Pseudo-cyclic Face-to-face Rigid Structure Caused by the Intramolecular Ion Pair Effect

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Abstract: Six 3-methylpyridine zwitterions and six quinoline zwitterions were synthesized through the reaction of 4-hydroxycoumarins, p-benzoquinone and the corresponding N-aromatics. The novel pseudo-cyclic face-to-face rigid structure of the zwitterion was elucidated by 1H-NMR at different temperatures, and assumed to be caused by both the intramolecular ion pair attraction and the steric interaction.

Keywords: 4-Hydroxycoumarins; Zwitterion; Molecular structure.

1. Introduction

Recently, the compounds with cyclic structures derived from the [2.2] paracyclophane backbone 1 (Figure 1) have stimulated considerable interest due to their special properties and applications. 4,12-Bis(diphenylphosphino)-[2.2]-paracyclophane was shown to be an excellent transition metal ligand for the catalytic asymmetric hydrogenation of carbonyl groups [1-4]. The bridge-fluorinated paracyclophanes display intriguing chemical reactivity [5-7] and commercial applications [8-9]. The bridging ligands derived from paracyclophane have afforded the opportunity to investigate the role of π-stacking interactions in mediating electronic communication, as charge-transport was observed in double-stranded DNA [10-12]. It is believed that the cyclic face-to-face rigid structure of the paracyclophane moiety plays an important role in properties of these derivatives.
In a recent communication [13], we reported the synthesis of zwitterionic 4-hydroxycoumarin derivatives. We now describe the novel pseudo-cyclic face-to-face rigid structures of these zwitterions (Figure 2).

2. Results and Discussion

The zwitterionic 4-hydroxycoumarin derivatives are composed of hydroquinone, pyridine and 4-hydroxycoumarin planes. The pyridine and 4-hydroxycoumarin planes are joined to the hydroquinone core to form the pseudo-cyclic face-to-face structure (Figure 2).

The different $^1$H-NMR shifts of the two $\alpha$-protons located on the pyridine ring of $2b$ [13] indicated that the pyridine plane cannot rotate freely at room temperature, as it is known that if the pyridine ring can rotate freely, the two $\alpha$-protons do not give separate $^1$H-NMR signals. Moreover, when N-heterocyclic aromatics such as 3-methylpyridine and quinoline (which lack a C$_2$-symmetric axis through the nitrogen atom) were treated with 4-hydroxycoumarins and $p$-benzoquinone, both cis and trans products were obtained, due to the restricted rotation about the C-N bond. The results of these reactions are summarized in Tables 1 and 2.

These cis and trans products could not be separated by silica gel column chromatography. The assignment of the respective stereochemistry and their isomer ratios could however be established from the $^1$H-NMR spectra. For the 3-methylpyridinium zwitterion $3a$, the $\alpha$-proton next to the methyl group on the pyridine ring was predicted to only show a single peak in the aromatic region (Figure 3). The appearance of the two aromatic singlets, at $\delta$ 8.92 and 8.51 ppm, respectively, implied that both cis and trans isomers might be generated. Furthermore, the two aromatic singlets had a total integrated area equal to 1H, consistent with a mixture of the two isomers. The peak at $\delta$ 8.92 was attributed to the $\alpha$-proton (H2) adjacent to the methyl group of cis isomer, in which H2 was is further away from the shielding region of the oxyanion, and came at low fields relative to H2’ of the trans isomer. Thus the area ratio of 1.3:1 of the two aromatic singlets represents the cis and trans isomer ratio.
Table 1. The synthesis of 3-methylpyridinium zwitterions.

\[
\text{Cis} : \text{Trans} = 1.3:1
\]

| Entry | 4-HCs | Yield(%) | Product | Cis/Trans |
|-------|-------|----------|---------|-----------|
| 1     | ![4-HCs](image) | 35       | ![Product](image) | 1.3:1     |
| 2     | ![4-HCs](image) | 29       | ![Product](image) | 1.2:1     |
| 3     | ![4-HCs](image) | 42       | ![Product](image) | 1.3:1     |
| 4     | ![4-HCs](image) | 37       | ![Product](image) | 1.1:1     |
| 5     | ![4-HCs](image) | 31       | ![Product](image) | 1.1:1     |

