VIP Polar–π Interactions

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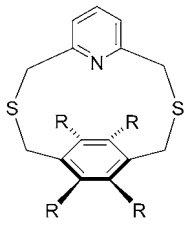
Basicity of (2,6-Pyridino)paracyclophanes: Lone Pair–π, Cation–π, and Solvation Effects**

Kim K. Baldridge, Franco Cozzi,* and Jay S. Siegel**

Polar–π effects often appear to explain the interaction between a π system, such as a benzene ring, and a polar group.[1] Perturbation of the electron density in the benzene ring by systematic "Hammett" substitution leads to reasonable correlations and slopes (ρ values) consistent with basic teachings of free-energy relationships.[2] In the present study, a simple analysis of the basicity of two (2,11)dithia[3,3](2,6-pyridino)paracyclophanes, one comprising a 2,6-substituted pyridine linked to a 1,4-substituted benzene (**1**), the other comprising the same pyridine linked to a tetrafluoro cognate of the benzene (**2**),[3] evokes exactly this analysis and lends additional support to the importance of benzene interactions in determining the stability of cations.[4] However, a control experiment measuring the basicity of 2,6-dimethylpyridine (lutidine)[5] forces a refinement of this analysis and emphasizes that solvation and environmental effects may dominate over internal electronic effects in such systems.[6]



1: R = H; **2**: R = F

The cyclophanes **1** and **2** adopt a ground-state conformation with C_s symmetry in which the pyridine ring is canted with respect to the benzene platform by 22° and 43°, respectively. This disposition of rings places the lone pair of the pyridine nitrogen atom convergent to the face of the benzene, but off-center (Figure 1). A C_2 conformation, with the pyridine ring normal to the benzene platform, is a higher energy intermediate on the path to pyridine ring flipping. The combined experimental and computational study of this isomerization reveals a sensitivity to polarity consistent with the polar–π hypothesis.[3]

The basicity of the lone pair of electrons on the nitrogen atom should also be sensitive to the presence and character of the platform ring. This effect would parallel the phenomenon seen for proton sponges like 1,8-bis(dimethylamino)naphthalene, in which convergent nitrogen lone pairs repel each other and raise the overall basicity of the system.[7] Additionally, the interaction of the protonated nitrogen atom (pyridinium ion) with the benzene platform could be modulated by ring substitution. The polar–π model says that the parent cyclophane **1** should be more basic than fluorinated cyclophane **2**, because the center of the benzene ring in **1** should have substantially greater δ^- character than in **2**.

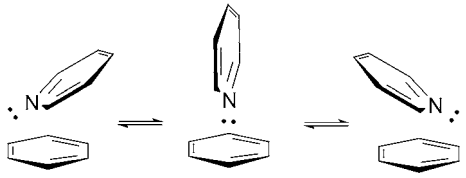
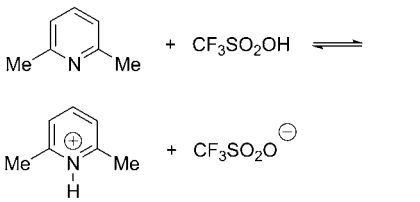


Figure 1. Pyridine-to-platform ring relative disposition and ring flip path ($C_s \rightarrow C_2 \rightarrow C_s$); only ring-to-ring disposition is shown.

To test this hypothesis, competitive titrations of **1** and **2** with triflic acid in DMSO were monitored by ^{1}H NMR (500 MHz) spectroscopy [Eqs. (1)–(2)]. The differential shifts of four hydrogen atoms were used to determine the relative pK_a values for **1** versus **2**. Titration of **1** relative to lutidine (Eq. 3) was used as a reference (pK_a of lutidine in DMSO = 4.46).[8] This method of competitive titration allows differences of 0.01 pK units to be distinguished.[9]

(1)

(2)



(3)

Cyclophane **1** was found to be more basic than **2** (ΔpK_a = 2.2). This finding agrees with the concept that the platform in **1** creates a more repulsive through-space Coulombic interaction with the pyridine nitrogen lone pair than that in **2**. The reference titration of **1** against lutidine showed that lutidine is

