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**GRAPHICAL ABSTRACT**

**Coumarin-based supramolecular gelator: A case of selective detection of F\(^-\) and HP\(_2\)O\(_7\)\(^{3-}\)**

Kumaresh Ghosh* and Santanu Panja

Coumarin-based small molecular gelator 1 has been designed and synthesized. Compound 1 forms stable gel from CHCl\(_3\) - petroleum ether (1:1, v/v). The fluorescent gel is anion responsive and is selectively disintegrated in the presence of F\(^-\) and hydrogen pyrophosphate.
Coumarin-based supramolecular gelator: A case of selective detection of F⁻ and HP₂O₇³⁻

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Coumarin appended 1,2,3-triazole coupled cholesterol 1 which acts as small molecular gelator has been designed and synthesized. Compound 1 has been noted to form gel from CHCl₃-petroleum ether (1:1, v/v). The stable gel is anion responsive. The gel state is transformed into the sol state selectively in the presence of F⁻ and hydrogen pyrophosphate and thus validates their visual sensing over a series of other anions. Fluorescence study in CH₃CN containing 0.5% DMSO also reveals substantial change in emission of 1 upon addition of both F⁻ and hydrogen pyrophosphate and distinguishes them from other anions studied.

Introduction

The design and synthesis of low molecular weight organic compound which is capable of forming supramolecular gel in a solvent and subsequently transformed to the sol state in the presence of ionic analytes is recently the subject of increasing attention in supramolecular chemistry.¹ Supramolecular gels are dimensionally controlled assemblies of low-molecular-weight molecules held together by noncovalent interactions, such as hydrogen bonding, metal coordination, van der Waals interaction, and π – π stacking.² Perturbation of these weak interactions using various stimuli such as light,³ redox,⁴ pH⁵ and different ions⁶ results in the destruction of supramolecular gel. These are called stimuli responsive gels. The stimuli responsive nature of the supramolecular gels is now-a-days highly attractive for the development of sensor devices. Many research groups in this domain have shown interest, especially, in the construction of anion-responsive supramolecular gels.⁶⁰⁻⁶⁷ Of the different anion responsive gels, fluoride and pyrophosphate-sensing gels have received a great deal of attention. Fluoride is an important anion which is involved in preventing dental caries and in medical treatment for osteoporosis.⁸ Similarly, pyrophosphate is critically important due to its crucial role in biological system.⁹ Careful scrutiny of the literature reveals that there are plenty of fluororeceptors which recognize fluoride¹⁰ and pyrophosphate anions in solution.¹¹ In relation to this, supramolecular gelators that are capable of detecting fluoride⁶c,¹² and some phosphate derivatives¹³ are less in number in the literature. To the best of our knowledge, pyrophosphate sensing gelators are unknown. In this account, we report a simple new architecture 1 (Fig. 1), which forms gel from CHCl₃-petroleum ether (1:1, v/v) mixture solvent. The gel is anion responsive. It is broken selectively in the presence of F⁻ and hydrogen pyrophosphate (HP₂O₇⁻) and validates their visual sensing over a series of other anions. Fluorescence study in CH₃CN containing 0.5% DMSO also reveals substantial change in emission of 1 upon addition of both F⁻ and HP₂O₇⁻:

Results and discussion

Compound 1 was achieved according to the Scheme 1. Cholesterol was initially converted to the chloride 2⁶c which on reaction with NaN₃ in CH₃CN afforded the cholesterol azide 3. Pursuance of click reaction of the azide 3 with propargyl alcohol gave 1,2,3-triazole linked cholesterol alcohol 4. Then the hydroxyl group in 4 was sequentially reacted with mesyl chloride and LiBr to give bromide derivative 6. Subsequent reaction of...
6,7-dihydroxycoumarin with bromide 6 in the presence of Cs₂CO₃ in CH₃CN under refluxing condition introduced the compound 1 in appreciable yield.

