Hydrogen Bonding Basicity of Amidines

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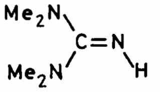
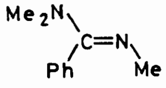
The hydrogen bonding basicity of amidines (**1**)—(**20**) has been measured by means of the frequency shift $\Delta\nu(OH)$ of methanol hydrogen bonded to amidines and of the formation constant *K* of their complexes with 4-fluorophenol. The electronic and steric effects of substituents on the imino nitrogen have been studied. Hydrogen bonding occurs at the imino nitrogen atom except for acetylformamidine (**16**) for which it occurs on the carbonyl group. For compounds $4\text{-}XC_6H_4N{=}CHNMe_2$, with X = NO_2, COMe, or C≡N, hydrogen bonding also takes place on the NO_2, COMe, or C≡N groups. From the $\log K/\Delta\nu(OH)$ correlation, two subsets, phenylformamidines and alkylformamidines, can be distinguished for the family of formamidines. For formamidines, Brönsted basicities correlate with $\Delta\nu(OH)$ as for the pyridines.

Hydrogen bonding basicity of amidines has only been measured for 1,1,3,3-tetramethylguanidine (**1**)[1] and for seven N^1,N^1-dimethyl-N^2-phenylformamidines, *para* and/or *meta* substituted on the phenyl ring.[2,3] We extend here these preliminary results to amidines (**2**)—(**20**). All the amidines have the same *E* stereochemical structure.[4—6]



(1)



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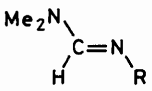


(3)—**(20)**

(**3**) ; R = $4\text{-}NO_2C_6H_4$
(**4**) ; R = $4\text{-}CNC_6H_4$
(**5**) ; R = $4\text{-}MeCOC_6H_4$
(**6**) ; R = $4\text{-}BrC_6H_4$
(**7**) ; R = Ph
(**8**) ; R = $4\text{-}MeC_6H_4$
(**9**) ; R = $2\text{-}BrC_6H_4$
(**10**) ; R = $2\text{-}MeC_6H_4$
(**11**) ; R = $3,5\text{-}Cl_2C_6H_3CH_2$
(**12**) ; R = $3\text{-}ClC_6H_4CH_2$
(**13**) ; R = $4\text{-}ClC_6H_4CH_2$
(**14**) ; R = $PhCH_2$
(**15**) ; R = $4\text{-}MeC_6H_4CH_2$
(**16**) ; R = COMe
(**17**) ; R = Pr^n
(**18**) ; R = Pr^i
(**19**) ; R = Bu^i
(**20**) ; R = Bu^t

We have measured: (a) $\Delta\nu(OH)$, a spectroscopic scale of hydrogen bonding basicity, from the frequency shift of the $\nu(OH)$ vibrator of methanol in CCl_4 at 20 °C; $\Delta\nu(OH) = \nu(OH, \text{free}) - \nu(OH, \text{hydrogen bonded})$ and, (b) log*K*, a thermodynamic scale of hydrogen bonding basicity from the formation constant *K* of hydrogen bonded complexes of 4-fluorophenol with amidines in CCl_4 at 25 °C. These quantities allow us (a) to study the influence of substitution on hydrogen bonding basicity, (b) to compare hydrogen bonding and Brönsted basicities, and (c) to investigate on which atom (imino nitrogen, amino nitrogen, or heteroatom in R) hydrogen bonding takes place.

Experimental

1,1,3,3-Tetramethylguanidine (**1**) was a commercial compound (Aldrich). Synthesis of amidines (**2**)—(**20**) has been already described.[4,7,8] Methanol and CCl_4 were spectroscopic grade compounds dried before use on molecular sieves. 4-Fluorophenol was purified by sublimation and dried *in vacuo* over P_2O_5.

I.r. spectra were recorded on a Fourier transform spectrometer Bruker IFS 45 WHR, with a 1 cm^{-1} resolution (256 scans). An infrasil quartz cell of 4 cm for $\Delta\nu(OH)$ measurements and 1 cm for *K* measurements was used.