[*] Prof. K. K. Baldridge, Prof. J. S. Siegel
Organic Chemistry Institute, University of Zurich
Winterthurerstrasse 190, 8057 Zurich (Switzerland)
E-mail: kimb@oci.uzh.ch
jss@oci.uzh.ch
Prof. F. Cozzi
Dipartimento di Chimica Organica e Industriale
Universitá degli Studi di Milano
via Golgi 19, 20133 Milano (Italy)
E-mail: franco.cozzi@unimi.it

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more basic than **1** in DMSO ($\Delta pK_a = 1.0$). Such a finding is difficult to explain with a model that only considers the molecules in isolation; the absence of the benzene platform in lutidine should have rendered it less basic. Thus, environmental factors such as solvation must be taken into account.

Computational methods were implemented to compare the energetics of the protonation reactions in Equations (1)–(3).[10] The reactions were assessed from consideration of the C_s conformations and of the C_2 conformations, independently, the former to model the experimental system where the nitrogen lone pair is partially exposed to solvent and the latter to understand the effect when the nitrogen lone pair is substantially buried into the platform ring.

Ab initio computational analysis supports the expectation that **1** is more basic than **2** in the gas phase. Subtraction of the ΔE for the reaction in Equation (1) from that in Equation (2) gives 7.2 (C_s) and 8.6 (C_2) kcal mol^{-1}, which corresponds to a difference in basicity of 5.2 and 6.3 pK units, in the gas phase, respectively.

The same reaction energetics were computed using a continuum solvation model.[11] The energy difference is moderated in solvent (Figure 2). The ΔE(Eq. (1)−Eq. (2)// sol) are 5.29, 4.08, 3.72, 3.65, 3.63, 3.60 (C_s series) and 6.81, 5.62, 5.24, 5.15, 5.12, 5.08 (C_2) kcal mol^{-1} in benzene, THF, acetone, acetonitrile, DMSO, and water, respectively, which corresponds to pK_a differences of 3.9, 3.0, 2.7, 2.7, 2.7, 2.6 (C_s) and 5.0, 4.1, 3.8, 3.8, 3.8, 3.7 (C_2) units, respectively (Table 1).

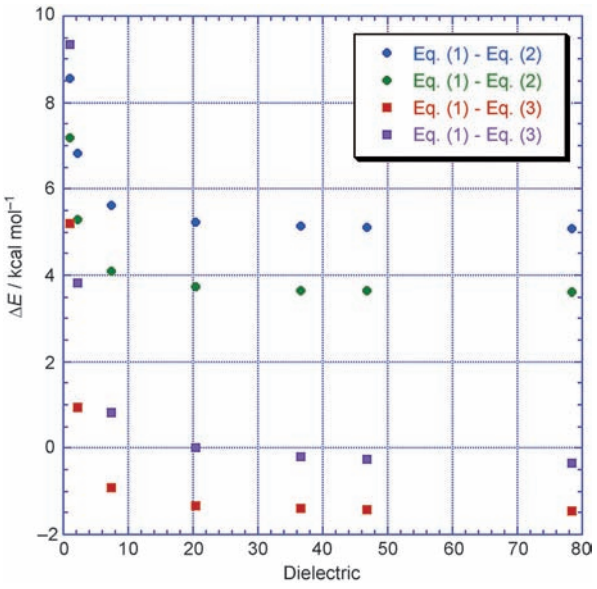

Figure 2. B97-D/Def2-TZVPPD[1] calculated ΔE, Eq. (1)−Eq. (2) versus the dielectric constant of the solvent.

