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Site of Protonation in Aniline and Substituted Anilines in the Gas Phase: A Study via the Local Hard and Soft Acids and Bases Concept

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In this paper we address the long standing problem regarding the site for gas-phase protonation in aniline and substituted anilines. Our study reveals that DFT-based reactivity descriptors can reproduce the experimentally observed preferable protonation sites. However, it is found that the quantity s_k^-/s_k^+, termed "relative nucleophilicity" and a measure of "local polarizability", produces more reliable results than the local softness, s_k^-. The problem which sometimes arises in taking s_k^-/s_k^+ as the reactivity descriptor is also discussed.

Introduction

Although aniline is a well-known nitrogen base in aqueous solution, the site of protonation of gaseous aniline is ambiguous and contradictory results are reported from time to time.[1a−h] The first experimental study on the gas-phase basicity of aniline suggested that the ring carbon may be the energetically feasible protonation site.[1a] Correlating the proton affinities of differently substituted anilines with nitrogen 1s electron ionization energies, Pollack et al.[1b] claimed that gaseous aniline preferably acts as a N-base and not as a C-base. Mass spectrometric studies involving collison−activated dissociation of partially deuterated aniline ions suggested preferential ring protonation under chemical ionization conditions, thus proposing thermodynamic control of the protonation.[1e,g,h] A recent study by Karpas et al.[1i] using the ion mobility/mass spectrometry technique showed that protonation of gaseous aniline at atmospheric pressure yields two isomeric ions involving nitrogen- and ring-protonated structures. On the basis of the assumption that the structure with lower mobility is that of a nitrogen-protonated species, they interpreted a preference for nitrogen protonation on aniline. Very recently Smith et al.[2] reported an experimental study in which they allow partially deuterium-labeled aniline ions to react with nitrogen bases in a dual-cell Fourier transform ion cyclotron resonance device. Their study unambiguously shows that nitrogen is the kinetically favored protonation site of gaseous aniline.

Only few theoretical studies, using molecular orbital methods,[1c,f] were reported hitherto. These minimal basis set ab initio or MNDO calculations showed that although the nitrogen atom is the thermodynamically preferred protonation site, it is only favored by 1−3 kcal/mol over the energetically most favorable site in the ring, the para position. It was argued that[1c] this energy difference is small enough to change the site of protonation by selective substitution in the meta position or by solvation (in the case of solution phase). The conclusiveness of those studies, however, remains questionable when considering the low level of calculation and also the small basis sets used.

More recently some studies using local reactivity descriptors have been published. Sjoberg et al.[3] used the local surface ionization energy $\bar{I}(r)$ concept and obtained for aniline a minimum on the para carbon atom promoting it to be the most reactive site toward electrophiles. On the other hand, Ritchie[4] has shown that the global minimum in the calculated molecular electrostatic potential value is found near the N atom, being then the most preferable site for protonation.

In this paper, we report the first study on the gas-phase protonation of aniline and substituted anilines (*m*- and *p*-F, Cl, CH_3, and OCH_3) using local reactivity descriptors based on the hard and soft acids and bases (HSAB) concept. We have used local softness values of the individual atoms to find out the most preferable protonation site in those systems. In a previous communication[5] we have shown that the recently defined reactivity descriptors "relative nucleophilicity" (s_k^-/s_k^+) and "relative electrophilicity" (s_k^+/s_k^-) offer a better description of the site selectivity in carbonyl compounds. In this study, however, the reliability of both s_k^- and s_k^-/s_k^+ will be considered (as the proton, H^+, is an electrophile) to find out the preferable protonation sites of aniline and substituted anilines.

In section 2 we briefly describe the HSAB indices highlighting the justification of these local indices as proper response functions. Section 3 is devoted to computational details. A critical analysis of the results along with plausible explanations is given in section 4.