The formation constant of complexes (AB) of 4-fluorophenol (A) with amidines (B) is defined as $K = C_{AB}/C_AC_B$. The initial molar concentration of A, C_A°, was *ca.* 4×10^{-3}M, while the initial molar concentration of B, C_B°, was varied from 2×10^{-3}—2×10^{-2}M. The equilibrium concentration C_A was obtained from the absorbance of the 3 614 cm^{-1} peak of 4-fluorophenol and the other equilibrium concentrations were deduced: $C_B = C_B^{\circ} - (C_A^{\circ} - C_A)$ and $C_{AB} = C_A^{\circ} - C_A$.

Solutions in CCl_4 were prepared in a dry box. In the spectrometer compartment the cell was under thermostatic control at 20 ± 0.5 °C for $\Delta\nu(OH)$ and 25 ± 0.5 °C for *K* measurements, by means of a Coleman thermoelectric cell holder and a Coleman digital controller.

Results and Discussion

Substituent Effects on Hydrogen Bonding Basicity.—Substitution at the imino nitrogen atom, where hydrogen bonding takes place (*vide infra*), changes the basicity of amidines. When R is benzyl [(**11**)—(**15**)] the effects of *meta* or *para* substituents can be predicted from the σ° substituent constant[10a,11] [equations (1) and (2)] since the phenyl ring is insulated from the amidino group by the methylene group.[10a]

$$\Delta\nu(OH) = 370 - 26.1\,\sigma^{\circ} \qquad n = 5,\ \text{s.d.} = 1.4\,\text{cm}^{-1},\ r = 0.991 \quad (1)$$

$$\log K = 2.29 - 0.45\,\sigma^{\circ} \qquad n = 5,\ \text{s.d.} = 0.06,\ r = 0.952 \quad (2)$$

Table. Hydrogen bonding basicity and Brönsted basicity of amidines (**1**)—(**20**)

Compd.	$\Delta\nu(OH)^a$ OH···N	$\Delta\nu(OH)^a$ OH···X	$\log K^b$	$pK_a{}^c$	σ°	$(\sigma^-)^d$	σ^{*e}
(**1**)	390		3.14^f	12.02^g			
(**2**)	390		2.62	10.17^d			
(**3**)	281	52	1.28	5.25^h	0.81	(1.24)	
(**4**)	284	99	1.49	5.70^g	0.71	(0.88)	
(**5**)	295	129	1.84	6.30^g	0.47		
(**6**)	304		1.65	6.69^h	0.26		
(**7**)	316		1.90	7.45^h	0.00		
(**8**)	325		2.07	7.75^h	−0.14		
(**9**)	268		1.37	5.58^i			
(**10**)	309		1.63	7.17^i			
(**11**)	350		2.00	9.26^g	0.74^j		
(**12**)	360		2.10	9.47^g	0.37		
(**13**)	365		2.12	9.71^h	0.24		
(**14**)	371		2.35	10.04^h	0.00		
(**15**)	372		2.36	10.28^h	−0.14		
(**16**)		166	*k*	*k*			
(**17**)	395		2.59	10.84^h			−0.115
(**18**)	385		*k*	10.95^h			−0.190
(**19**)	390		2.52	10.70^h			−0.125
(**20**)	387		*k*	11.15^g			−0.300

[a] $\Delta\nu(OH)$ measured for methanol in CCl_4 at 20 °C. $\Delta\nu(OH)/cm^{-1} = 3\,644 - \Delta\nu(OH\cdots)$. These shifts are reproducible to ± 5 cm^{-1} or better. [b] $\log K$ was measured for 4-fluorophenol in CCl_4 at 25 °C. Each *K* value is the mean of 3—6 determinations. From the s.d. of the mean, $\log K$ is believed to be reproducible to $\pm$ 0.04. [c] pK_a was measured by a potentiometric method in azeotropic ethanol at 20 °C.[7–9] [d] σ° (or σ^-) values refer to the substituent 4- or 3-X in the phenyl or benzyl system as R. [e] σ^* values are for R as a whole. [f] Ref. 1. [g] Ref. 9. [h] Ref. 7. [i] Ref. 8. [j] The effects of *meta* substituents are assumed to be additive. [k] Not measured.

