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Sterically Hindered Resonance in Methyl-Substituted Anilines in the Gas Phase

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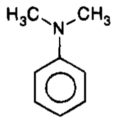
The steric hindrance to resonance and other substituent effects in *o*-methylanilines and *N,N*-dimethylanilines were reinvestigated on the basis of gas-phase basicities and acidities (Fourier transform ion cyclotron resonance equilibrium data) and enthalpies of formation calculated by the semiempirical methods PM3 and AM1. In the gas phase, the phenomenon of hindered resonance is actually operating in the isolated molecules of *N,N*,2-trimethyl- and *N,N*,2,6-tetramethylaniline: it can be also observed via their basicities in water, but previous values were overestimated. The second ortho methyl group, in these cases, causes a lesser effect than the first. In the case of ortho-substituted anilines, a controversy was settled in favor of the steric hindrance to solvation of the cation as the most important effect in solution. However, steric effects also operate in both the isolated molecules and the anions: in these cases the second ortho methyl group causes a greater effect than the first. By the combination of different steric effects in the neutral base molecule and in the cation, an unexpected order in the basicity values can arise. The principle of inhibited resonance is fruitful and generally valid but should be revised quantitatively in every case with respect to the actual conformation and to a real estimate of the resonance energy.

Steric hindrance to resonance was often defined and demonstrated on the acidity or basicity of aromatic compounds whose functional groups are twisted out of the ring plane.[1] We criticized recently[2] this concept since it has been used in the literature too broadly. In our opinion, one should prove in every case that (a) the sterically hindered molecule is actually nonplanar while the unhindered reference molecule is planar and (b) the steric hindrance, estimated in energy units, is consistent with the estimate of the undisturbed resonance energy.

Along these lines, we reinvestigated[2] methyl-substituted benzoic acids using experimental gas-phase acidities[2] and the principle of isodesmic reactions,[2,3] based on known enthalpies of formation. It turned out that the steric hindrance to resonance only takes place in sterically more crowded molecules and often represents a lesser part of the total observed effect.

When we tried to extend the investigation to the resonance in aromatic amines, we encountered in the literature both a more complex experimental pattern and more sophisticated explanations.[4,5] The observed basic dissociation constants in water were interpreted, in two classical sources,[1] in similar terms. Steric hindrance to resonance (in other terminology called secondary steric effect[6]) was evident only in *N,N*,2-trimethylaniline (**2**), which is a stronger base than *N,N*-dimethylaniline (**1**). However, *N,N*,2,6-tetramethylaniline (**3**), is a weaker base than **2**: this was explained by steric crowding (so-called primary steric effect[6]) in the hydrated cation prevailing over the hindrance to resonance.



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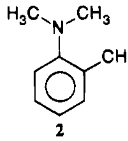

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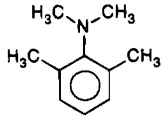
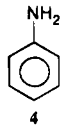


3

5.12 6.11 5.86, 6.10

pK_a of the protonated form in water[4a]

In the primary amines **4**−**6** the functional group is too small for any effective inhibition of resonance. Both **5** and **6** are weaker bases than **4**, and this was attributed again to the primary steric effect.[6]



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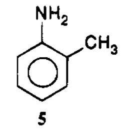

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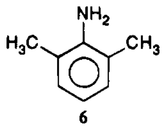

6

4.60 4.44 3.89

pK_a of the protonated form in water[4a]

A more accurate explanation must also take into account the polar effect[7] of ortho-standing methyl groups, but this does not change the qualitative interpretation.

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(6) These terms (ref 1a) are now somewhat obsolete. "Secondary steric effect" has practically the identical meaning as steric hindrance to resonance. "Primary steric effect" meant originally the van der Waals interaction but may also sometimes include other steric effects.

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The most detailed analysis was carried out by Wepster,[4a,b] who preferred for **5** and **6** the term steric hindrance to solvation rather than the former term, primary steric effect.[1b] For **2** and **3** steric hindrance to solvation should also be operative, opposed by the hindrance to resonance. When the latter was estimated from UV spectra, the two effects were of comparable magnitude, the former prevailing in **3**, the latter in **2**.[4a] In the case of *N,N*-dimethylanilines, this explanation seems to have been generally accepted. In the case of anilines, however, debate continued as to whether solvation in the cation is a more or less significant effect.[5] Alternatively, an effect in the neutral base molecule[5a] instead of in the cation might explain the observed trend.

