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Correlation of Dissociation Constants of 2- and 2,6-Substituted Anilines in Water by Methods Based on the Similarity Principle and Quantum-Chemistry Calculations

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In the context of studies of the ortho effect, two series of 2-monosubstituted (H, CH_3, CF_3, OH, CH_3O, F, Cl, NH_2, CN, NO_2) and 2,6-disubstituted anilines (containing all combinations of CH_3, CH_3O, Cl, and NO_2 substituents) were chosen for this work. Commercially unavailable derivatives were synthesized, and dissociation constants in water were determined for those substances for which the proper measurements had not yet been carried out. A critical compilation of pK_a literature data has been summarized and compared with the authors' own data. The analysis and interpretation of the *ortho* substitution effect and its manifestation in the dissociation constants of the studied anilines (as log K_a) was based on two different approaches—correlation analysis (similarity principle) and quantum-chemistry calculations. The classical correlation equation with substituent constants σ_I and σ_R was extended by the parameter υ describing the steric effects, but the correlation was not close enough ($s = 0.514$, $R = 0.986$). The AISE theory (alternative interpretation of substituent effects), extended by parameter υ for the steric effects description, significantly improved the correlation ($s = 0.139$, $R = 0.9991$). The B3LYP/6-311G(d,p) method was used for the calculation of physical−chemical properties of protonated and nonprotonated forms of aniline derivatives. Quantum chemically calculated properties were correlated with experimental data. The data mining regression method showed that the statistically most suitable interpreting variables are the Gibbs energy of the dissociation equilibrium (ΔG_{eq}) and the sum of the natural charges of the nonprotonated amino group hydrogen atoms ($Q_n(\sum H)$) and the dipole moment of the aniline protonated form (μ_+). This correlation is closer ($s = 0.316$, $R = 0.995$) than that based on the similarity principle. The correlation with quantum-chemical characteristics indicates a close interrelation of the dissociation constant with the energy of the equilibrium participants and the delocalization energy of the nonprotonated form of aniline. The meaning of the $\sum$H quantity in the correlation relation is related to the presence of a nitro substituent (intramolecular hydrogen bond with the reaction center). The dipole moment of the aniline protonated form μ_+ is in relation with nonspecific solvation in an aqueous medium.

Introduction

Aniline represents not only a significant chemical product but also an important chemical model. The interaction between the aromatic ring and the amino group is interesting from the point of view of molecular geometry, electron distribution, spectral properties, acid−base properties, and substituent effects. In studies of the aforementioned properties, an increasingly important role has been played by quantum-chemistry methods. The molecular geometry of aniline calculated at the semiempirical level or at the ab initio level agrees well with experimentally available quantities.[1−7] The amino group in aniline possesses a pyramidal structure, the dihedral angle between the plane formed by H−N−H atoms and the benzene ring being 42.4 ± 0.3° (ref 8). The group also exhibits inversion and torsion vibrations, whose detailed quantum-chemical analysis has been published elsewhere.[6] Due to its resonance with the amino group, the benzene ring possesses a slightly quinoid structure, with increased π-electron density at the 2-, 4-, and 6-positions, where electrophilic aromatic substitution reactions usually take place. In this context it is worth noting that an aniline molecule in the gas phase is preferably protonated at the 4-position, not at the nitrogen atom.[9]

Development of quantum-chemical methods has made it possible to study the effect of substitution upon the molecular structure and associated quantities (particularly acid−base properties) of anilines. Theoretical calculations of molecular structure, electron distribution, and several other physicochemical properties were carried out for para substituted anilines at a semiempirical level[10−14] (MINDO/3, AM1, PM3) and at an ab initio level,[12,15,16] as well as by other methods.[17] From the results published, it follows that electron-acceptor substituents in an aniline molecule diminish the dihedral angle between the H−N−H plane and the benzene ring, shorten the N−C bond length, simultaneously increase the dipole moment, and lower the HOMO energy and so forth.

The acid−base properties of aniline and its substitution derivatives are among the most important properties. The basicity in solution can easily be measured experimentally and expressed quantitatively by means of the dissociation constant of the conjugated base. Also it is possible to experimentally

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determine the relative basicity in the gas phase expressed by the value of the enthalpy change (ΔH_{prot}) of the proton transfer in the isodesmic reaction.[18] This quantity can be acceptably approximated by the energy difference of the participating molecules calculated using an appropriate quantum-chemical method.[19] A detailed quantum-chemical study of the B3LYP functional for predicting acidities and basicities in the gas phase has been published.[20] This study shows that the B3LYP/6-31G-(d) method is of sufficient quality for semiquantitative calculations of neutral bases' basicity.

