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Gas-phase basicity of aromatic azines: A short review on structural effects

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Dedicated to Professor José Manuel Riveros for his contribution to gas-phase ion chemistry.

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ABSTRACT

A large number of experimental and computational gas-phase basicity data for monocyclic and polycyclic aromatic azines, including values taken from the recent literature, were examined to explore how internal (structural) effects influence gas-phase basicity (GB) and/or proton affinity (PA) of aza nitrogen. Substituent electron withdrawing effects on the pyridine ring may induce a decrease in PA as large as 200 kJ mol^{-1}. Polarizability of alkyl and aryl groups increases experimental PA by up to 100 kJ mol^{-1}, as in the case of 1- and 2-aza[6]helicene. The many computational studies involving azines, often performed in search of "superbasicity", were reviewed. Calculations at the DFT level, carried out on chelating azine systems bearing strong electron donor substituents, yielded PAs much higher than the current upper limit of the experimental scale. The structural variety of aromatic azines, from hexaazabenzene to the phosphazeno derivative of azacalix[3](2,6)pyridine, generates aza-nitrogen PAs ranging from ca. 650 up to 1300 kJ mol^{-1}.

1. Introduction

As soon as determinations of experimental basicities became feasible in the gas phase, nitrogen bases were scrutinized in detail. With the John Brauman group at Stanford University, José Riveros was a pioneer of such measurements for amines [1]. These early studies inspired many other researchers and contributed to the development of physical organic chemistry [2]. In particular, Robert W. Taft at the University of California, Irvine (UCI) and his co-workers launched systematic experimental investigations of substituent effects in pyridine derivatives [3]. Owing to the relative structural simplicity of the aromatic systems, pyridines were also investigated in parallel by quantum chemical methods. In this short review, we examine the progress made in understanding the structural effects on the gas-phase basicity in the aromatic azine series.

In aromatic azines, the sp^2 aza nitrogen atom is *a priori* the most favored protonation site. Depending on structure, aromatic azines exhibit variable basicity strength in aqueous solution, from weak (pK_a close to zero) to medium (pK_a close to 10) [4]. The situation is different in the gas phase. For example, pyridine is a weaker base than ammonia in aqueous solution (by 4 pK_a units [4]), whereas in the gas phase, it displays a stronger basicity (by ca. 80 kJ mol^{-1} [5]). The difference in basicity in these two extreme environments is in part a consequence of the polarizability of the heteroaromatic ring. This effect is very important in the gas phase whereas in aqueous solution it is reduced almost to zero. For more complex azines, the differences between their strength in aqueous solution and in the gas phase result also from the various structural (internal) effects possible in the gas phase, most of them being strongly attenuated by solvent molecules, *e.g.*, polarizability of alkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl groups, as well as intramolecular H-bond(s). The structural variety of aromatic azines induces a large spectrum of gas-phase basicity, ranging from that of the weak base hexaazabenzene (PA close to that of benzene), through that of medium and strong bases (PAs close to those of amines), to that of the exceptionally basic polyfunctional chelating azacalix[3](2,6)pyridines with PAs close to that of phosphazenes [6].

In this work, we review the most important internal effects that dictate the gas-phase basicity of the nitrogen atom as the site of protonation in aromatic azines: presence of additional nitrogen atom(s) in the ring, presence of additional aromatic ring(s), pushing (electron donating) effect of specific groups {*e.g.*, NR_2, N=CH–NR_2, N=C(NR_2)$_2$, N=P(NR_2)$_3$, R = H or Alkyl}, electronic effects of other substituents (*e.g.*, NO_2, CN, CF_3, F, Me, Alkyl), and intramolecular

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repulsive or attractive interactions (like H-bonding) in bifunctional ligands. These effects help to explain the exceptional gas-phase basicity and to predict the favored site of protonation for more complex polyfunctional derivatives.

2. Experimental determinations of gas-phase basicities

In gas-phase acid-base chemistry [5,7], the Gibbs energy change for the deprotonation reaction of the conjugate acid of a neutral base: $BH^+ \rightarrow B + H^+$ is called gas-phase basicity (GB), $GB = \Delta G^\circ = PA - T\Delta S^\circ$, and proton affinity (PA) is the enthalpy change of this reaction. Both, GB and PA refer also to the negative of the Gibbs energy and enthalpy change of the protonation reaction of B, respectively. When the basicity strength of B increases, GBs and PAs also increase.

GBs and PAs can be experimentally determined using various methodologies and MS techniques [3,5–7]. In early ion cyclotron resonance (ICR) and high-pressure mass spectrometry (HPMS) experiments, the equilibrium method was employed [3,5–9]. Based on proton-transfer equilibrium constant determinations between two bases of close basicities, the relative gas-phase basicity ΔGB can be determined. Basicity ladders were established step-by-step by adding these basicity differences, and improvement of the self-consistency of the scale was confirmed by measurement overlaps. The kinetic method, proposed by Cooks and co-workers [10], has been widely applied later. Twenty years ago, Bouchoux and co-workers proposed the thermokinetic method [11].

