ChemPubSoc Europe

DOI: 10.1002/chem.201304462

CHEMISTRY
A European Journal
Communication

Aromatic Interactions

Stabilisation of 2,6-Diarylpyridinium Cation by Through-Space Polar–π Interactions

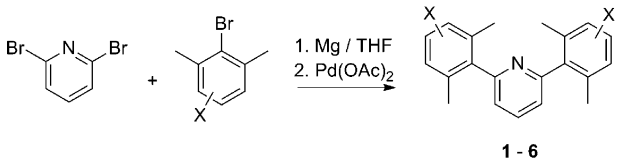
Joan Simó Padial,[a] René de Gelder,[a] Célia Fonseca Guerra,[b] F. Matthias Bickelhaupt,[a, b] and Jasmin Mecinović*[a]

Abstract: The through-space polar–π interactions between pyridinium ion and the adjacent aromatic rings in 2,6-diarylpyridines affect the pK_a values. Hammett analysis illustrates that the basicity of pyridines correlates well with the sigma values of the substituents at the *para* position of the flanking aryl rings.

Weak non-covalent interactions dominate biological molecular recognition events, including enzyme catalysis, DNA double helix structure, protein folding, protein–protein interactions and association of proteins and ligands.[1] Among functionalities that often participate in molecular recognition are aromatic rings, which provide a dominant stabilising effect for many polar functional groups via polar–π interactions (i.e., energetically-favourable interaction between polar group and π system of the aromatic ring).[2] In this regard, the most detailed structural and energetics studies were performed on small molecule systems that involve interactions between aromatic rings and diverse sets of functional groups, including alkyl, aryl, perfluoroaryl, thiol, hydroxyl, carboxyl, silyl, borenium and various cations and anions.[3] The mechanisms by which substituents on the aryl group affect polar groups include, depending on the substitution pattern of the system, contributions from through-bond and/or through-space effects.

Early studies on the substituted pyridines demonstrated that pyridine's basicity can be significantly altered in the presence of substituents located at the *ortho*, *meta* or *para* positions of the aromatic ring.[4] In addition to causing different pK_a values, substituted pyridines also exhibit substantially different reactivities relative to unsubstituted pyridine towards electrophiles in the nucleophilic substitution type reactions. Most, if not all, of these studies suggested that the underlying mechanism of the substituent effect on the pyridine system is based on through-bond effect; either via induction or resonance effects, or a combination of both. In contrast, stabilisation of pyridines (or pyridinium cations) via through-space effect has not been commonly a subject of investigations employing rigorous physical-organic chemistry approaches. Recently, it was determined that (2,6-pyridino)paracyclophane that contains an aryl group in front of the pyridine's nitrogen is about two orders of magnitude more basic than cyclophane that bears the tetrafluoroaryl group at the same position; this result can be in part attributed to through-space effect.[5]

We have envisaged that the basicity of pyridines that possess two flanking aryl groups might be perturbed by substituents positioned at the distinct *para* position of these rings *via* the mechanism by which through-space polar–π interactions provide a dominant contribution. 2,6-Diarylpyridines **1**–**6** were synthesised from 2,6-dibromopyridine and *meta*- or *para*-substituted bromoxylenes under initial Grignard reaction, followed by Kumada coupling (Scheme 1).



Scheme 1. Synthesis of 2,6-diarylpyridines **1**–**6** under Grignard–Kumada conditions.