Let us now consider in more detail what these data reveal to us about the intramolecular interactions and solvation in these systems. Four principal interactions can be postulated: lone pair–platform, cation–platform, lone pair–solvent, and cation–solvent. In general, ions interact with their surroundings more strongly than neutral species. Therefore, one would expect the interactions of the cations to drive the trends in the data.[8]

Table 1: Calculated (B97-D/Def2-TZVPPD[a]) relative pK_a values of **1** and **2** as a function of solvent.[b]

Solvent	Eq. (1)− Eq. (2) (C_s)	Eq. (1)− Eq. (2) (C_2)	Eq. (1)− Eq. (3) (C_s)	Eq. (1)− Eq. (3) (C_2)
gas phase	5.2	6.3	3.8	6.9
benzene	3.9	5.0	0.7	2.8
THF	3.0	4.1	−0.7	0.6
acetone	2.7	3.9	−1.0	0.0
acetonitrile	2.7	3.8	−1.0	−0.1
DMSO	2.7[c]	3.8	−1.0[d]	−0.2
water	2.6	3.7	−1.1	−0.2

[a] See Ref. [10]. [b] See Ref. [11]. [c] Experimental value = 2.2. [d] Experimental value = −1.0. DMSO = dimethylsulfoxide, THF = tetrahydrofuran.

Whereas in the gas phase the stability of the cation is dependent on intramolecular interactions, in solution the solvent can play a decisive role. This is well illustrated in the comparison of the basicity of lutidine, **1** and **2**, where in the gas phase the order of basicity is **1** > lutidine > **2**.[12] This trend is fully consistent with the polar–π hypothesis. In solution the trend changes for solvents more polar than benzene to lutidine > **1** > **2**. This change in order can be understood in that **1** and **2** with similar geometries are also affected similarly by solvation, whereas lutidine with a substantially more exposed N-H$^+$ cation is affected to a greater extent. In so far as solvation leads to a stabilization of the cation, solvation favors the lutidinium more than the **1**-H$^+$ cation. Roughly speaking, the crossover point, where lutidine becomes more basic than **1** serves as an estimate of the internal solvation ability of the platform. Thus, the benzene platform in these cyclophanes is not substantially different from bulk benzene as solvent. For solvents of increasingly higher dielectric constants the effect appears to saturate, as expected from a Coulombic interaction with the solvent.

Consideration of the C_2 conformation provides further insight into the issue of differential solvation. In the C_2 conformation, the lone pair of the nitrogen in the neutral state and the N-H$^+$ cation in the protonated state are sterically buried into the face of the benzene ring platform and therefore inaccessible to solvent. For **1** and **2** the geometry is essentially identical and as such the change in solvent accessible surface should parallel one another. The data in Table 1 show that for Eq. (1)−Eq. (2) the difference in pK_a values from the gas phase to water track directly with one another (ΔpK_a(gas-water) = 2.6 [C_s] versus 2.6 [C_2] pK units). In contrast, for Eq. (1)−Eq. (3), the comparison of **1** to lutidine, the more solvent accessible C_s conformation shows a smaller differential solvation effect than the buried C_2 conformation (ΔpK_a(gas-water) = 4.9 [C_s] versus 7.1 [C_2] pK units).

Looking to the magnitude of the range for Eq. (1)–Eq. (3) in the C_s versus C_2 conformation one sees that relative to lutidine, **1** seems to become more basic on passing from C_s to C_2. Thus the reference basicity and the sensitivity to environment are affected by the conformation **1** adopts. This implies that the apparent importance of the presence of the benzene

platform is dependent on the nature of the anchoring scaffold. Something similar to this is seen in previous studies involving arene–arene interactions modeled by 1,8-disubstituted naphthalenes compared to 1,8-disubstituted biphenylenes (Figure 3).[2] In the former, the arenes are forced inside van der Waals contacts and the slope of the sensitivity correlation

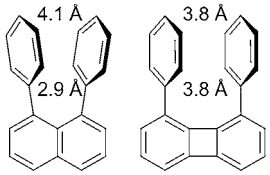

Figure 3. Models for arene–arene interactions based on 1,8-disubstituted naphthalenes and 1,8-disubstituted biphenylenes.

is high; in the latter, the rings sit at roughly the van der Waals contact distance and the slope is lower, or the correlation is not apparent (i.e., slope ca. 0). These studies point to a general caveat to conclusions based on molecular recognition models and the partitioning of biochemical effects: the structure of the system may alter the magnitude of the observed effect.