Scheme 1. (i) Chloroacetyl chloride, pyridine, dry CH₂Cl₂, rt, 10h; (ii) CH₂CN, Na₂SO₃, reflux, 5h; (iii) propargyl alcohol, CuSO₄, Cu turning, EtOH-H₂O, reflux, 90°C, 6h; (iv) Dry CH₂Cl₂, methanesulfonyl chloride, NEt₃, rt, 30 min; (v) Dry THF, LiBr, stirring, 8h; (vi) 6,7-dihydroxycoumarin, dry CH₂CN, Cs₂CO₃, reflux, 36h.

Compound 1 consists of different components of which the anion binding site is comprised of phenolic OH and triazole C=H as hydrogen bond donors (Fig. 1). The cholesterol group has been added adjacent to the binding site for its potential for strong hydrophobic interactions. Coumarin moiety has been introduced as the fluorescent signalling unit to execute the sensing behavior of compound 1. It is noteworthy that cholesteryl motif bearing compound 1 with such an arrangement is observed to form brown colored gel from chloroform/petroleum ether (1:1 v/v) mixture solvent. A range of other solvents or solvent mixtures as summarized in Table 1 were unable to bring gelation of 1. The gel was stable at room temperature and transformed into the sol state at 48 °C (Tgel). Upon cooling the sol is slowly transformed into the gel state and thereby indicated that the gel forming and gel collapsing are thermo reversible. Figure 2 shows the scanning electron microscopy (SEM) image of the xerogel of 1. Three dimensional network shows fibrous aggregate.

Table 1. Results of gelation test for 1

<table>
<thead>
<tr>
<th>Solvents</th>
<th>Result° (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHCl₃</td>
<td>S</td>
</tr>
<tr>
<td>2% CH₃OH in CHCl₃</td>
<td>S</td>
</tr>
<tr>
<td>CHCl₃ : Petroleum ether (1:1, v/v)</td>
<td>G (18 mg/mL)</td>
</tr>
<tr>
<td>CH₃COCH₃</td>
<td>S</td>
</tr>
<tr>
<td>DMF</td>
<td>S</td>
</tr>
<tr>
<td>DMF : H₂O (1:1, v/v)</td>
<td>P</td>
</tr>
<tr>
<td>CH₂CN</td>
<td>I</td>
</tr>
<tr>
<td>CH₂CN : CHCl₃ (1:1, v/v)</td>
<td>S</td>
</tr>
<tr>
<td>CH₃OH</td>
<td>I</td>
</tr>
<tr>
<td>CH₃OH : H₂O (1:1, v/v)</td>
<td>I</td>
</tr>
<tr>
<td>DMSO</td>
<td>S</td>
</tr>
<tr>
<td>1% DMSO in CH₂CN</td>
<td>S</td>
</tr>
</tbody>
</table>

a. S = solution; G = transparent gel (minimum gelation concentration); I = insoluble; P = precipitation.

To our belief, out of several possibilities, the phenolic OH and the triazole ring nitrogen in 1 may be intimately involved in hydrogen bonding to make an intermolecular association according to the mode shown in Fig. 3. This gives a network into the solution. The hydrophobic-hydrophobic interaction between

![Image](315x606 to 427x690)

Fig. 2. SEM images of xerogel of 1 prepared from CHCl₃—petroleum ether (1:1, v/v): (a) in 100 µm and (b) 2 µm scales.

![Image](436x606 to 548x690)

Fig. 3. Probable mode of interaction of 1.

![Image](559x606 to 671x690)

Fig. 4. Comparison of (a) UV-vis and (b) fluorescence spectra of 1 in the sol and gel states.

The cholesterol units and weak π-stacking interaction of coumarins presumably stabilize the hydrogen bonded network. A shouldering at 378 nm in UV-vis spectrum of 1 in the gel state with respect to its sol state is likely to be due to aggregate stacking of the gel (Fig. 4a). In fluorescence, red-shifted emission at 446 nm for the gel state is also in accordance with the proposed π-stacking aggregation (Fig. 4b). In FTIR, while the stretching for –OH in the amorphous state of 1 was noted at 3391 cm⁻¹ as broad signal, in the gel state it appeared at 3393 cm⁻¹ (Fig. 5). This small change in stretching frequency for –OH group is presumably due to its participation in hydrogen bonding. On the other hand, stretching frequency for ester carbonyls of both the

![Image](559x606 to 671x690)
coumarin and cholesteryl parts merged together and appeared at 1725 cm$^{-1}$ as broad signal. In the gel state, this signal was reduced to the lower frequency (1714 cm$^{-1}$). This lowering of stretching for ester carbonyl in 1 is the consequence of hydrogen bonding.