Potentiometric methods to measure pK_a values in different solvents were found inapplicable, because either starting 2,6-diarylpyridines or their hydrochloride salts were insoluble in these media. Another method, that was previously used for the determination of differences of pK_a values of pyridines and imidazoles in DMSO by ^{1}H NMR spectroscopy, was found to work very well.[5,6] This NMR method utilizes the titration of triflic acid into a mixture of two pyridines of interest and provides information about the differences in their pK_a values (i.e. ΔpK_a). Our hypothesis that the substituents at the *para* position of the flanking aryl rings influence the pK_a values of pyridines in a predictable manner can be tested in the presence of the standard pyridine base. Measurements of pyridines **1**–**6** in the presence of 2,6-dimethylpyridine (lutidine) as an internal reference gave poor results, presumably because the difference in the pK_a values between 2,6-diarylpyridines and lutidine

[a] J. S. Padial, Dr. R. de Gelder, Prof. Dr. F. M. Bickelhaupt, Dr. J. Mecinović
Institute for Molecules and Materials
Radboud University Nijmegen
Heyendaalseweg 135, 6525 AJ Nijmegen (The Netherlands)
Fax: (+31) 24-365-3393
E-mail: j.mecinovic@science.ru.nl

[b] Dr. C. Fonseca Guerra, Prof. Dr. F. M. Bickelhaupt
Department of Theoretical Chemistry
and Amsterdam Center for Multiscale Modeling
VU University Amsterdam
De Boelelaan 1083, 1081 HV Amsterdam (The Netherlands)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201304462.

was too large for a good determination of ΔpK_a (in competition experiments, shifts of 4-CH proton was only observed for lutidine, but not for the set of pyridines **1**–**6**). 2,6-Di-*tert*-butylpyridine, a bulkier analogue of lutidine, is about two orders of magnitude ($\Delta pK_a = 2.2$) less basic than lutidine in 50% aqueous ethanol.[7] Thus, we have conceived that 2,6-di-*tert*-butylpyridine might be a better reference for our set of pyridines, due to smaller differences in their basicity/acidity constants. Competitive titrations between an individual pyridine in the series of **1**–**6** and 2,6-di-*tert*-butylpyridine gave excellent results, as exemplified by a linear correlation ($R^2 > 0.97$) between the shift of the aromatic CH protons in pyridines **1**–**6** and the reference by ^{1}H NMR (Table 1, see the Supporting Information). The plot that shows a dependence of pK_a of pyridines **1**–**5** on the 2σ illustrates that the acidity constant of the pyridinium ion is in a strong correlation ($R^2 = 0.99$) with the Hammett sigma values giving the ρ value of 1.1 (Figure 1). Overall these

Table 1. pK_a values for pyridines **1**–**6**.

Compound	X	σ	pK_a[a]
1	H	0.00	2.40
2	*p*-OMe	−0.27	3.04
3	*p*-Me	−0.17	2.83
4	*p*-F	0.06	2.26
5	*p*-Cl	0.23	1.99
6	*m*-OMe	0.12	3.02

[a] Determined in [D_6]DMSO.

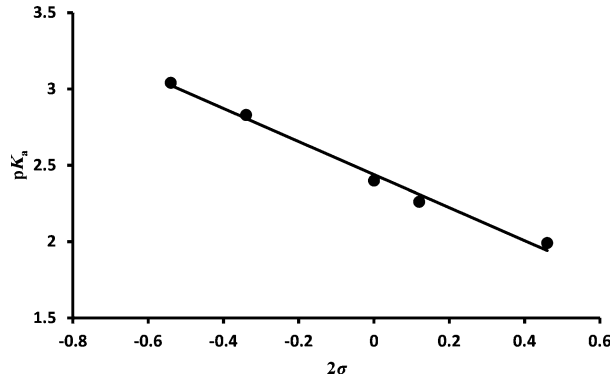


Figure 1. Dependence of pK_a values on the Hammett sigma values of *para*-substituted pyridines **1**–**5**. 2σ is the sum of the Hammett sigma values of *para* substituents on both flanking rings.

results demonstrate that pyridines that contain electron-donating groups (e.g. OMe, Me) are significantly more basic than pyridines that bear electron-withdrawing groups (e.g. Cl), and that there is a linear relationship between the acidity and the Hammett sigma values. Notably, the pyridine that possesses a OMe substituent at the *meta* position (**6**) exhibits a similar pK_a value as the *para* analogue (**2**), despite the value of σ_{meta} (0.12) being significantly different from the value of σ_{para} (−0.27) for this substituent.