When R is phenyl [(**3**)—(**8**)] a better correlation with σ° than with σ^- [10b] is observed [equations (3) and (4)]

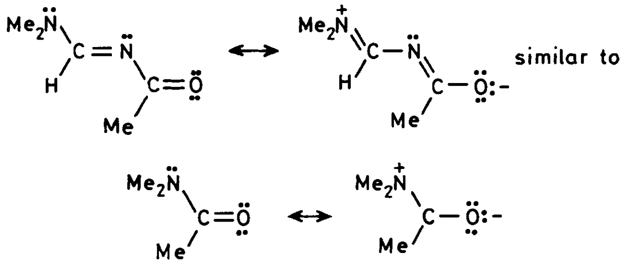
$$\Delta\nu(OH) = 317 - 45.9\,\sigma^\circ$$
$$n = 6,\ \text{s.d.} = 1.4\ \text{cm}^{-1},\ r = 0.988\ (0.976\ \text{with}\ \sigma^-) \qquad (3)$$

$$\log K = 1.91 - 0.81\,\sigma^\circ$$
$$n = 4,\ \text{s.d.} = 0.05,\ r = 0.992\ (0.967\ \text{with}\ \sigma^-) \qquad (4)$$

These σ° rather than σ^- correlations indicate that hydrogen bonding takes place on a lone pair not conjugated with *para* electron-acceptor resonance substituents of the phenyl group, and this is expected for the lone pair of the imino nitrogen.

When R is an alkyl group [(**17**)—(**20**)] the basicity does not follow the σ^* [12] electronic order [the value $r = 0.66$ for the correlation of $\Delta\nu(OH)$ with σ^* is not significantly different from zero, for $n = 4$]. It seems that hydrogen bonding formation is also sensitive to the steric effects of substituents on the imino nitrogen. Steric effects also seem partly responsible for the lower basicity of the *ortho-* substituted compounds (**9**) and (**10**) in comparison with the *para* compounds (**6**) and (**8**); $\log K$ decreases from 1.65—1.37 and from 2.07—1.63 for Me and Br groups respectively on going from the 4- to the 2-position.

When R is acetyl [compound (**16**)], the $\Delta\nu(OH)$ value of 166 cm^{-1}, comparable to that of dimethyl acetamide (177 cm^{-1}), suggests that the strong resonance and inductive electron-withdrawing effects of COMe makes the imino nitrogen so weakly basic that hydrogen bonding takes place on the carbonyl group, and this is further enhanced as the basicity of oxygen is increased as shown by the resonance formulae opposite.



In fact the N^1,N^1-dimethylformamidino group (Me_2N-CH=N) is less electron-donating than the dimethylamino group ($\Delta\nu$ 166 is lower than 177 cm^{-1}), as shown by the σ^+ substituent scale.[10c] A σ_p^+ value can be calculated for the $Me_2NCH{=}N$ group from the measurement of the wavenumber of the stretching vibration of the carbonyl group in (**5**) (1 678.8 cm^{-1} in CCl_4) and from the correlation (5) between $\nu(C{=}O)$ of *para*-substituted acetophenones in CCl_4 and σ_p^+.[13] Thus we find σ_p^+ ($Me_2NCH{=}N$) = −1.1, a value not as large as that of Me_2N($\sigma_p^+ = -1.7$) and comparable to that of NH_2($\sigma_p^+ = -1.3$).[10c]

$$\nu(C{=}O) = 1\,691.3 + 11.1\,\sigma_p^+, \qquad n = 17,\ r = 0.996 \qquad (5)$$

