>1.54178</td>
</tr>
<tr>
<td>Orthorhombic, Pnma (No 62)</td>
<td></td>
<td>Monoclinic, P2(_1)/n (No14)</td>
<td>Monoclinic, P2(_1)/n (No14)</td>
</tr>
<tr>
<td>a (Å)</td>
<td>157.66(1)</td>
<td>157.66(1)</td>
<td>157.66(1)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>131.63(1)</td>
<td>131.63(1)</td>
<td>131.63(1)</td>
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<tr>
<td>c (Å)</td>
<td>104.15(1)</td>
<td>104.15(1)</td>
<td>104.15(1)</td>
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<tr>
<td>F(200)</td>
<td>47127/9068 (0.04)</td>
<td>47127/9068 (0.04)</td>
<td>47127/9068 (0.04)</td>
</tr>
<tr>
<td>R(f00)</td>
<td>1.396</td>
<td>1.396</td>
<td>1.396</td>
</tr>
<tr>
<td>Crystal size (mm)</td>
<td>0.35 x 0.30 x 0.30</td>
<td>0.35 x 0.30 x 0.30</td>
<td>0.35 x 0.30 x 0.30</td>
</tr>
<tr>
<td>Theta range for data collection (°)</td>
<td>1.65-28.21</td>
<td>1.65-28.21</td>
<td>1.65-28.21</td>
</tr>
<tr>
<td>Least-squares parameters</td>
<td>27 x 24 x 27</td>
<td>27 x 24 x 27</td>
<td>27 x 24 x 27</td>
</tr>
<tr>
<td>Reflections collected (R)</td>
<td>21.000(2004) (0.059)</td>
<td>22.000(2004) (0.059)</td>
<td>22.000(2004) (0.059)</td>
</tr>
<tr>
<td>Completeness to theta = 28.21</td>
<td>99.9%</td>
<td>99.9%</td>
<td>99.9%</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.995 and 0.981</td>
<td>0.995 and 0.981</td>
<td>0.995 and 0.981</td>
</tr>
<tr>
<td>Full-matrix least-squares on F^2</td>
<td>1.023</td>
<td>1.023</td>
<td>1.023</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>0.051 and 0.081</td>
<td>0.051 and 0.081</td>
<td>0.051 and 0.081</td>
</tr>
<tr>
<td>Largest diff peak and hole (e Å(^{-3}))</td>
<td>0.58 and -0.38</td>
<td>0.58 and -0.38</td>
<td>0.58 and -0.38</td>
</tr>
</tbody>
</table>

\(^{*}\) Structure solution and refinement were performed using sas97 and olex-97.
CH—O [2.34 Å, 159° (C20-H20C—O4) and 2.42 Å, 124° (C18-H18—O2)], CH—N [2.45 Å, 115° (C20-H20A—N7)], and NH—O [2.21 Å, 174° (N12-H12—O21)] interactions. Acetone is found to interact from the top of the macrocycle and the carbonyl oxygen is bonded to two amide NHs through two coplanar hydrogen bonds. Two hydrogens of each methyl group form unconventional C—H—O and C—H—N hydrogen bonds which result in a seven-membered hydrogen bonded ring. The angled molecules lead to corrugated packing. The acetone molecule and the centre of the macrocycle are packed in the [100] direction. This inclusion of acetone was due to contamination of the solvent used either during workup or during purification of 1. This was proved by repeating the synthesis, isolation and purification of 1 using acetone-free solvents. Characterization was achieved by 1H NMR, 13C NMR and mass spectrometries, which revealed that the structure 1 was free from acetone. The inclusion of acetone into the cavity of macrocycle 1 was further tested using the same crystallizing solvent contaminated with acetone which gave the same result. To determine the robustness of the acetone complex of 1, thermal analysis was performed and the weight losses at different temperatures are shown in Figure 3. The weight loss between 152°C and 233°C is presumably due to loss of acetone.