Attempts to obtain a direct evidence for polar–π interactions were then carried out using X-ray crystallography. Pyridinium complex **3**·HCl crystallised from methanol at room temperature, whereas crystals of **3**·$HClO_4$ and **3**·HSO_3(OEt) were obtained from ethanol at 4 °C.[8] Crystallographic analyses of all three salts illustrate that both flanking rings at the *ortho* position of the pyridinium ion display dihedral angles between 61° and 82°, and that both rings are approximately in "antiparallel" or "staggered" positions (Figure 2A and Supporting Information).

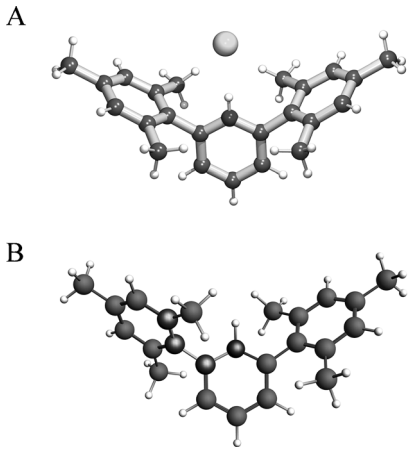


Figure 2. A) Crystal structure of **3**·HCl. B) Calculated most stable conformation of pyridinium cation **3**. Dihedral angle φ is calculated from N-C_2-C_α-C_β.

tion). Average distances between the pyridinium proton and carbon atoms on the neighbouring rings are: NH-C_α 2.5 Å, NH-C_β 3.3 Å, NH-C_γ 4.4 Å, and NH-C_δ 4.9 Å. These data support the view that the substituents at the *para* position (i.e., C_δ) do not directly interact with the pyridinium ion, and that the rings' proximity and orientation stabilises the pyridinium ion. All three crystal structures also suggested that in the crystal form there is an interaction between pyridinium NH and the anion. Distances between pyridinium NH proton and the anionic species were 2.14 Å for Cl^-, 1.98 Å for oxygen in ClO_4^-, and 1.78 Å for oxygen in $HSO_3(OEt)^-$. These observations are in agreement with the structure of the salt between cationic **3** and tetrachloro gallate anion.[9] Our crystal structures also revealed that solvent molecules do not interact with the cation.

Computational studies on our pyridine system, using the Amsterdam Density Functional (ADF) program, support the interpretation of our experimental findings.[10] The optimisation of the geometry for pyridinium ion **1**, computed at BP86/TZ2P, provided the conformation of the energetically most stable form. The dihedral angle between the pyridinium C2 and the adjacent aryl ring (i.e., N-C_2-C_α-C_β) for the energetically most stable structure was found to be 65° for a set of six pyridines (Figure 2B). Our computed angles for the most stable conformation are compatible with those derived from crystal structures. Importantly, the computations reveal that the potential energy well, associated with varying the dihedral angle around the absolute minimum at 65°, is extremely shallow. Thus, whereas conformers with angles below 30° are energetically

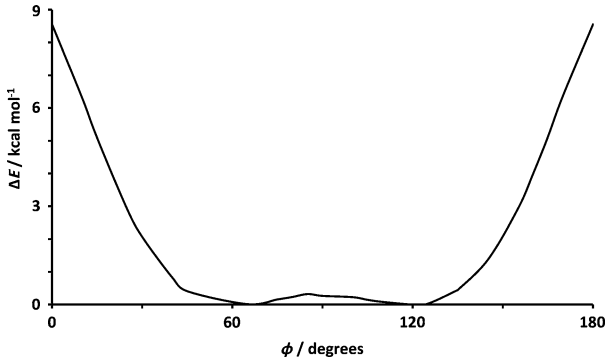


Figure 3. Relative energy ΔE of pyridinium cation **1** in the gas phase as a function of the dihedral angle φ, computed at BP86/TZ2P.

unfavourable, the difference in energy between conformers that possess dihedral angles between 45° and 90° was calculated to be only 0.4 kcal mol^{-1} (Figure 3). Similarly, pyridinium ions **4** and **5** were calculated to be energetically stable between 45° and 90°; the difference in energy between conformers in this range was found to be 0.6 kcal mol^{-1} (see the Supporting Information).