2. Theoretical Background

Although the hard and soft acids and bases concept was introduced more than three decades ago by Pearson,[6] the first unambiguous definition of hardness and softness was given by Parr and Pearson in the early 80s.[7] They defined global hardness η as

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{\nu(\bar{r})} = \left(\frac{\partial \mu}{\partial N}\right)_{\nu(\bar{r})} \tag{1}$$

where E is the total energy, N the number of electrons of the chemical species, and $\nu(\bar{r})$ the external potential (i.e., due to nuclei plus any other if present). μ is the chemical potential, which is identified as the negative of the electronegativity[8] (χ) as defined by Iczkowski and Margrave.[9]

The corresponding global softness (S), which bears an inverse relationship with the global hardness (η), is defined as[7]

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$$S = \frac{1}{2\eta} = \left(\frac{\partial N}{\partial \mu}\right)_{v(\bar{r})} \tag{2}$$

The operational definitions of η and S are obtained by finite difference approximations to eq 1 as

$$\eta = \frac{\mathrm{IP} - \mathrm{EA}}{2} \tag{3}$$

$$S = \frac{1}{\mathrm{IP} - \mathrm{EA}} \tag{4}$$

where IP and EA are the vertical ionization potential and electron affinity respectively, of the chemical species.

In our present study we are interested in site selectivities of chemical species toward an electrophilic attack (in casu by H^+). This aspect can be described better by local responses of a chemical species toward attack by an another species. Local softness ($s(\bar{r})$) and Fukui functions ($f(\bar{r})$) are such a type of local reactivity descriptors. A large number of theoretical studies in our group using these local reactivity descriptors were already performed.[10] Local softness is defined as[11]

$$s(\bar{r}) = \left(\frac{\partial \rho(\bar{r})}{\partial \mu}\right)_{v(\bar{r})} \tag{5}$$

where $\rho(\bar{r})$ is the electron density. Consequently, $\int s(\bar{r})\, d\bar{r} = S$.

Combining eqs 5 and 2 we can write

$$s(\bar{r}) = \left(\frac{\partial \rho(\bar{r})}{\partial N}\right)_{v(\bar{r})} \left(\frac{\partial N}{\partial \mu}\right)_{v(\bar{r})} = f(\bar{r})S \tag{6}$$

where $f(\bar{r})$ is the Fukui Function introduced by Parr and Yang.[12] It is obvious from eq 6 that both $s(\bar{r})$ and $f(\bar{r})$ can be used for studying intramolecular reactivity sequences (i.e., relative site selectivity in a molecule), but only $s(\bar{r})$ (which contains in its definition the information of global softness, S) can be used as an indicator when comparing the reactivity of different molecules with respect to a common reaction partner.[13]

Considering the fact that $\rho(\bar{r})$ is a discontinuous function of N, three different types of $f(\bar{r})$ can be defined for any atom or molecule corresponding to a nucleophilic, electrophilic, or radical attack. Within a finite difference approximation the condensed form of these three functions, when multiplied by S, provides three different local softnesses for any particular atom (k)[14]

$$s_k^+ = [\rho_k(N_0 + 1) - \rho_k(N_0)]S \tag{7a}$$

(suited for studies of nucleophilic attack)

$$s_k^- = [\rho_k(N_0) - \rho_k(N_0 - 1)]S \tag{7b}$$

(suited for studies of electrophilic attack)

$$s_k^0 = \frac{1}{2}[\rho_k(N_0 + 1) - \rho_k(N_0 - 1)]S \tag{7c}$$

(suited for studies of radical attack)

where $\rho_k(N_0)$, $\rho_k(N_0 - 1)$, and $\rho_k(N_0 + 1)$ represent the electronic population on atom k for the N_0, $N_0 - 1$, and $N_0 + 1$ electron systems, respectively.

From eqs 7a, 7b, and 7c (which are of interest here), we see that s_k^+, s_k^-, and s_k^0 are indicative of the response of any particular site toward addition or subtraction of one electron to or from the system. It can be stated that other known methods of finding site selectivities, e.g., from atomic charges or molecular electrostatic potential values[15] on the individual sites of the neutral system only, lack some physical reality as these methods consider only the electron density of the neutral systems and thus neglect the response of the system (through redistribution of its electron density) to perturbations in the number of electrons.

In this paper, the concept of "local polarizability" is introduced. From our previous work on gas-phase acid–base equilibria,[16] we can state that the electronic effects in the charged form of the acid–base equilibrium are often responsible for the observed acid–base sequences. Introducing a positive or negative charge in the system creates an additional stabilization of the system via the charge-induced dipole interaction, which is dependent on the polarizability. Since polarizability correlates with softness,[17a–h] one can expect that softer groups in the basic center tend to stabilize the positive charge in the protonated form. Since in the case of substituted anilines two sites can be expected to be protonated,[1a–h] a measure of local polarizability is needed, for which we use the local softness. The protonation of aniline will thus occur at the site where

(1) the initial attraction toward the proton is the largest, a characteristic of the uncharged form of the acid–base equilibria;

(2) the local polarizability is the highest as measured by the local softness.

