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COMMUNICATION

Anion- π Interactions and Positive Electrostatic Potentials of *N*-Heterocycles Arise from the Positions of the Nuclei, not Changes in the π -electron Distribution

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We show that the positive electrostatic potentials and molecular quadrupole moments characteristic of π -acidic azines, which underlie the ability of these rings to bind anions above their centres, arise from the position of nuclear charges, not changes in the π -electron density distribution.

Anion- π interactions¹ are attractive non-covalent interactions between anions and the faces of π -acidic rings.² They often involve azabenzene (azines) such as s-triazine and s-tetrazine,¹⁵ and have emerged as powerful tools for anion binding, recognition and transport, and even catalysis.³ Despite rapidly-growing interest in these non-covalent interactions, there is a dearth of rigorous explanations of their origin.⁴ Most authors^{2g,2h} ascribe anion- π interactions to a combination of electrostatic and induction effects (anion-induced polarization of the arene).⁵ The electrostatic component of these interactions is generally characterized by the Q_{zz} component of the quadrupole moments of the arenes, which is correlated with the strength of anion- π interactions.^{2g,2h} Alternatively, the electrostatic component of these interactions can be described in terms of electrostatic potentials (ESPs), which are widely employed in analyses of a variety of other non-covalent interactions.⁶

Although the correlation of the strength of anion- π interactions with arene Q_{zz} and ESP values seems straightforward, questions remain regarding the origin of the positive Q_{zz} and ESP values that are characteristic of π -acidic *N*-heterocycles. Many equate positive Q_{zz} and ESP values with π -electron deficiency,^{1b-d,3a-f} and “ π -acidic” is often implicitly defined in terms of positive ESP and Q_{zz} values.^{3f} The problem is that both ESPs and molecular quadrupole moments reflect the balance between the large and opposing effects of the distribution of positive (nuclear) and negative (electronic) charge throughout the molecule. As a result, a positive Q_{zz} value can indicate the depletion of electron density above the ring centre (*e.g.*, reduction of the π -electron density) or the movement of nuclear charge towards the ring centre. Similarly, a positive ESP above an aromatic ring can arise from changes in either the electron or nuclear charge distributions.⁷ These distinctions are rarely made in discussions of anion- π interactions,¹⁻² which focus almost exclusively on the concepts of π -acidity and π -electron-deficiency.

Previously, Wheeler and Houk showed⁸ that substituent-induced changes in the ESPs of substituted arenes are dominated

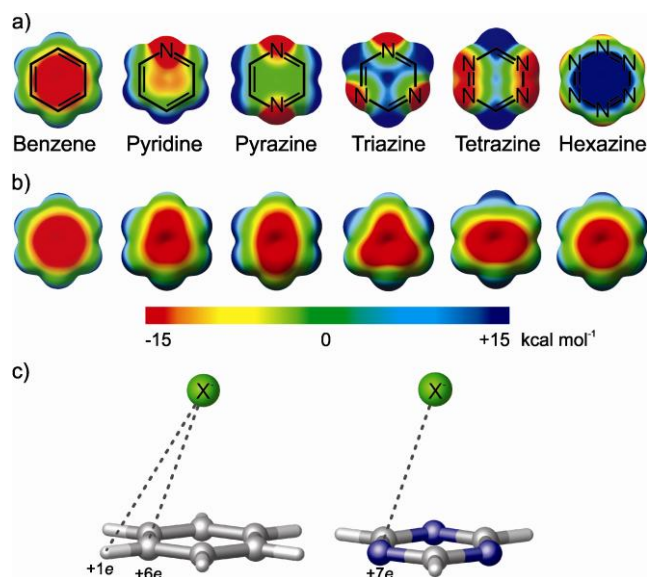


Fig. 1 (a) Total ESPs of benzene and five azines, mapped onto the corresponding electron density isosurfaces; (b) Fictitious EPSs resulting from the replacement of only the π -electron density of benzene with that of the corresponding azine, while leaving the σ -electron density and nuclear charges unchanged. (c) Comparison of proximity of nuclear charges to an anion above the centres of benzene and triazine.

by through-space effects, not changes in the π -electron density. Similarly, they also demonstrated^{4a} that anion-binding by substituted benzenes is due to interactions of the anion with the substituents; the interaction of the anion with the phenyl ring itself remains repulsive regardless of the substituents. Unfortunately, neither of these studies addressed the impact of heteroatoms, despite the importance of *N*-heterocycles in supramolecular chemistry. Consequently, key questions remain regarding the origin of the positive ESPs and Q_{zz} values of π -acidic *N*-heterocycles, as well as the ability of these arenes to bind anions. Here, we tackle these questions by separating the impact of σ - and π -electron density on ESPs and Q_{zz} values based on the symmetry of the underlying molecular orbitals (see ESI for more details). The results are contrary to conventional descriptions of anion- π interactions involving *N*-heterocycles,¹⁻² as well as prevailing descriptions of π -acidic azines.

