Intramolecular cation–π interactions control the conformation of nonrestricted (phenylalkyl)pyridines†

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NOEsy and fluorescence spectroscopy reveal that conversion of conformationally flexible (phenylalkyl)pyridines into their corresponding *N*-methyl-pyridinium iodides results in intramolecular π-stacking.

Aromatic interactions have been widely used for template directed and asymmetric syntheses,[1–4] with the conformation of interacting molecules having been proposed to be controlled by aromatic stacking interactions.[5–7] This type of stacking interaction is also important in biological systems, where they have been implicated in a number of biomolecular recognition events.[8,9] A number of model systems have been proposed to explore these stacking phenomena,[10–12] with a range of spectroscopic techniques used to probe both inter- and intramolecular interactions.[10,13,14] However, as Cozzi and co-workers have recently discussed,[15] it is often difficult to demonstrate that aromatic–aromatic interactions are solely responsible for conformational control.[16]

One potentially powerful class of stacking effects employs supramolecular cation–π interactions.[17] This type of stacking event is known to be important in biological systems,[18,19] playing important roles in binding of the pyridinium ring of NAD^+ to tryptophan in the active sites of enzymes,[20] as well as in the stacking of positively charged alkylated DNA bases in excision repair enzymes.[21] Pyridinium cation–π interactions have also been used as a control element for supramolecular chemistry to form host–guest complexes of anions,[22] and to control the helical architecture of polyphenylenes that contain a central dimethylaminopyridinium fragment.[23] Yamada *et al.* have also demonstrated that pyridinium cation–π interactions can be used to bias the conformation of amide derivatives **1** and **2** (Fig. 1) that has proven to be useful for asymmetric synthesis.[17,24–27]

However, it should be noted that many of the pyridinium cation–π interactions described to date have been reported for conformationally restricted substrates that favour the occurrence of stacking (Fig. 1). Consequently, we decided to determine whether pyridinium cation–π interactions could be used to control conformationally non-restricted pyridiniums, since this would enable this design element to be applied to a wider range of systems.

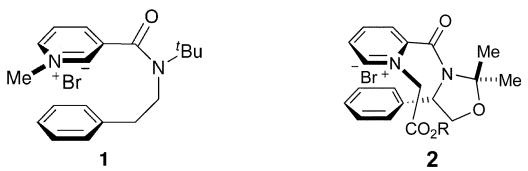

Fig. 1 Conformationally restricted π-stacked pyridinium systems.

The simple intramolecular strategy that was proposed to explore stacking interactions in conformationally mobile pyridyl species is shown in Fig. 2. In this approach, we wished to determine whether *N*-methylation of a non-restricted *para*-substituted pyridine species **3** linked to an aryl group *via* an alkyl chain would result in formation of a stacked pyridinium species **4**.[28]

Therefore, pyridines containing ethyl, *n*-propyl and *n*-butyl linkers were prepared in 35–40% overall yield, *via* Grignard addition of the appropriate phenylalkyl magnesium bromide to isonicotinonitrile, followed by Wolff–Kishner reduction of the resultant ketones. The resultant pyridines **5a–c** were then converted to their corresponding *N*-methyl-pyridinium iodides **6a–c** in 70–94% yield *via* treatment with methyl iodide in acetone (Scheme 1).[29,30]

The presence of any aromatic–aromatic association within pyridinium salts **6a–c** in solution was probed *via* NOEsy, since this approach had been used previously to demonstrate the presence of stacking in more rigid pyridinium species. It was first demonstrated that pyridines **5a–c** exhibited no NOEsy crosspeaks between their pyridyl and phenyl rings, thus indicating that no intramolecular aromatic–aromatic interactions were present. Conversely, analysis of the NOEsy spectra of *N*-methyl-pyridinium salts **6a–c** revealed distinct crosspeaks between the H_3 protons of their pyridinium fragments and their $H_{2'}$ phenyl protons (shown for **6b** in Fig. 3).[31]

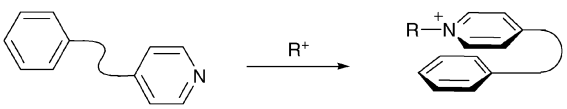

Fig. 2 Does alkylation of conformationally mobile phenylalkylpyridine **3** result in intramolecular stacking of the *N*-alkyl-pyridinium salt **4**?

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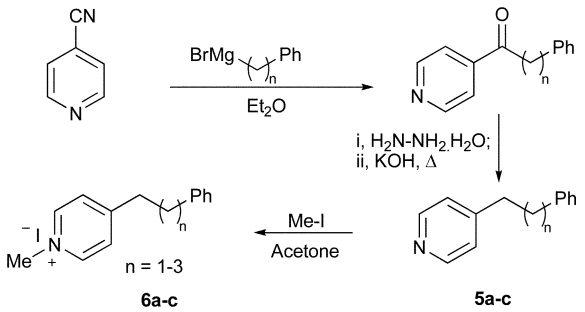

Scheme 1 Synthesis of *N*-methyl-pyridinium salts **6a–c**.

