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Protonation of alkylpyridines: polarizability and steric effects in the base and in the cation[†]

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epoc ABSTRACT: The energies of alkyl-substituted pyridines in the 2-, 3-, 4- and 2,6-positions, of their protonated forms and of reference derivatives of benzene were calculated at the RHF/6–31G(d,p) and B3LYP/6–31G(d,p) levels. The results were processed by isodesmic reactions, expressing the substituent effect separately for the base molecules, their protonated forms and for the gas-phase basicity. The substituent effect is greatest in the protonated forms, and in the uncharged bases it is approximately three times smaller. In both cases, it is stabilizing: basicity is given by the difference. No actual steric effect was revealed, merely a stabilizing effect in the 2-position, which can be explained in terms of polarization. This effect is almost equal in the protonated and unprotonated forms, so that it is not operative in the basicity. In water solution, all effects are attenuated and steric inhibition of solvation appears, particularly with 2,6-di-*tert*-butylpyridine and 2,6-diisopropylpyridine. Copyright © 2001 John Wiley & Sons, Ltd.
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KEYWORDS: pyridine derivatives; DFT calculations; gas-phase basicity; substituent effects

INTRODUCTION

The classical terms of steric effects and steric inhibition of resonance were defined mostly on acidities or basicities in solution.[1,2] On the one hand, they were loaded with unknown solvent effects, and on the other hand, the effects in the acids (bases) could not be separated from those in the anions (cations). We undertook a systematic reinvestigation, based on the gas-phase acidities (basicities) and on the gas-phase enthalpies of formation.[3] Using alkyl-substituted benzoic acids as model compounds,[4,5] we concluded that their acidity is not controlled by classical steric effects (van der Waals interaction) since the steric volumes of the COOH and COO^- groups are practically equal:[5d] increased acidity of *ortho* derivatives is best described as pole–induced dipole interaction stabilizing the anion.[5,6]

In this work, we used 2-substituted pyridines as reference compounds without any possible steric inhibition to resonance and with a steric effect anticipated to be small or negligible. These compounds were suggested as such references by McDaniel and Brown:[7] the substituent effects in them were explained in terms of a short-range field-inductive effect. Even when the substitution was restricted to alkylpyridines in which the polar effects are minute, no steric effects were revealed: the substituent effects were explained in terms of inductive effect and hyperconjugation, the former increasing from methyl to *tert*-butyl, and the latter decreasing in the same sequence.[8] An apparent exception was found later in 2,6-di-*tert*-butylpyridine[9] and attributed to the steric hindrance to solvation.[10] All these considerations were based on dissociation constants in water, and only exceptionally on p*K* values in other solvents.[11] More recently, the protonation was investigated also in the gas phase[12,13] and compared with the basicity in water,[14,15] with the main conclusion that solvation is mainly due to hydrogen bonding of the cation[14a] and steric hindrance to solvation is operative not only in 2,6-di-*tert*-butylpyridine but also in some other 2,6- and 2-alkyl derivatives.[12] Basicities in the gas phase were correlated with substituent constants σ_α, σ_F and σ_R: according to these correlations, the effect of alkyl groups should be controlled mainly by their polarizability.[13] Recent analysis of basicities in water also rejected any hyperconjugation of alkyl groups.[16]

An essential drawback of all considerations based on basicities or acidities, even in the gas phase, is that they interpret only differences between the energies of a

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[†] Dedicated to Dr John Shorter on the occasion of his 75th birthday in recognition of his outstanding merits for the correlation analysis.

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Table 1. Calculated and experimental reaction energies of isodesmic reactions (298 K, kJ mol^{-1})[a]

