^1H and ^{13}C Dynamic Nuclear Magnetic Resonance Study of Hindered Internal Rotation in (*N,N*-Dimethylamino)pyrimidines

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The free energies of activation $\Delta G^{\ddagger}$ for hindered rotation around the C–N exocyclic bond in a series of 2- and 4-(*N,N*-dimethylamino)pyrimidines have been determined by ^1H and ^{13}C n.m.r. line-shape analysis. Good linear correlations have been obtained between the coupling constant ^1J(C,H) for the dimethylamino group and the $\Delta G^{\ddagger}$ parameter. Such correlations have been used to estimate $\Delta G^{\ddagger}$ values of symmetrical or unsymmetrical pyrimidines for which an experimental determination of this thermodynamic parameter is either impossible or extremely difficult. In addition, substituent effects on the barrier heights indicate that: (i) the difference between the $\Delta G^{\ddagger}_4$ and $\Delta G^{\ddagger}_2$ values decreases with increasing electron-withdrawing power of the substituent, and (ii) substituent effects are larger through a ring nitrogen than through a ring carbon atom. Correlation of the $\Delta G^{\ddagger}$ values with Hammett constants is discussed.

Previous studies on the hindered internal rotation about the exocyclic C–N bond in *N,N*-dimethylamino-substituted pyrimidines demonstrated that the degree of conjugation of the dimethylamino group with the pyrimidine ring is dependent on its position of attachment, *i.e.* in our case the 2- or 4-position.[1] This difference in conjugation is enhanced when protonation occurs.[2] In order to understand the influence of substituents on this property, we have determined the height of the rotational barrier about the C–N exocyclic bond in two series of 4- and 2-(*N,N*-dimethylamino)pyrimidines [**(1a)**—**(19a)** and **(1b)**—**(20b)** respectively] by n.m.r.

Some of these compounds are of pharmaceutical interest, *e.g.* **(6a)** is a known rodenticide,[3] and **(6b)** shows tranquilizing properties.[3] Bipyrimidines similar to compound **(12b)** have been shown to enhance the antibacterial and antitumoral activity of phleomycin.[4] Lastly, **(17)** is a potent hypolipidemic agent and exhibits significant activity on serum triglycerides.[5]

Results

Hindered rotation about the C–N exocyclic bond in compounds **(1)**—**(20)** was studied by ^1H and ^{13}C dynamic nuclear magnetic resonance (DNMR). Three methods were used to determine the values of the chemical exchange rate k from the shape of the n.m.r. signal.

Method A.—The k values are determined at the coalescence temperature T_c by the approximate expression established by Gutowsky and Holm[6] $(k)_{Tc} = \pi\Delta\nu_\infty/2$ which is valid only if the linewidth W_0 is much smaller than the chemical shift $\Delta\nu_\infty$ in the absence of exchange.

Method B.—When $\Delta\nu_\infty$ has the same order of magnitude as W_0, the k values at the coalescence temperature are calculated using equation (1)[7a] where W is the linewidth of the exchange-broadened signal at coalescence.

$$k = \frac{\pi\Delta\nu_\infty^2(W + W_0)\left[1 + 2\left(\frac{W}{\Delta\nu_\infty}\right)^2 - \left(\frac{W}{\Delta\nu_\infty}\right)^4\right]^{1/2}}{2(W^2 - W_0^2)} \quad (1)$$

Method C.—Complete analysis of the n.m.r. line-shapes (TLS method)[7] permits the determination of the k values at different temperatures. The activation parameter $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values are calculated by a least-squares fit from the well known Eyring equation.

The standard deviation for $\Delta G^{\ddagger}$ ($_s\Delta G^{\ddagger}$) is then estimated from expression (2) where ρ is the correlation coefficient observed

$$[{}_s\Delta G^{\ddagger}]^2 = [{}_s\Delta H^{\ddagger}]^2 + T^2[{}_s\Delta S^{\ddagger}]^2 - 2T\rho\,[{}_s\Delta H^{\ddagger}][{}_s\Delta S^{\ddagger}] \quad (2)$$

between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.[8] The last term can be very large (from 0.8—16 kJ^2 mol^{-2} K^{-1}) and should not be ignored.

It has been shown[8] that uncertainties in the determination of k and T values can lead to systematic errors in the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ due to their correlation; such errors are larger than random ones. Consequently, the results, whatever the method used (A, B, or C), are discussed in terms of the free energies of activation at the coalescence temperature $\Delta G^{\ddagger}_{Tc}$. The range of T_c in this study does not invalidate such a comparison since the entropies $\Delta S^{\ddagger}$ are small for dimethylamino rotational processes (see Table 2 and ref. 1).

