isomerized TB3N solutions is identical with that of the spectrum of TB3DN·⁻. This indicates that the major isomerization product is that in which both *tert*-butyl groups are in the Dewar portion of the compound as was found in the photochemical synthesis.

The reaction of TB4N·⁻ and TB3N·⁻ in DME was not studied in detail. Apparently the solvent is sufficiently acidic to cause protonation of the strained 1 or 8 position of the naphthalene nucleus. The mechanism by which the *tert*-butyl group is removed is not clear.

Conclusions

Reduction of 1,3,6,8-tetra-*tert*-butylnaphthalene and 1,3,8-tri-*tert*-butylnaphthalene by NaK in dimethoxyethane or dimethoxyethane–tetrahydrofuran was studied. These solutions exhibited secondary spectra following reduction to the primary radical anion. In dimethoxyethane, the secondary spectra were assigned to *tert*-butylnaphthalene anions in which a *tert*-butyl group in either the 1 or 8 position was replaced by a proton. In 40% dimethoxyethane–tetrahydrofuran spectra were assigned to the formation of a hemi-Dewar naphthalene valence bond isomer. This conclusion was derived from the analysis of the hyperfine splittings and the g factors of the radical ions.

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Ionization of Methyl Derivatives of Imidazole, Histidine, Thyreotropin Releasing Factor, and Related Compounds

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Abstract: The pK_a values for imidazole and for its 1- and 2-methyl derivatives were determined electrometrically at seven temperatures in the range of 10–40 °C. The results are discussed in terms of inductive and resonance effects, and hydrogen bonding of water molecules to the protonated imidazolium nitrogen atoms. From the contribution of N-methyl groups to imidazole basicity a correction factor was derived to improve the estimation of imidazole tautomer ratios from the pK_a of the parent compound and that of the N^{τ}- or the N^{π}-methyl derivative. This analysis was applied to 4-nitroimidazole, histamine, histidine, *tert*-butoxycarbonylhistidine, and thyreotropin releasing factor.

The introduction of an alkyl substituent in one of the nitrogens of imidazole, and of some of its derivatives, does not produce significant changes in the basicity at the other nitrogen atom. Thus, the pK_a of 1-methylimidazole is only about 0.1 unit higher than that of imidazole.[1,2] However, correction for the statistical factor due to the presence of two equivalent protons in the imidazolium ion yields a pK_a 0.2 unit higher for imidazole than for its 1-methylderivative, leading to the conclusion that the methyl group must effectively reduce the basicity of the other nitrogen atom.[3] This is contrary to the expected inductive effect and to the reported good correlation between the pK_a values of 1-substituted imidazoles with either σ_I or σ_m values for the substituents.[4] However, this correlation does not hold for the case of imidazole when the statistical correction is made. This was observed on simple Hammett correlations using σ_I or σ_m, as well as with a dual substituent parameter treatment,[5a] which takes into account both inductive and resonance effects. Figure 1 shows that a very good fit of the data was obtained, except for imidazole, whose pK_a is 0.62 unit higher than predicted by the correlation. In order to

Table I. Effect of Temperature on the pK_a of Imidazole, 1-Methylimidazole, and 2-Methylimidazole in 0.15 M KCl

Compound	pK_a 10 °C	15 °C	20 °C	25 °C	30 °C	35 °C	40 °C	r^a	ΔH,[b,c] kcal/mol	ΔG (25 °C),[c] kcal/mol	ΔS (25 °C),[c] (eu)
Imidazole	7.46	7.37	7.25	7.14	7.03	6.94	6.83	0.999	8.65 ± 0.14	9.74 ± 0.03	−3.66 ± 0.57
1-Methyl-imidazole	7.48	7.40	7.30	7.20	7.11	7.02	6.93	0.999	7.55 ± 0.12	9.82 ± 0.02	−7.61 ± 0.47
2-Methyl-imidazole	8.41	8.29	8.16	8.02	7.90	7.79	7.68	1.000	9.99 ± 0.10	10.94 ± 0.02	−3.19 ± 0.40

[a] Correlation coefficient for the linear dependence of pK_a on $1/T$. [b] Obtained from the best fit of the data to van't Hoff's equation by the method of least squares. [c] Errors indicated are standard deviations.