Proton affinity energies (ΔE^{PA}) for a set of pyridines were then calculated in the gas phase and in DMSO, again at BP86/TZ2P and using COSMO to simulate the effect of solvation (Table 2). Dependence of proton affinity energies in the gas phase on the Hammett sigma values shows a strong linear relationship with the slope of −11.0 (Figure 4 A). In DMSO, the slope is significantly shallower with a value of −1.8 (Figure 4 B). These results are compatible with the picture that the NH cation strongly interacts with electron-rich aromatic rings at the adjacent positions, and that this interaction is more profound in the gas phase than in DMSO.

Table 2. Proton affinity energies ΔE^{PA} [in kcal mol^{-1}] computed at BP86/TZ2P.

Compound	X	ΔE^{PA} in gas phase	ΔE^{PA} in DMSO[a]
1	H	238.6	22.3
2	*p*-OMe	244.5	23.9
3	*p*-Me	241.2	22.8
4	*p*-F	236.4	22.2
5	*p*-Cl	234.4	21.9
6	*m*-OMe	243.0	22.1[b]

[a] Solvation in DMSO is simulated using COSMO. [b] Lower ΔE^{PA} for **6** than for **2** may be ascribed to discontinuous change in COSMO cavity for *meta* pyridine **6** as compared to *para* pyridines **1**–**5**.

In principle, six mechanisms can be involved in the stabilisation of pyridinium cation by the adjacent aryl groups: 1) resonance effect, 2) inductive effect, 3) field effect, 4) polarisability effect, 5) steric effect and 6) solvation effect. Our analysis that 1) compares all sets of pyridines relative to a reference under the same experimental conditions, and 2) the fact that a substituent at the distant *para* position of the flanking rings does

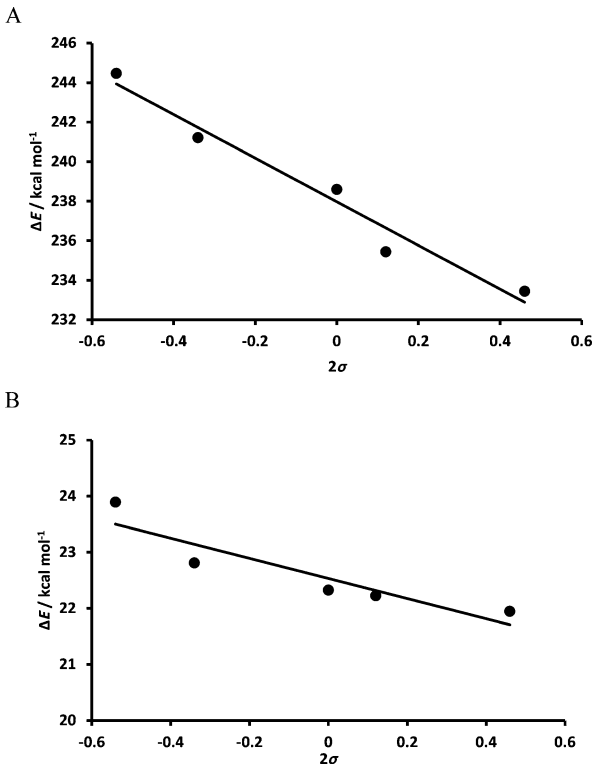


Figure 4. Dependence of proton affinity energies (ΔE) in the gas phase (A) and in DMSO (B) on the Hammett sigma values of *para*-substituted pyridines **1**–**5**. 2σ is the sum of the Hammett sigma values of *para* substituents on both flanking rings.