If the protonation of aniline takes place in solution, it involves additional changes in the solvation of all the participants, particularly of the reaction center. The solvation changes also involve specific interaction at the molecular level and nonspecific electrostatic interaction connected with the relative permittivity and polarizability of the medium.[21-23] In principle, the interaction of aniline with a proton is a very simple reaction. The protonation involves a change in the overall energy of the molecule, as well as a significant reorganization of its orbitals (the frontier orbitals in particular), redistribution of electrons, and changes in its other properties. Thus, it can be expected that the experimental pK_a value would correlate with the energy difference between the protonated and nonprotonated forms of aniline, with the HOMO energy of the nonprotonated form (E_{HOMO}), and with some other appropriate characteristics. This presumption was confirmed in the cases of *meta* and *para* substituted anilines by a number of relatively close correlations between the pK_a values (water) and charges at the NH_2 group[16] ($Q(NH_2)$), relative enthalpies of proton transfer (ΔH_{prot}), $r_{\text{C-N}}$ bond lengths, the inversion energy of the amino group (E_{inv}), natural partial charges at the N atom of the amino group[24] (Q_n-(N)), and some other quantities.[19,25] The best residual standard deviations in pK_a units so far published are $s = 0.29$ (18 derivatives)[19] and $s = 0.26$ (19 derivatives).[24]

In contrast to the cases of meta and para substitution, the effect of ortho substitution on the acid-base properties of aniline has been given less attention so far. Published data include the pK_a values of the most obvious 2-substituted derivatives in water.[16,26-29] However, values for 2,6-disubstituted anilines[26,29] with common substituents have not been published in a compact form so far. Quantum-chemistry calculations were carried out for some 2-substituted anilines,[13,14,16] but a systematic study of the *ortho* effect is still missing. The reason obviously lies in the specific manifestations of the *ortho* effect connected with the potential formation of an intramolecular hydrogen bond,[30-33] steric effects leading to the steric hindrance of resonance, and changes in the solvation of the amino group and/or its protonated form.[34] The aforementioned effects are more pronounced in benzoic acids.[35-39] This causes difficulties in the description of benzoic acids by means of correlation relations based on the similarity principle.[35-37]

The aim of the present work is to compile existing pK_a data (in water) and provide missing data for 2-mono- and 2,6-disubstituted anilines containing CH_3, CH_3O, Cl, and NO_2 substituents and their combinations, respectively. Attention is paid to the description and interpretation of the substituent effects acting from the 2 and 6 positions by methods based on the similarity principle as well as quantum-chemistry calculations by techniques derived from density-functional theory (DFT).

Experimental Section

2-Mono- and 2,6-Disubstituted Anilines with CH_3, CH_3O, Cl, and NO_2 Substituents. All 2-substituted anilines, 2,6-dimethylaniline, and 2-chloro-6-methylaniline were purchased from Aldrich, Merck, or Fluka. 2-Methoxy-6-methylaniline,[40] 2,6-dimethoxyaniline,[41] and 2-chloro-6-methoxyaniline[42] were synthesized by known procedures; their purity was checked by liquid chromatography, and they were identified by melting point determination and ^{1}H NMR spectra. The syntheses and properties of other 2,6-disubstituted anilines are described elsewhere.[29]

Measurements of Dissociation Constants. Dissociation constants of substituted derivatives having p$K_a > 2$ were measured spectrophotometrically in Britton-Robinson buffers at 25 °C. For the measurements, 8-18 buffers were used, having pH values approximately in the range of p$K_a \pm 1$. The measured value of the dissociation constant of *o*-phenylenediamine was corrected statistically (splitting off of the proton from one nitrogen atom; protonation at one of the two nitrogen atoms present). The dissociation constants of other derivatives were determined from the acidity function by a procedure published elsewhere.[29]

Computational Methods

The density-functional theory (DFT) method was employed for calculations because it gives results including the electron-correlation effect and is quicker than the perturbation (e.g. MP*n*), configuration interaction (CI), or coupled clusters (CC) methods. The geometries of anilines were optimized using the DFT-B3LYP method. B3LYP is a combination of Becke's three-parameter hybrid functional[43] and the Lee-Yang-Parr correlation functional.[44] Hybrid schemes have proved to be very accurate in predicting the structural properties of substituted anilines.[16] The 6-311G(d,p) basis set was employed for optimization. Thermochemistry and frequentional analysis were performed at the same level of B3LYP/6-311G(d,p) theory. No scaling was applied to the obtained frequencies or zero-point energies for the calculation of thermodynamic parameters. The thermodynamic parameters obtained were temperature corrected to 298.15 K. The optimized geometries were used to obtain the Mulliken (Q_M), natural (Q_n), and electrostatic potential-derived charges (Q_{ESP}) as well as dipole moments (μ), energies of frontier orbitals (E_{HOMO}, E_{LUMO}), and geometrical parameters. Electrostatic potential-derived partial charges were calculated according to the Merz-Singh-Kollman scheme.[45,46] The tilting degree of the amino group related to the phenylene plane was described by the two angles δ and θ (Figure 1). The angle δ was defined as an angle between the two planes A(N,H1,H2) and B(phenylene ring); the angle θ was defined as an angle between the plane B(phenylene ring) and the line L(C1,N) (cf. ref 16).

Gas phase basicities (ΔG_{eq}) were calculated at the same level of theory as that for the Gibbs energy change for the reaction of aniline with a proton on the amino group. The experimental gas phase basicities were obtained from the literature.[47] All calculations were performed using Gaussian 98 (ref 48).