More recent investigations confirmed the nonplanar conformation of **2** and **3** by UV,[4b] photoelectron,[8] ^{13}C NMR and ^{15}N NMR spectroscopies,[9,10] dipole moments,[11] and molar refraction.[4a] The twisting angle φ was given values from 30° to 68° for **2** and from 68° to 81° for **3**. On the other hand, **1** is most probably planar:[8,11,12] small values of φ obtained in one study were attributed by the authors to be due merely to experimental uncertainties.[9a] Aniline itself has a pyramidal configuration[13] on N. Its derivatives **5** and **6** do not show any steric hindrance and retain a similar form.[8b,9a]

Summarizing the above reasoning, we see at least two reasons why the problem should be revisited. First, the effect of hindered hydration can be reliably estimated by referring to the basicities in the gas phase since a pioneering work[14] has proven that **1**, **4**, and further derivatives are protonated on the nitrogen. Second, the effects operating in the neutral molecule and in the anion can be approximately separated by means of suitably constructed isodesmic reactions. For this purpose, we measured here the gas-phase basicities of **1**–**6**, unless they had been already reported, by the equilibrium method using Fourier transform ion cyclotron resonance[15] (FT-ICR). In the case of **4**–**6**, their gas-phase acidities were also investigated. The relative energies of neutral molecules and of their protonated or deprotonated forms were obtained computationally using suitable isodesmic reactions. When necessary, enthalpies of formation were taken from the thermodynamic tables[16] for some of the compounds. MO calculations were performed on all compounds using the semiempirical PM3 and AM1 methods.[17] These procedures were recently found satisfactory for similar problems with compounds of this size.[2,18]

Table 1. Gas-Phase Acidities (in kJ mol^{-1}) of Methyl-Substituted Anilines (AH)

AH	RefH	$\Delta\Delta_{acid}G°(338\ K)^a$	$\Delta_{acid}G°(AH)^b$
5	CH_3CHO	-4.8 ± 0.1	
	4	-4.4 ± 0.2	1500.4
6	**4**	-6.8 ± 0.1	
	5	-0.9 ± 0.3	1498.9

[a] Gibbs energies for the reactions $AH + Ref^- = RefH + A^-$; quoted uncertainties correspond to the standard deviation for three–four measurements. [b] Absolute Gibbs energies of acidity ($AH \rightarrow A^- + H^+$) (at 298 K) from absolute acidities of RefH in the GIANT table (ref 23b): no temperature correction was applied.

Table 2. Gas-Phase Basicities (in kJ mol^{-1}) of Methyl-Substituted Anilines (B)

B	Ref	$\Delta GB(338\ K)^a$	$GB(B)^b$
2	$(n\text{-}Pr)_2NH$	-2.5 ± 0.2	
	piperidine	$+4.3 \pm 0.2$	
	2-picoline	$+8.9 \pm 0.1$	917.2
5	propargylamine	$+6.0 \pm 0.4$	
	$(c\text{-}Pr)_2CO$	$+8.1 \pm 0.1$	856.0
6	$(c\text{-}Pr)NH_2$	$+1.1 \pm 0.1$	
	5	$+10.0 \pm 0.3$	866.2

[a] Gibbs energies for the reaction $BH + Ref = RefH^+ + B$; quoted uncertainties correspond to the standard deviation for three–four measurements. [b] Absolute Gibbs energies of basicity ($BH^+ \rightarrow B + H^+$) (at 298 K) from absolute GBs from Ref in ref 23a: no temperature correction was applied.

Experimental Section

N,N,2-Trimethylaniline (**2**) was prepared by the standard procedure;[19] the other compounds were of commercial origin.

Proton transfer equilibria were monitored by FT-ICR as in the preceding paper.[2] Details on the technique were given previously for the acidity[20] and basicity[21] measurements, respectively. The results are listed in Table 1 (acidities) and in Table 2 (basicities).