Fig. 5. Partial FTIR spectra of 1 in its (a) amorphous and (b) gel states.

In an effort to understand the stimuli responsive nature of the gel, we added different anions as their tetrabutylammonium salts to the gel state of 1. Among the anions taken in the study, only addition of F$^-$ and HP$_2$O$_7^{3-}$ led to the rapid transformation of the gel into solution (Fig. 6). Fluoride being strongly basic deprotonates the phenolic -OH and disrupts the self-assembly of 1. This deprotonation mediated gel disruption was further supported by addition of tetrabutylammonium hydroxide. Similarly, HP$_2$O$_7^{3-}$ rather than H$_2$PO$_4^{-}$ strongly interacts with the triazole coupled phenolic OH motif of 1 via hydrogen bond formation and destroys the network through deprotonation of the phenolic –OH. It is mentionable that hydrogen bonding affinities of triazole motif for HP$_2$O$_7^{3-}$ is well established. 

As the compound 1 contains coumarin motif, a well defined fluorophore with good quantum yield, we further investigated its interaction with the said anions in CH$_3$CN containing 0.5% DMSO (used for homogeneity of the solution). In fluorescence, while compound 1 showed measurable interaction with F$^-$ and HP$_2$O$_7^{3-}$, other anions perturbed the emission weakly. Figure 8 highlights the change in fluorescence ratio of 1 at 428 nm. As can

Fluoride induced broken gel was recovered on keeping the sol after addition of either trifluoroacetic acid (TFA) or BF$_3$. Importantly, while TFA recovered the gel state after ~1h, BF$_3$ was able to gelate the sol after 1.5h (Fig. 7). We believe that regeneration of phenolic OH either by protonation using TFA or by scavenging F$^-$ ions from the mixture as BF$_4$ enables the compound 1 to attain its original structural feature for which gelation takes place. Likewise, HP$_2$O$_7^{3-}$ induced broken gel was recovered upon addition of TFA, shown in Fig. 7a. During recovery, the color of the gel became light brown rather than deep brown.

Fig. 6. Photograph showing the changes in the CHCl$_3$-petroleum ether (1:1, v/v) gel of 1 (18 mg/mL) after addition of 1 equiv. amount of different anions ($c = 3.5 \times 10^{-2}$ M).

Fig. 7. Phase changes of the gel of 1 [18 mg/mL in CHCl$_3$/pet ether (1:1, v/v)] on successive addition of (a) HP$_2$O$_7^{3-}$ (c = 3.5 $\times$ 10$^{-2}$ M) and TFA (The gel to sol conversion was completed within 15 min and reappeared upon addition of TFA after 1h); (b) TBAF (c = 3.5 $\times$ 10$^{-2}$ M) and TFA (The gel to sol conversion was completed within 10 min and reappeared upon addition of TFA after 1.5h).

Fig. 8. Fluorescence ratio [I/I$$_0$] of 1 ($c = 1.94 \times 10^{-5}$ M) at 428 nm upon addition of 10 equiv. amounts of a particular anion ($c = 7.76 \times 10^{-4}$ M) in CH$_3$CN containing 0.5% DMSO.