To remove acetone from the cavity of 1, urea dust was added to its chloroform solution and the solution was sonicated thoroughly for 15 min. The excess urea was filtered off and the solvent was evaporated to dryness. The solid mass obtained was redissolved in dry CDCl3 and a 1H NMR was taken. A smaller downfield shift of the amide protons (\(\Delta S = 0.45 \) ppm) of 1 was observed but no signal for the urea NH was found in the 1H NMR. Even the signal at 2.15 ppm for the \(-\text{CH}_3\) of acetone was present. On keeping the same solution for 10 days, a signal at 5.65 ppm for the urea NHs was observed along with the absence of the peak at 2.15 ppm for the \(-\text{CH}_3\) of complexed acetone. The integration ratio of urea protons to receptor protons showed a clear 2:1 (1 urea).
Figure 6. UV-vis spectra of the acetone complex of 1 on dilution with CHCl₃. Inset—change in absorbance with concentration of acetone complex 1 at 287 nm.

A sharp change in absorbance (Fig. 6) shows a linear change in absorbance at 287 nm with complex concentration. The binding constants were not estimated and compared due to the different stoichiometries of the complexes of acetone and urea with the macroyclic receptor 1.

In conclusion, we have shown that the synergy of both conventional and unconventional hydrogen bonds in simple macrocycle 1 plays an important role for effective binding of acetone, which can have practical application in complexation of a chiral ketone by a chiral receptor. Additionally, the biologically important metabolite, urea, can also be complexed by the same macrocycle with a moderate binding constant value involving conventional hydrogen bonds only. To the best of our knowledge, this example is unknown in the literature. Further modification of 1 is under progress in our laboratory.

Acknowledgement

We thank CSIR, New Delhi, for financial support.

Supplementary data

¹H NMR and ¹³C NMR spectra of the macrocycle 1 Supplementary version, at doi:10.1016/j.tetlet.2008.06.030

References and notes


22. Semi-empirical AM1 calculations were performed using Gaussian 03 version 8.0

23. Macrocycle 1 Mp 150 °C. ¹H NMR (400 MHz, CDCl₃, in ppm) 9.03 (2H, -CONH-), 8.77 (4H, s, 8.35-8.30 (2H, m, 7.76-7.67 (2H, s, 0.20 (2H, d, 7.12)), 6.63 (4H, s), 7.77 (8H, s, 13C NMR (75 MHz, CDCl₃) 164.3, 135.5, 151.1, 138.2, 122.2, 121.1, 21.4, 118.0, 112.8, 75.3, 71.1, 69.0, 5058

24. FTIR (cm⁻¹, KBr) 3387, 2921-2850 1650 1597 1544 1458

25. To establish the spectral properties of the inclusion complexes of acetone and urea, UV-vis spectra were taken in CHCl₃.

The macrocycle 1/urea 2:1 inclusion compound (melting point 130-140 °C) crystallizes in the monoclinic space group P2₁/a (No 14)

The ¹H NMR spectra of 1 in the presence of both acetone and urea are shown in Figure 4. Crystallization of 1 from CHCl₃ is known in the literature Further modification of 1 is under progress in our laboratory.

Absorbance peak at 287 nm which on dilution with CHCl₃ is present in the colloidal form in the CHCl₃ solution.

The stoichiometry of these experimental observations indicates that acetone is slowly replaced by urea from the macrocyclic cavity which is present in the colloidal form in the CHCl₃ solution.

The macrocycle 1/urea 2:1 inclusion compound (melting point 130-140 °C) crystallizes in the monoclinic space group P2₁/a (No 14).

Due to the greater number of 'traditional' hydrogen bonds are formed (Fig 5) Two independent molecules of macrocycle 1 show strong inclusion for urea involving NH—O (2.03 Å, 159° (N54-H54A—N25B), and 218 Å, 141° (N53-H53B—N7A)) and NH-N 12.32 Å, 171° (N23A-H23A—O51). and 218 Å, 174° (N12B-H12B—O51). These experimental observations indicate that acetone is slowly replaced by urea from the macrocyclic cavity which is present in the colloidal form in the CHCl₃ solution.

The stoichiometry of these experimental observations indicate that acetone is slowly replaced by urea from the macrocyclic cavity which is present in the colloidal form in the CHCl₃ solution.