Linear and nonlinear regressions were calculated using standard procedures.

Results and Discussion

Dissociation Constants of 2-Mono- and 2,6-Disubstituted Anilines and Their Critical Compilation. Table 1 presents the pK_a values of 2-mono- and 2,6-disubstituted anilines in water taken from the literature. From the table it is obvious that there is a good accordance in the pK_a values of common monosubstituted anilines containing H, CH_3, CH_3O, Cl, and NO_2 substituents: for these compounds the standard deviation of the

TABLE 1: Comparison of the pK_a Values (and Their Standard Deviations s_{pK}) Found in the Present Work and in Ref 29 for 2-Substituted (X_6 = H) and 2,6-Disubstituted (X_2, $X_6 \neq$ H) Anilines in Water with Those Published in the References Given[a]

no.	X_2, X_6	pK_a (s_{pK})	pK_a, ref
1	H, H	*4.62* (0.03)	4.56,[49] 4.58,[50−52] 4.59,[53] 4.60,[54−57] 4.62,[58,59] 4.63,[60] 4.72[61]
2	H, CH_3	*4.45* (0.03)	4.39,[62−64] 4.44,[65,66] 4.45,[67] 4.46,[68] 4.53[69]
3	H, CF_3	*2.39* (0.23)	1.74,[49] 2.85[65]
4	H, OH	*4.80* (0.08)	3.66,[70] 4.66,[68] 4.74,[69] 4.781,[71] 4.84[72]
5	H, CH_3O	*4.49* (0.03)	4.39,[73] 4.45,[69] 4.48,[68] 4.49,[62,63,74] 4.52,[67] 4.527,[28] 4.56[64]
6	H, F	*3.37* (0.06)	2.47,[75] 3.17,[68] 3.20[67]
7	H, Cl	*2.64* (0.05)	2.60,[69] 2.62,[62,63,76] 2.65,[50,65−67] 2.661,[28] 2.70[68]
8	H, NH_2	*4.88* (0.17)	3.64,[65] 4.47,[77] 4.74[69]
9	H, CN		0.77,[68] *0.95*,[69] 1.80[78]
10	H, NO_2	−*0.30* (0.05)	−0.35,[79] −0.33,[80] −0.32,[81] −0.31,[81,82] −0.30,[83,84] −0.29,[81,86−89] −0.28,[65,90] −0.25[81]
11	CH_3, CH_3	*3.91* (0.05)	3.89,[57] 3.95,[66,68,91,92] 4.25[65]
12	CH_3, CH_3O	*4.32* (0.06)	
13	CH_3, Cl	*2.22* (0.01)	
14	CH_3, NO_2	−*0.69* (0.04)	
15	CH_3O, CH_3O	*4.75* (0.03)	
16	CH_3O, Cl	*2.64* (0.02)	
17	CH_3O, NO_2	−*0.48* (0.04)	
18	Cl, Cl	*0.35* (0.07)	0.40[93]
19	Cl, NO_2	−*2.57* (0.07)	−2.60,[95] −2.54,[80] −2.49,[94] −2.43,[87] −2.38,[83] −2.26[96]
20	NO_2, NO_2	−*5.38* (0.06)	−5.90,[95] −5.64,[80] −5.39,[83,94] −5.37,[79] −5.25,[87,94] −5.23[90]

[a] The values in italic type were used in further correlations.

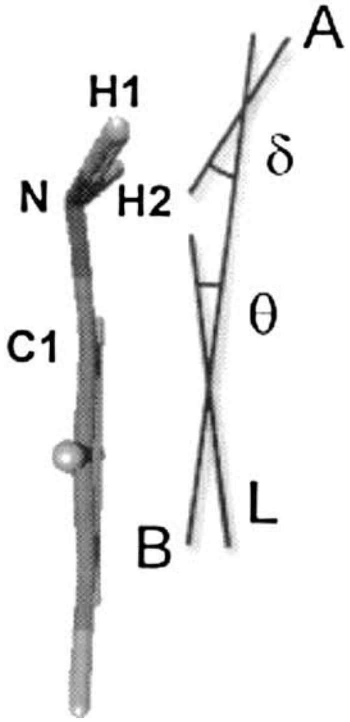

Figure 1. The (non)planarity of the aniline amino group is described by two angles δ and θ. The angle δ is defined as an angle between two planes A(N,H1,H2) and B(phenylene ring); the angle θ is defined as an angle between the phenylene plane and the line L(C1,N).

data in the group does not exceed the value of 0.05. The derivatives containing less usual substituents (CF_3, F, CN) or ionizing substituents (OH, NH_2) show a reproducibility of the results lower by 1 order of magnitude, and the standard deviation is in the range of (0.5−1)pK_a units. Naturally, the largest differences in pK_a values are observed for lower basic derivatives, as the results depend strongly on the acidity function adopted.[29] In this case, the reproducibility varies roughly within (0.05−2)pK_a units. The reproducibility values given are important for the evaluation of the fit of the correlation relations used for the interpretation of the substituent effect on dissociation constants. If ref 97 claims the validity of the Hammett equation to be (0.05)pK_a units, then it is obvious that the correlation fit for the studied series depends particularly on the experimental precision given by the range of (0.05−0.2)pK_a units.