Experimental determination of gas-phase basicities for aromatic azines started more than forty years ago. For substituted pyridines, GBs have mostly been determined by Taft and co-workers at UCI by the equilibrium method using ICR mass spectrometry and later its Fourier transform upgrading (FT-ICR) [8,12]. A large number of experiments have also been performed by Aue, Bowers (University of California, Santa Barbara – UCSB) [9,13], Meot-Ner (formerly at the National Bureau of Standard, now National Institute of Standard and Technology; currently at Virginia Commonwealth University, Richmond, VA) and their co-workers [14]. They also applied the equilibrium method and various MS techniques, especially ICR and HPMS. Gas-phase experiments for very strong bidentate pyridine bases have been performed at the University Nice Sophia Antipolis (UNS, now member of Université Côte d'Azur) by FT-ICR mass spectrometry using the equilibrium method [15,16]. Investigations by Meot-Ner for polycyclic monoazines and polyazines started also about forty years ago [14] and were continued in other laboratories [5,17,18]. Meot-Ner and co-workers [14] first used the equilibrium method for polycyclic azines and polyazines, and later Gronert, Meot-Ner and co-workers used calculations and bracketing for polycyclic aromatic nitrogen heterocycles [17]. For chiral superbases, 1- and 2-aza[6]helicenes, the kinetic method was chosen [18] by Roithová et al. The gas-phase basicity of melamine has been determined by the kinetic method [19].

Biomolecules containing the pyridine moiety, including nicotine and its derivatives, have been experimentally investigated at UCI [12], UNS [20], and also at UCSB [21]. For these studies, the equilibrium method and FT-ICR-MS technique were applied. Experimental gas-phase basicities of RNA and DNA bases were already known in 1970s [22,23], and have been re-examined later [24]. Recent experimental gas-phase basicity determinations by the kinetic and bracketing methods for nucleobases and their models together with theoretical studies confirmed that adenine and cytosine behave as pyridine bases [25–27]. Owing to the complexity of the multiple sites of protonation in these systems, as well as specific experimental difficulties, this topic cannot be treated appropriately in a limited space. Only a few simple nucleobases are examined in this short review.

In the family of substituted monocyclic aromatic azines, the lowest experimental GB was found for pentafluoropyridine (733.0 kJ mol^{-1} [5]) and the largest one for 2-N′,N′-dimethylformamidinopyrimidine (974.9 kJ mol^{-1} [15]). For polycyclic monoazines, the experimental GBs of 1-aza[6]helicene (1000 ± 4 kJ mol^{-1}) and 2-aza[6]helicene (992 ± 4 kJ mol^{-1}) [18] are close to that of the "proton sponge" 1,8-bis(dimethylamino)-naphthalene (995.8 kJ mol^{-1} [5]). For monocyclic polyazines, the lowest experimental GB was observed for *s*-triazine (819.6 kJ mol^{-1} [5]) and the largest one for melamine (913.8 kJ mol^{-1} [19]). Representative experimental GBs for aromatic azines, including some simple biomolecules, are given in Table 1.

3. Theoretical estimations of gas-phase basicities

Very frequently quantum-chemical calculations were performed for aromatic azines in parallel to experimental determinations [5,12a,16–18,20,25–27]. For monofunctional azines, high level calculations confirm experimental results with "chemical" ($\leq$5 kJ mol^{-1}) or "benchmark" accuracy (1 kJ mol^{-1}). For polyfunctional azines, quantum-chemical calculations help to analyze the favored site of protonation and all possible intramolecular interactions. Proton affinity (PA) can be estimated from the enthalpies (H_{298}) calculated at 298 K for the ionic (BH^+ and H^+) and neutral (B) species: $PA(B) = H_{298}(B) + H_{298}(H^+) - H_{298}(BH^+)$, and gas-phase basicity (GB) from their Gibbs energies (G_{298}): $GB(B) = G_{298}(B) + G_{298}(H^+) - G_{298}(BH^+)$. For the proton, its enthalpy $\{H_{298}(H^+) = 5/2RT = 6.2$ kJ mol$^{-1}\}$, entropy $\{S_{transl}(H^+) = 108.95$ J mol^{-1} K$^{-1}\}$ and Gibbs energy $\{G_{298}(H^+) = H_{298}(H^+) - TS_{transl}(H^+)\}$ at 298 K are known [5,28]. Various quantum-chemical methods were applied for PA and GB estimations. The most frequently employed are DFT (density functional theory), *ab initio* MP2 (second-order Møller-Plesset perturbation), and Gaussian-theory variants (abbreviated as G-n, n = 1–4) [6]. For small molecules, coupled cluster {CCSD(T)} or quadratic configuration interaction {QCISD(T)} calculations were also performed [6,29].

Currently, with the progress of computing power, there are many theoretical data for polyfunctional azines not yet experimentally confirmed. For example, Despotović and Vianello using DFT method investigated derivatives of pyridine and 1,8-diazanaphthalene containing strong pushing tetramethylguanidino {N=C(NMe$_2$)$_2$} and hexamethylaminophosphazeno {N=P(NMe$_2$)$_3$} groups (Table 2) [30]. The Authors estimated gas-phase basicities for two potential basic sites, ring aza and chain imino nitrogens, and showed that the aza nitrogen is preferentially protonated.

Analogous estimations, performed by Maksić and co-workers [31] for amino and guanidino derivatives of *s*-triazine, led to the same conclusion that the aza nitrogen is the favored protonation site. Multifunctional aminoazines investigated by Maksić and co-workers seem to be the strongest bases in the family of aromatic polycyclic polyazines [31,32]. Their calculated PAs are considerably larger than 1150 kJ mol^{-1}, the limit for the current experimental GB ladder [6,33]. In a computational study of electrophilic aromatic substitution, Vianello applied the G3B3 composite procedure for the calculation of PA and GB of a few simple azines, one of the aims of the work being the determination of the proton affinities of the nitrogen (or heteroatom) and of the carbon sites [34]. The results were in good agreement with the available experimental data.

4. Effects of additional aza nitrogen(s)

Gas-phase basicity measurements performed for mono- and polyazines [5] gave the possibility for estimating the effects of additional aza nitrogen(s) that strongly depend on the position