Compound	Substituents	$\Delta_1 E$ (DFT)	$\Delta_1 H^o$ calc.	$\Delta_1 H^o$(g) exp.[b]	$\Delta_2 E$ (DFT)	$\Delta_3 E$ (DFT)	$\Delta_3 H^o$(g) exp.[c]	Steric effects SE_4	SE_5	SE_7	$\Delta_3 G^o$(w)[d]	SE_7(w)
2a	2-Me	−7.9	−8.2	−8.6	−26.8	−18.9	−19.1	−4.1	−4.4	−0.3	−4.2	0.2
2b	2-Et	−8.6[e]	−8.8[e]	—	−31.0[e]	−22.4[e]	−22.4	−5.0	−5.5	−0.5	−4.2	0.2
2c	2-*i*-Pr	−11.7	−11.9	—	−36.5	−24.8	−26.4	−7.8	−7.3	+0.5	−3.5	0.9
2d	2-*t*-Bu	−14.7	−15.0	—	−42.8	−28.1	−31.7	−9.6	−8.9	+0.7	−3.1	1.2
3a	3-Me	−1.1	−3.6	−1.1	−14.6	−13.5	−13.4	0	0	0	−2.7	0
3b	3-Et	−1.5	−1.5	—	−18.8	−17.3	−17.4	0	0	0	−2.8	0
3c	3-*i*-Pr	−0.8	−0.7	—	−21.7	−20.9	—	0	0	0	−2.9	0
3d	3-*t*-Bu	−1.9	−1.9	—	−26.5	−24.6	—	0	0	0	−3.4	0
4a	4-Me	−3.8	−6.2	−3.6	−22.4	−18.6	−17.2	0	0	0	−4.4	0
4b	4-Et	−3.6	−3.3	—	−25.6	−22.0	−21.1	0	0	0	−4.4	0
4c	4-*i*-Pr	−4.0	−3.7	—	−29.2	−25.2	−25.7	0	0	0	−4.4	0
4d	4-*t*-Bu	−5.1	−4.9	—	−33.9	−28.8	−27.7	0	0	0	−4.3	0
5a	2,6-Me_2	−16.1	−11.7	−16.0	−52.3	−36.2	−33.0	−8.6	−7.5	+1.1	−8.3	0.5
5b	2,6-Et_2	−17.4	−17.6	—	−59.1	−41.7	−43.3	−10.2	−8.0	+2.2	−8.0[f]	0.8
5c	2,6-*i*-Pr_2	−15.0	−15.6	—	−67.5	−52.5	−49.0	−7.1	−9.1	−2.0	−6.0[f]	2.8
5d	2,6-*t*-Bu_2	−23.0	−24.4	—	−83.0	−59.9	−52.9	−12.8	−15.2	−2.7	+4.1[f]	12.7

[a] Subscripts on Δ in all symbols refer to the number of the pertinent isodesmic reaction.

[b] Calculated from $\Delta_f H^o$(g) of Ref. 22.

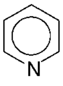
[c] Ref. 23.

[d] Calculated from p*K* values in water, Ref. 8.

[e] Calculated with the value for a secondary minimum of the ethylbenzene molecule, see Table SI (supplementary data).

[f] These values were estimated from the basicities in 50% ethanol, Ref. 9; our estimates differ from those of Ref. 12.

neutral molecule and of a cation. Separation of these energies has already been attempted[17] in terms of isodesmic reactions in which a pyridine derivative is formally synthesized from pyridine and a monosubstituted benzene [see later, Eqn. 1]. The energies of the species involved were calculated at lower levels, RHF/STO-3G or 4–31G//STO-3G;[17] in addition to methyl derivatives, only polar substituents in the 3- or 4-positions were investigated. In our previous work, we extended and systematically applied this principle[3] in studying the steric effects in alkyl-substituted benzoic acids,[4,5,18] alkylanilines[19] and methoxybenzoic acids;[20] experimental enthalpies of formation were sometimes substituted for by DFT-calculated energies.[18]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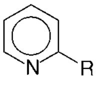
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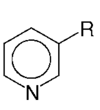
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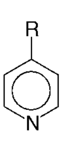
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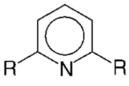

5

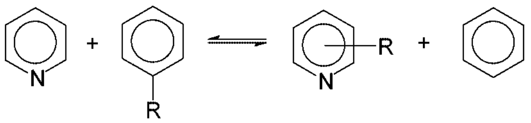
a R CH_3
b R = C_2H_5
c R = $CH(CH_3)_2$
d R = $C(CH_3)_3$