\(^a\)Isolated. \(^b\)Determined by \(^1\)H-NMR
Table 2. The synthesis of quinolinium zwitterions.

\[
\text{4b(cis)} + \text{4b'(trans)} + \text{aqu. acetone} \rightarrow \text{rt, 24hr, 15%} \]

| Entry | 4-HCs | Yield(%)\(^a\) | Product | Cis/Trans\(^b\) |
|-------|-------|----------------|---------|-----------------|
| 1     | ![Image](image1.png) | 12 | ![Image](image2.png) | ![Image](image3.png) | 1:1.3 |
| 2     | ![Image](image4.png) | 9 | ![Image](image5.png) | ![Image](image6.png) | 1:1.4 |
| 3     | ![Image](image7.png) | 16 | ![Image](image8.png) | ![Image](image9.png) | 1:1.7 |
| 4     | ![Image](image10.png) | 13 | ![Image](image11.png) | ![Image](image12.png) | 1:1.3 |
| 5     | ![Image](image13.png) | 12 | ![Image](image14.png) | ![Image](image15.png) | 1:1.5 |

\(^a\)Isolated yield. \(^b\)Determined by \(^1\)H-NMR.
Figure 3. The $^1$H-NMR spectra of compounds 2a and 3a.

The chemical shifts and the integration of the peaks of the $^1$H-NMR spectrum did not change even when the sample of 2b and 4a was warmed. (Figures 4 and 5.) This showed that the zwitterionic 4-hydroxycoumarin derivatives were very stable. However, pyridium zwitterions are generally considered to be reactive species and unstable [14]. The characteristic features of the $^1$H-NMR spectra of the zwitterions at different temperatures indicated that the zwitterionic 4-hydroxycoumarin derivatives possessed a rigid backbone containing two defined face-to-face planes, just like [2.2]paracyclophanes do. However, [2.2]paracyclophane is a macrocyclic ring, and the zwitterions just were pseudo-cyclic.

Figure 4. The $^1$H-NMR spectra of compound 2b at 30 °C and 70 °C.
Figure 5. The $^1$H-NMR spectra of compound 4a at 30 °C and 80 °C.

Emadi et al. [15] have reported a trimeric compound 5 (Figure 6), with structural features similar to those of zwitterionic 4-hydroxycoumarin derivatives. In compound 5 the presence of conjugation between the naphthoquinone and the two (2-hydroxynaphthoquinone) subunits was suggested. This conjugation implied that the subunit could rotate along the bond joining the subunit to the quinone core and a rigid structure wasn’t generated.
Figure 6. The structure of compound 5.

The face-to-face rigid backbone of the zwitterions was assumed to be caused by both the intramolecular ion pair attraction and the steric interaction (Figure 7). The ion pair attraction made the 4-hydroxycoumarin ring tilt toward the pyridine ring until the equilibration between the ion pair attraction and the steric interaction was reached and the rings could remain stable at a certain angle. Conversely, the tilted 4-hydroxycoumarin ring constrained the pyridine from rotating freely through steric interactions.

Figure 7. The intramolecular ion pair attraction and steric interaction of the zwitterion.

3. Experimental

3.1. General

$^1$H-NMR spectra were measured at room temperature (except for the temperature dependence studies) on a Varian UNITY INOVA 500 MHz spectrometer using TMS as an internal standard. For the electrospray (ESI) MS analysis, a Finnigan LCQ Deca XP ion trap mass spectrometer equipped with a Microsoft Windows NT data system and an ESI interface was used. Elementary analysis was recorded on an Elementar Vario EL elementary analysis device. IR spectra were recorded on a Bruker TENSOR 37 spectrophotometer.

3.2. General procedure: synthesis of 4-hydroxycoumarin zwitterions

A mixture of 4-hydroxycoumarin (5 mmol), $p$-benzoquinone (1.08 g, 10 mmol) and the appropriate $N$-heterocyclic aromatic (10 mmol) was magnetically stirred in aqueous acetone (30 mL, v:v = 1:1) at room temperature for 24 h. The reaction mixture was filtered to afford a brown crude product which
was purified by column chromatography (silica gel, methanol-chloroform = 1:10) to give yellow compounds.

