DOI: 10.1002/asia.200800255

Solid-State Structures and Solution Analyses of a Phenylpropylpyridine *N*-Oxide and an *N*-Methyl Phenylpropylpyridine

Isabella Richter,[a] Mark R. Warren,[a] Jusaku Minari,[b] Souad A. Elfeky,[a] Wenbo Chen,[a] Mary F. Mahon,[a] Paul R. Raithby,*[a] Tony D. James,[a] Kazuo Sakurai,[b] Simon J. Teat,[c] Steven D. Bull,[a] and John S. Fossey*[a]

Abstract: The crystal structures of phenylpropylpyridine-*N*-oxide and *N*-methyl-phenylpropylpyridinium iodide are compared, revealing that hydrogen bonding with the solvent molecule plays an important role in the *N*-oxide compound, whilst electrostatic interactions are predominant in controlling the solid-state orientation of the *N*-methylated compound. Fluorescence spectroscopy and NOESY indicate that in contrast to the previously reported pyridinium iodide, the *N*-oxide is not subject to intramolecular π-stacking, as judged by excimer emission and a lack of corresponding cross peaks, respectively.

Keywords: cations · fluorescence · hydrogen bonds · alkylpyridines · π-stacking

Introduction

Aromatic–aromatic interactions are often required for a high degree of control in asymmetric synthesis,[1–4] and π-stacking interactions have been implicated in a number of template directed syntheses.[5–7] Stacking interactions are also proposed to be vital in many biological recognition scenarios.[8–12] Model systems have been developed to probe these interactions;[13–15] however the difficulty for demonstrating that aromatic–aromatic interactions are solely responsible for conformational control is well known.[16,17] In contrast to more conformationally biased systems that have been exploited for asymmetric synthesis and control supramolecular architecture,[18–21] we recently demonstrated that subtle intramolecular cation–π interactions of flexibly linked, conformationally mobile pyridinium species (e.g., compound **1** in Figure 1) could be detected using fluorescence spectroscopy.[22,23]

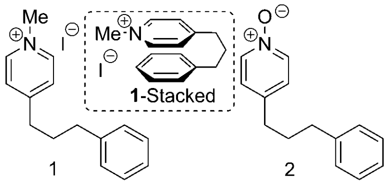

Figure 1. Phenylalkylpyridine derivatives **1** and **2**.

Whilst our interest in *N*-alkylpyridinium structures (**1**) stems from a desire to understand the conformation of catalytic species and their implications for (stereo)selectivity, we wished to probe the solid-state properties of cation–π motifs to enable comparison of solution and solid-state data. Avasthi et al. have shown that propylene linked pyrazolo [3,4-*d*]pyrimidines favor folded conformations in the solid state.[24,25] We had previously reported strong evidence for π-stacking of the cationic compound **1** in solution, hence we

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[a] I. Richter, M. R. Warren, S. A. Elfeky, W. Chen, M. F. Mahon,
Prof. P. R. Raithby, T. D. James, S. D. Bull, Dr. J. S. Fossey[+]
Department of Chemistry
The University of Bath
Claverton Down, Bath, BA2 7AY (UK)
Fax: (+44) 1225386231
E-mail: j.s.fossey@bham.ac.uk
p.r.raithby@bath.ac.uk

[b] J. Minari, K. Sakurai
Current Address: Faculty of Environmental Engineering
Department of Chemical Process and Environments
The University of Kitakyushu, 1-1, Hibikino, Wakamatsu-ku
Kitakyushu, Fukuoka, (Japan)

[c] S. J. Teat
Advanced Light Source
Lawrence Berkeley National Laboratory
Berkeley, CA 94720 (USA)

[+] *New Address*: School of Chemistry
University of Birmingham
Edgbaston, Birmingham, B15 2TT (UK)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.200800255.

anticipated that this structure might also display π-stacking in the solid state, and therefore decided to probe its solid-state structure/orientation. Consequently, we now report the solid-state structure of *N*-methyl-pyridinium salt **1** and the closely related neutral phenylalkylpyridine *N*-oxide derivative **2**.