In the present paper, we apply the above principles to pyridine derivatives **2–4** with the methyl, ethyl, isopropyl and *tert*-butyl substituents in the 2-, 3- and 4-positions. Since the anticipated steric effects are weak, we included also the 2,6-bis-derivatives **5**. The main problem was whether the relative basicities are controlled essentially by the substituent effects in the pyridinium cation or whether the effect in the neutral base molecule is also of importance. Further, we intended to estimate the steric effect in the 2-position by comparison with the 4-position, and the additivity of the effects in the 2,6-positions as compared with one substituent in the 2-position. Ultimately, there was the question of whether 2,6-di-*tert*-butylpyridine reveals any exceptional behavior. Although our concept was the same as in previous work,[3,4,18–20] the concrete approach was different. Previously the task was to determine gas-phase basicities or acidities while the enthalpies of formation were known from the literature. In the present case, experimental proton affinities *PA* were known,[12] and enthalpies of formation were tentatively replaced either by the energies *E*(RHF) or *E*(DFT) calculated within the framework of the RHF and density functional theory, respectively, or by the sums of electronic and thermal enthalpies at 298 K, ΔH^o_{298}(g), calculated from them by standard statistical thermodynamics. The values of *E*(RHF), *E*(DFT) and ΔH^o_{298}(g) for individual compounds are listed in Table SI (supplementary material), and the reaction energies derived from them for the isodesmic reactions are given in Table 1.

RESULTS AND DISCUSSION

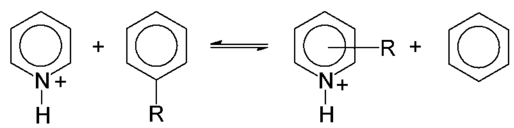
Principle of isodesmic reactions

In terms of this principle,[3,13] a pyridine derivative is symbolically synthesized from a benzene derivative and pyridine in the isodesmic reaction shown in Eqn. 1:



(1)

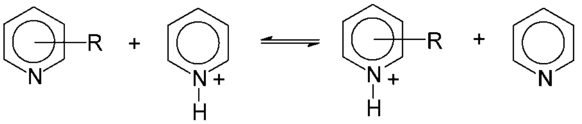
This reaction is not only isodesmic but also homodesmotic.[21] Its reaction enthalpy in the gas phase, $\Delta_1H^o(g)$, is believed to represent the substituent effect of the alkyl group on the heterocyclic nitrogen atom. Experimental values of $\Delta_1H^o(g)$ were obtained as a sum of available enthalpies of formation in the gas phase[22] and are listed in Table 1, column 5. The corresponding calculated values were obtained from the data in Table SI (supplementary material) and are given in columns 3 and 4, in terms of the energy Δ_1E(DFT) or enthalpy $\Delta_1H^o_{298}$, respectively. In the same way, Eqn. 2 expresses the substituent effect in a pyridinium cation:



(2)

Its reaction enthalpies are directly accessible only by calculation and are listed in Table 1, column 6, as the energies Δ_2E(DFT).

By combining Eqns 1 and 2, we obtain the isodesmic equation shown in Eqn. 3, defining the relative basicity of a pyridine derivative, related to pyridine:

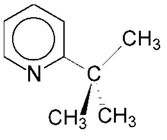


(3)

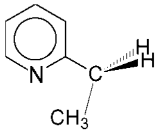
Its calculated reaction energies Δ_3E(DFT) (Table 1, column 7), were obtained as a difference Δ_2E(DFT) $-\Delta_1E$(DFT). The corresponding experimental values, $\Delta_3H^o(g)$, are available from the gas-phase basicities[23] as a difference of the two proton affinities *PA*, with a reversed sign (Table 1, column 8).

Problem of the conformation

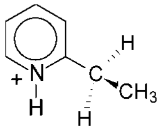
When estimating reaction enthalpies of Eqns (1)–(3), we encountered a particular problem connected with the conformation around the $C_{sp^2}-C_{sp^3}$ bond. The rotational barrier is low and several conformations are possible. The experimental enthalpies relate to the thermal equilibrium of all conformers; simple calculations relate to the lowest energy conformer, although the equilibrium can also be calculated. The problem is not in comparison of experimental and calculated values but in evaluating the substituent effects. When, for instance, Eqn. 1 should represent a construction of the structure of an alkyl pyridine from its two moieties, the conformation of these moieties should be the same on both sides of the equation. Of course, it is possible always to calculate energies of similar conformers even when one of them is not that of the lowest energy. However, energies calculated in this way cannot be compared with experiments.