Therefore, irradiation of the pyridinium H_3-protons (~7.80 ppm) of *N*-methyl-pyridinium salts **6a**, **6b** and **6c** resulted in 0.28%, 0.15% and 0.07% NOE enhancements of their respective phenyl $H_{2'}$-protons (~7.20 ppm). Consequently, these NOEsy studies clearly indicated that *N*-methylation of pyridines **5a–c** had resulted in conformational change occurring to bring the pyridinium and phenyl fragments of their resultant iodide salts **6a–c** into close proximity.

Whilst these NOEsy experiments suggested the presence of intramolecular cation–π interactions, we sought further evidence for this phenomenon using fluorescence spectroscopic techniques that had been used previously to probe cation–π interactions in other types of pyridinium systems. In these cases, the presence of excimer fluorescent emissions was used to confirm that aromatic–aromatic interactions were present.[32,33]

Excitation of 0.6 μM solutions of the parent pyridines **5a–c** in dichloromethane at 260 nm resulted in no significant fluorescence. However, excitation of the corresponding *N*-methyl-pyridinium salts **6a–c** resulted in significant (6 to 50 fold) fluorescent enhancements under identical conditions (Fig. 4). Importantly, the fluorescence spectrum of *N*-methyl-pyridinium iodide (in the presence and absence of 1.0 equiv. of benzene) revealed no significant fluorescent enhancement. This suggests that the large fluorescent enhancement observed for pyridinium salts **6a–c** was a consequence of intramolecular π–π-stacking excimer emission. The relative order of fluorescent enhancement of pyridinium salts **6b** > **6a** > **6c** (50, 23 and 6 fold, respectively) may reflect the fact that pyridinium salt **6b** contains a C_3-linker that is the optimal length for 'face–face' π–π interactions to occur,[34] which in turn would lead to the largest fluorescence response. This is in contrast to the non-optimal orientations of the aryl rings of pyridinium salts **6a** and **6c** that contain C_2- and C_4-linkers,

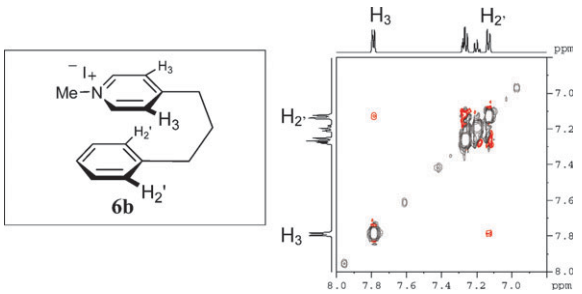

Fig. 3 Structure and selected region of the NOEsy spectrum of *N*-methyl-pyridinium iodide **6b**.

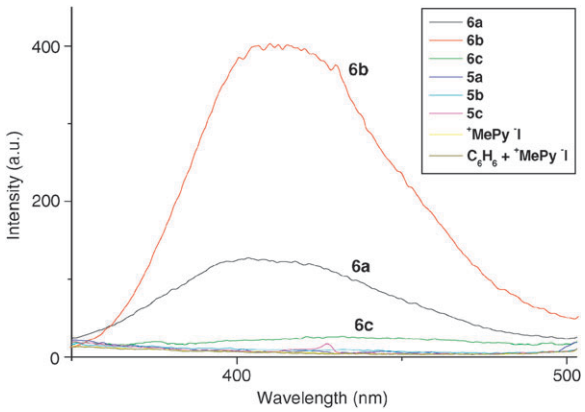

Fig. 4 Comparative fluorescence spectra of pyridines **5a–c** and *N*-methyl-pyridinium salts **6a–c** (λ_{ex} = 260 nm, 1 × 10^{-6} M, CH_2Cl_2).

respectively, whose lower fluorescence responses are likely to result from non-parallel interactions leading to weaker emissions. Indeed, whilst pyridinium salt **6a** exhibits the largest NOE enhancement between its $H_3/H_{2'}$ protons, indicating that its aryl fragments are in close proximity, it displays a lower fluorescent enhancement than the C_3-linked pyridinium salt **6b**, which implies that its C_2-linker is too short to maximise parallel face–face π-interactions. Conversely, the C_4-linker of pyridinium salt **6c** appears to be too long for efficient interaction of its pyridinium and aryl fragments to occur, with the weakest NOE and fluorescent responses being observed accordingly.

In conclusion, we have used NOEsy and fluorescence spectroscopy to demonstrate that *N*-methyl-pyridinium salts exhibit intramolecular stacking in solution. We anticipate that this demonstration of the generality of this effect in simple systems will result in this tool for conformational control being used more widely for applications in other synthetic, catalytic and bioorganic scenarios.