Results and Discussion

Single Crystal X-Ray Diffraction

Though compound **1** was a little sensitive to light in solution, small plate-like crystals were obtained and found to be stable in ambient conditions. These crystals of **1** were suitable for diffraction analysis utilising the diffraction facilities on Beamline 11.3.1 at the ALS, Lawrence Berkeley National Laboratory, and its molecular and crystal structures are illustrated in Figures 2 and 3, respectively.

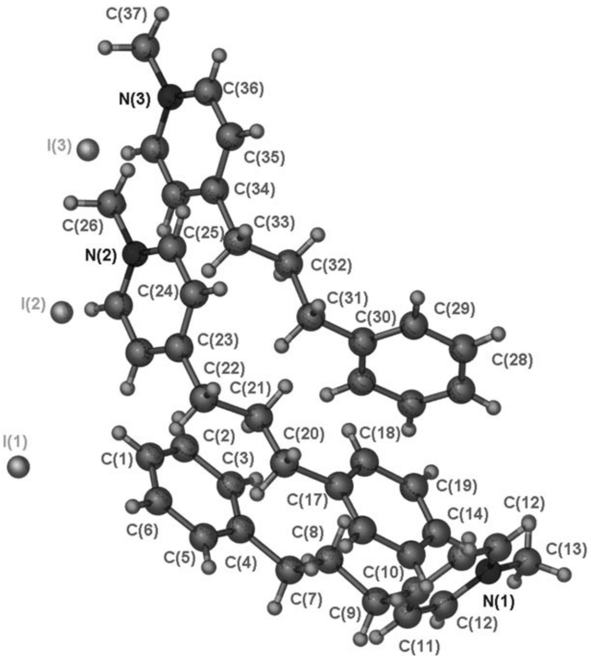

Figure 2. The crystal structure of $[(C_6H_5)(CH_2)_3(C_5H_4N(CH_3))]^+I^-$ **1** showing the three units with atomic numbering scheme. The two halves of the pyridine ring (N(1), C(10)–C(12)) are related by the symmetry operation *x*, 1.5−*y*, *z*, and all the other halves of the rings by the symmetry operation *x*, 0.5−*y*, *z*.

Abstract in Japanese:

不斉合成においては芳香環どうしの相互作用が重要な役割をになう。特にπスタッキングは多くの鋳型合成において中心的な働きをする。我々はこのような芳香環相互作用のモデルとして、フェニルアルキルピリジン誘導体の立体配座を蛍光分光法を用いて調べてきた。フェニルアルキルピリジンN-オキサイドとNメチルフェニルアルキルピリジンの結晶構造を精密なX線回折法によって決定したところ、固体中での構造形成においては、N-オキサイド化合物では溶媒との水素結合が重要な役割をしているのに対して、N メチル化合物では静電的相互作用が重要であることが判明した。蛍光分光法や2次元 NMR から、N-オキサイド化合物は分子内での芳香環相互作用がないことが分かっていたが、この原因は、今回の構造解析より、溶媒との相互作用が支配的であるためと考えらる。

Compound **1** crystallises in the orthorhombic space group *Pnma* with $Z=12$, that is, with three structurally similar, independent half molecules in the crystallographic asymmetric unit. Each cation sits on a crystallographic mirror plane, which generates the other half of the molecule. However, there are subtle differences between the three molecules. In two of the three cations, namely, cation (a) (C(1)–C(13)) and cation (b) (C(14)–C(26)), the phenyl rings C(1)–C(6) and C(14)–C(19), respectively, lie in the crystallographic mirror planes, while the corresponding pyridine rings (N(1), C(10)–C(12)) and (N(2), C(23)–C(25)) are bisected by the crystallographic mirror plane. This means that the dihedral angle between the phenyl and pyridine ring in each molecule is precisely 90° by crystallographic symmetry. However, in the third molecule, cation (c) (C(27)–C(37)) both the phenyl ring (C(27)–C(30)) and the pyridine ring (N(3), C(34)–C(36)) are bisected by crystallographic mirror planes so that these planes are not required to be perpendicular by crystal symmetry and the dihedral angle between the planes of these two rings is 62.5°. The torsion angles along the aliphatic chains in the three molecules are all 180° by crystal symmetry. The three half iodine anions also sit on crystallographic mirrors. The bond parameters within the cations lie within the normal ranges.