Correlation by Methods Based on the Similarity Principle (Similarity Principle-Based Methods). The correlation relationships were constructed using our own pK_a values (Table 1) with respect to consistency of data; the remaining pK_a value for 2-cyanoaniline was selected from the literature data. Due to the substitution at the 2- and/or 6-position, connected with the *ortho* effect, the interpretation of substituent effects cannot be carried out by the Hammett equation. A standard approach for such correlations is based on the separation of effects, that is, the inductive effect described by the substituent σ_I constant and the mesomeric effect described by the substituent σ_R constant (for parametrization see ref 97). In the case of 2,6-disubstituted derivatives it is necessary to presume the additivity of both substituent effects, which tends to be fulfilled in practice.[36,37] The correlation of the logarithms of dissociation constants K_a (as log K_a, i.e., negative values of pK_a data in Table 1) with the substituent constants σ_I and σ_R under the given conditions is described by relation 1

$$\log K_a = -(4.12 \pm 0.28) + (5.87 \pm 0.38)\sum\sigma_I + (4.06 \pm 0.45)\sum\sigma_R \quad (1)$$

$$n = 20, \quad s = 0.608, \quad R = 0.979, \quad F(2,17) = 197.7$$

where n is the number of points in the regression, s is the residual standard deviation, R is the multiple correlation coefficient, and F is the Fisher−Snedecore criterion of regression significance. The correlation is not too close, and the jackknife residuals indicate the value of log K_a for the 2,6-dimethylaniline as an outlier. This finding emphasizes, as can be expected,[27,34] the non-negligible role of a steric effect. Hence, the correlation relation was extended by the υ parameter describing the steric effect.[98] After this extension, the correlation reads as follows

$$\log K_a = -(4.56 \pm 0.31) + (5.51 \pm 0.36)\sum\sigma_I + (4.28 \pm 0.41)\sum\sigma_R + (1.05 \pm 0.43)\sum\upsilon \quad (2)$$

$$n = 20, \quad s = 0.536, \quad R = 0.985, \quad F(3,16) = 171.9.$$

The addition of the term describing the steric effect somewhat improves the residual standard deviation, but the latter is still higher than the precision limit of the $\mathrm{p}K_a$ determination. The analysis of residuals did not reveal any differences between the mono- and disubstituted derivatives, wherefrom it can be deduced that the effects in disubstituted derivatives are additive within experimental error. The calculated values of the reaction constants (ρ) are high: in comparison to analogous correlations of *meta* and *para* substituted derivatives by the Hammett equation, the ρ_I and ρ_R values are higher, as expected ($\rho = 3.03$, ref 19; $\rho = 3.24$, ref 24). This is probably due to the fact that the reaction center and *ortho* substituents are closer to each other and can be mutually affected by nonbonding interactions. The high values of the reaction constants ρ_I and ρ_R indicate high sensitivity to substitution, and their small difference indicates a comparable contribution of both effects, which is usual, for example, for substitution from the *para* position. The reaction constant Ψ describing the extent of the steric effect on dissociation is relatively large and positive. Therefore, the steric strain between the solvated ammonium group and *ortho*-standing substituents increases the Gibbs energy of the protonated form of aniline (cf. benzoic acids[37]) and also the dissociation constant.

The AISE theory (alternative interpretation of substituent effects)[99,100] is based on the idea that a substituent possesses a single property described in terms of the quantitative description of substituent effects by a single substituent constant σ^i. This property of the substituent affects the reaction center in three different ways, according to the interaction type in the triad reaction center−basic skeleton−substituent. For the interpretation it is essential to distinguish if the substituent possesses π-electrons at the atom connected to the basic skeleton. First class substituents possess no such electron pairs and act only through σ-bonds by an effect which could be identified with an inductive effect (e.g. hydrogen, alkyl groups). Second class substituents include the so-called inner nucleophiles, that is, substituents possessing a free electron pair at the atom connected to the basic skeleton (e.g. halogens, amino group, hydroxy group, etc.). Third class substituents are the so-called inner electrophiles which possess a polarized multiple bond between the first and the second atom, the polarization being oriented out from the molecule (all substituents involving carbonyl grouping, nitro group, etc.). The AISE theory is expressed mathematically by a bundle of straight lines corresponding to the three classes of substituents and having a common point of intersection σ_0^i, y_0. In the case of disubstitution, additivity of effects is presumed, as in the previous section. The application of the AISE method to the data from Table 1 leads to relation 3

$$\begin{aligned}\log K_a = {}& -(0.95 \pm 1.32) + \\ & (4.35 \pm 1.12)\delta_I[\textstyle\sum\sigma^i - (0.37 \pm 0.06)] + \\ & (11.8 \pm 1.1)\delta_N[\textstyle\sum\sigma^i - (0.37 \pm 0.06)] + \\ & (13.2 \pm 1.1)\delta_E[\textstyle\sum\sigma^i - (0.37 \pm 0.06)]\end{aligned} \quad (3)$$

