Synthesis and structural study of 3-anisyl-4-(4'-pyridyl(pyridinium))thieno[2,3-b]thienophenes

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A new class of co-facially oriented donor-acceptor thienothiophene 2 and its ionic analog 3 have been synthesized to investigate the presence of through-space vs through-bond charge transfer interaction. The key step is the double Dieckman cyclization on the ketene dithioacetal 5. Comparative 1H NMR spectral analysis of 2 and 3 suggests through-bond charge transfer between the π-deficient pyridinium ring and π-rich thienophene ring being the dominant interaction with the through-space charge transfer interaction in 3 making a relatively small contribution. The interpretation of UV-Visible data 2 and 3 also seem to support such a conclusion.

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Charge transfer (ct) interaction involving π-rich and π-deficient aromatic rings have been a subject of continuing interest on account of the involvement of this interaction in conducting materials, photonic devices, the host guest phenomena, crystal packing and self organized supramolecular systems1,2. In addition, ct phenomena are also widely implicated in reaction mechanisms and in a variety of biological functions3. The most attractive molecular systems which have been designed to display significant ct interaction include cyclophanes, tryptene analogs and 1,8-diarylnapthalenes4-7. In these systems, the ct interaction originates on account of fixation of donor (D) and (A) substituents at a short distance either in face-to-face (co-facial) or lateral orientations. Molecular systems in which D and A chromophores are separated by an extended saturated hydrocarbon spacers have also been studied for spectacular through-bond ct interactions8.

We envisaged that thienothiophene framework9, an analog of 10π-naphthalene system could also be exploited to develop potentially interesting ct systems by placing D and A groups at the peri (C3 and C4) positions. Towards this end, we have recently reported synthesis and structural analysis of 3-anisyl-4-(3'-N-methylypyridinium) thieno[2,3-b]thiophene iodide salt 1 (ref.10). However, detail 1H NMR, UV-Visible and single X-ray crystal structural analysis revealed the presence of weak intramolecular ct interaction in molecule 1. The key structural factors that work against effective through-space ct interaction include (a) much increased van der Waals separation (4.08 Å) between the pyridyl and anisyl chromophores and (b) unusually smaller torsional angles (being in the range of 39-44°) of pyridyl and anisyl groups with respect to the plane of the thienothiophene ring. These factors are responsible for poor HOMO-LUMO overlap leading to weak ct interaction in 1. In order to further probe the existence of through-space vs through-bond ct interaction, we now report synthesis and spectral studies of isomeric, 3-anisyl-4-(4'-pyridyl) thieno[2,3-b]thiophene 2 and its N-methyl salt 3 (Chart I).

Synthesis of 2 and 3

The synthetic scheme towards the target 2 (Scheme I) is similar to that used earlier for 1 (ref.10) and it entails the double Dieckman cyclization11 as the key step on the ketene dithioacetal intermediate 5. To start with, the known diketone 4 (ref.12) was condensed with CS2 and 2 equivalents of ethyl bromoacetate under anhydrous K2CO3/DMF conditions to afford ketene dithioacetal 5 as an oil. Upon treatment with sodium ethoxide in dry THF solvent, 5 underwent spontaneous double Dieckman cyclization to provide the desired thienothiophene diester 6 as a light yellow crystalline solid, mp 143-45 °C in 45% yield. Hydrolysis of 6 was achieved readily under
basic condition (KOH in DMSO, 100°C) to afford upon acidification diacid 7. Finally, thermal decarboxylation of 7 followed by SiO₂ chromatographic purification of the crude product gave the desired thienothiophene 2 in 30% yield, mp 72-74°C, M⁺ at m/z 323. Next, we converted compound 2 into the corresponding ionic N-methyl pyridinium salt 3 by treatment with methyl iodide in CH₃CN. The purpose to synthesise ionic salt 3 was to enhance the acceptor properties of the pyridyl ring in order to increase the ct interaction vis-a-vis the neutral analog 2. The neutral molecule 5 can be taken as a reference standard whose spectral properties can be compared with that of its ionic counterpart 3 to evaluate the extent of ct interaction in the latter system.