From our experience[16] it is possible to say that the second effect will be the most important in describing the acid–base sequences. The question then arises for a good descriptor of local polarizability. As protonation involves an attack by electrophile, El^+, the first obvious choice is s_k^-. However, in a previous communication[5] we have shown that the ratio s_k^-/s_k^+ (termed as "relative nucleophilicity") of the individual atoms is a more reliable descriptor of intramolecular "nucleophilicity" (in the case of protonation we can read it as "basicity") than s_k^- itself. Here, it is to be noted that by "relative nucleophilicity" we intend to describe the affinity of any site (i.e., atom in present case) toward an electrophile (El^+) relative to its affinity toward a nucleophile (Nu^-). Now relative affinity of any site toward an electrophile (El^+) as compared to a nucleophile (Nu^-) depends on the relative values of s_k^- and s_k^+. The theoretical justification in favor of taking s_k^-/s_k^+ as a measure of relative nucleophilicity is that in this way we may cancel (to some extent) the errors in the individual values of s_k^+ and s_k^-, incurred in the process of their evaluation (e.g., due to insufficiently taking into account electron correlation, basis set limitations, etc.). In the present study we will examine the reliability of both s_k^- and s_k^-/s_k^+ as a measure of local polarizability as defined above.

3. Methodology and Computational Details

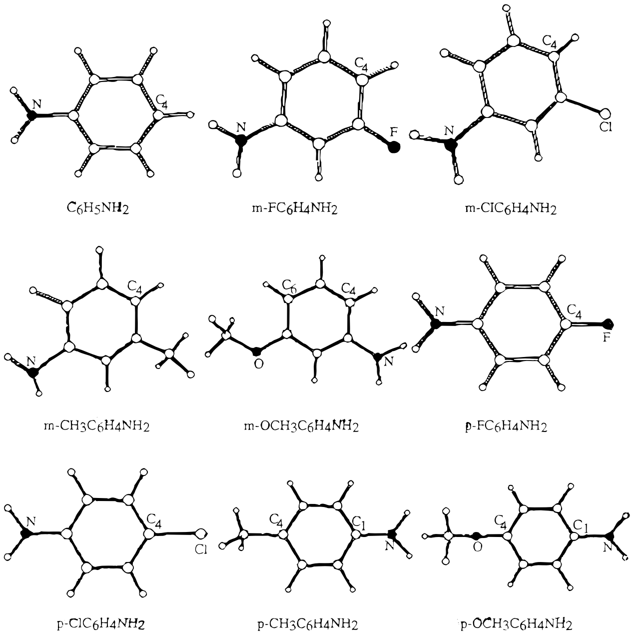
In our present study we have chosen aniline ($C_6H_5NH_2$) and *m*- and *p*- substituted ($-F$, $-Cl$, $-CH_3$, and OCH_3) anilines to examine their preferable protonation sites in the gas phase. The initial geometries have been generated using the Unichem program system.[18] Subsequently these geometries are optimized both at Hartree–Fock and DFT levels. In the former case a RHF/DZP methodology (Huzinaga's double-ζ basis set[19] plus polarization functions as introduced by Dunning[20]) is used. In the latter case a DFT approach is used (the B3LYP functional,[21a–c] together with Dunning's correlation consistent polarized valence double-ζ basis[22]) denoted as B3LYP/cc-pVDZ. The s_k^+ and s_k^- values are evaluated at the above two levels. However, to increase the reliability of the results we also evaluated s_k^+ and