$$n = 20, \quad s = 0.427, \quad R = 0.991, \quad F(4,15) = 205.7$$

where the symbols δ_I, δ_N, and δ_E are Kronecker's deltas denoting membership of classes I, II, and III of the substituents. This correlation is closer than the previous one, but still it does not reach the experimental accuracy. The extension of the AISE correlation by a term describing steric effects results in relationship 4

$$\begin{aligned}\log K_a = {}& -(0.86 \pm 1.17) + \\ & (3.96 \pm 0.87)\delta_I[\textstyle\sum\sigma^i - (0.38 \pm 0.06)] + \\ & (9.96 \pm 0.94)\delta_N[\textstyle\sum\sigma^i - (0.38 \pm 0.06)] + \\ & (14.1 \pm 1.5)\delta_E[\textstyle\sum\sigma^i - (0.38 \pm 0.06)] + \\ & (0.91 \pm 0.28)[\textstyle\sum\upsilon - (0.38 \pm 0.06)]\end{aligned} \quad (4)$$

$$n = 20, \quad s = 0.333, \quad R = 0.995, \quad F(5,14) = 271.7$$

As in the previous case, the additional interpreting variable improves the correlation, which is now the closest of those given so far. The analysis of residuals indicates *o*-phenylenediamine as the outlier. The difference between the experimental and predicted values is 0.82 units, the $\mathrm{p}K_a$ measured being lower (= a stronger conjugated acid) than the value predicted. This is not very surprising, since it is difficult to determine the dissociation constant of a substance having two identical groups at adjacent positions on the benzene ring: the data given by different authors differ considerably (see Table 1). From the physical point of view, the higher acidity of the conjugated base is due to the formation of a hydrogen bond between the ammonium group and the *ortho*-standing amino group. A partial proton transfer to the nitrogen atom of the amino group changes its properties as a substituent: this group behaves as a stronger electron-acceptor with increased acidity of the two remaining hydrogen atoms in the ammonium group. After excluding the *o*-phenylenediamine from the calculation, the statistical characteristics of the correlation fit improved ($s = 0.209$, $R = 0.998$), but the analysis of residuals indicated another outlier belonging to 2-hydroxyaniline. The difference between the experimental and predicted values is 0.50 unit in this case, the $\mathrm{p}K_a$ measured being lower again than the value predicted. The reason lies in the formation of an intramolecular hydrogen bond between the hydroxy group and the amino group. Exclusion of both OH and NH_2 substituents from the AISE calculation leads to eq 5

$$\begin{aligned}\log K_a = {}& -(1.23 \pm 0.36) + \\ & (3.87 \pm 0.33)\delta_I[\textstyle\sum\sigma^i - (0.36 \pm 0.01)] + \\ & (12.4 \pm 0.4)\delta_N[\textstyle\sum\sigma^i - (0.36 \pm 0.01)] + \\ & (13.4 \pm 0.3)\delta_E[\textstyle\sum\sigma^i - (0.36 \pm 0.01)] + \\ & (1.04 \pm 0.11)[\textstyle\sum\upsilon - (0.36 \pm 0.01)]\end{aligned} \quad (5)$$

$$n = 18, \quad s = 0.123, \quad R = 0.9994, \quad F(5,12) = 1843.8$$

None of the remaining substituents exhibited a difference higher than 0.3 units between the experimental and predicted values. Thus, eq 5 made it possible to interpret the substituent effects with a residual standard deviation comparable with the experimental precision and to interpret the deviations. The correlation fit confirms the justifiability of the application of the additive model for disubstituted derivatives. From eq 5 it follows that the dissociation of *ortho* substituted and disubstituted anilines is strongly sensitive to substituents with the inclusion of their steric effects. The sensitivity to inner nucleophiles and inner electrophiles is almost the same, being twice as high as the sensitivity to substituents exerting an inductive effect only. This means that the position of dissociation equilibrium is predominantly controlled by the interactions of substituents mediated by π-electrons. The value of the reaction constant Ψ, describing the sensitivity to steric effects, is