**NMR and UV-Visible spectral analysis of 2 and 3**

*A priori*, both through-space and through-bond ct interactions can be operative in ionic 3. In the event of through-space ct interaction, the protons associated with the anisyl ring in 3 are expected to experience deshielding effects (i.e., downfield shifts) in comparison to the neutral 2 on account of the overlap of HOMO of anisyl ring with the LUMO of acceptor pyridinium rings in 3. The magnitude of ∆δ (the
deshielding coefficient\(^{13}\) would give a qualitatively indication of the extent of through-space ct interaction in 3. On the other hand, through-bond ct interaction between the \(\pi\) -deficient pyridinium ring and the \(\pi\)-rich thienothiophene ring in 3 would result in the downfield shifts of the thienothiophene proton(s) as a consequence of electron withdrawal by the positively charged pyridinium ring. Accordingly, the downfield shifts of the protons associated with \(p\)-anisyl ring or the thienothiophene ring can form a basis for the qualitative assessment of through-space vs through-bond ct interaction in ionic 3 relative to the neutral reference 2.

The \(^1\)H NMR spectral data for compounds 2 and 3 are compiled in Table I and the signal assignments are based on relevant chemical shift positions and multiplicities of various protons. A perusal of Table I gives the relative position of various protons in the NMR spectra of compounds 2 and 3. Firstly, as expected, H(2') and H(3') protons on the pyridinium ring in 3 appear downfield by 0.68 and 0.42\(\delta\), respectively compared to 2 on account of electron withdrawal by the positively charged nitrogen of pyridinium ring. The thiopheno proton H(a) in molecule 3 experiences significant downfield shift of 0.43\(\delta\) relative to the neutral ring 2, so also the H(b) proton in 3 suffers deshielding, though to a lesser extent by 0.14\(\delta\). The deshielding of thienothiophene protons in molecule 3 may be attributed to direct \(\pi\)-delocalisation (through-bond charge transfer) from the thienothiophene ring to pyridinium ring. However, in context of though-space ct interaction, the deshieldings observed for the anisyl protons H(2) and H(3) in ionic 3 compared to the reference 2 are found to be rather small, being in the region of 0.06 to 0.10\(\delta\) only. In donor-acceptor \(\pi\)-stacked paracyclopahnes and 1,8-diarylnaphthalenes, the deshielding coefficients, \(\Delta\delta\) are reported to vary in the region between 0.5 to 1.5 \(\delta\) thereby indicating moderate to large through-space ct interaction in these systems\(^{6,7,14}\). Since, the magnitude of \(\Delta\delta\) for the anisyl protons in the case of 3 is rather small (a maximum of about 0.1\(\delta\)), we can infer that the through-space ct interaction in this molecule is not appreciable. However, large downfield resonance shifts of thienothiophene protons in 3 (0.42 to 0.68\(\delta\)) lead us to suggest the presence a dominant through-bond conjugation between the pyridinium ring and the thienothiophene in 3.

The UV-Vis spectrum of the neutral 2 showed two major absorptions at 234 nm (\(\varepsilon\) max 2\(\times\)10\(^4\)) and 275 nm (\(\varepsilon\) max 9\(\times\)10\(^3\)) as depicted in Figure 1. The lower wavelength absorption band could be predominantly of the n-\(\pi^*\) transition, whereas the longer wavelength absorption band may be attributed to \(\pi\)-\(\pi^*\) transitions. The UV-Vis spectrum of N-methyl pyridinium analog 3 showed three main absorption bands at 236.5 (\(\varepsilon\) max 3.6\(\times\)10\(^3\)), 275 (\(\varepsilon\) max 1.35\(\times\)10\(^3\)) and 348 nm (\(\varepsilon\) max 3.8\(\times\)10\(^3\)). Thieno[2,3-b]thiophene system\(^{15}\) is reported