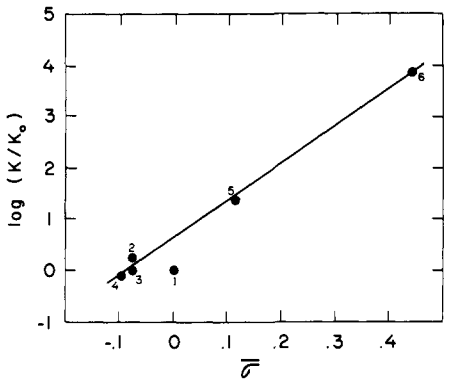


Figure 1. Dissociation constants (at 25 °C, $\Gamma/2 = 0$) of 1-substituted imidazoles (K), relative to that of imidazole (K_0), as a semilogarithmic function of $\bar{\sigma}$, obtained from $\sigma^-_{R(A)}$ scale.[5] (1) H (imidazole pK_a, corrected for statistical effect); (2) methyl; (3) ethyl (ref 6); (4) *tert*-butyl (ref 6); (5) phenyl (ref 7); (6) acetyl (ref 16). The data were fitted to the equation: $\log (K/K_0) = \rho_I\bar{\sigma} + c$ by a least-squares method, which yielded $c = 0.62$ (SD = 0.09, $f = 0.05$[5a]).

better understand the origin for this behavior we have studied the ionization of imidazole and of some imidazole-containing compounds, as well as their methyl derivatives.

Our results indicate that the anomalous position of imidazole in the correlation shown in Figure 1 may be attributed mainly to solvation effects, which are also responsible for masking the inductive effect in 1-methylimidazole. We have also found that a correction for this effect must be introduced in the method for estimating the tautomer ratio of imidazole compounds from the pK_a values of their 1- or 3-methyl derivatives.[8-10]

Experimental Section

Materials. N^π- and N^τ-methyl-L-histidines,[11] imidazole, 1-methylimidazole, and 2-methylimidazole were from Sigma Chemical Co., and L-histidine was from Calbiochem. These compounds were found to be homogeneous by TLC on silica gel with three different solvent systems and by paper electrophoresis at pH 5, and they were used without any further treatment. N^π- and N^τ-methyl-N^α-*tert*-butoxycarbonylhistidines were bought from Bachem Inc., and they were purified by column chromatography on silica with 1-butanol:acetic acid:water (4:1:5). N^α-*tert*-butoxycarbonylhistidine was prepared as described by Handford et al.[12] Thyreotropin releasing factor (TRF), [2-N^τ-methylhistidine]-TRF, and [2-N^π-methylhistidine]-TRF were synthesized by the solid-phase method as described by Rivier et al.[13]

Methods. The electrometric titrations and the treatment of titration data were done as previously described.[14,15] Not less than four independent titrations were made for each compound, at each temperature, in 0.15 M KCl. The titrations were made with more than 80 points for the amino acids and peptides, and with about 40 points for imidazole and its 1- and 2-methyl derivatives. The 95% fiducial limits for the pK_a values, in the range 3–9.5, were found to be ±0.03. These fiducial limits were obtained by the statistical treatment of a large number of titrations done in conditions used for the experiments described in this paper.[15] For the comparison of pK_a values determined at different ionic strengths, the reported values were reduced to zero ionic strength by means of a simplified Debye equation: $pK_{\mu=0} = pK_{obsd} - 0.5\mu^{1/2}/(1 + \mu^{1/2})$.

Table II. Parameters for Transference of a Proton from Imidazolium to Methylimidazoles at 25 °C

Compound	ΔpK_a[a]	ΔG, cal/mol	ΔH,[b] cal/mol	$T\Delta S$, cal/mol	ΔS, eu
1-Methylimidazole	0.24	327	1100	773	2.59
2-Methylimidazole	−0.88	−1201	−1340	−139	−0.47
4-Methylimidazole	−0.24	−327	50	377	1.27

[a] Obtained by substracting the pK_a value of the compound from that of imidazole corrected for the statistical factor by adding 0.3. [b] Obtained by subtracting the ΔH of dissociation of the compound from that of imidazole.