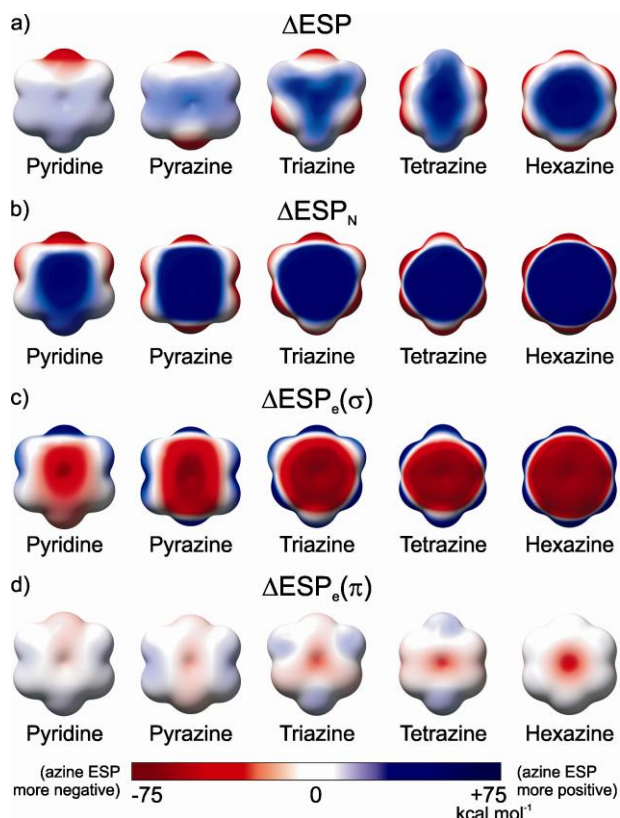


Fig. 2 (a) Differences in ESPs of five azines, relative to benzene (ΔESP), as well as (b) the nuclear (ΔESP_N), (c) σ -electronic [$\Delta\text{ESP}_\sigma(\sigma)$], and (d) π -electronic [$\Delta\text{ESP}_\sigma(\pi)$] contributions to ΔESP , all mapped onto total electron density isosurfaces.

The azines pyridine, pyrazine, s-triazine, s-tetrazine, and the hypothetical molecule (planar) hexazine provide a convenient platform for understanding the origin of anion- π interactions and the nature of π -acidic N -heterocycles. Notably, these five arenes exhibit drastically different ESPs and Q_{zz} quadrupole moments (see Fig. 1a and Table 1), despite being σ - and π -isoelectronic with benzene. Moreover, the isoelectronic nature of these rings enables the direct evaluation of the impact of nuclear and electronic charge distributions on ESPs and Q_{zz} values. When an anion such as Cl^- is constrained to lie above the ring centroid, these arenes provide a systematic and linear progression from unfavourable anion- π interactions (for benzene), to strongly attractive interactions for triazine, tetrazine and hexazine.^{4d} Because of the strong correlation between interaction energies for such model anion- π complexes and ESP and Q_{zz} values for the rings (see ESI), explaining the impact of N -substitutions on anion- π interactions is equivalent to explaining their impact on ESPs and Q_{zz} values.⁹ Of course, cation- π interactions, which are vital to sundry chemical and biological processes,¹⁰ are also strongly correlated with ESP and Q_{zz} values.^{4b,11} Indeed, electrostatic effects play a key role in many non-covalent interactions involving N -heterocycles. As such, the analysis below has important implications for our understanding of many non-covalent interactions.^{4c,4d}

ESP maps for benzene and the five azines are depicted in Fig. 1a, and show a clear progression from a negative ESP above benzene to positive ESPs above triazine, tetrazine, and hexazine. This is consistent with the well-established trend in the ability of

these rings to bind anions, and seemingly jives with the classic description of the N -heterocycles as π -electron-deficient. However, closer examination of the components of these ESPs reveals a starkly different picture. Differences in computed ESPs (ΔESP) for the five azines are plotted in Fig. 2a, relative to the ESP of benzene. These ESP differences arise from three sources: differences in the position of the nuclei (ΔESP_N), differences in the σ -electron density [$\Delta\text{ESP}_\sigma(\sigma)$], and differences in the π -electron density [$\Delta\text{ESP}_\sigma(\pi)$]. These contributions to ΔESP are plotted in Fig. 2b, 2c, and 2d, respectively. Analogous plots in the plane bisecting these rings are provided for selected systems in ESI. The only one of these components that leads to more positive ESPs above the centres of these rings is the nuclear contribution, ΔESP_N ; both the σ - and π -electronic contributions lead to more negative ESPs and weaker anion- π interactions, compared to benzene. Additionally, the impact of the σ -electron density differences on the ESPs is much more substantial than variations in π -electron distributions.

The reason for the positive values of ΔESP_N above the ring centres is simple: each time a CH group is replaced with a nitrogen atom, there is effectively a movement of $+1e$ charge about 1 Å towards the ring centre, arising from the consolidation of the hydrogen and carbon nuclei into a $+7$ nitrogen nucleus (see Fig. 1c). The proximity of a greater quantity of nuclear charge near the centres of the azines leads to substantially more positive ESP values above the ring, and much more favourable anion- π interactions, as compared to benzene.