Quantum chemical calculations were performed by means of a MOPAC6 standard program for the AM1[17a] and PM3[17b] methods. The corresponding MO models were first optimized with respect to all geometrical degrees of freedom. Both planar

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(7) The exact meanings of the terms "polar effect" and "inductive effect" may be doubted with respect to the quantum chemical theory. We advocate operational definitions based on experimental facts. Accordingly, the polar effect is that exerted also by more distant substituents; the inductive effect is a part of it, present also in the absence of any conjugated system: Exner, O. *Correlation Analysis of Chemical Data;* Plenum Press: New York, 1988; Chapter 2.

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Table 3. Enthalpies for Methyl-Substituted Anilines and for Their Protonated and Deprotonated Forms (kJ mol^{-1}, 298 K)

	$\Delta_f H^\circ$		$-\delta PA$[c]			$\Delta H_{(1)}$[d]			
compound	exp[a]	calc[b]	exp	calc[b]	$\delta\Delta H_{acid}$[c]	exp	calc[b]	$\Delta H_{(2)}$[d]	$\Delta H_{(3)}$[d]
N,N-dimethylaniline (**1**)	100.5[e]	83.8 (130.2)	0	0			0	0	
N,N,4-trimethylaniline		45.2 (99.2)	−9.2[f]	−0.8 (−6.5)			0.5 (0.8)	−8.7[g] (−8.4)[g]	
N,N,2-trimethylaniline (**2**)		55.9 (109.6)	−16.0	−14.2 (−13.6)			11.2 (11.2)	−4.8[g] (−4.8)[g]	
N,N,2,6-tetramethylaniline (**3**)		21.3 (84.6)	−13.0[f]	−9.3 (−7.9)			15.6 (17.8)	2.6[g] (4.8)[g]	
aniline (**4**)	87.0	89.2 (85.8)	0	0	0	0	0	0	0
4-methylaniline	41.8	50.5 (54.4)	−14.2[f]	−7.4 (−6.8)	−5.0[f]	−12.6	0.4 (0.4)	−26.8	−7.6
2-methylaniline (**5**)	54.8	55.1 (55.2)	−8.7	−4.2 (−6.5)	−4.6	0.4	5.0 (1.2)	−8.3	−4.2
2,6-dimethylaniline (**6**)		22.2 (25.1)	−18.9	−11.5 (−12.6)	−6.1	6.5[h] (1.9)[h]		−12.4[g] (−17.0)[g]	0.4[g] (−4.2)[g]

[a] Reference 16. [b] PM3 (in parentheses AM1). [c] Relative experimental values related to aniline or *N,N*-dimethylaniline, respectively. [d] Enthalpies of the isodesmic reactions, eqs 1−3, respectively. They represent the overall interaction energy between the functional group and ortho methyl groups in the molecule of base, protonated form, or deprotonated form. Experimental values unless otherwise noted; uncertainty approximately 4 kJ mol^{-1}; in the calculated values uncertainty unknown. [e] Reference 24. [f] Based on the data of ref 23. [g] From experimental basicities (acidities) and PM3 (in parentheses AM1) calculated $\Delta H_{(1)}$. [h] Combined values from the experimental value for **5** and the difference calculated by PM3 (in parentheses AM1).

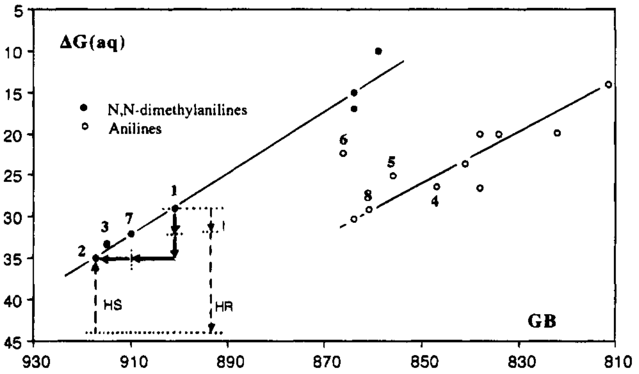

Figure 1. Plots of the basicities in kJ mol^{-1} of methyl-substituted anilines and *N,N*-dimethylanilines; aqueous (ΔG(aq)) vs gas phase (GB); data from refs 22, 23, and this work. (Plain lines) approximate dependence for meta and para derivatives with polar substituents. (Dashed arrows) inductive effect (I), steric hindrance to resonance (HR), and steric hindrance to solvation (HS) as calculated by Wepster, ref 4a. (Bold arrows) a more realistic estimate (this work) of inductive effect and steric hindrance to resonance in water (vertical, no evident hindrance to solvation) and in the gas phase (horizontal), respectively.