TABLE 2: Anilines' Partial Charges Computed Using the B3LYP/6-311G(d,p) Method

X_2, X_6	$Q_n(N)$[a]	$Q_n(\Sigma H)$[b]	$Q_n(N^+)$[c]	$Q_n(\Sigma H^+)$[d]	$Q_M(N)$	$Q_M(\Sigma H)$	$Q_M(N^+)$	$Q_M(\Sigma H^+)$[e]
H, H	−0.782	0.726	−0.669	1.321	−0.468	0.407	−0.361	0.932
H, CH_3	−0.788	0.728	−0.669	1.314	−0.479	0.405	−0.383	0.919
H, CF_3	−0.773	0.755	−0.680	1.345	−0.481	0.426	−0.403	0.936
H, OH	−0.784	0.741	−0.674	1.334	−0.467	0.418	−0.361	0.932
H, CH_3O	−0.784	0.741	−0.676	1.330	−0.467	0.416	−0.361	0.924
H, F	−0.780	0.743	−0.670	1.337	−0.462	0.424	−0.357	0.945
H, Cl	−0.777	0.752	−0.671	1.335	−0.469	0.437	−0.358	0.930
H, NH_2	−0.809	0.726	−0.700	1.329	−0.498	0.412	−0.367	0.893
H, CN	−0.767	0.767	−0.680	1.349	−0.486	0.446	−0.385	0.939
H, NO_2	−0.744	0.801	−0.702	1.337	−0.476	0.478	−0.385	0.938
CH_3, CH_3	−0.792	0.734	−0.675	1.315	−0.490	0.405	−0.396	0.904
CH_3, CH_3O	−0.791	0.744	−0.677	1.324	−0.479	0.415	−0.380	0.912
CH_3, Cl	−0.784	0.744	−0.679	1.326	−0.479	0.434	−0.378	0.916
CH_3, NO_2	−0.751	0.808	−0.703	1.327	−0.491	0.478	−0.406	0.923
CH_3O, CH_3O	−0.783	0.752	−0.667	1.326	−0.462	0.420	−0.348	0.913
CH_3O, Cl	−0.777	0.766	−0.676	1.343	−0.463	0.443	−0.367	0.936
CH_3O, NO_2	−0.741	0.820	−0.690	1.340	−0.470	0.488	−0.359	0.924
Cl, Cl	−0.772	0.777	−0.680	1.346	−0.470	0.465	−0.368	0.942
Cl, NO_2	−0.741	0.821	−0.702	1.349	−0.475	0.501	−0.406	0.923
NO_2, NO_2	−0.712	0.846	−0.706	1.378	−0.440	0.514	−0.365	0.945

[a] $Q_n(N)$ is the natural partial charge (NPC) for the amino group nitrogen in e (electron charge, 1 e = 1.602188×10^{-19} C). [b] $Q_n(\Sigma H)$ is the sum of the NPCs for amino group hydrogen atoms. [c] $Q_n(N^+)$ is the NPC for the ammonium group nitrogen atom. [d] $Q_n(\Sigma H^+)$ is the sum of the NPCs for ammonium group hydrogen atoms. [e] Q_M means Mulliken's partial charges for the same atoms.

TABLE 3: Selected Properties of Anilines Computed by the B3LYP/6-311G(d,p) Method

X_2, X_6	r_{C-N}[a]	δ[b]	θ[b]	ΔG_{eq}[c]	E_{HOMO}[d]	μ[e]	μ_+[e]
H, H	1.397	38.12	2.18	206.09	−0.207	1.713	7.123
H, CH_3	1.400	38.82	2.46	207.40	−0.204	1.746	6.651
H, CF_3	1.383	33.18	0.30	200.38	−0.223	2.747	7.500
H, OH	1.394	39.31	2.34	210.97	−0.196	1.369	5.363
H, CH_3O	1.393	38.85	2.46	213.07	−0.193	1.689	5.503
H, F	1.391	37.77	2.49	202.27	−0.213	1.715	6.337
H, Cl	1.385	34.62	2.32	201.54	−0.217	2.080	6.433
H, NH_2	1.409	47.68	6.15	212.61	−0.194	1.387	5.047
H, CN	1.375	27.36	0.95	195.13	−0.228	4.208	6.651
H, NO_2	1.355	6.42	0.75	196.89	−0.230	4.722	7.341
CH_3, CH_3	1.401	37.80	1.68	209.60	−0.201	1.787	6.144
CH_3, CH_3O	1.397	40.27	2.87	215.07	−0.192	1.568	5.090
CH_3, Cl	1.388	35.83	1.87	203.68	−0.214	2.280	5.740
CH_3, NO_2	1.356	0.32	0.83	200.16	−0.226	5.069	6.620
CH_3O, CH_3O	1.391	39.92	3.44	220.52	−0.184	1.022	4.164
CH_3O, Cl	1.382	35.20	2.78	209.17	−0.204	3.251	5.015
CH_3O, NO_2	1.351	0.00	0.00	203.19	−0.216	6.273	6.393
Cl, Cl	1.374	30.25	2.20	197.77	−0.225	0.761	3.723
Cl, NO_2	1.349	0.64	0.52	193.68	−0.239	3.080	3.356
NO_2, NO_2	1.337	0.31	0.40	187.19	−0.258	1.810	0.828

[a] r_{C-N} (in Å) is the distance between the aromatic carbon and the amino group nitrogen. [b] δ and θ (in deg) are angles describing the (non)planarity of the amino group (cf. Figure 1). [c] ΔG_{eq} (in kcal mol^{-1}) is the gas phase basicity calculated as the Gibbs energy change for the reaction of aniline with a proton on the amino group. [d] E_{HOMO} (in hartrees, 1 hartree = 27.2116 eV) is the energy of the highest-occupied molecular orbital (HOMO). [e] μ and μ_+ (in D) are the dipole moments for the base and its conjugated acid, respectively.

statistically identical to the value calculated from eq 2 and can also be identically interpreted.