Take this a bit further and one sees that if left to choose, simple arenes would not associate especially strongly nor would their association be strongly dependent on the substituent details. Even benzene/hexafluorobenzene associate weakly in solution,[13] and the naphthalene/paraquat systems operate as charge-to-neutral complexes in moderately competitive polar solvents.[14] The situation changes when groups are anchored close to one another or when a substrate is forced into an enzyme pocket. Confronted with a perturbing group in a confined proximity, the system's response may be exaggerated compared to a "free" association. Thus, the effect observed is not quantitatively transferable from system to system, and complex biological systems may not lend themselves to partitioning into a set of elementary effects that sum back to the whole.

Can consideration of solvation give us more insight into the role of solvent in cation–π effects? The binding energy of K^+-to-benzene (expt: 19, calc: 20 kcal mol^{-1}) versus K^+-to-water (expt: 17, calc: 15 kcal mol^{-1}) in the gas phase is often cited as fundamental evidence for how strong the cation–π effect can be.[15] Two issues arise from this study: 1) the maximal number of coordinating benzene molecules to K^+ is sterically limited to four and even four times the K^+-to-benzene binding energy is lower than the solvation energy of K^+ in bulk water (80 kcal mol^{-1}); 2) from only these two data points, benzene and water, one is unsure if the experiment is teaching us if K^+-to-benzene (gas phase) is stronger than expected, or if K^+-to-water (gas phase) is weaker than expected.

The first point makes it unlikely that benzene is a competent ionophore. Much less cited work from the same laboratory sheds light on the second issue and offers up a provocative correlation associated with the first issue.[16] The binding energy of K^+-to-ligand in the gas phase was measured for DMSO, DMF, acetone, and THF. Placed in rough order from highest to lowest binding energy, the series follows DMSO, DMF, acetone, and THF. In every case, four times the gas phase value exceeds the solvation energy of K^+ in bulk water. Extending the series with the benzene and water data, we obtain, again in rank order: DMSO, DMF, acetone, THF// benzene, and water. The two additional points come at the lower end of the series and in neither case is four times the gas phase value higher than the solvation energy of K^+ ion in bulk water.

The more complete series described above focuses attention on the apparent weak-binding character of water in the gas phase, and elicits no sense of benzene being a particularly strong binder. Furthermore, the functional groups of solvent molecules, for which tetrahedral coordination around K^+ could provide a local solvation energy higher than K^+ in bulk water, appear as components of natural product ionophores.[17] For benzene, an analogous hypothesis has been formulated, but has it undergone proper scrutiny?

What about the poor performance of water in the gas phase? Our introductory chemistry instruction actually prepared us well to understand that much of the special character of water comes from its cooperative action in the bulk and its small steric profile. The auto-dissociation of water and the Grotthuss chain mechanism for proton transfer highlight the importance for water to act as part of an aggregate.[18] The coordination chemistry of water as a ligand is also special in giving rise to octahedral fields even for K^+. This combination of higher coordination numbers and second sphere cooperative solvation give water special properties, which are not at play in the simple K^+-to-benzene versus K^+-to-water comparison.

It is generally accepted that π systems are more polar than their saturated counterparts (e.g. benzene to cyclohexane or ethene to ethane), but not of comparable polarity to the lone pairs of atoms like oxygen or nitrogen. Comparison of computed K^+–ethene (10.0 kcal mol^{-1}) to K^+–ethane (7.1 kcal mol^{-1}) binding energies shows a preference of K^+ for ethene of 3 kcal mol^{-1}.[10] The analogous computation for K^+–benzene versus K^+–cyclohexane suggests a preference for benzene by 10 kcal mol^{-1}. Thus roughly 50% of the 20 kcal mol^{-1} binding energy in K^+–benzene, and 70% of the 10 kcal mol^{-1} binding energy in K^+–ethene, is attainable from non-π interactions, among which dispersion must be considered. In contrast, comparison of the binding energy in K^+–water to K^+–methane (5.2 kcal mol^{-1}) indicates that over 70% of the binding energy can be rationalized as coming from polar terms.[10]

Dispersion interactions[19] and competitive solvation interactions are often neglected because they are more difficult to get a handle on or too costly to handle computationally. Be that as it may, the simple polar–π or cation–π model should be employed with the caveat that it may well be too simple for most biological chemistry systems.[20] In general, it is worth remembering that correlation alone does not require causation or significance.[21]

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