The crystal packing (Figure 3) shows that electrostatic cation–anion interactions dominate in the molecule. The anions lie in the channels parallel to the crystallographic *c* axis with the polar $(C_5H_4N(CH_3))$ groups pointing towards these anion channels. The cations are arranged so that adjacent groups have their polar end groups pointing in opposite directions. There is little indication of either hydrogen bonding or of CH–π interactions between the cations.[26]

To allow comparison between different functionality, crystallisation of a number of structural variations was attempted. Despite failing to obtain suitable crystals from related cationic alkyl and benzyl halide and triflate salts, we were delighted to obtain crystals of the aquated compound **2** suitable for X-ray diffraction analysis, the molecular and crystal structure of which is shown in Figures 4 and 5.

The aquated compound $[(C_6H_5)(CH_2)_3(C_5H_4N^+{-}O^-)]H_2O$ **2** crystallises in the orthorhombic space group *Pcab* (non-standard setting of *Pbca*, No. 61) with $Z=8$. The bond parameters in the unique molecule lie within the expected ranges and the dihedral angle between the phenyl ring (C(9)–C(14)) and the pyridine ring (N(1), C(1)–C(5)) is only 4.3°, so that within the molecule in the solid state, these rings are almost parallel but the distance between the centroids of the two rings, at 6.08 Å, excludes the possibility of intramolecular π–π-stacking. The observed dihedral angle is comparable to the crystallographically constrained angles of 62.5° and 90.0° in **1**. The torsion angles C(9)−C(8)−C(7)−C(6) and C(3)−C(6)−C(7)−C(8) are 67.2° and 70.3°, respectively.

The intermolecular interactions are dominated by the hydrogen bonding network between the solvent water molecule and the oxygen atom of the *N*-oxide compound. Strands of hydrogen bonds run along the *a* axis through the

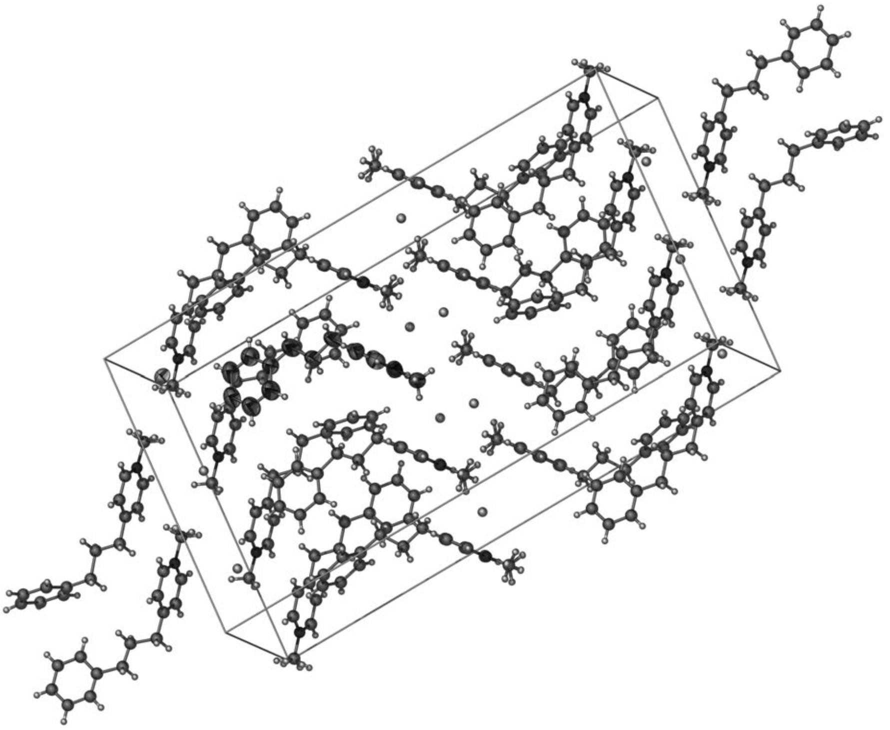

Figure 3. Crystal packing of **1** showing the channels of I^- ions running parallel to the *c* axis.