and pyramidal starting geometries on the nitrogen atom were tested, and they led to the same energy minima in all cases, corresponding to a slightly nonplanar configuration. The calculated energies are collected in Table 3; the geometrical parameters are not reported.

Results and Discussion

Basicities in the Gas Phase and in Solution. The significance of the solvation energy and of its steric hindrance can be assessed very simply from a plot of the basicities in water vs those in the gas phase (Figure 1). As a reference let us consider anilines substituted in either the meta or para position by dipolar groups (mostly electron attracting). Within the framework of the Hammett equation,[7] the respective points should lie on a straight line with the slope equal to the ratio of the two reaction constants ϱ. In fact, substituent effects in the gas phase are more complex and can be expressed by a three-term equation.[25] Furthermore, the substituent effects are not exactly transferable from the gas phase to solution since they are not quite independent of the solvent.[7,26,27] Nevertheless, considering also the lack of data, we believe that the approximate linear dependence in Figure 1 is sufficient for our purpose. Its slope, 0.35, represents the solvent attenuation factor,[26] determined mainly by specific solvation. It is only slightly smaller than the value obtained for substituted pyridines[26a] and points to a relatively delocalized charge on the cation. For meta- and para-substituted *N,N*-dimethylanilines, another straight line is obtained with a practically equal slope (Figure 1). The vertical distance between the two lines (approximately 15 kJ mol^{-1}) can be interpreted as the steric hindrance to solvation, exerted by the two methyl groups on nitrogen.

The points for the two ortho derivatives **5** and **6** deviate markedly from the meta−para line, **6** twice more than **5**: these compounds are relatively weaker bases in water than in the gas phase. The deviations can be interpreted as the steric hindrance to solvation exerted by the ortho methyl groups. Another explanation was considered[26a] for the effects observed on substituted pyridines. There, the reason for the deviations should not be the decreased basicity in water but an increased basicity in the gas phase caused by the polarizability of the near methyl groups. In our case this explanation can be rejected by referring to 4-methylaniline which is slightly more basic in the gas phase than 2-methylaniline. The long standing controversy is thus in our opinion resolved in favor of Wepster's steric hindrance to solvation[4,5b] against the alternatives.[1b,5a]

On the other hand, the points for **2** and **3** lie on the line for *N,N*-dimethylanilines (Figure 1); hence there appears to be no hindrance to solvation. Since **2** is more basic than its 4-methyl isomer, both in the gas phase and in water, steric hindrance to resonance is an acceptable

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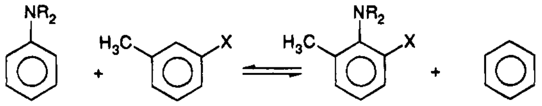
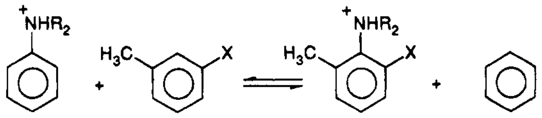
explanation. Its magnitude may be estimated from the difference to be 7 kJ mol^{-1} in the gas phase and 3 kJ mol^{-1} in water. Wepster[4a] estimated the hindrance to resonance from electronic spectra and obtained an unreasonably large value (10 kJ mol^{-1} in water) for which he had to compensate by a nonrealistic steric hindrance to solvation (dashed arrows in Figure 1). According to our measurements, the latter effect is practically absent, the inductive effect can be estimated from the 4-methyl isomer, and the steric hindrance to resonance is obtained with more reliability (bold arrows). However, the puzzling order of basicities, **3** less basic than **2**, appears even in the gas phase. For its explanation, a deeper analysis is necessary as described in the next section.