Sites of Hydrogen Bonding.—Amidines possess two potential sites for hydrogen bonding (imino and amino nitrogen atoms) and amidines (**3**)—(**5**) and (**16**) have a third potential site, *i.e.* the nitro group for (**3**), the cyano group for (**4**), and the carbonyl group for (**5**) and (**16**). Except for compounds (**3**)—(**5**) the i.r. spectra of amidines have one associated $\nu(OH\cdots)$ band, showing that one site is strongly favoured. With the exception of compound (**16**) for which the site is oxygen (*vide supra*), there is little doubt that this site is the imino nitrogen on the basis of the following observations:

(a) The rotation barrier around the C–N^1 bond (*ca.* 54—67 kJ)[2] is in favour of the resonance $N^1{-}C{=}N^2 \longleftrightarrow {}^+N^1{=}C{-}N^2$ showing that the electron density on N^2 (imino) is reinforced at the expense of N^1 (amino).

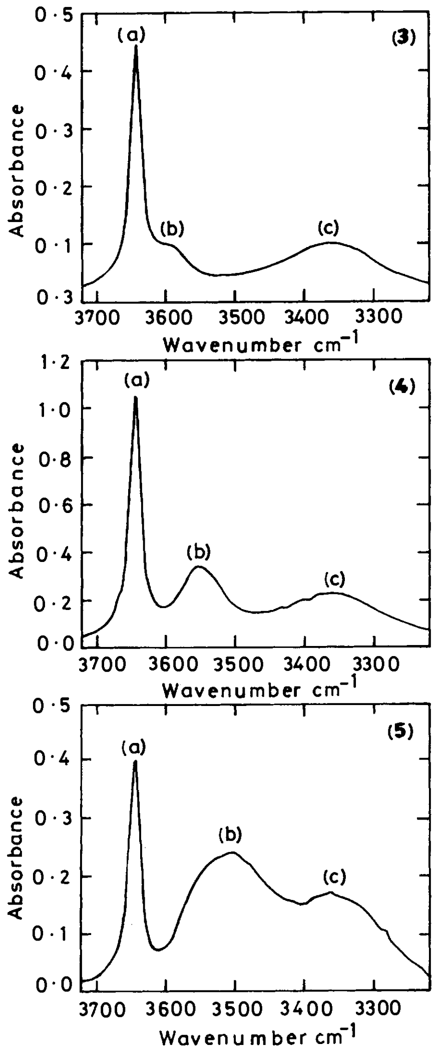


Figure 1. I.r. spectra of the ν(OH) bands of methanol in CCl_4 solutions of amidines (3)—(5) (a) ν(OH) free; (b) (3) ν(OH ··· O_2N), (4) ν(OH ··· N≡C), and (5) ν(OH ··· O=C); (c) ν(OH ··· N imino)

(b) When R is Ph and the hydrogen bond donor is phenol, Vaes *et al.*[2] have shown that the ρ constant of the Hammett equation applied to the formation constant of phenol–amidine complexes is close to that of phenol–aniline complexes. The ρ-value would have been lower if the site had been the more remote N^1 (amino).

(c) The dipole moments of the phenol–formamidine complexes are interpreted by hydrogen bonding on the N^2 (imino).[2]

(d) The substituent effect is of the σ^0 type and not of the σ^- type in compounds (**3**)—(**8**) (*vide supra*).

(e) The hydrogen bonding basicity is sensitive to the steric effects of substituents on N^2 in compouns (**9**), (**10**), (**17**)—(**20**) (*vide supra*).

However, the i.r. spectra of methanol hydrogen bonded to amidines (**3**)—(**5**) show two ν(OH ···) bands (Figure 1). The Δν(OH) values allow us to attibute the more remote band to hydrogen bonding on the imino nitrogen and the other one to hydrogen bonding on the NO_2, C≡N, or C=O groups respectively for (**3**), (**4**), or (**5**), since the values Δν(OH) = 52, 99, or 129 cm⁻¹ are close to Δν(OH) = 53, 100, or 134 cm⁻¹ found respectively for *N*,*N*-dimethyl-4-nitroaniline, 4-dimethylaminobenzonitrile, and 4-dimethylaminoacetophenone.