crystal (Figure 5) and the parameters for the O(2)–H(2B)···O1 and O(2)–H(2A)···O(1) hydrogen bonds are H(2B)···O(1), 2.01 Å, O(2)···O(1), 2.91 Å, O(2)–H(2B)···O(1), 173.9°, and H(2A)···O(1), 2.01 Å, O(2)···O(1), 2.89 Å, O(2)–H(2A)···O(1), 165.3°, respectively, where the two O(1) atoms are related to the O(2) atom by the symmetry operations x, y, z and $0.5+x$, $1.5-y$, z.[27]

Spectroscopy

We previously reported that NOE provided us with qualitative information on intramolecular interactions in **1** and related structures.[22] Under comparable conditions, we could not confidently ascribe a stacking nature between the pyridyl *N*-oxide and phenyl rings based on the NOESY spectrum of **2**, which suggests that intramolecular interactions in the cation of **1** are not equivalent to those of the overall neutral unimolecular *N*-oxide **2**.

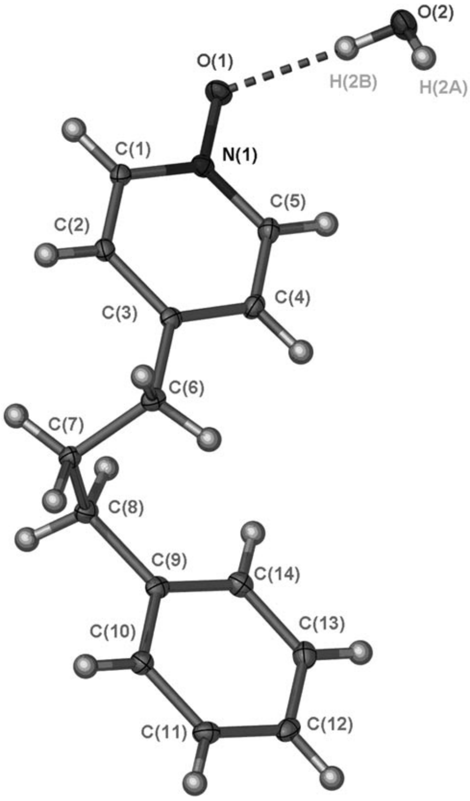

Figure 4. Crystal structure of one unit of $[(C_6H_5)(CH_2)_3(C_5H_4N^+\text{-}O^-)]H_2O$ **2**. Anisotropic displacement parameters have been drawn at the 50 % probability level and atom numbering scheme is also shown.

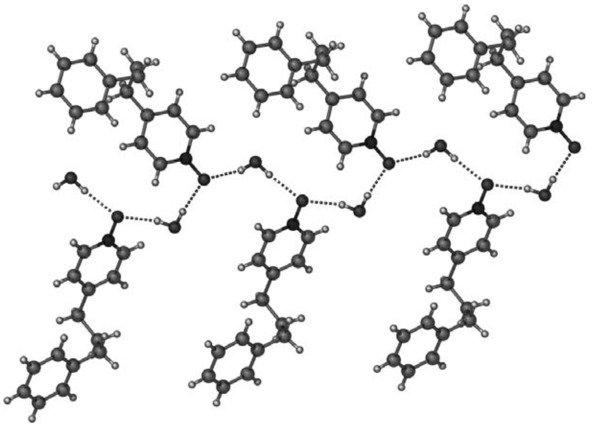

Figure 5. The crystal packing of **2**.H_2O showing hydrogen bonding along the *a* axis.