Results and Discussion

Table I shows the pK_a values for imidazole, 1-methylimidazole, and 2-methylimidazole at seven different temperatures in the range 10–40 °C. Very good linear correlations between pK_a and $1/T$ were observed (as indicated by the correlation coefficients in Table I), allowing an estimation of ΔH and ΔS values.

The pK_a values found at 25 °C for the three compounds of Table I are in very good agreement with the best reported measurements.[16] The $\Delta H = 8.65 \pm 0.14$ kcal/mol is 1 kcal larger than the value reported for imidazole by Nozaki et al.,[1] but it is in close agreement with the results of Datta and Grzybowski.[17] To our knowledge, no measurements of ΔH have been previously reported for 1- and 2-methylimidazoles.

From the data of Table I, and from those of Nozaki et al.,[1] it is possible to calculate the thermodynamic parameters for the transference of a proton from the imidazolium ion to the unprotonated methylimidazoles. Table II shows that 2- and 4-methylimidazoles are more basic than imidazole, as expected from the inductive effect of the methyl group. Also, 2-methylimidazole is more basic than 4-methylimidazole. An idea of the factors responsible for these relationships may be obtained by an analysis of the thermodynamic quantities. The finding that ΔH accounted for most of the ΔG, in the case of 2-methylimidazole, indicates that interaction with solvent is not very important in this case, since solvation effects should make contributions to ΔH and ΔS that would nearly cancel each other.[18,19] In the case of 4-methylimidazole, however, the larger ΔS value indicates significant solvation effects. A semi-quantitative idea of these effects may be obtained by treatment of the data to evaluate the external (ΔH_{ext}) and internal (ΔH_{int}) contributions to ΔH in terms of Hepler's theory:[18]

$$\Delta H = \Delta H_{int} + \Delta H_{ext} = \Delta H_{int} + \beta\Delta S \qquad (1)$$

Table III. Effect of Ring-Nitrogen Methylation on the Imidazole pK_a[a] of Some 4-Substituted Imidazoles

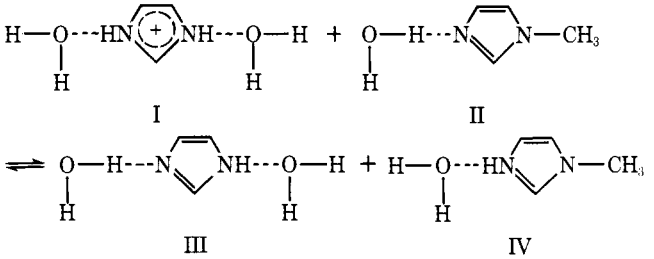
Compound	pK_a	pK_τ[b]	pK_π[c]	$-\log k$[d]
4-Nitroimidazole[e]	−0.16	2.12	−0.58	0.42
Histamine	6.04[f]	6.51[g]	5.87[g]	0.26
Histidine	6.01	6.47	5.86	0.25
Boc-histidine	7.04	7.14	6.94	0.31
TRF	6.26	6.55	6.09	0.30

[a] Reduced to zero ionic strength except for 4-nitroimidazole, which was titrated at an unspecified ionic strength. [b] pK_a of the N^π-methyl derivative. [c] pK_a of the N^τ-methyl derivative. [d] Calculated by eq 3. [e] Reference 9. [f] Reference 23. [g] Reference 10.