Fig. 9. Change in emission of 1 ($c = 1.94 \times 10^{-5}$ M) upon addition of 10 equiv. amounts of (a) HP$_2$O$_7^{3-}$, (b) F$^-$ ($c = 7.76 \times 10^{-4}$ M) in CH$_3$CN containing 0.5% DMSO ( Insets show the change in colour of the solutions under UV radiation).
be seen from Fig. 9, the emission at 428 nm is significantly quenched with a red shift of 24 nm upon interaction. This indicated strong interaction of HP$_{2}$O$_{5}^{2-}$ and F$^{-}$ at the binding site of I involving the phenolic OH and triazole C-H as the hydrogen bond donors. In presence of both F$^{-}$ and HP$_{2}$O$_{5}^{2-}$, blue colored solution of I became light greenish blue when looked in under UV light (insets of Fig. 9). During interaction with these anions, the phenolic OH of I was deprotonated rather than participation in hydrogen bonding when they were present in excess in solution. In $^1$H NMR, the disappearance of the signal at 6.20 ppm for –OH in the presence of equivalent amount of F$^{-}$ and HP$_{2}$O$_{5}^{2-}$ supported the deprotonation phenomena (Fig. 10). On deprotonation of phenolic OH, the coumarin ring protons H$_{a}$, H$_{b}$ moved upfield significantly. On the other hand, downfield chemical shift of the proton H$_{g}$ in triazole ring (Δδ for F$^{-}$ = 0.2 ppm and HP$_{2}$O$_{5}^{2-}$ = 0.15 ppm) indicated its involvement in hydrogen bonding with the anions.

![Fig. 10. Partial $^1$H NMR (400 MHz, CDCl$_3$) of (a) compound I ($c = 6.54 \times 10^{-4}$ M), (b) I with TBAF (1:1) and (c) I with TBA-hydrogen pyrophosphate (1:1).](image)

In UV-vis titration, while in presence of HP$_{2}$O$_{5}^{2-}$ and F$^{-}$ ions the intensity of the peak at 340 nm was decreased, a new peak at 412 nm appeared with significant intensity (Fig. 11). A similar ratiometric change was observed in the presence of tetrabutylammonium hydroxide (ESI). The peak at 412 nm is due to the formation of phenoxide ion that exerts auxochromic effect in UV-vis spectra. This was not observed for other anions taken in the study (ESI). Acetate ion being less basic responded weakly in deprotonation as supported by minor change in absorbance of I at 412 nm in the presence of AcO$^{-}$ ion (ESI).

To realize the strength of interaction, the emission titration data for HP$_{2}$O$_{5}^{2-}$ and F$^{-}$ with I were analysed. The binding constant values were observed to be $(1.78 \pm 0.19) \times 10^{4}$ M$^{-1}$ and $(8.49 \pm 1.11) \times 10^{3}$ M$^{-1}$ for HP$_{2}$O$_{5}^{2-}$ and F$^{-}$, respectively with 1:1 stoichiometries. Due to small change in emission the binding constant values for other anions were not determined. In the process, the detection limits for F$^{-}$ and HP$_{2}$O$_{5}^{2-}$ were determined to be $1.06 \times 10^{-4}$ M and $7.51 \times 10^{-5}$ M, respectively (ESI). Interference study as shown in Fig. 6S (ESI) corroborates that F$^{-}$ and HP$_{2}$O$_{5}^{2-}$ are mutually interfering. Other anions in the study were non interfering.

**Conclusion**

In conclusion, coumarin-based fluorescent organogelator I has been designed and synthesized. The gelator forms stable gel from CHCl$_3$ -petroleum ether (1:1, v/v). Cooperative hydrogen bonding between phenolic –OH and 1,2,3-triazole ring as well as hydrophobic-hydrophobic interaction of the cholesteryl groups in I play crucial role in the formation of organogel. The stable gel is anion responsive. The gel phase is rapidly transformed into the sol state selectively in the presence of F$^{-}$ and HP$_{2}$O$_{5}^{2-}$ and thus validates their visual sensing over a series of other anions. Fluorescence study in solution also distinguishes these two anions from the other anions by showing considerable change in emission. In CH$_3$CN containing 0.5% DMSO, substantial quenching of emission of I in presence of F$^{-}$ is noticeable and useful in its distinction from other halides. In a similar way greater quenching of emission in presence of HP$_{2}$O$_{5}^{2-}$ ion is mentionable for its diagnosis from H$_2$PO$_4$ ion. Thus the compound I in this account is undoubtedly a new system that detects F$^{-}$ and HP$_{2}$O$_{5}^{2-}$ fluorimetrically as well as gel breaking process under appropriate conditions. Further insight along this direction is underway in our laboratory.