Consequently we utilised fluorescence spectroscopy as a tool for the analysis of π–π interactions in solution, that is, excimer emission as evidence for π-stacking as depicted in the stacked representation in Figure 1.

A pre-scan of **2** (conc $= 1\times10^{-4}$ M in CH_2Cl_2) suggested an excitation wavelength of 315 nm leading to an emission at ≈380 nm should be used. If this observed emission were a result of π-stacking (excimer emission), a corresponding shorter wavelength peak should be observed in *N*-oxide **4** which would not be subject to the same kind of intramolecular π-stacking. To bench mark the fluorescence spectroscopy results, spectra of *N*-methyl phenylpropylpyridinium iodide **1**, *N*-methyl phenylpropylpyridine **3**, and pyridine *N*-methyl pyridinium iodide **5** were recorded under the same conditions and the results are presented in Figure 6. Under these conditions, **1**, **3** and **5** elicit the same kind of response as we already reported under different conditions, namely, excimer emission from **1** (≈400 nm), accompanied by an absence of emission from **3** and **5** at the same wavelength. However, pyridine *N*-oxide **4** has a relatively intense fluorescence in the same region, which is accompanied with a less intense peak from phenylpropylpyridine *N*-oxide **2** in the same region of the spectrum, and as such, no excimer peaks were detected.

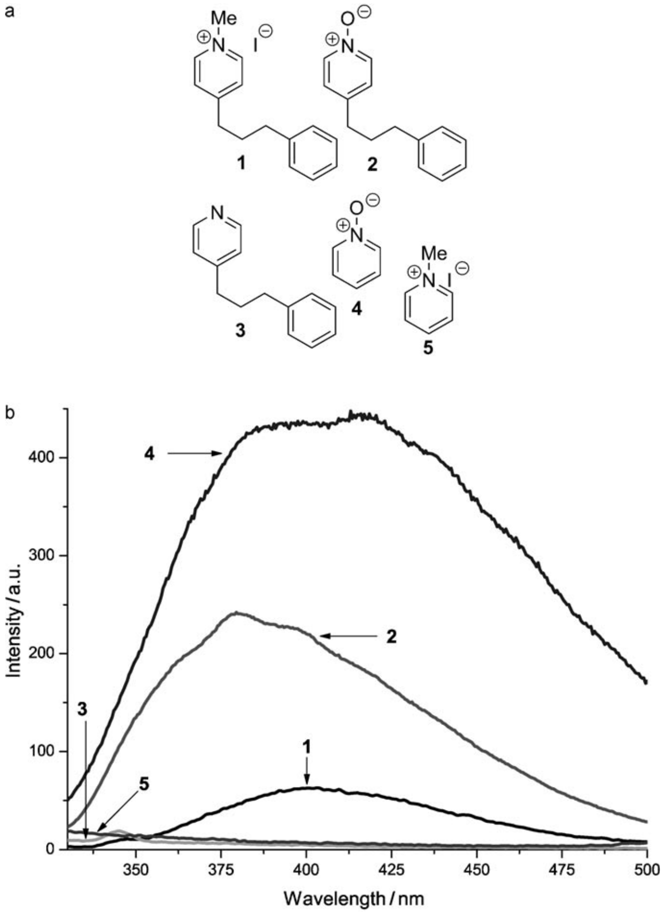

Figure 6. a) Compounds compared by Fluorescence Spectroscopy. b) Emission spectra of compounds **1**--**5**, 1×10^{-4} M (CH_2Cl_2), excitation at 315 nm.

Conclusions

Through the analysis of the solid-state structures of $[(C_6H_5)(CH_2)_3(C_5H_4N(CH_3))]^+I^-$ **1** and $[(C_6H_5)(CH_2)_3(C_5H_4N^+{-}O^-)]H_2O$ **2**, it is apparent that different intermolecular interactions dominate in the two cases. In **1**, electrostatic interactions between the $[(C_6H_5)(CH_2)_3(C_5H_4N(CH_3))]^+$ cations and the I^- ions represents the major packing interaction.