According to this theory, ΔH_{int} arises from the enthalpy differences between the protonated and unprotonated forms of the molecules, including the inductive effect of the methyl group on imidazole basicity, while ΔH_{ext} is associated with differences in solute-solvent interactions. The value of the proportionality constant β may vary from one reaction to another,[20] but may be approximated by the slope of the linear relationship between ΔH and ΔS of dissociation of a series of related compounds.[21] This slope, for a series of 13 histidine-containing peptides, was found to be 250 ± 9 at 25 °C.[15] Using this value for β in eq 1, the 4-methylimidazole data (Table II) yields $\Delta H_{int} = -268$ cal/mol and $\Delta H_{ext} = 318$ cal/mol. The negative value of ΔH_{int} indicates that methylation of imidazole at position 4 also produces an inductive increase in basicity, although smaller than that observed in 2-methylimidazole. For this latter compound, $\Delta H_{int} = -1222.5$ cal/mol and $\Delta H_{ext} = -117.5$ cal/mol.

Methylation of imidazole's position 1 resulted in a decrease of basicity, as indicated by the positive ΔG (Table II) due mostly to a $\Delta H_{int} = 452$ cal/mol. A decrease in basicity would be expected from a smaller resonance stabilization of the 1-methylimidazolium (relative to the imidazolium) ion. However, interactions with the solvent such as hydrogen bonding to water molecules, which would also contribute to ΔH_{int}, should be considered. The internal (gas phase) and solvation terms of the thermodynamic parameters of ionization of amines have been thoroughly dissected,[22] leading to the conclusion that the difference in solvation free energies between primary, secondary, and tertiary amines depends mainly on the number of possible $NH^+\cdots OH_2$ hydrogen bonds, which contribute about 6–7 kcal/mol to the enthalpy of solvation. This enthalpy is not compensated by $T\Delta S$ and should be included in ΔH_{int}. In the case of the imidazolium ion, two $NH^+\cdots OH_2$ bonds are possible, of which one is lost when a proton is transferred to 1-methylimidazole (compare I and IV, Scheme I). Since the enthalpy of the hydrogen bonds shown

Scheme I



in II and III should be negligible in comparison with those of I and IV, a positive ΔH_{int} of the order of that found in amines should be expected. The finding of a much smaller value indicates a considerable negative contribution of the methyl group's inductive effect.

In order to have more information about the effect of *N*-methylation on imidazole pK_a, we have titrated, at 25 °C, histidine, *N-tert*-butoxycarbonylhistidine, and TRF, and their respective N^π- and N^τ-methyl derivatives. The imidazole pK_a's of these compounds, as well as those of two other 4-substituted imidazoles and their methyl derivatives taken from the literature, are shown in Table III. We have determined a pK_a for N^π-methylhistidine that is in excellent agreement with those reported earlier.[24,25] For N^τ-methylhistidine our value of 5.86 differs from that of 5.7 obtained previously,[26] at an unspecified ionic strength. The pK_a values determined by us for TRF, N^π-methyl-TRF, and N^τ-methyl-TRF (Table III) are in good agreement with those reported by Grant et al.[27]

The analysis of the effect of methylation of one of the imidazole nitrogens upon the other's basicity cannot be done in histidine and histamine as simply as it was for imidazole itself, because of the asymmetry introduced by the substituent side chain at position 4 of the ring, giving rise to two different *N*-methyl derivatives. The effect of methylation of the imidazole nitrogen may, however, be assessed, with the reasonable and generally accepted assumption[3,8-10] that solvation changes should be similar for the dissociation of the two ring-nitrogen atoms, and that methylation of either of the two nitrogens would have the same effect on the other's basicity. Consequently, the dissociation constant of the parent compound should be the sum of the dissociation constants of the π (K_π) and of the τ (K_τ) nitrogens, corrected by a factor (k) that represents the effect of the methylation of one nitrogen on the other's dissociation constant:

$$K_a = k(K_\pi + K_\tau) \qquad (2)$$

The negative logarithm of this factor is the effect of methylation of one ring nitrogen on the pK_a of imidazole and can be obtained by eq 3 from the experimentally determined values

$$-\log k = pK_a + \log (10^{-pK\pi} + 10^{pK\tau}) \qquad (3)$$

of pK_a, pK_π, and pK_τ, the latter two being those of the N^τ- and N^π-methyl derivatives, respectively. With the exception of 4-nitroimidazole (for which larger errors in pK_a should be expected in view of their very low values) the calculated effects of ring-nitrogen methylation on imidazole pK_a of the compounds listed on Table III did not vary significantly and were close to the value 0.24 found for imidazole (Table II). This validates the assumption used to derive eq 2 and indicates that methylation of one ring nitrogen of any imidazole derivative should result in $\Delta pK_a = 0.27$ (SD = 0.03), which is an average of the values for imidazole and for the compounds of Table III, with the exception of 4-nitroimidazole. This corresponds to a change of 371 cal/mol in the free energy of dissociation and to $k = 0.537$.