**Experimental**

**Syntheses:**

Chloro-acetic acid 17-(1,5-dimethyl-hexyl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopent[a]phenanthren-3-yl ester (2):

To a stirred solution of cholesterol (0.5 g, 1.29 mmol) in 20 mL dry CH$_2$Cl$_2$ was added chloroacetyl chloride (0.16 mL, 1.93 mmol) and pyridine (0.05 mL, 0.65 mmol) under nitrogenous atmosphere. The mixture was allowed to stir for 10 h at room temperature. After completion of reaction, the solvent was evaporated and the crude was extracted with CHCl$_3$ (3 × 30 mL). The organic layer was washed several times with water and separated and dried over Na$_2$SO$_4$. Evaporation of the solvent gave white solid compound. Recrystallization from petroleum ether afforded pure product 2 (0.58 g, yield 96%), mp 148 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ 5.37 (m, 1H), 4.72 (m, 1H), 4.03 (s, 2H),
To a stirred solution of compound 2 (0.5 g, 1.08 mmol) in CH$_2$CN (20 mL) NaN$_3$ was added (0.11 g, 1.6 mmol) and the reaction mixture was refluxed for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with 2% CH$_3$OH. Evaporation of the solvent gave the crude product which was purified by column chromatography using CHCl$_3$ to 1% CH$_3$OH in CHCl$_3$ as eluents to afford the pure compound 1 in 71% yield (0.027 g), mp 192°C.

Compound 3 (0.6 g, 1.28 mmol) was dissolved in ethanol (40 mL) and propargyl alcohol (0.12 mL, 1.92 mmol) was added to this solution followed by addition of 4 mL of saturated CaSO$_4$ solution and Cu turning (0.75 mg). Then the reaction mixture was refluxed for 6 h at 90°C. After completion, reaction mixture was filtered through celite bed. The filtrate was evaporated off and the crude mass was extracted with 2% CH$_3$OH in CHCl$_3$ and dried over anhydrous Na$_2$SO$_4$. Evaporation of the solvent gave the crude product which was purified by column chromatography using 70% ethyl acetate in petroleum ether to afford compound 4 (0.53 g, yield 78%), mp 178°C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.68 (s, 1H), 5.37 (d, 1H, $J$ = 4 Hz), 5.14 (s, 2H), 4.81 (s, 2H), 4.70 (m, 2H), 2.36 (d, 2H, $J$ = 8 Hz), 1.99–0.85 (m, 38H), 0.67 (s, 3H) (signal for –OH is not found due to broadening); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 165.7, 161.4, 149.2, 148.7, 144.9, 143.3, 142.4, 138.8, 124.9, 123.3, 113.8, 112.7, 112.1, 100.8, 62.8, 62.6, 56.6, 56.1, 51.0, 49.9, 42.2, 39.6, 39.5, 37.8, 36.8, 36.5, 36.1, 35.8, 31.8, 31.7, 28.2, 28.0, 27.6, 24.2, 23.8, 22.8, 21.0, 19.2, 18.7, 11.8; FTIR (KBr, cm$^{-1}$): 3391, 2935, 2867, 1725, 1627; HRMS (TOF MS$^+$): required 685.4091 (M$^+$ + Na$^+$), found 685.3961 (M$^+$ + Na$^+$).

A mixture of 6,7-Dihydroxycoumarin (0.1 g, 0.56 mmol) and Cs$_2$CO$_3$ (0.36 g, 1.12 mmol) was refluxed in dry CH$_2$CN for 2 h and then compound 6 (0.49 g, 0.84 mmol) was added to it. The reaction mixture was then allowed to reflux for 36 h. Then the organic solvent was evaporated under reduced pressure and water was added to the crude mass. Then reaction mixture was extracted with 2% CH$_3$OH in CHCl$_3$. Evaporation of the solvent gave the crude product which was purified by column chromatography using CHCl$_3$ to 1% CH$_3$OH in CHCl$_3$ as eluents to afford the pure compound 1 in 71% yield (0.027 g), mp 192°C.

References