Separation of the Effects Operating in the Neutral Molecule and in the Protonated Form. In the same way as in the preceding papers,[2,3,28] the substituent effect in the neutral molecule can be expressed by the isodesmic reaction, eq 1. Its reaction enthalpy, $\Delta H_{(1)}$, represents the interaction of the amino (or dimethylamino) group with the methyl groups in the ortho position, whatever the origin of this interaction may be. The value of $\Delta H_{(1)}$ could be calculated from the tabulated[16] enthalpies of formation only in the case of **5** (Table 3); for the other compounds we must refer to semiempirical calculations. The values obtained by PM3 and AM1, respectively, are quite close for aniline derivatives but very different for *N,N*-dimethylanilines (Table 3). It is well known that AM1 overestimates interactions between hydrogen atoms: this was possibly one of the reasons why the PM3 method was devised.[17b] The experimental value, available only for one of our compounds (**1**), falls just between the AM1 and PM3 results. When we proceed to the isodesmic reactions, the errors largely cancel and the two calculations differ only little. Comparison with experimental data, possible only for **5** and 4-methylaniline, is even here not quite satisfactory,[29] with AM1 showing a better agreement. The most reliable estimates of $\Delta H_{(1)}$ are in our opinion as follows: for **5** the experimental value, for **6** a sum of the latter value and of the calculated difference between **6** and **5**, and for the *N,N*-dimethylaniline derivatives **2** and **3** the calculated values (Table 3).



(1)



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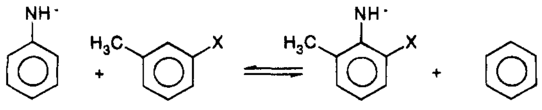

(3)

Once $\Delta H_{(1)}$ have been estimated, the enthalpies of the isodesmic reactions for the protonated forms, eq 2, and for the deprotonated forms, eq 3, can be obtained from experimental basicities or acidities through a thermodynamic cycle. No additional uncertainty is introduced by this procedure. The main error thus arises from quantum chemical calculations and may be in the order of magnitude of 5 kJ mol^{-1}. Nevertheless, a comparison of $\Delta H_{(1)}$ and $\Delta H_{(2)}$ for all the compounds yields the following, very consistent picture.

Quite generally, the interaction of ortho substituents in anilines is much smaller than in *N,N*-dimethylanilines where it is considerable and destabilizing. In the cations or anions, stabilization prevails due to the polarizability of the methyl groups.

Concerning aniline derivatives, a marked stabilization is observed in 4-methylaniline which is evidently due to the polar effect[7] transmitted through the benzene ring. The steric effect of the ortho methyl groups is destabilizing (repulsion between the lone electron pair and methyl hydrogens).

In the protonated forms of anilines, the effect is strongly stabilizing for 4-methylaniline and less stabilizing for **5** and **6** (polarizability vs steric hindrance). This "steric hindrance" could include also an electrostatic component since it is evidently greater than an estimate on 1,2-dimethylbenzene[16] or 1,2,3-trimethylbenzene[16] as model compounds. Nevertheless, the steric effects are of similar intensity in the cations as in the bases because their influence on the basicity is relatively small (see the rather close basicities of 2- and 4-methylanilines).

In *N,N*-dimethylanilines one ortho methyl group is strongly destabilizing but two methyls have only a slightly greater effect than one (11 and 16 kJ mol^{-1}). Steric hindrance to resonance is an acceptable explanation.

In the protonated forms of the *N,N*-dimethylanilines, the polarizability effects are weaker than those in anilines: one could say that a distant methyl group contributes less to charge delocalization when the two near *N*-methyl groups are already present. The steric hindrance in the cations increases by a greater amount on addition of the second methyl group than on addition of the first, while in the neutral base molecule the ratio was opposite. By the combination of these two effects, the apparent anomaly in the order of basicities (**3** less basic than **2**) comes into existence. The original explanation[1,4] seems to be qualitatively valid, even in the gas phase.