Cis and trans 3-(3,6-Dihydroxy-2-(3-methylpyridinium-1-yl)phenyl)-2-oxo-2H-chromen-4-olate (3a and 3a’): yield 39%; 3a:3a’ = 1.3:1; \(^1\)H-NMR (DMSO-\(d_6\)) \(\delta\) 2.25 (3H, s) ppm; IR: 3404, 3060, 1649, 1597, 1505, 1445 cm\(^{-1}\); ESI-MS (\(m/e\)): 360 (M-1); Anal. Calcd. for C\(_{21}\)H\(_{15}\)NO\(_5\): C, 69.80%; H, 4.18%; N, 3.88%. Found: C, 69.47%; H, 4.35%; N, 4.02%.

Cis and trans 3-(3,6-dihydroxy-2-(3-methylpyridinium-1-yl)phenyl)-8-methyl-2-oxo-2H-chromen-4-olate (3b and 3b’): yield 35%, 3b:3b’ = 1.3:1; \(^1\)H-NMR (DMSO-\(d_6\)) \(\delta\) 2.25 (3H, s), 2.21 (3H, s) ppm; IR: 3062, 1620, 1504, 1424, 1335, 1278 cm\(^{-1}\); ESI-MS (\(m/e\)): 374 (M-1); Anal. Calcd. for C\(_{22}\)H\(_{17}\)NO\(_5\): C, 70.39%; H, 4.56%; N, 3.73%. Found: C, 69.56%; H, 4.73%; N, 3.95%.

Cis and trans 3-(3,6-dihydroxy-2-(3-methylpyridinium-1-yl)phenyl)-7-methyl-2-oxo-2H-chromen-4-olate (3c and 3c’): yield 29%; 3c:3c’ = 1.2:1; \(^1\)H-NMR (DMSO-\(d_6\)) \(\delta\) 2.67 (3H, s), 2.29 (3H, s) ppm; IR: 2924, 1603, 1501, 1434, 1272 cm\(^{-1}\); ESI-MS (\(m/e\)): 374 (M-1); Anal. Calcd. for C\(_{22}\)H\(_{17}\)NO\(_5\): C, 70.39%; H, 4.56%; N, 3.73%. Found: C, 70.15%; H, 4.81%; N, 3.87%.
Cis and trans 3-(3,6-dihydroxy-2-(3-methylpyridinium-1-yl)phenyl)-6-methyl-2-oxo-2H-chromen-4-olate (3d and 3d\'): yield 42%; 3d:3d' = 1.3:1; ¹H-NMR (DMSO-d₆) δ 2.32 (3H, s), 2.24 (3H, s) ppm; IR: 3394, 1641, 1504, 1512, 1270 cm⁻¹; ESI-MS (m/e): 374 (M-1); Anal. Calcd. for C₂₂H₁₇NO₅: C, 70.39%; H, 4.56%; N, 3.73%. Found: C, 70.22%; H, 4.63%; N, 3.81%.

Cis and trans 3-(3,6-dihydroxy-2-(3-methylpyridinium-1-yl)phenyl)-2-oxo-2H-benzo[h]chromen-4-olate (3e and 3e\'): yield 37%; 3e:3e' = 1.1:1; ¹H-NMR (DMSO-d₆) δ 2.22 (3H, s) ppm; IR: 3068, 1638, 1478, 1271 cm⁻¹; ESI-MS (m/e): 410 (M-1); Anal. Calcd. for C₂₅H₁₇NO₅: C, 72.99%; H, 4.16%; N, 3.40%. Found: C, 72.67%; H, 4.57%; N, 3.76%.
Cis and trans 2-(3,6-dihydroxy-2-(3-methylpyridinium-1-yl)phenyl)-3-oxo-3H-benzo[f]chromen-1-olate (3f and 3f'): yield 31%; 3f:3f' = 1.1:1; $^1$H-NMR (DMSO-$d_6$) $\delta$ 2.24 (3H, s) ppm; IR: 3059, 1632, 1507, 1266 cm$^{-1}$; ESI-MS ($m/e$): 410 (M-1)$^-$; Anal. Calcd for C$_{25}$H$_{17}$NO$_5$: C, 72.99%; H, 4.16%; N, 3.40%. Found: C, 72.63%; H, 4.51%; N, 3.69%.