TABLE 1: s_k^+ and s_k^- Values (in atomic units) of the Relevant Atomic Positions of Aniline and *m*-Substituted Anilines

		basis set					
		DZP		cc-pVDZ		cc-pVTZ	
compound	atomic center	s_k^+	s_k^-	s_k^+	s_k^-	s_k^+	s_k^-
$C_6H_5NH_2$	N	0.0350	0.2549	0.0482	0.3775	0.0761	0.5007
	C_4	−0.1124	0.4753	−0.0057	0.2474	−0.0068	0.3623
m-$FC_6H_4NH_2$	N	0.0333	0.2378	0.0478	0.3657	0.0236	0.4862
	C_4	0.1034	0.4918	0.1045	0.3003	0.1667	0.4332
m-$ClC_6H_4NH_2$	N	0.0261	0.2019	0.0513	0.3620	0.0809	0.4786
	C_4	0.1725	0.4102	0.0447	0.2948	0.0860	0.4403
m-$MeC_6H_4NH_2$	N	0.0333	0.2197	0.0476	0.3673	0.0753	0.4867
	C_4	−0.0645	0.5206	0.0303	0.2953	0.0355	0.4319
m-$OMeC_6H_4NH_2$	N	0.0325	0.1686	0.0481	0.3002	0.0369	0.4019
	C_4	0.1945	0.3520	0.1273	0.2556	0.1470	0.3670
	C_6	0.0740	0.4938	0.0618	0.2997	0.0914	0.4206

s_k^- values at B3LYP/cc-pVTZ (Dunning's correlation consistent polarized valence triple-ζ basis set[22]) using the geometry optimized at the B3LYP/cc-pVDZ level. The effectiveness of B3LYP/cc-pVDZ and B3LYP/cc-pVTZ methods to produce reliable Fukui functions is already reported by this group.[23] In the calculations at DZP level, the RHF (restricted Hartree−Fock) method is used for the neutral systems (closed shell), whereas the ROHF (restricted open-shell Hartree−Fock) method is used for the corresponding cations and anions (open-shell).[24] Abbreviations for the methods that will be used are HF/DZP ≡ A, B3LYP/cc-pVDZ ≡ B, and B3LYP/cc-pVTZ ≡ C. Condensed Fukui functions were evaluated using Mulliken's population analysis.[25] All calculations were performed with the Gaussian 94 Program[26] on the CRAY JP916/8-1024 computer of the Free Universities of Brussels.

While the geometries are optimized, frequencies are simultaneously checked (so that there is no imaginary frequency in the optimized geometry) to be sure that the geometry corresponding to a minimum energy is reached. Local softness values (both s_k^+ and s_k^-) are, in a straightforward way, calculated for all the atoms using eqs 7a and 7b.



$C_6H_5NH_2$ m-$FC_6H_4NH_2$ m-$ClC_6H_4NH_2$

m-$CH_3C_6H_4NH_2$ m-$OCH_3C_6H_4NH_2$ p-$FC_6H_4NH_2$

p-$ClC_6H_4NH_2$ p-$CH_3C_6H_4NH_2$ p-$OCH_3C_6H_4NH_2$

Figure 1. Numbering of atoms in aniline and *m*- and *p*-substituted anilines.

4. Results and Discussion

A. Aniline and *m*-Substituted Anilines. Figure 1 shows the numbering of the atoms in the molecules considered. Only positions in which we are interested, i.e., only those atoms having comparable s_k^- values in the higher range and at the same time fulfilling the condition $s_k^- > s_k^+$, are depicted. If these two conditions are satisfied then those atoms are considered to act as a preferable "nucleophilic" center. The same criteria will be applied for *p*-substituted anilines. The local softness values (both s_k^+ and s_k^-) of the individual atoms are tabulated in Table 1. These will provide us information regarding the response of individual atoms toward protonation. The corresponding s_k^-/s_k^+ values are presented in Table 2.

TABLE 2: s_k^-/s_k^+ Values of the Relevant Atomic Positions of Aniline and *m*-Substituted Anilines

		basis set		
		DZP	cc-pVDZ	cc-pVTZP
compound	atomic center	s_k^-/s_k^+	s_k^-/s_k^+	s_k^-/s_k^+
$C_6H_5NH_2$	N	7.2747	7.8311	6.5806
	C_4	−4.2288	−43.3036	−53.4138
m-$FC_6H_4NH_2$	N	7.1401	7.6554	20.5685
	C_4	4.7567	2.8732	2.5981
m-$ClC_6H_4NH_2$	N	7.7472	7.0622	5.9189
	C_4	2.3786	6.5966	5.1182
m-$MeC_6H_4NH_2$	N	6.5923	7.7108	6.4669
	C_4	−8.0672	9.7466	12.1657
m-$OMeC_6H_4NH_2$	N	5.1895	6.2490	10.8960
	C_4	1.8095	2.0082	2.4963
	C_6	6.6702	4.8511	4.6013