2d



2b



2bH$^+$

Problems of this kind were encountered particularly in the RHF calculations and led to irregularities in the sequence of substituents methyl–ethyl–isopropyl–*tert*-butyl. This was the main reason why we proceeded to the higher level DFT model in which the lowest energy conformations of corresponding molecules are mostly the same, or at least the energy differences are minute. The conformation of *tert*-butyl derivatives is now uniform: always one methyl group is situated in the ring plane, and always it is the more remote position from the nitrogen atom; see the structure **2d** as an example. The lowest energy conformation of methyl derivatives is similar: one hydrogen atom lies in the ring plane, in the remote position from the nitrogen atom. In isopropyl derivatives, the only hydrogen atom is in the same position. The only problem remains with the ethyl derivatives. In 2-ethylpyridine and ethylbenzene, the stable conformers have the β-carbon atom in the ring plane (see formula **2b**), whereas in 2-ethylpyridinium ion this conformer is 0.9 kJ mol^{-1} less stable than the conformer with the methyl group perpendicular to the ring plane (formula **2bH$^+$**). When we calculated the substituent effect Δ_1H^o from equal conformations (Table 1, footnote e), the corresponding relative acidity Δ_3H^o should be 22.4 kJ mol^{-1}. The calculated energy difference between molecules in the lowest energy conformation is 23.3 kJ mol^{-1}, and that between the equilibrium mixtures of conformers is 23.5 kJ mol^{-1}. The differences are minute and cannot influence comparison with the experimental quantities since they are within the limits of experimental uncertainty. In 2,6-diethylpyridine and in 1,3-dimethylbenzene, the stable conformations are again those with the β-carbon atoms perpendicular to the ring plane, one below and one above. In the 2,6-diethylpyridinium ion this conformation also has the lowest energy but is only 0.1 kJ mol^{-1} more stable that another conformation with these carbon atoms in the ring plane in the direction toward the nitrogen atom. The consequences for the energy are negligible.

Comparison of calculated and experimental results

There are two possibilities of comparison with experimental results, at least for some compounds. Reaction enthalpies Δ_1H^o(g) of Eqn. 1 are available from the experimental enthalpies of formation,[22] Δ_fH^o(g), in the case of four derivatives; see Table 1, column 5. They can be compared with the calculated electronic energies Δ_1E(RHF) or Δ_1E(DFT) or with the corresponding enthalpies $\Delta_1H^o_{298}$. An evidently better agreement was found with Δ_1E(DFT) than with $\Delta_1H^o_{298}$ (Table 1, columns 3 and 4, respectively); at the RHF level the agreement was still worse. This result may seem surprising. Generally it is assumed (and sometimes confirmed[25]) that the contributions from the partition functions approximately cancel in an isodesmic reaction; hence correlation with Δ_1E(DFT) and with $\Delta_1H^o_{298}$ should be equally good. We cannot draw any conclusion from a few data, taking into account also the experimental uncertainty of the enthalpies of formation which may amount several kJ mol^{-1}. Nevertheless, some imperfection in the calculation of $\Delta_1H^o_{298}$ within the framework of B3LYP theory may be suspected.

The second possibility is comparison of Δ_3H^o with the experimental relative proton affinities δPA (enthalpies of protonation in the gas phase). We used the values recalculated in a critical review[23] (Table 1, column 8); they sometimes differ appreciably from the original literature.[12] The agreement is very good for both Δ_3E(DFT) and $\Delta_3H^o_{298}$, and it is impossible to decide which of the two is better: the correlation coefficients, 0.9891 and 0.9897, are not significantly different. We chose the electronic energy E(DFT) for calculating all derived quantities but this choice has no consequence for further conclusions. In general, we believe that our calculations are well supported by experiments and all conclusions can be based on the calculated values without combination with experimental values; the latter approach was used in some previous cases.[19]

Substituent effects in the base and in the cation

As expected, all substituent effects are stabilizing, both in the base molecules and in the protonated forms (Table 1, columns 3 and 6, respectively); they increase regularly with the size of the alkyl group according to the inductive, not the hyperconjugative, order. In Fig. 1 the substituent effects in the base, Δ_1E(DFT), and in the cation, Δ_2E(DFT), are plotted. The effects in the cations are greater and are deciding for the basicity as found already on a different set of heterocyclic compounds.[17] Effects in the base molecules are not only smaller but also less regular. Between the two there are only rough relationships, separate for the individual positions. All this would be compatible with the inductive effect or with the polarizability effect. No evident steric effects are observed; even 2,6-di-*tert*-butyl pyridine does not show any exceptional behavior.