Cis and trans 3-(3,6-dihydroxy-2-(quinolinium-1-yl)phenyl)-2-oxo-2H-chromen-4-olate (4a and 4a'): yield 15%, 4a(cis):4a'(trans) = 1:1.6; IR: 3093, 1639, 1513, 1274 cm$^{-1}$; ESI-MS ($m/e$): 396 (M-1)$^-$; Anal. Calcd for C$_{24}$H$_{15}$NO$_5$: C, 72.54%; H, 3.80%; N, 3.52%. Found: C, 72.55%; H, 3.91%; N, 3.65%.
Cis and trans 3-(3,6-dihydroxy-2-(quinolinium-1-yl)phenyl)-8-methyl-2-oxo-2H-chromen-4-olate (4b and 4b') : yield 12%; 4b(cis):4b'(trans) = 1:1.3; \(^1\)H-NMR (DMSO-\(d_6\)) \(\delta\) 9.39 (0.56H, s), 8.83 (0.44H, br), 2.10 (3H, s) ppm; IR: 3391, 1635, 1516, 1274 cm\(^{-1}\); ESI-MS (\(m/e\)): 410 (M-1\(^-\)), Anal. Calcd for C\(_{25}\)H\(_{17}\)NO\(_5\): C, 72.99%; H, 4.16%; N, 3.40%. Found: C, 72.74%; H, 4.32%; N, 3.55%.

Cis and trans 3-(3,6-dihydroxy-2-(quinolinium-1-yl)phenyl)-7-methyl-2-oxo-2H-chromen-4-olate (4c and 4c') : yield 9%; 4c (cis):4c'(trans) = 1:1.4; \(^1\)H-NMR (DMSO-\(d_6\)) \(\delta\) 2.24 (3H, s) ppm, IR: 3432, 1605, 1508 cm\(^{-1}\); ESI-MS (\(m/e\)): 410 (M-1\(^-\)); Anal. Calcd. for C\(_{25}\)H\(_{17}\)NO\(_5\): C, 72.99%; H, 4.16%; N, 3.40%. Found: C, 72.77%; H, 4.33%; N, 3.46%.
Cis and trans 3-(3,6-dihydroxy-2-(quinolinium-1-yl)phenyl)-6-methyl-2-oxo-2H-chromen-4-olate (4d and 4d'): yield 16%, 4d:4d' = 1:1.7; $^1$H-NMR (DMSO-$_d_6$) $\delta$ 2.25 (3H, s) ppm; IR: 3366, 1641, 1512, 1277 cm$^{-1}$; ESI-MS ($m/e$): 410 (M-1)$^-$; Anal. Calcd. for C$_{25}$H$_{17}$NO$_5$: C, 72.99%; H, 4.16%; N, 3.40%. Found: C, 72.83%; H, 4.26%; N, 3.43%.

Cis and trans 3-(3,6-dihydroxy-2-(quinolinium-1-yl)phenyl)-2-oxo-2H-benzo[h]chromen-4-olate (4e and 4e'): yield 13%; 4e:4e' = 1.3:1; IR: 3090, 1638, 1578, 1524, 1272 cm$^{-1}$; ESI-MS ($m/e$): 410 (M-1)$^-$;
Anal. Calcd. for C$_{28}$H$_{17}$NO$_5$: C, 75.16%; H, 3.83%; N, 3.13%. Found: C, 75.06%; H, 3.93%; N, 3.28%.

*Cis* and *trans* 2-(3,6-dihydroxy-2-(quinolinium-1-yl)phenyl)-3-oxo-3H-benzo[f]chromen-1-olate (4f and 4f'): yield 12%, 4f:4f' = 1:1.5; IR: 3094, 1629, 1512, 1270 cm$^{-1}$; ESI-MS (m/e): 410 (M-1); Anal. Calcd for C$_{28}$H$_{17}$NO$_5$: C, 75.16%; H, 3.83%; N, 3.13%. Found: C, 75.31%; H, 3.98%; N, 3.24%.
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*Sample Availability:* Samples of the compounds are available from the authors.

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