We have compared the results obtained from Table 1 with the experimental relative proton affinities of competitive atoms in gas phase as observed by Summerhays et al.[1c] It is to be mentioned that the experimental studies carried by them are based on the correlation of gas-phase free energies of *m*- and *p*- substituted anilines with the corresponding free energies in aqueous solution. Anilines and substituted anilines (those which are considered in the present study) are well-known for their N-protonation in aqueous solution.[27] So the systems, for which gas-phase relative base strengths correlate well with those obtained in aqueous solution, are believed to demonstrate preferable N-protonation in gas-phase. On the basis of their observation Summerhays et al.[1c] concluded that aniline, all *p*-substituted anilines, and *m*-fluoro and *m*-chloro anilines preferably undergo N-protonation in gas-phase. On the other hand *m*-toluidine and *m*- anisidine are preferably protonated in the para position since the relative gas-phase base strengths of these two compounds do not show a fair correlation with those obtained in aqueous solution phase. One plausible explanation may be that because of their high electronegativity, F and Cl atoms draw electrons from the aromatic ring in *m*-fluoro and *m*-chloro anilines and thus prevent the para position from being protonated. Being +I and +M substituents, respectively, the CH_3 and OCH_3 groups increase the electron density of the para position, thus enhancing the chance of para protonation. But in the case of para-substituted anilines, as the para position is already occupied, the preferable site of protonation will be the N atom. In our present study the argument is that the higher the values of local polarizability (as measured by s_k^- or s_k^-/s_k^+) of any atom, the more tendency it has to be protonated. If we summarize the results for s_k^- from Table 1 the following trends become obvious:

molecule	method	preferrence for protonation
$C_6H_5NH_2$	A	$N < C_4$
	B	$N > C_4$
	C	$N > C_4$
m-$FC_6H_4NH_2$	A	$N < C_4$
	B	$N > C_4$
	C	$N > C_4$
m-$ClC_6H_4NH_2$	A	$N < C_4$
	B	$N > C_4$
	C	$N > C_4$
m-$CH_3C_6H_4NH_2$	A	$N < C_4$
	B	$N > C_4$
	C	$N > C_4$
m-$OCH_3C_6H_4NH_2$	A	$C_6 > (C_4, N)^a$
	B	$N > (C_6, C_4)^a$
	C	$C_6 > (N, C_4)^a$

[a] Relative base-strength of position C_4 is not discussed in the experimental study of Summerhays et al.[1c]

From these results it is clear that DZP level calculations fail in most cases. Only in the cases of *m*-toluidine and *m*-anisidine do theory and experiment match. Whether the ortho position (C_4) in *m*-anisidine should have a higher proton affinity than the N atom is not clearly known from experiment. The DFT level calculations with the cc-pVDZ basis reproduce all experimental trends except in *m*-toluidine and *m*-anisidine. The *m*-anisidine case is corrected at the cc-pVTZ level. We will see from Table 2 that passing to s_k^-/s_k^+ will correct this irregular trend in most cases. The summary of observations from Table 2 is as follows:

molecule	method	preference for protonation
$C_6H_5NH_2$	A	$N > C_4$
	B	$N > C_4$
	C	$N > C_4$
m-$FC_6H_4NH_2$	A	$N > C_4$
	B	$N > C_4$
	C	$N > C_4$
m-$ClC_6H_4NH_2$	A	$N > C_4$
	B	$N > C_4$
	C	$N > C_4$
m-$CH_3C_6H_4NH_2$	A	$N > C_4$
	B	$N < C_4$
	C	$N < C_4$
m-$OCH_3C_6H_4NH_2$	A	$C_6 > (N > C_4)^a$
	B	$N > (C_6 > C_4)^a$
	C	$N > (C_6 > C_4)^a$

[a] Relative base-strength of position C_4 is not discussed in the experimental study of Summerhays et al.[1c]

Here we see that in most cases the trend has become correct except for *m*-anisidine, where N has emerged to be the strongest nucleophilic center instead of the para carbon (C_6) atom as experimentally observed. In aniline (in all the three basis sets) and *m*-toluidine (at DZP level) a problem arises owing to the negative sign of s_k^+. In our earlier work we argued in favor of taking the ratio of s_k^- and s_k^+ (i.e., to consider s_k^-/s_k^+), instead of only s_k^-, as a measure of nucleophilicity of a particular site (atom), because in that way the effect of correlation and of basis set can be compensated. Also in our present study we see that the irregular trends obtained by considering only s_k^- values are corrected in most cases by taking s_k^-/s_k^+ values (except those cases where s_k^+ has negative values).