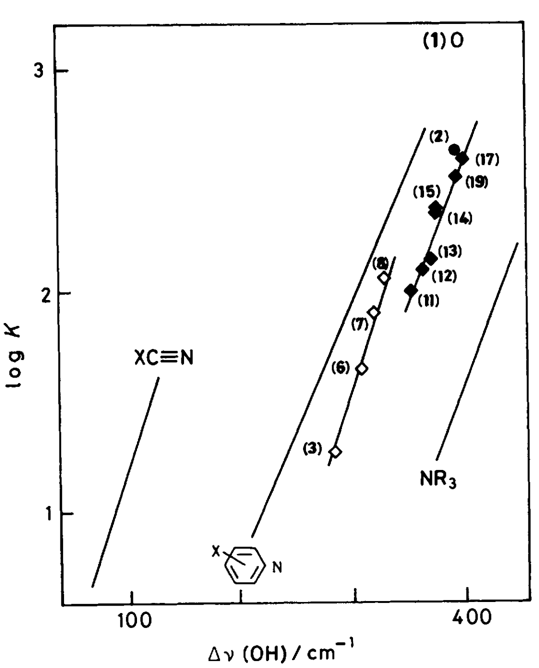


Figure 2. Correlation log*K* *vs.* Δν(OH) for nitriles, pyridines, amidines, and aliphatic tertiary amines

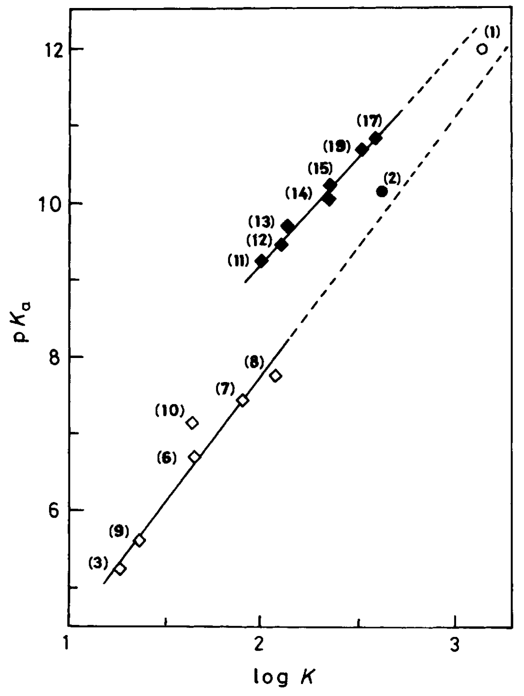
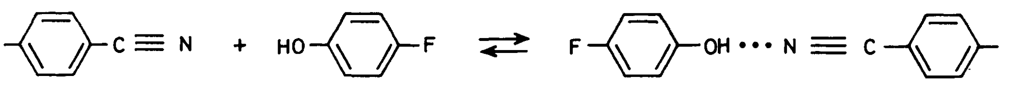
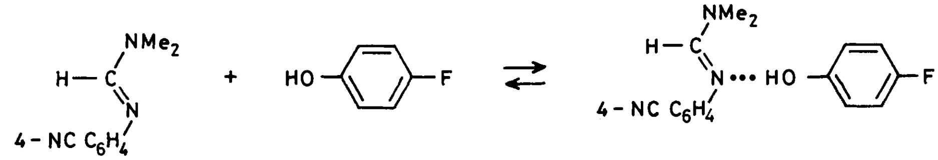


Figure 3. Correlation pK_a *vs.* log*K* for amidines

Comparison of the Thermodynamic and Spectroscopic Scales of Hydrogen Bonding Basicity.—Perfect agreement between the two scales does not occur, since the correlation of log*K*/Δν(OH) is family dependent. We have shown[14] that the correlation of log*K*/Δν(OH) allows us to characterize the state of hybridization of the hydrogen bond acceptor atom. In Figure 2 we have plotted log*K* *versus* Δν(OH) (data from ref. 14) for four families of nitrogen bases where nitrogen is in various states of hybridization: *sp* (nitriles), sp^2 (pyridines), sp^3 (tertiary aliphatic amines) and sp^x (amidines). It is seen that the *p* character of the