not alter the structural feature of the pyridinium cation provides direct information about the impact of the electronic effect, and eliminates the contribution on the basicity from the solvent effect (we do, however, note that solvent has a substantial effect on basicity of pyridines as exemplified by the large difference in calculated proton affinities in the gas phase relative to DMSO; see above). A resonance effect is excluded, because the system is not planar as demonstrated by both, crystallographic and computational studies. Furthermore, a resonance effect is also eliminated by the observation that pyridines **2** and **6** that bear *meta* and *para*-substituted methoxy group, respectively, have the same basicity. Contributions from the inductive effect are also excluded, because through-bond effects diminish with the number of bonds (there are five bonds between pyridinium NH and the aryl C_δ). Similarly, involvement of the steric effect is eliminated due to a substantial distance (>5 Å) between the NH and the substituent at the *para* position whereas we nevertheless observe a significant dependence of the basicity of the set of pyridines **1**–**5** on the electronic properties of the *para* substituent. Our results, a decreasing basicity with increasing Hammett sigma values, are compatible with the mechanism by which the field effect and the polarisability effect via through-space polar–π interactions determine the stability and basicity of 2,6-diarylpyridines.

We have demonstrated that the acidity of 2,6-diarylpyridinium cations that bear two flanking aryl rings is substantially influenced by substituents positioned at the distant *para* posi-

tion of these two rings. In this set of pyridines, the pyridinium NH cation is stabilised by aromatic rings via through-space polar–π interactions caused by the neighbouring aryl groups. In depth understanding of the molecular level mechanism by which through-space interactions (either intramolecular or intermolecular) stabilise polar functionalities might be useful in designing small-molecule ligands and inhibitors that bind to proteins specifically and with high affinity. In this respect, our study demonstrates that pyridinium ions favourably interact with electron-rich aromatic rings that are located in close proximity to pyridinium NH (<5 Å) and possess a proper orientation (T-shape or distorted T-shape).[11] Because pyridine derivatives construct the skeleton of many drugs, it is important to consider that the pyridinium ion (as substituted pyridines can partially exist in protonated form under physiological conditions) can be stabilised by aromatic amino acids (i.e., Phe, Tyr, Trp) that constitute the binding sites of several biologically important proteins.

Acknowledgements

We thank Radboud University Nijmegen, the Netherlands Organization for Scientific Research (NWO-CW), and the National Research School Combination Catalysis (NRSC-C) for financial support, Jan M. M. Smits for assistance with crystallography, and Professor Alan E. Rowan for helpful discussions.

Keywords: basicity · Hammett analysis · non-covalent interactions · polar–π interactions · pyridines

[1] A. Karshikoff in *Non-Covalent Interactions in Proteins*, Imperial College Press, London, **2006**.

[2] a) E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem.* **2003**, *115*, 1244 – 1287; *Angew. Chem. Int. Ed.* **2003**, *42*, 1210 – 1250; b) L. M. Salonen, M. Ellermann, F. Diederich, *Angew. Chem.* **2011**, *123*, 4908 – 4944; *Angew. Chem. Int. Ed.* **2011**, *50*, 4808 – 4842; c) S. E. Wheeler, *Acc. Chem. Res.* **2013**, *46*, 1029 – 1038.