In the crystal structure of **2**, the presence of water is of considerable importance. The major crystal structure-determining feature is the hydrogen bonding network formed between the water molecule and the *N*-oxide oxygen atom. Hu et al.[28] and others have also implicated hydrogen bonding as the key factor for the characteristic T-shaped interactions and π-stacking in conformationally rigid systems.[29,30] There is also evidence for the presence of weak CH–π interactions between the phenyl and pyridine rings on adjacent molecules. Despite the presence of aromatic rings, there is no evidence of graphitic-like π–π-stacking interactions. This interaction may be precluded by weak electrostatic repulsions from the $O^{\delta-}$ *N*-oxide oxygen atom.

The solid-state structures of **1** and **2**.H_2O are dominated by electrostatic and hydrogen bonding channel-like architectures, respectively, which results in molecular conformations that do not display the archetypal intermolecular π-stacking interactions previously revealed in the solution state of **1** by fluorescence spectroscopy.[22] Hence, the solution and solid-state structures must be very different. It remains unclear what the effect on the solid-state structure would be if water was removed from **2**.

In solution, NOESY failed to provide evidence of *N*-oxide π-stacking along with a reduction in relative fluorescence between phenyl containing **2** versus pyridine *N*-oxide **5**. It may be concluded that a system which is ideally suited, on steric grounds, to possess intramolecular π-stacking appears not to offer any evidence for its presence. Although another kind of inter- or intra- molecular interaction may be operating that could explain the relative reduction in fluorescence, conformationally flexible phenyl-linked *N*-oxides appear unsuitable as π-stacking building blocks for solid-state materials.

Experimental Section

Synthesis

1: 4-(3-Phenylpropyl)pyridine methyl iodide. As previously reported.[22]

2: 4-(3-Phenylpropyl)pyridine *N*-oxide.[31–33] 4-(3-Phenylpropyl)pyridine (1.0 g, 5 mmol) was dissolved in acetonitrile/water (2 mL:8 mL) and heated to 75 °C. Hydrogen peroxide (3 mL (35 %), 0.1 mmol) was added dropwise with stirring. After 72 h the mixture was evaporated to dryness and the residue purified by flash chromatography (silica gel, ethyl acetate/methanol = 50:50) to afford **2**. ^{1}H NMR (500 MHz; $CDCl_3$): $\delta=1.97$ (quin, $J=7.7$ Hz, 2H, CH_2), 2.65 (m, 4H, 2xCH_2), 7.08 (d, $J=6.6$ Hz, 2H, Py C*H*), 7.16 (d, $J=7.9$ Hz, 2H, PhC*H*), 7.21 (t, $J=7.3$ Hz, 1H, Ph C*H*), 7.30 (m, 2H, Ph C*H*), 8.12 ppm (d, $J=6.7$ Hz, 2H, NC*H*); ^{13}C{^{1}H} NMR (75 MHz; $CDCl_3$): $\delta=142.28$, 141.52, 139.22, 128.91, 128.76, 126.55, 126.38, 35.47, 34.10, 32.01 ppm; m.p. = 60–61 °C; Acc. mass: Bruker, Daltonics, MICROTOF(ESI, positive): *m*/*z* (%) calcd for $C_{14}H_{15}NO$: 214.1231 $[M+H]^+$; found: 214.1227.