Relationship between Quantum-Chemistry Quantities. The selected quantum-chemistry characteristics obtained by the methods described above are presented in Tables 2 and 3. Table 2 gives partial charges of various types calculated by the B3LYP/6-311G(d,p) method. The ESP charges are not given there because their contribution was statistically negligible in all of the correlations carried out. The pair correlation coefficients between partial natural charges and Mulliken's partial charges at the same center are generally very low: $r_{Q(N)} = 0.464$, $r_{Q(\Sigma H)} = 0.981$, $r_{Q(N^+)} = 0.418$, $r_{Q(\Sigma H^+)} = 0.647$. The assignment of electron density to individual atoms is somewhat artificial, and the quantities calculated need not have any relationship to those physically measurable (for discussion of population analyses and partial atomic charge schemes usage, cf. Jensen's textbook[101]).

Among the quantities given in Table 3, a close correlation is provided between the Gibbs energy of the dissociation equilibrium in the gas phase ΔG_{eq} and the HOMO energy (E_{HOMO}, correlation coefficient $r = 0.983$) and between the bond length r_{C-N} and the δ angle of (non-)planarity of the amino group ($r = 0.963$). The close correlation between the Gibbs energy of the dissociation equilibrium and the HOMO energy is logical and indicates the dominant energy change caused by destruction of the HOMO localized at the amino nitrogen during protonation. In other words, the dissociation equilibrium in the gas phase is fundamentally affected by the destruction of the free electron pair at the nitrogen atom of the amino group and the subsequent loss of delocalization energy. Electron-acceptor substituents lower the HOMO energy. The positive correlation between the bond length r_{C-N} and the δ angle can be explained by the extent of the participation of the free electron pair at the nitrogen atom of the amino group in the conjugation with the π-electron system of a nucleus. The longer bond corresponds to a lower extent of interaction, and a higher localization of electrons at the nitrogen atom causes a shift from a planar to a pyramidal structure of the amino group. Electron-acceptor substituents shorten the bond length r_{C-N} and diminish the δ angle due to the enforced shift of electrons from the nitrogen of the amino group to the benzene ring.

It is worth mentioning that the dipole moments of the nonprotonated and protonated forms of anilines do not mutually correlate to a statistically significant extent ($r = 0.371$). The dipole moments of conjugated acids of anilines are markedly higher than those of the respective parent anilines in the cases of substances without a nitro group. In the case of nitro derivatives, the mentioned differences are substantially smaller, and for 2,6-dinitroaniline the difference is even reversed. Large differences in the polarity of the molecules at equilibrium usually result in a strong dependence of the equilibrium constant upon solvent, particularly its relative permittivity.[21]

Correlation with Quantum-Chemistry Quantities. Thermodynamics provides a linear relationship between the pK_a

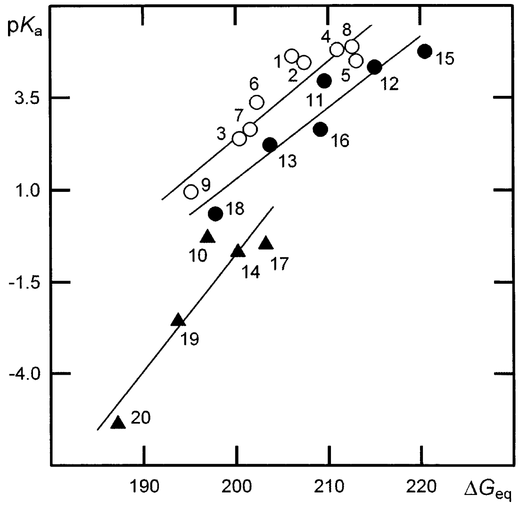

Figure 2. Dependence of pK_a values on the values of the Gibbs energy of the dissociation equilibrium (ΔG_{eq} in kcal mol^{-1}): ○, monosubstituted derivatives without a nitro group; ●, disubstituted derivatives without a nitro group; ▲, nitro derivatives.

values and Gibbs energies of dissociation equilibria ΔG_{eq}. The relationship between the pK_a values from Table 1 and the ΔG_{eq} gas phase values from Table 3 is depicted in Figure 2. This plot shows that the dependence is divided into three groups involving (i) monosubstituted derivatives without a nitro group, (ii) disubstituted derivatives without a nitro group, and (iii) nitro derivatives. These groups are highlighted in the plot by regression straight lines.

The ΔG_{eq} values calculated by the B3LYP/6-311G(d,p) method correspond to the dissociation in the gas phase, and they should contain all intramolecular interactions, including electronic and nonbonding ones.