The above cases (i.e., those having negative s_k^+ values) point to the apparent problem of taking s_k^-/s_k^+ values of any atom as a measure of its affinity to an electrophile (El^+), because in such cases the value of s_k^-/s_k^+ is negative. Now if we go back to the equation of s_k^+ (eq 7a), we see that negative s_k^+ values arise when $\rho_k(N_0 + 1) < \rho_k(N_0)$, i.e., when the electron density on any particular atom decreases even though the overall number of electrons of the system is increased by one. Although to the best of our knowledge no proof has been given that the Fukui function should be always positive, it is difficult to accept negative values on an intuitive basis. An artifact of methodology (finite difference approach), basis set limitation and lack of correlation seems plausible. In the cases where s_k^-/s_k^+ is negative, only s_k^- is considered.

B. *p*-Substituted Anilines. The s_k^+ and s_k^- values of the competitive atoms of *p*-substituted anilines are presented in Table 3. The corresponding s_k^-/s_k^+ values are given in Table 4. In their experimental study Summerhays et al.[1c] only discussed N-protonation (which was arrived at by correlating relative gas-phase base strengths with the corresponding solution-phase values). However, in our present study we will see that some other sites also become important in a few cases. From the results on s_k^- in Table 3 we get the following trends:

molecule	method	preference for protonation
p-$FC_6H_4NH_2$	A	$C_4 > N > F$
	B	$N > F > C_4$
	C	$N > F > C_4$
p-$ClC_6H_4NH_2$	A	$Cl > N > C_4$
	B	$Cl > N$
	C	$Cl > N$
p-$CH_3C_6H_4NH_2$	A	$C_4 > C_1 > N$
	B	N
	C	N
p-$OCH_3C_6H_4NH_2$	A	$C_4 > C_1 > N$
	B	$N > C_4$
	C	$N > C_4$

We see that in most cases the DZP basis does not yield experimental trends. Results at B3LYP/cc-pVDZ and B3LYP/cc-pVTZ levels are improved except for *p*-fluoroaniline and *p*-chloroaniline. In the former although N is seen to be the strongest basic center, the calculated trend $F > C_4$ (the carbon atom in para position to the NH_2 group) is not clearly understood. Similarly highest basicity of the Cl atom in *p*-chloroaniline is difficult to accept. We will see from Table 4 that s_k^-/s_k^+ values correct this unexpected trend in some cases.

TABLE 3: s_k^+ and s_k^- Values (in atomic units) of the Relevant Atomic Positions of *p*-Substituted Anilines

		basis set					
		DZP		cc-pVDZ		cc-pVTZ	
compound	atomic center	s_k^+	s_k^-	s_k^+	s_k^-	s_k^+	s_k^-
p-$FC_6H_4NH_2$	N	0.0413	0.2736	0.0516	0.3731	0.0837	0.4975
	F	0.1099	0.2033	0.1466	0.2541	0.1623	0.2840
	C_4	0.0024	0.4370	0.0583	0.2199	−0.0591	0.2019
p-$ClC_6H_4NH_2$	N	0.0382	0.2510	0.0516	0.3504	0.0829	0.4662
	C_l	0.3243	0.5105	0.3915	0.6317	0.4011	0.6634
	C_4	−0.1803	0.2463		*a*		*a*
p-$MeC_6H_4NH_2$	N	0.0379	0.2312	0.0483	0.3533	0.0771	0.4714
	C_1	−0.0107	0.2501		*a*		*a*
	C_4	−0.2469	0.2970		*a*		*a*
p-$OMeC_6H_4NH_2$	N	0.0413	0.2410	0.0490	0.3546	0.0793	0.4734
	C_1	−0.0260	0.2420		*a*		*a*
	C_4	−0.0277	0.4504	0.0420	0.2141	−0.0428	0.2173

[a] Values are significantly smaller and thus are omitted.