X-Ray Crystallography

Data collection and reduction: A suitable single crystal of **1** was glued onto the end of a glass fibre while a crystal of **2** in inert oil was mounted on a glass fibre. Data were measured on a Bruker AXS APEXII CCD diffractometer on Station 11.3.1 at the ALS, Lawrence Berkeley National Laboratory (**1**) using silicon monochromated radiation of wavelength $\lambda=0.7749$ Å or using Mo-K_α radiation ($\lambda=0.71069$ Å) with a Bruker Nonius Kappa CCD diffractometer at the University of Bath (**2**) and both instruments were fitted with an Oxford Cryostream low-temperature attachment although the data for **1** was collected at room temperature because the crystal underwent a destructive phase change at lower temperatures. *Structure solution and refinement*: Structures were solved by direct methods (*SHELXS-86*)[34] and subjected to full-matrix least-squares refinement on F^2 (program *SHELXL-97*).[35] For both structures all the non-hydrogen atoms were refined with anisotropic displacement parameters. In the structure of **1**, all the hydrogen atoms were placed in idealised positions and allowed to ride on the relevant carbon atom with the isotropic displacement parameter refined as 1.2 times that of the attached carbon atom for the methylene and aromatic hydrogen atoms and 1.5 times for the methyl hydrogen atoms. In each cation, the methyl group attached to the pyridine ring was disordered across a mirror plane and so each hydrogen was refined over two positions with an occupancy of 0.25. The same parameters were used to refine the hydrogen atoms in **2** except for the hydrogen atoms attached to the oxygen of the water molecule. The water hydrogen atoms were located in the electron density difference map, and their positions were DFIXed at 0.9 Å from the oxygen atom and they were each assigned an independent isotropic displacement parameter. Refinement continued until convergence was reached. A weighting scheme which gave a relatively flat analysis of variance was introduced in the final cycles of refinement. The final electron density difference map for each structure showed no significant regions of residual electron density.

Crystal data for **1**: $C_{15}H_{18}IN$, $M=399.20$, crystal dimensions: $0.20\times0.10\times0.01$ mm, orthorhombic, space group *Pnma*, $T=288$ K, $a=32.183(7)$, $b=8.1961(17)$, $c=17.375(4)$ Å, $V=4583.3(16)$ Å^3, $Z=12$, $\rho_{\text{calcd}}=1.475$ g cm^{-3}, $\mu=2.586$ cm^{-1}, $2.76<\theta<25.50°$, 17483 reflections measured, $R(\text{int})=0.045$, 3496 unique reflections, 2705 observed reflections ($I>2\sigma(I)$), $R1=0.036$ for observed data and $wR2=0.101$ for all data.

Crystal data for **2**: $C_{14}H_{17}NO_2$, $M=231.29$, crystal dimensions: $0.50\times0.30\times0.30$ mm, orthorhombic, space group *Pcab*, $T=150$ K, $a=9.3420(1)$, $b=11.7920(2)$, $c=21.8200(4)$ Å, $V=2403.71(7)$ Å^3, $Z=8$, $\rho_{\text{calcd}}=1.278$ g cm^{-3}, $\mu(\text{Mo-}K_\alpha)=0.085$ cm^{-1}, $3.74<\theta<27.46°$, 33661 refleed data and $wR2=0.0983$ for all data.

Fluorescence Spectroscopy

Fluorescence spectra were recorded on a Perkin–Elmer Luminescent Spectrophotometer LS50B, utilising Starna Silica (quartz) cuvets (four faces polished) with 10 mm path lengths. Data was collected using the Perkin–Elmer FL Winlab software package. Sample solutions were prepared in dichloromethane (HPLC grade) and were analysed at a concentration of 10^{-4} M.

Correspondence regarding crystallography should be addressed to PRR and synthesis and spectroscopy to JSF.

Acknowledgements

The Advanced Light Source is acknowledged for granting beamtime which is supported by the Director, Office of Science, Office of Basic Energy Sciences, of the U.S. Department of Energy under Contract No. DE-AC02-05CH11231. Dr. J. P. Lowe and Dr. A. T. Lubben are thanked for assistance with NMR spectroscopy and mass spectrometry, respectively. We are grateful to the DAAD (IR scholarship), the Royal Society (JM, KS, SDB Joint Project and JSF Research Grant 2007/R2), the Egyptian Government (SAE fellowship), the EPSRC (PRR Senior Research Fellowship, PA and MRW studentships), and the Leverhulme Trust (JSF and WC F/00351/P).

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Received: July 4, 2008