<table>
<thead>
<tr>
<th>Proton</th>
<th>2 (^1)H NMR ((\delta), ppm)</th>
<th>3 (^1)H NMR ((\delta), ppm)</th>
<th>Chemical shift difference ((\Delta\delta)) between 3 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>H (a)</td>
<td>7.80 (1H, s)</td>
<td>8.23 (1H, s)</td>
<td>0.43</td>
</tr>
<tr>
<td>H(b)</td>
<td>7.55 (1H, s)</td>
<td>7.69 (1H, s)</td>
<td>0.14</td>
</tr>
<tr>
<td>H(2)</td>
<td>6.67 (2H, d, (J=8)Hz)</td>
<td>6.77 (2H, d, (J=8)Hz)</td>
<td>0.10</td>
</tr>
<tr>
<td>H(3)</td>
<td>6.96 (2H, d, (J=8)Hz)</td>
<td>7.02 (2H, d, (J=8)Hz)</td>
<td>0.06</td>
</tr>
<tr>
<td>H(2')</td>
<td>6.99 (2H, d, (J=5.5)Hz)</td>
<td>7.65 (2H, d, (J=5.5)Hz)</td>
<td>0.66</td>
</tr>
<tr>
<td>H(3')</td>
<td>8.26 (2H, d, (J=5.5)Hz)</td>
<td>8.68 (2H, d, (J=5.5)Hz)</td>
<td>0.42</td>
</tr>
<tr>
<td>O-CH₃</td>
<td>3.72 (3H, s)</td>
<td>3.76 (3H, s)</td>
<td>0.04</td>
</tr>
<tr>
<td>N-CH₃</td>
<td>-</td>
<td>4.23 (3H, s)</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 1 — UV-Vis spectra of 2 and 3 (plot I and II) in MeCN
to show main absorption bands at 278 and 292 nm, whereas the UV spectrum of N-methyl pyridinium iodide\textsuperscript{16} is reported to show a single major absorption at 258.8 nm. Thus, clearly the absorption band at 348 nm extending up to 400 nm in 3 is a new band which is not arising from any transition either from pyridinium ring or the thienothiophene ring. We propose that this new long wavelength band in 3 has its origin in the charge delocalised structure 3a which arises from "S" lone pair participation, as shown in Chart II. The resonance contribution from the delocalised structure 3a also finds support in the observed downfield shifts of thienothiophene protons in the \(^1\)H NMR of 3. It may be noted that long wavelength absorption bands are widely encountered in the planar donor-acceptor chromophoric systems by direct resonance delocalisation (through-bond interaction) as exemplified by cyanine dyes and push-pull systems\textsuperscript{17,18}. Thus, the presence of a new long wavelength band and downfield shifts of the thienothiophene protons together suggest the presence of a dominant through-bond charge transfer in 3. The presence of a weak through-space charge transfer interaction however cannot be discounted. It is noteworthy that unlike 3, no longer wavelength charge transfer absorption was observed in the recently reported isomeric system 1. This is presumably on account of the odd position of the nitrogen in the pyridinium ring which precludes direct \(\pi\)-electron delocalisation from the thienothiophene ring into the pyridinium ring.

In conclusion, we have developed the synthesis of a new class of donor-acceptor thienothiophene 2 and the ionic N-methyl pyridinium salt 3. A comparative analysis of high resolution \(^1\)H NMR and UV-Visible spectral studies of 2 and 3 reveal at best poor through-space ct interaction in 3. The dominant interaction seems to be arising from through-bond ct interaction. Currently, work is in progress to study conformational analysis and nonlinear optic properties of donor-acceptor thienothiophene systems.

**Experimental Section**

The chemicals and solvents for synthesis and column chromatography were purchased from S/D Fine Chemicals and Merck (India) and used as received. Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. IR spectra were recorded on a Shimadzu FTIR-420 spectrophotometer; \(^1\)H NMR spectra on a Bruker-AMX-500 spectrometer with TMS as an internal standard; mass spectra on GCMS-QP 5050A Shimadzu spectrophotometer; and UV-Visible spectra on a Shimadzu UV-Visible spectrophotometer UV-2100.