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Notes and references

1 D. B. Amabilino and J. F. Stoddart, *Chem. Rev.*, 1995, **95**, 2725–2828.
2 H. C. Kolb, P. G. Andersson and K. B. Sharpless, *J. Am. Chem. Soc.*, 1994, **116**, 1278–1291.
3 B. M. Trost, D. O'Krongly and J. L. Belletire, *J. Am. Chem. Soc.*, 1980, **102**, 7595–7596.
4 M. Keller, C. Lehmann and M. Mutter, *Tetrahedron*, 1999, **55**, 413–422.
5 G. J. Gabriel and B. L. Iverson, *J. Am. Chem. Soc.*, 2002, **124**, 15174–15175.
6 G. J. Gabriel, S. Sorey and B. L. Iverson, *J. Am. Chem. Soc.*, 2005, **127**, 2637–2640.
7 M. Weck, A. R. Dunn, K. Matsumoto, G. W. Coates, E. B. Lobkovsky and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 1999, **38**, 2741–2745.
8 K. M. Guckian, B. A. Schweitzer, R. X. F. Ren, C. J. Sheils, D. C. Tahmassebi and E. T. Kool, *J. Am. Chem. Soc.*, 2000, **122**, 2213–2222.
9 G. B. McGaughey, M. Gagne and A. K. Rappe, *J. Biol. Chem.*, 1998, **273**, 15458–15463.
10 C. A. Hunter, K. R. Lawson, J. Perkins and C. J. Urch, *J. Chem. Soc., Perkin Trans. 2*, 2001, 651–669.

11 E. A. Meyer, R. K. Castellano and F. Diederich, *Angew. Chem., Int. Ed.*, 2003, **42**, 1210–1250.
12 M. L. Waters, *Curr. Opin. Chem. Biol.*, 2002, **6**, 736–741.
13 S. L. Cockroft, J. Perkins, C. Zonta, H. Adams, S. E. Spey, C. M. R. Low, J. G. Vinter, K. R. Lawson, C. J. Urch and C. A. Hunter, *Org. Biomol. Chem.*, 2007, **5**, 1062–1080.
14 C. A. Hunter, *Chem. Soc. Rev.*, 1994, **23**, 101–109.
15 G. Dell'Anna, M. Benaglia, L. Raimondi and F. Cozzi, *Org. Biomol. Chem.*, 2007, **5**, 2205–2206.
16 Y. El-Azizi, A. Schmitzer and S. K. Collins, *Angew. Chem., Int. Ed.*, 2006, **45**, 968–973.
17 S. Yamada, T. Misono and S. Tsuzuki, *J. Am. Chem. Soc.*, 2004, **126**, 9862–9872.
18 H. Ritter, F. Koch-Nolte, V. E. Marquez and G. E. Schulz, *Biochemistry*, 2003, **42**, 10155–10162.
19 D. T. Major and J. L. Gao, *J. Am. Chem. Soc.*, 2006, **128**, 16345–16357.
20 S. Yamamoto-Katayama, M. Ariyoshi, K. Ishihara, T. Hirano, H. Jingami and K. Morikawa, *J. Mol. Biol.*, 2002, **316**, 711–723.
21 B. F. Eichman, E. J. O'Rourke, J. P. Radicella and T. Ellenberger, *EMBO J.*, 2003, **22**, 4898–4909.
22 W. J. Belcher, M. Fabre, T. Farhan and J. W. Steed, *Org. Biomol. Chem.*, 2006, **4**, 781–786.
23 J. M. Heemstra and J. S. Moore, *Chem. Commun.*, 2004, 1480–1481.
24 S. Yamada, *Org. Biomol. Chem.*, 2007, **5**, 2903–2912.
25 S. Yamada, Y. Morimoto and T. Misono, *Tetrahedron Lett.*, 2005, **46**, 5673–5676.
26 S. Yamada, J. Yamamoto and E. Ohta, *Tetrahedron Lett.*, 2007, **48**, 855–858.
27 S. Yamada and C. Morita, *J. Am. Chem. Soc.*, 2002, **124**, 8184–8185.
28 For a related study that explored the cation–π interactions of sterically constrained pyridinium species see: M. J. Rashkin, R. M. Hughes, N. T. Calloway and M. L. Waters, *J. Am. Chem. Soc.*, 2004, **126**, 13320–13325.
29 E. Reimann, J. Speckbacher and H. Lotter, *Arch. Pharm.*, 1987, **320**, 385–393.
30 E. Reimann, J. Speckbacher and J. Schunemann, *Arch. Pharm.*, 1990, **323**, 35–39.
31 The resonances of pyridines **5a–c** and *N*-methyl-pyridiniums **6a–c** were assigned by consideration of their chemical shifts and coupling constants of their ^{1}H NMR spectra.
32 A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher and T. E. Rice, *Chem. Rev.*, 1997, **97**, 1515–1566.
33 Fluorescence spectroscopy has been used to probe intermolecular π–cation interactions of pyridiniums. See: T. Ishida, S. Ibe and M. Inoue, *J. Chem. Soc., Perkin Trans. 2*, 1984, 297–304; I. Willner, S. Marx-Tibbon, S. Cohen, Y. Eichen and M. Kaftori, *J. Phys. Org. Chem.*, 1997, **10**, 435–444.
34 Recent *ab initio* calculations on π–cation interactions of *N*-methyl-pyridiniums with benzene revealed that a slipped parallel 'face–face' orientation of their aryl rings was predicted to be most favourable, see: S. Tsuzuki, M. Mikami and S. Yamada, *J. Am. Chem. Soc.*, 2007, **129**, 8656–8662.