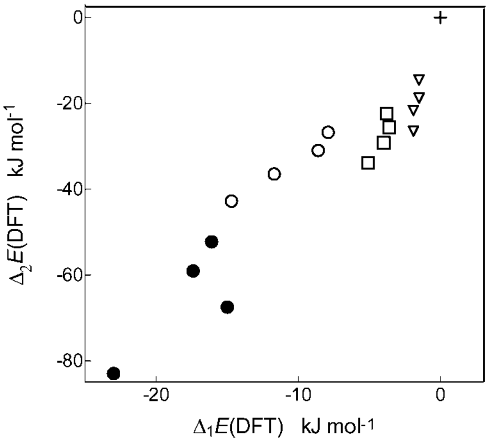
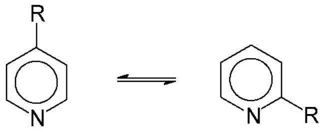


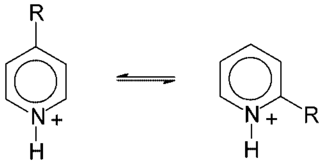
Figure 1. Plot of the substituent effect in alkyl-substituted pyridines Δ_1E(DFT) vs the substituent effect in their cations, Δ_2E(DFT). ○, 2-Derivatives; ▽, 3-derivatives; □, 4-derivatives; ● 2,6-bis derivatives; +, pyridine

Gas-phase basicities of substituted pyridines were expressed by a correlation equation giving comparable importance to inductive effect and resonance and less importance to polarizability.[13] For alkyl substituents, the inductive effect equals zero. We hold the interpretation by polarizability to be most appropriate but we have not found any confirmation of resonance (hyperconjugation). In particular, no significant changes of the geometric parameters were observed (Table SII, supplementary material). It is true that the bonds C-2—C-3 and C-5—C-6 in 4-alkyl derivatives are slightly shortened, as would be required by the hyperconjugation formulas, in the cations somewhat more than in the base molecules. However, there is not the anticipated decrease in this effect from the methyl derivatives to the higher alkyls. In 2-alkyl derivatives this effect is weaker. The exocyclic bonds, C_{ar}—C_{al}, are slightly shorter than in the corresponding derivatives of benzene but do not reveal the anticipated differences between 3- and 4-derivatives. The most significant feature is the stretched C_{ar}—C_{al} bond in all *tert*-butyl derivatives, that has obvious steric reasons. In our opinion, the cited correlation equation[13] was supported mainly by polar substituents and does not fit well to alkyl groups: all basicities are underestimated by 5 kJ mol^{-1} on average. There are further defects of this equation: it assigns the same resonance contribution to all alkyl groups and assumes a stronger resonance in the 3- than in the 4-position.

Concerning the steric effects, we previously attempted their separation in various aromatic compounds, based on the assumption that polar effects are equal in the *ortho* and *para* positions.[4,5] This approximation is common and has been applied even in the case of pyridine derivatives,[10] although the polar effects in the *ortho* position of benzene derivatives were also claimed[27] to be greater or smaller than those in the *para* position. When the approximation is accepted, the steric effect *SE* in a 2-alkyl derivative is expressed by $\Delta_4 H$ of the simple isomerization reaction, Eqn. 4, and in the pyridinium cation by Eqn. 5:

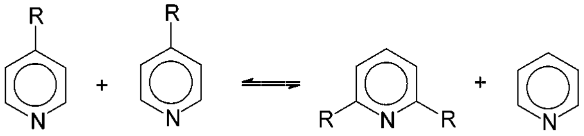

(4)

$$SE_4 \equiv \Delta_4 H°(\mathrm{g})$$

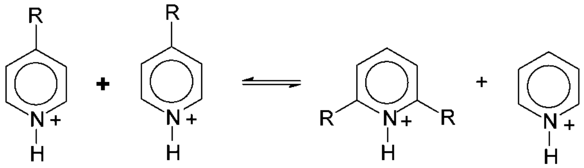

(5)

$$SE_5 \equiv \Delta_5 H°(\mathrm{g})$$

For 2,6-bis derivatives, the reactions are more complex, as shown in Eqns (4a) and (5a), respectively:


(4a)

$$SE_4 \equiv \Delta_4 H°(\mathrm{g})$$


(5a)

$$SE_5 \equiv \Delta_5 H°(\mathrm{g})$$

The values of *SE* calculated according to these equations (Table 1, columns 9 and 10, respectively) differ sharply from those obtained previously in the case of 2-alkylbenzoic acids[4,5] or 2-alkylanilines[19] in that they are negative (stabilizing). Such an interaction cannot be denoted as a steric effect: a suitable indifferent term would be *ortho* effect. In the case of cations, Eqns 5 and (5a), the most suitable interpretation is through pole–induced dipole interaction.[5,6] In a correct form,[5b] this interaction may be expressed as function of the polarizability α of the alkyl group, charge of the pole q, its distance r and effective relative permittivity $\varepsilon_{\mathrm{ef}}$ (in the gas phase a value between 1 and 2):

$$\Delta E = -\alpha q^2/32\pi^2\varepsilon_0{}^2\varepsilon_{\mathrm{ef}}{}^2 r^4 \qquad (6)$$

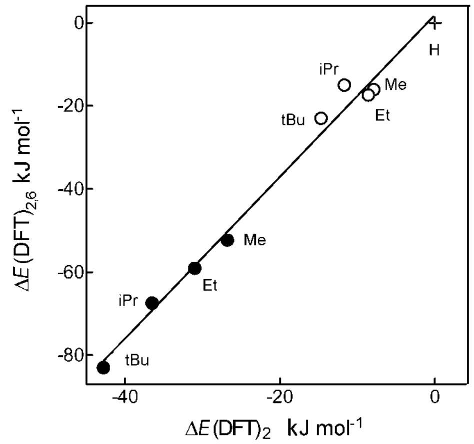


Figure 2. Additivity of substituent effects in the *ortho* positions: plot of the calculated substituent effect, $\Delta_1 E$(DFT) or $\Delta_2 E$(DFT), in 2,6-dialkyl derivatives vs the substituent effect in 2-alkyl derivatives. ○, Alkylpyridines; ●, alkylpyridinium cations

Actual calculations according to this equation are not feasible owing to the sensitivity to r and to the poorly defined position of the charge. Nevertheless, Eqn. 6 explains qualitatively the strong dependence on the distance r and strong attenuation in the solvents with a greater $\varepsilon_{\mathrm{ef}}$. The *ortho* effect in the neutral molecules, Eqns 4 and (4a), must be explained within the framework of the same theory, assuming either fractional charges or point dipoles in the pyridine ring; in the latter case the effect would decrease still more steeply with the distance (with r^6).

The steric effect on the basicity SE_7 is given by the difference, Eqn. 7:

$$SE_7 = SE_5 - SE_4 \qquad (7)$$

The values given in Table 1, column 11 reveal that SE_7 is a difference of two almost equal numbers. It is virtually equal to zero for all 2-derivatives; even for 2,6-bis derivatives it does not exceed significantly the uncertainty included in the approach. Moreover, some of the values are positive and some negative. Even 2,6-di-*tert*-butylpyridine does not show any steric effect.

Additive behavior and the buttressing effect

These concepts have significance only in the case of 2,6-bis derivatives. Additivity requires in this simple case that the substituent effects are double as in 2-derivatives. This is fulfilled fairly well both for the base molecules and for the cations (Fig. 2). What is most important, 2,6-di-*tert*-butylpyridine does not show any deviation even in this plot.

The buttressing effect was originally defined as an additional steric effect of a further adjoining group, in aromatic compound typically in 2,3-bis derivatives.[28] The term was redefined to hold for any trisubstituted compound in relation to all pertinent bis derivatives.[29] The definition can also be represented by an isodesmic reaction which is relatively complex. In the case of a 2,6-dialkylpyridine, its energy is compared with the energies of the pertinent 2-alkylpyridine (taken twice) and of 1,3-dialkylbenzene. In this particular case, the difference against the additivity principle is negligible and the buttressing effect is also zero within experimental uncertainty for all compounds investigated. Even in this case, 2,6-bis-*tert*-butylpyridine does not represent any exceptional case.