The availability of a value for k allows one to introduce a correction in the equation used to calculate the tautomer ratio (K_T) of imidazole derivatives from the dissociation constants of the compound and that of either its N^π- or its N^τ-methyl derivatives.[8,9] Equations 4 and 5 are, respectively, the corrected forms of the equations for use with pK_τ and pK_π:

$$K_T = (K_a/kK_\tau) - 1 \qquad (4)$$

$$K_T = 1/[(K_a/kK_\pi) - 1] \qquad (5)$$

To check the validity of these equations we have used them to calculate K_T for the five 4-substituted compounds with $k = 0.537$ (corrected form) or $k = 1$ (uncorrected) and compared the results with those obtained by the ratio K_π/K_τ. This ratio is the best way to calculate K_T as attested by the very good agreement between the value thus calculated for histidine and that estimated from the pH dependence of ^{13}C chemical shifts.[28] Table IV shows that the introduction of the factor to correct for the effect of ring-nitrogen methylation ($k = 0.537$)

Table IV. Use of Eq 4 and 5 to Estimate Tautomer Ratio of 4-Substituted Imidazole Derivatives

Compound	K_π/K_τ	Eq 4		Eq 5	
		$k = 0.537$	$k = 1$	$k = 0.537$	$k = 1$
4-Nitroimidazole	501	353	189	−3.42	−1.61
Histamine	4.37	4.50	1.95	3.86	−3.09
Histidine	4.07	4.37	1.88	3.14	−3.42
Boc-histidine	1.58	1.34	0.26	2.09	−4.86
TRF	2.88	2.63	0.95	3.86	−3.09

greatly improves the use of eq 4 or 5 to calculate tautomer ratio, when the dissociation constants of the appropriate methyl derivatives are not available. It also shows that eq 4 is better than eq 5 for the estimation of tautomer ratios.

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Deuterium Isotope Effects in the General Base Catalyzed Deprotonation of Methylcreatininium Ion

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Abstract: The general base catalyzed deprotonation of methylcreatininium ion (I) has been measured with 39 bases that include aliphatic carboxylates, ortho-, meta-, and para-substituted benzoates and substituted pyridines, and the salt effect, solvent isotope effect, and the temperature effect on the catalytic rate constants determined. Except for the ortho-substituted benzoates the variation in isotope effect, k_H/k_D, for I-d_2 (I containing deuterium at the methylene site) is normal for proton abstraction from carbon—the lower the equilibrium basicity of the reagent, the smaller the catalytic constant and the smaller the isotope effect. Ortho-substituted benzoates exhibit increased catalytic activity and lower isotope effects, the reasons for which are unclear. Proton tunneling does not appear to be significant in the reaction. An estimate of 17 is made for the pK of the methylene group in creatinine, based on its kinetic acidity and that of I.

The kinetics of the general base catalyzed exchange of the methylene protons in I, the quaternary methyl derivative of creatinine, have previously been studied in D_2O using NMR (Scheme I).[1,2] We now report the result of an iodination study of the reaction of I and I-d_2 with 39 general bases in H_2O. (I-d_2 is deuterated at the methylene position.)

The present results, which are consistent with Scheme I, allow us to compare the two methods, but more importantly we are now able to examine the relation between deuterium isotope effect and reaction rate over a wide range of reactivities, and with a large number of bases. The extent to which isotope effects and Bronsted coefficients can be used to probe transition-state structure is a matter of considerable current interest,[3] and we believe the present work is pertinent in this regard.