The extent of the original, not hindered resonance in aniline could be estimated for instance from the isodesmic reaction, eq 4. However, $\Delta H_{(4)}$ depends strongly on the reference alkyl group:[30] the most reasonable choice would probably between i-C_3H_7 and t-C_4H_9. Taking into account that resonance in *N,N*-dimethylaniline is certainly stronger than in aniline, its steric hindrance can acquire values of 10−15 kJ mol^{-1} which were found in the above analysis.

$$\begin{gathered} RNH_2 + C_6H_6 = C_6H_5NH_2 + RH \\ R = \mathrm{Me, Et, i\text{-}Pr, t\text{-}Bu} \\ \Delta H_{(4)} = -48, -34, -16, -10\ \mathrm{kJ\ mol^{-1}} \end{gathered} \tag{4}$$

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(28) Decouzon, M.; Exner, O.; Gal, J.-F.; Maria, P.-C.; Waisser, K. *J. Phys. Org. Chem.* **1994**, *7*, 511−517.

(29) The experimental enthalpies of formation for methylanilines are not very dependable since the difference between the isomers 3 and 4 is too great: Draeger, J. A. *J. Chem. Thermodyn.* **1984**, *16*, 1067−1073.

(30) The stabilizing interaction between larger alkyls and heteroatoms was called the φ -effect; any explanation is not known: Istomin, B. I.; Palm, V. A. *Reaktsionnaya Sposobnost Org. Soedinenii (Tartu)* **1971**, *8*, 845−866; **1972**, *9*, 433−467, 847−870; *Chem. Abstr.* **1972**, *77*, 61180v; **1973**, *79*, 145798g, 24129f.

Possibility of Calculating Gas-Phase Basicities. We needed the semiempirical calculations mainly for estimating the enthalpies of formation. Nevertheless, they can also furnish the energies of the cations and thus predict the gas-phase basicities as in some previous examples.[18] The results in Table 3 are better for *N,N*-dimethylanilines than for anilines. In no case are they able to replace the experimental determination since their error can exceed the experimental uncertainty by more than 10 times. There is practically no difference between PM3 and AM1 in this respect.

Gas-Phase Acidities of Anilines. These were processed in the same way as the basicities. The substituent effects were bisected into those operating in the neutral molecule and those operating in the deprotonated form by means of isodesmic reactions, eqs 1 and 3. The steric effect is weaker in the deprotonated form (approximately 3 kJ mol^{-1} for **5**) than in either the protonated or neutral molecules (18 or 13 kJ mol^{-1}, respectively): due to electrostatic interaction between the H atoms and the lone electron pairs on the nitrogen, the overall effect of the ortho methyl groups is stabilizing. The second ortho methyl group causes a greater effect than the first one; their ratio is still more pronounced than in the case of the cations. The reason is evidently again due to the conformation. As a result of this, the second methyl group has a much weaker effect on strengthening acidity than the first one.

Conclusions

The precision of our approach must not be overestimated but certain, merely semiquantitative conclusions are apparent. The commonly known nonadditive character of steric effects has been confirmed. In ortho derivatives the effects of the first and second methyl groups are always unequal. In the case of steric hindrance to resonance, the second methyl is less effective (when the functional group is already twisted out of the ring plane). In the case of van der Waals interaction, or possibly other steric effects, it is more effective (the effect of one methyl group can be minimalized in a certain conformation, with two methyls it is no longer possible). When the basicities or acidities are considered, their values represent a fine balance of two effects and may sometimes reveal an unexpected pattern. The mentioned irregularity in the basicities of **1**, **2**, and **3** can be explained in these terms: the steric hindrance to resonance (in the base molecule) and van der Waals interaction (in the cation) show different sensitivity to steric crowding, i.e. to the effects of the first and second methyl group. When only dissociation constants in solution are experimentally accessible, these effects are further leveled and made less clear.

Concerning the steric hindrance to resonance, this simple theoretical model is useful and applicable. However, each case should be experimentally checked from two points of view: conformation and energy. The hindered resonance effect need not be actually present in every case when a plausible chemical formula can be written, and every case is to be checked on the basis of experimental facts. In the case of *N,N*-dimethylanilines, we believe that this concept is the best explanation.

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