Substituent effects in water solution

All the above isodesmic reactions can in principle be defined also for water solution. This is simplest with Eqn. 3, in which $\Delta_3G^o(w)$ means relative basicity in water. The values in Table 1, column 12, were obtained from the published p*K* values, as far as possible taken from one source.[8,9] When they are compared with the basicities in the gas phase, column 8, the attenuation effect of the solvent is evident, although the attenuation is weaker than in many other classes of compounds.[15] The main part of the attenuation is ascribed to the absence of polarizability effects.[13] We tried to isolate the possible substituent steric effect in the same way as in the gas phase, by comparing 2- and 4-derivatives, Eqn. 7. The steric effects in water, $SE_7(w)$, are listed in Table 1, last column. In contrast to the effects in the gas phase, $SE_7(g)$, they are not negligible; particularly the value for 2,6-di-*tert*-butylpyridine **5d** is striking. The interpretation of Meot-Ner and Sieck,[12] based on a graphical representation, is thus confirmed: the low basicity of this compound is due to strong steric inhibition of solvation. This inhibition must take place in the protonated form and probably belongs to the entropy.[14b] We can also observe a weaker hindrance to solvation with 2,6-diisopropylpyridine and 2-*tert*-butylpyridine, in contradistinction to Meot-Ner and Sieck[12] not with 2-ethylpyridine. Note that the experimental basicity of **5d** is not completely reliable and its direct determination met with difficulties.[14c] Our estimate in Table 1 ($4.1\ \mathrm{kJ\ mol^{-1}}$) is based on a close correlation of p*K*s in 50% ethanol[9] and in water. It differs only slightly from another estimate[12] but more from a titration in water ($1.3\ \mathrm{kJ\ mol^{-1}}$). However, this disagreement does not affect the qualitative conclusions.

It is not feasible at present to estimate substituent effects in water separately for unprotonated and protonated forms. It would be necessary to transform Eqn. 1 for water solution by adding the enthalpies or Gibbs energies of solvation, $\Delta H^o_{g\rightarrow w}$, or $\Delta G^o_{g\rightarrow w}$ for all molecules involved. The easiest way is to assume that $\Delta_1H^o(g)$ and $\Delta_1G^o(g)$ are equal;[3] then one can proceed to $\Delta_1G^o(w)$ by adding the experimental Gibbs energies of solvation, $\Delta G^o_{g\rightarrow w}$. The latter values were determined experimentally only for some methylpyridines and the conclusion was drawn that the solvent effects on basicity are caused by one quarter by the hydration of pyridine bases and by three quarters to hydration of the cations.[14a] More data are available[14b] for $\Delta H^o_{g\rightarrow w}$, particularly for larger alkyls. When we added these values to Eqn. 1, we obtained a zero substituent effect in water, $\Delta_1H^o(w)$, in **5d**: basicity in water is thus given exclusively by the effect in the protonated form.

CONCLUSIONS

The approach used in this paper differs from the previous ones mainly by consequent separation of substituent effects in the base and in its protonated forms. This approach is satisfactory for the isolated molecules, i.e. in the gas phase. Under these conditions, the separated substituent effects are described in a simpler way than the basicity, which is a difference between two, sometimes fairly similar, quantities. In water solution, the separation is less easy since the necessary energies of solvation are difficult to determine and often not sufficiently precise. Discussion restricted to the basicity and operating only with solution data are generally less trustworthy. Our approach, somewhat more precise, essentially supported the previous concepts: absence of steric effects in alkyl-substituted pyridines in the gas phase and the steric hindrance to solvation in solution.

CALCULATIONS

Calculations were performed at the levels RHF/6–31G(d,p) and B3LYP/6–31G(d,p) (according to Becke[30]) by means of the Gaussian 98 program.[31] Vibrational analyses were carried out in all cases; even the less stable conformers represented local minima at the potential-energy surface. Sums of electronic and vibrational energies at 298 K, $\Delta H^o_{298}(g)$, were calculated with the same program. The results are listed in Table SI (supplementary material) and the reaction energies of the isodesmic reactions, Eqs 1 and 2, are given in Table 1. Some important geometric parameters are given in Table SII (supplementary material).

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