[3] a) I. K. Mati, S. L. Cockroft, *Chem. Soc. Rev.* **2010**, *39*, 4195 – 4205; b) 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, C. A. Hunter, *Org. Biomol. Chem.* **2007**, *5*, 1062 – 1080; c) F. Cozzi, R. Annunziata, M. Benaglia, M. Cinquini, L. Raimondi, K. K. Baldridge, J. S. Siegel, *Org. Biomol. Chem.* **2003**, *1*, 157 – 162; d) K. S. Kim, P. Tarakeshwar, J. Y. Lett, *Chem. Rev.* **2000**, *100*, 4145 – 4185; e) C. T. Chen, J. S. Siegel, *J. Am. Chem. Soc.* **1994**, *116*, 5959 – 5960; f) S. Duttwyler, Q. Q. Do, A. Linden, K. K. Baldridge, J. S. Siegel, *Angew. Chem.* **2008**, *120*, 1743 – 1746; *Angew. Chem. Int. Ed.* **2008**, *47*, 1719 – 1722; g) S. L. Cockroft, C. A. Hunter, K. R. Lawson, J. Perkins, C. J. Urch, *J. Am. Chem. Soc.* **2005**, *127*, 8594 – 8595; h) C. A. Hunter, C. M. Low, C. Rotgers, J. G. Vinter, C. Zonta, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4873 – 4876; i) H. B. Mansaray, A. D. L. Rowe, N. Phillips, J. Niemeyer, M. Kelly, D. A. Addy, J. I. Bates, S. Aldridge, *Chem. Commun.* **2011**, *47*, 12295 – 12297; j) J. C. Ma, D. A. Dougherty, *Chem. Rev.* **1997**, *97*, 1303 – 1324; k) A. Frontera, P. Gamez, M. Mascal, T. J. Mooibroek, J. Reedijk, *Angew. Chem.* **2011**, *123*, 9736 – 9756; *Angew. Chem. Int. Ed.* **2011**, *50*, 9564 – 9583.

[4] a) A. Fischer, W. J. Galloway, J. Waughan, *J. Chem. Soc.* **1964**, 3591 – 3596; b) D. H. Aue, H. M. Webb, M. T. Bowers, C. L. Liotta, C. J. Alexander, H. P. Hopkins, *J. Am. Chem. Soc.* **1976**, *98*, 854 – 856; c) A. R. Katritzky, D. E. Leahy, *J. Chem. Res. (S)* **1985**, 28 – 29; d) C. D. Johnson, I. Roberts, P. G. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1981**, 409 – 413.

[5] a) K. K. Baldridge, F. Cozzi, J. S. Siegel, *Angew. Chem.* **2012**, *124*, 2957 – 2960; *Angew. Chem. Int. Ed.* **2012**, *51*, 2903 – 2906; b) R. Annunziata, M. Benaglia, F. Cozzi, A. Mazzanti, *Chem. Eur. J.* **2009**, *15*, 4373 – 4381.

[6] C. L. Perrin, M. A. Fabian, K. B. Armstrong, *J. Org. Chem.* **1994**, *59*, 5246 – 5253.

[7] H. C. Brown, B. Kanner, *J. Am. Chem. Soc.* **1953**, *75*, 3865 – 3865.

[8] CCDC 958095, 958096 and 958097 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] T. Pell, D. P. Mills, A. J. Blake, W. Lewis, S. T. Liddle, *Polyhedron* **2010**, *29*, 120 – 125.

[10] a) G. te Velde, F. M. Bickelhaupt, E. J. Baerends, C. Fonseca Guerra, S. J. A. van Gisbergen, J. G. Snijders, T. Ziegler, *J. Comput. Chem.* **2001**, *22*, 931 – 967; b) Computer code ADF 2013.01: see http://www.scm.com.; c) M. Swart, F. M. Bickelhaupt, *J. Chem. Theory Comput.* **2006**, *2*, 281 – 287; d) M. Swart, E. Rösler, F. M. Bickelhaupt, *J. Comput. Chem.* **2006**, *27*, 1486 – 1493; e) A. Klamt, *J. Phys. Chem.* **1995**, *99*, 2224 – 2235; f) M. Swart, E. Rösler, F. M. Bickelhaupt, *Eur. J. Inorg. Chem.* **2007**, 3646 – 3654.

[11] S. Tsuzuki, M. Mikami, S. Yamada, *J. Am. Chem. Soc.* **2007**, *129*, 8656 – 8662.

Received: November 14, 2013
Revised: March 25, 2014
Published online on April 15, 2014