**Ketene thioacetal 5.** A solution of known diketone\textsuperscript{12} 4 (3.06 g, 12 mmoles) and freshly distilled carbon disulfide (1.52 mL, 30 mmoles) in dry DMF (15 mL) was added at room temperature to a vigorously stirred mixture of dry DMF (15 mL) containing anhyd. K\(_2\)CO\(_3\) (2.5 g) and a catalytic amount of tetrabutylammonium bromide (100 mg). The addition was completed during 30 min and then ethyl bromoacetate (2.67 ml, 24 mmoles) was added dropwise during 30 min. The reaction mixture was stirred for 24 hr, diluted with cold 5% aq. NaOH solution and extracted with diethyl ether. After water washing, the organic extract was dried over anhyd. Na\(_2\)SO\(_4\). Removal of the solvent gave a red oil which was purified by silica gel column chromatography (eluant: ethyl acetate-petroleum ether; 30:70) to afford 5 (60 %) as an unstable yellow oil. IR (oil film, \(\nu\) cm\(^{-1}\)): 2900, 1720, 1685, 1663, 1547, 1383, 1185, 1124, 1040, 955. The crude 5 was immediately used as such for the next reaction.

**3-(4-Methoxyphenyl)-4-(4-pyridyl)thieno[2,3-b]thiophene-2,5-diethylester 6.** The crude 5 (2.04 g, 4 mmoles, purity ca. 90 %) was dissolved in dry THF (20 mL) and added dropwise at 0 °C during 10 min to a stirred solution of sodium ethoxide prepared from 300 mg Na in dry THF (20 mL). The reaction was stirred at this temperature for 50 min and then poured onto crushed ice. A yellowish brown solid that separated out was filtered and washed thoroughly with water. The crude solid was purified by repeated crystallization from ethyl acetate-petroleum ether (1:3) to provide 6 as a light yellow solid, mp 143-45 °C in 45 % yield,IR (KBr, \(\nu\) cm\(^{-1}\)): 2905, 1706, 1685, 1663, 1547, 1222, 1167, 844; \(^1\)H NMR (200 MHz, CDCl\(_3\)):\(\delta\) 1.2 (3H, t, \(J= 7.5\) Hz), 2.85 (3H, t, \(J= 7.5\) Hz), 3.73 (3H, s) 4.1-4.2 (4H, two
Preparation of the diacid 7. The diester 6 (1.32 g, 3 mmoles) was dissolved in 20 mL of DMSO containing 10% aq. KOH (10 mL) and the reaction mixture heated at 100 °C for 10 hr. The reaction mixture was cooled, diluted with water and acidified with HCl to ca. pH 3. The precipitated diacid 7 was obtained as a light brown solid in 83% yield, mp 240-50 °C.

Preparation of the N-CH₃ salt 3. The thieno[2,3-b]thiophene 2 (1.32 mg) was dissolved in dry acetonitrile (2 mL) and freshly distilled CH₃I (2 mL) was added. The reaction mixture, which had turned dark brown, was cooled to room temperature, extracted with chloroform and filtered to remove the small amount of insoluble residue. The filtrate was concentrated and the crude product purified by SiO₂ column chromatography using petroleum ether as an eluant to provide the required product 2 as a pale yellow solid, m.p 72-74 °C in 30% yield, IR (KBr, ν cm⁻¹): 2980, 1603, 1403, 1350, 1180, 1100, 997, 920, 840, 821; ¹H NMR (500 MHz, CDCl₃): see Table I. MS (EI, 70 eV, m/z (%): 323(M⁺, 100), 293 (51) 279 (18), 246 (16), 149 (18), 132 (9); UV-Vis (CH₃CN): see Figure 1. Anal. Calcd for C₁₈H₁₃NO₅S₂: C, 16.37; H, 4.02; N, 4.33; S, 19.81. Found: C, 17.07; H, 4.25; N, 4.59; S, 20.07%.

Preparation of the diacid 7. The diester 6 (1.32 g, 3 mmoles) was dissolved in 20 mL of DMSO containing 10% aq. KOH (10 mL) and the reaction mixture heated at 100 °C for 10 hr. The reaction mixture was cooled, diluted with water and acidified with HCl to ca. pH 3. The precipitated diacid 7 was obtained as a light brown solid in 83% yield, mp 240-50 °C.

References