The summary of the results indicates that method B predicts correct trends in the case of *p*-fluoroaniline

molecule	method	preference for protonation
p-$FC_6H_4NH_2$	A	$C_4 \gg N > F$
	B	$N > C_4 > F$
	C	$N > F > C_4$
p-$ClC_6H_4NH_2$	A	$N > Cl > C_4$
	B	$N > Cl$
	C	$N > Cl$
p-$CH_3C_6H_4NH_2$	A	$N > C_4 > C_1$
	B	N
	C	N
p-$OCH_3C_6H_4NH_2$	A	$N > C_1 > C_4$
	B	$N > C_4$
	C	$N > C_4$

(although the s_k^- trends remain the same in methods A and C). For *p*-chloroaniline the trend has become closer to experiment. In both systems the N-atom emerges as the most preferable site for protonation (except for *p*-fluoroaniline in method A), though F and Cl also show a high proton affinity. As far as *p*-toluidine is concerned, the results for the s_k^- values showing N to be unambiguously the most preferable protonation site at all levels are confirmed here also. For *p*-anisidine using method A, the problem due to negative s_k^+ values arises. However, in all four systems the N-atom emerges as the most preferable protonation site (except at the lower DZP level in *p*-fluoroaniline and *p*-anisidine), in agreement with experiment.

From the previous analysis our overall impression is that with improvement of methodology and basis set the calculated s_k^- and s_k^-/s_k^+ values of any particular atom become more reliable and hence can be compared, with confidence, to find out the preferable gas−phase protonation sites. In the case of *m*-anisidine, though s_k^- values at the B3LYP/cc-pVTZ level produce experimental trends, it is not so if we compare s_k^-/s_k^+ values. Similarly, though s_k^- values at the B3LYP/cc-pVTZ level reproduce experimental trends in most cases, they fail for *m*-toluidine and *p*-chloroaniline. It is really interesting that s_k^-/s_k^+ values termed as relative nucleophilicity and considered to be a measure of local polarizability correct these irregular trends.

Further investigations using other approaches to the molecular charge distributions (e.g., MEP, based charges)[28,29] may provide additional insight into the concept of relative nucleophilicity.

TABLE 4: s_k^-/s_k^+ Values of the Relevant Atomic Positions of *p*-Substituted Anilines

		basis set		
		DZP	cc-pVDZ	cc-pVTZP
compound	atomic center	s_k^-/s_k^+	s_k^-/s_k^+	s_k^-/s_k^+
p-$FC_6H_4NH_2$	N	6.6249	7.2313	5.9475
	F	1.8503	1.7335	1.7501
	C_4	179.3371	3.7711	−3.4196
p-$ClC_6H_4NH_2$	N	6.5791	6.7878	5.6224
	Cl	1.5743	1.6137	1.6540
	C_4	−1.3657	*a*	*a*
p-$MeC_6H_4NH_2$	N	6.0943	7.3126	6.1129
	C_1	−23.3010	*a*	*a*
	C_4	−1.2031	*a*	*a*
p-$OMeC_6H_4NH_2$	N	5.8300	7.2327	5.9719
	C_1	−9.3267	*a*	*a*
	C_4	−16.2752	5.1038	−5.0845

[a] Because of very small values of s_k^- (Table 3), these s_k^-/s_k^+ values are insignificant and thus are omitted.

5. Conclusion

It is observed that the DFT-based local reactivity descriptors s_k^- or more specifically s_k^-/s_k^+, if evaluated with DFT methods of sufficient level and adequate basis set, reproduce the experimental trends of preferable protonation sites in most cases. The present results complete those of a previous one where we have studied the preferable sites for nucleophilic addition in carbonyl compounds, which shows that relative nucleophilicity (s_k^-/s_k^+) and relative electrophilicity (s_k^+/s_k^-) can be used more reliably as local reactivity descriptors than the individual s_k^+ and s_k^- values, respectively. Correlation and basis set errors are possibly minimized in this way. Though in the present study the B3LYP/cc-pVDZ and B3LYP/cc-pVTZ methods take care of correlation effects, the level may not be sufficient if we consider the highly competitive nature of the preferable protonation sites. It is interesting to see that the s_k^-/s_k^+ values, if calculated at the B3LYP/cc-pVTZ level (the best of the three methods used in the present study), reproduce experimental trends in all the cases except for *m*-anisidine.

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