(A)


(B)

hydrogen bond acceptor nitrogen increases from the left to the right on the Figure 2. In this figure the amidines line is close to the pyridines; the state of hybridization of the imino nitrogen lone pair is therefore close to sp^2. The X-ray structure of N^1-(hexamethylene)-N^2-p-nitrophenylformamidine [similar to (3)] gives effectively a value of 117.5 ° for the $C{=}N^2{-}C_{ar}$ angle.[15] The separation of formamidines into two subsets, the subset of phenylformamidines and that of benzyl- and alkyl-formamidines [which includes also the trimethylbenzamidine (2)], is therefore interpreted by slightly different states of hybridization of the imino nitrogen lone pair for the two subsets.

*Prediction of log*K *for Each Site of Bi-site Amidines.*— Another interesting feature of the $\log K/\Delta\nu(OH)$ correlation is to allow the calculation of $\log K$ for each site of the bi-site amidines. From the $\log K/\Delta\nu(OH)$ correlation for nitriles[14] and from $\Delta\nu_1(OH) = 99\ cm^{-1}$, we calculate $K_1 = 15.8\ l\ mol^{-1}$ for equilibrium (A).

From the $\log K/\Delta\nu(OH)$ correlation for amidines (**6**)—(**8**) (Figure 2) and from $\Delta\nu_2(OH) = 284\ cm^{-1}$, we calculate $K_2 = 20.9\ l\ mol^{-1}$ for equilibrium (**B**).

It is easy to show that the macroscopic measured constant K is the sum of K_1 and K_2 and we calculate $\log K = 1.56$ for compound (**4**). This calculated value is in good agreement with the experimental value (1.49). In the same way for compound (**5**), from the $\log K/\Delta\nu(OH)$ correlation for ketones[14] and from $\Delta\nu_1(OH) = 129\ cm^{-1}$ we calculate $K_1 = 46.8\ l\ mol^{-1}$ and from the $\log K/\Delta\nu(OH)$ correlation for amidines and from $\Delta\nu_2(OH) = 295\ cm^{-1}$ we calculate $K_2 = 33.1\ l\ mol^{-1}$. The sum of K_1 and K_2 gives $\log K = 1.90$ for (**5**), a value which compares well with the experimental value (1.84).

We have not yet established the $\log K/\Delta\nu(OH)$ correlation for nitrobenzenes and we cannot calculate K_1 for (**3**). However, K_1 is expected to be very low and the experimental $\log K$ value is close to $\log K_2$.

Comparison of Hydrogen Bonding and Brönsted Basicities.— There is no general linear free energy relationship between the Brönsted basicity of amidines (measured as the pK_a in ethanol) and hydrogen bonding basicity (measured as $\log K$). The pK_a *vs.* $\log K$ correlation (Figure 3) reveals the existence of two subsets, phenyl formamidines and alkyl formamidines) in the family of formamidines, and the behaviour of benzamidines [such as (**2**)] and guanidines [such as (**1**)] needs further study. In contrast formamidines remain homogeneous in the correlation of pK_a *vs.* $\Delta\nu(OH)$ [equation (6)].

$$pK_a = -7.87 + 0.0483\ \Delta\nu(OH) \qquad n = 17,\ s.d. = 0.26,\ r = 0.933 \quad (6)$$

Pyridines are another family of nitrogen bases where pK_a and $\Delta\nu(OH)$ are strongly correlated.*

$$pK_a = -8.73 + 0.0485\ \Delta\nu(OH) \qquad n = 25,\ s.d. = 0.42,\ r = 0.982 \quad (7)$$

The slopes and intercepts of equations (6) and (7) are not directly comparable because the pK_a determinations are in water for pyridines and in ethanol for amidines. We plan to measure the pK_a of amidines in water to check if the correlation between pK_a and $\Delta\nu(OH)$ is family independent for various families of nitrogen bases.

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* For pyridines $\Delta\nu(OH)$ are taken from reference 16 and the pK_a value from reference 17.