The effects of the nuclear positions are tempered by the accompanying changes in the electron distribution. That is, changes in both the σ - and π -electron density distribution resulting from incorporation of nitrogen atoms depress the value of the ESP above the ring centres, reducing the strength of anion-binding. For example, the change in the π -electron distribution resulting from the replacement of a single CH group with nitrogen (*i.e.*, converting benzene to pyridine) leads to a 3.0 kcal mol⁻¹ reduction in the electrostatic component of the binding of Cl^- at a distance of 3.5 Å above the ring centre (see ESI). This effect grows linearly with the number of nitrogen atoms, to the point that the electrostatic interaction of a simple anion with the π -electron cloud of hexazine is almost 17 kcal mol⁻¹ more repulsive than the π -electron cloud of benzene. In other words, azines do not bind anions above their centres because of changes in the π -electron distribution, but despite greater repulsion between the anion and the π -electron density!

Of course, differences in the π -electron distribution of these rings do impact on the electronic character of these rings, which presumably underlies the chemistry of π -acidic N -heterocycles. However, these differences are not responsible for the positive ESPs above the N -heterocycles, nor are they responsible for the ability of these arenes to bind anions. This can be seen explicitly in Fig. 1b, in which we plot ESPs of artificial molecular systems in which the π -electron density of benzene has been replaced with the π -electron density of each of the four azines while keeping the nuclear positions and σ -electron density unchanged. These plots clearly show that simply changing the π -electron density of benzene to that of the N -heterocycles does not result in the positive ESPs that are characteristic of these “ π -electron-deficient” rings.

Table 1 Q_{zz} quadrupole moments for the five azines, relative to benzene (ΔQ , in Buckingham), as well as nuclear and electronic contributions to ΔQ_{zz} (ΔQ_N and ΔQ_e) and σ - and π -contributions to ΔQ_e [$\Delta Q_e(\sigma)$ and $\Delta Q_e(\pi)$].^a

	ΔQ	ΔQ_N	ΔQ_e	$\Delta Q_e(\sigma)$	$\Delta Q_e(\pi)$
pyridine	+3.0	+17.8	-14.9	-14.6	-0.3
pyrazine	+6.1	+35.0	-29.0	-28.5	-0.5
s-triazine	+9.2	+53.2	-44.0	-43.3	-0.7
s-tetrazine	+11.4	+63.8	-52.4	-51.8	-0.6
hexazine	+15.9	+86.9	-71.0	-70.4	-0.6

^a For benzene, $Q_{zz} = -8.9$ B. For pyridine, Q_{zz} is computed relative to the centre of mass.

The same conclusions can be drawn from the nuclear and electronic contributions to Q_{zz} (see Table 1). The positive Q_{zz} values of the azines are a result of the nuclear positions, while changes in both the σ - and π -electron density distributions depress the Q_{zz} values of the azines, as compared to benzene. Similarly, the impact of the π -electron density on Q_{zz} is miniscule compared to that of the σ -electrons, reflecting the relatively minor perturbations of the aromatic π -cloud accompanying the introduction of nitrogen atoms into these rings.¹² That differences in the nuclear positions give rise to the positive Q_{zz} values of these π -acidic azines is also in agreement with previous work from Vrbanich and Ritchie¹³ on substituted benzenes.

Conclusions

Anion- π interactions are a vital tool for supramolecular chemistry,¹⁻³ and means of exploiting these interactions in a myriad of contexts will be facilitated by a sound understanding of their origin. Unfortunately, prevailing discussions¹⁻² of anion- π interactions involving N -heterocycles, which are based on changes in π -electron distributions induced by the introduction of heteroatoms, are not consistent with detailed computational analyses. Instead, we have shown that the ability of the N -heterocyclic azines to bind anions above their centres does not stem from changes in π -electron density. Instead, the positive Q_{zz} and ESP values of these azines, which underlie their anion-binding ability, are due to the proximity of a greater amount of nuclear charge near the ring centre, as compared to benzene. Moreover, the σ - and π -electron clouds of the azines actually repel anions to a greater extent than those of benzene. In other words, N -heterocycles do not bind anions because of changes in the π -electron density distribution, but despite greater σ - and π -electron repulsion, as compared to benzene. This conclusion could be tested by using fictitious nuclear charges.¹⁴ Moreover, these results have important implications for all non-covalent interactions with N -heterocycles in which electrostatic interactions play key roles, including XH- π interactions, cation- π interactions, and π -stacking interactions, among others.

Notes and references

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† Electronic Supplementary Information (ESI) available: Additional computational details, additional figures and data, and Cartesian coordinates. See DOI: 10.1039/b000000x/

‡ Electron density isosurfaces correspond to $\rho = 0.001$ e/au³, and were plotted using Chimera.¹⁵ ESP and Q_{zz} computations were performed at the HF/aug-cc-pVTZ level of theory using a locally-modified version of

Psi3.¹⁶ This work was supported by the National Science Foundation (Grant CHE-1254897). We also thank the Texas A&M Supercomputing Facility for computational resources

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