The validity of this statement can be documented (at least for some derivatives) by comparison to experimental values ΔG_{eq}(exp) available in the literature[47] (X_2, X_6 = H, H; H, NH_2; H, OH; H, Me; H, MeO; Me, Me). The agreement between calculated and experimental values of ΔG_{eq} is quite good, the average relative deviation being 1.64%. Obviously, in an aqueous medium other effects not involved in this quantity are also pronounced. A systematic selection of quantum-chemistry characteristics among all possible combinations of the quantities given in Tables 2 and 3 revealed the sum of natural partial charges at the hydrogen atoms of the amino group ($Q_n(\Sigma H)$) and the dipole moment (μ_+) of the protonated form as the most appropriate characteristics. The dependence on dipole moment indicates nonspecific solvation. According to the Born and/or Kirkwood theory, the change of equilibrium Gibbs energy connected with solvation is proportional to the difference of the squares of dipole moments of both components at equilibrium,[21] in our case the protonated and nonprotonated forms of aniline. After involving the description of nonspecific solvation, we obtain eq 6

$$\log K_a = (1.19 \pm 8.42) - (0.161 \pm 0.018)\Delta G_{eq} + (39.9 \pm 6.3)Q_n(\textstyle\sum H) - [(3.07 \pm 1.12) \times 10^{-2}](\mu_+^2 - \mu^2) \quad (6)$$

$$n = 20, \quad s = 0.383, \quad R = 0.992, \quad F(3,16) = 339.9.$$

The statistically significant term $Q_n(\Sigma H)$ in eq 6 describes some specific properties of the nitro group, which are not involved in ΔG_{eq} but still act in solution. Differences can be clearly seen between the nitro derivatives and other derivatives in Figure 3, where the sum of values ($\Sigma\sigma^i$) represents the electron effects of substituents.

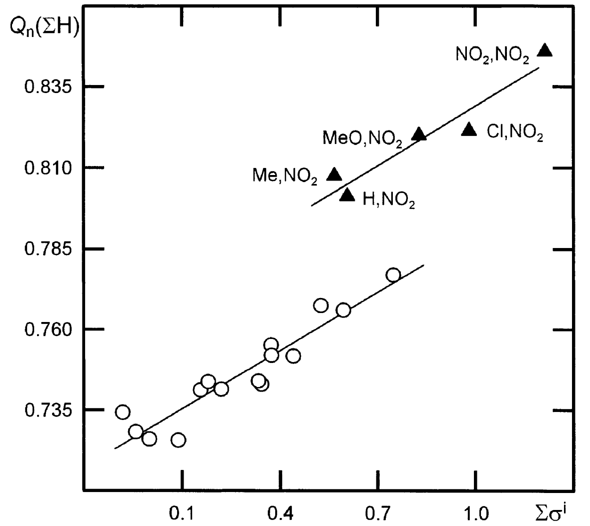

Figure 3. Dependence of $Q_n(\Sigma H)$ values on the sum of the substituent constants, $\Sigma\sigma^i$, from the positions: ▲, nitro derivatives.

The increase in acidity of amino hydrogen atoms for nitro derivatives as compared with the expected value can be explained by the formation of an intramolecular hydrogen bond between the hydrogen atoms of the amino group and the oxygen atoms of the nitro group.[16,30,31] This effect is manifested by the change of amino and nitro group specific solvation and by a subsequent additional decrease in the basicity of the respective aniline (see Figure 2). The interaction given cannot be described by calculating the properties of the isolated molecule, and it will appear as an additional term in the correlation equation.

A somewhat closer correlation than that in eq 6 can be obtained by applying the explaining variables E_{HOMO}, $Q_n(\Sigma H)$, and ($\mu_+^2 - \mu^2$) according to eq 7.

$$\log K_a = -(41.0 \pm 2.45) - (90.5 \pm 5.9)E_{HOMO} + (27.3 \pm 4.3)Q_n(\textstyle\sum H) - [(3.69 \pm 0.69) \times 10^{-2}](\mu_+^2 - \mu^2) \quad (7)$$

$$n = 20, \quad s = 0.231, \quad R = 0.996, \quad F(3,16) = 945.5$$

The dependence of the dissociation constant on the HOMO energy is connected with the localization of this orbital at the nitrogen atom of the amino group. The protonation consists of electron transfer from this orbital into the LUMO of the proton acting as electrophile, in analogy with the charge-transfer complexes. The higher the E_{HOMO} of aniline will be, the smaller the ionization potential will become and the easier the electron transfer into the bond with the proton. Consequently, the respective aniline will be more basic and its conjugated acid will be less acidic. The meaning of the other terms is identical with those of eq 6.

Conclusion

The critical comparison of our own experimental pK_a values with the literature data for selected 2-mono- and 2,6-disubstituted anilines has shown a relatively considerable scattering of results given by various authors for the same substance. Data taken from different sources are not suitable for a systematic analysis and interpretation of effects of *ortho* substitution and disubstitution upon the dissociation constants of the studied anilines, and that is why we preferred the data obtained from our own experiments. This paper shows the difficulties in the description of ortho substitution and disubstitution by means of correlation relations based on similarity, particularly if it is impossible to find (within the validity range) and explicitly interpret physicochemically justified deviations (intramolecular hydrogen bond, steric effects, solvation differences, of molecular moieties). The quantum-chemical approach has the advantage that its results implicitly involve all manifestations of substituents, inclusive of the formation of hydrogen bonds between molecular moieties, nonbonding interactions, and so forth. A useful fact is that quantum-chemical calculations carried out for isolated molecules give results of similar quality to that of results obtained by classical correlation relations based on the similarity principle.

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