The $_s\Delta G^{\ddagger}$ values (Tables 1 and 2) are calculated according to the following equation for the variance $(_s\Delta S^{\ddagger})^2$:[7b]

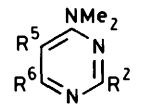
$$[{}_s\Delta G^{\ddagger}]^2 = [RT]^2\left\{\left[\left(\ln\frac{k_B T}{hk} + 1\right)\frac{\Delta T}{T}\right]^2 + \left[\frac{\Delta k}{k}\right]^2\right\} \quad (3)$$

Therefore, the error in the temperature, ΔT (0.5—2 K), is taken into account as well as that in the rate constant Δk, which in turn is dependent upon errors in $\Delta\nu_\infty$, W, and W_0.

Discussion

32 Pyrimidines were examined in order to compare the substituent effects on the degree of conjugation of the dimethylamino group with the heterocycle *per se*. For those pyrimidines, in which experimental determination of the $\Delta G^{\ddagger}$ value was not possible, an estimation was made based on the correlation observed between $\Delta G^{\ddagger}$ and the ^1J(C,H) coupling constant of the dimethylamino group.[1]

Linear Correlation of the Free Energies of Activation $\Delta G^{\ddagger}$ with the ^1J(C,H) Coupling Constants of the Dimethylamino Group.—



(1a) $R^2 = R^5 = R^6 = H$

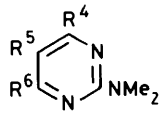
(2a) $R^2 = Cl, R^5 = R^6 = H$

(5a) $R^2 = R^6 = Me, R^5 = H$

(6a) $R^2 = Cl, R^5 = H, R^6 = Me$

(7a) $R^2 = R^6 = Cl, R^5 = H$

(8a) $R^2 = Cl, R^5 = H, R^6 = OCH_2Ph$



(1b) $R^4 = R^5 = R^6 = H$

(2b) $R^4 = Cl, R^5 = R^6 = H$

(3b) $R^4 = CN, R^5 = R^6 = H$

(4b) $R^4 = NHNH_2, R^5 = R^6 = H$

(6b) $R^4 = Cl, R^5 = H, R^6 = Me$

(7b) $R^4 = R^6 = Cl, R^5 = H$

(8b) $R^4 = Cl, R^5 = H, R^6 = OCH_2Ph$

(9b) R^4 = piperidin-1′-yl, $R^5 = H, R^6 = Cl$

(10b) R^4 = 4′,6′-Cl_2-pyrimidin-2′-yl, $R^5 = R^6 = H$

(11b) R^4 = 4′-NMe_2-6′-Cl-pyrimidin-2′-yl, $R^5 = R^6 = H$

(12b) R^4 = 4′-NMe_2-6′-$NHCH_2CH_2NMe_2$-pyrimidin-2′-yl, $R^5 = R^6 = H$

(13) $R^2 = R^4 = NMe_2, R^5 = R^6 = H$

(14) $R^2 = R^4 = NMe_2, R^5 = Me, R^6 = H$

(15) $R^2 = R^4 = NMe_2, R^5 = H, R^6 = Me$

(16) $R^2 = R^4 = NMe_2, R^5 = NO_2, R^6 = H$

(17) $R^2 = R^4 = NMe_2, R^5 = H, R^6 = Cl$

(18) $R^2 = R^4 = R^6 = NMe_2, R^5 = H$

(19a) $R^2 = R^6 = Cl, R^5 = SMe$

(19b) $R^4 = R^6 = Cl, R^5 = SMe$

(20b) $R^4 = OH, R^5 = R^6 = H$

Table 1. N.m.r. parameters and free energies of activation for the hindered internal rotation of the dimethylamino group in 4-(*N*,*N*-dimethylamino)-pyrimidines

Compd.	Nucleus	Solvent (v/v)	$\Delta\nu_\infty(T_c)^a$/Hz	$k(T_c)^b$/s^{-1}	T_c/K	$\Delta G_4^\ddagger(T_c)^c$/kJ mol^{-1}
(6a)	^{13}C	CD_3OD	12.9 ± 0.5	29 ± 1	267 ± 1	57.7 ± 0.3
(7a)	^{13}C	$CDCl_3$–CH_2Cl_2 (2:1)	7.0 ± 0.5	15.5 ± 1	272.5 ± 0.5	60.3 ± 0.2
(8a)	^{13}C	CD_3OD	9.9 ± 0.5	22 ± 1	257 ± 1	56.0 ± 0.3
(14)	^{13}C	CD_3OD	(21)	(46.7)	<182	<(31.5)[d]
(15)	^1H[e]	CD_3OD	16.2 ± 0.5	36 ± 1	222 ± 2	47.3 ± 0.5
	^{13}C	CD_3OD	21.0 ± 0.5	47 ± 1	227 ± 2	47.8 ± 0.5
	^{13}C	$(CD_3)_2CO$	17.5 ± 0.5	39 ± 1	224 ± 1	47.5 ± 0.2
(16)	^{13}C	$CDCl_3$–CH_2Cl_2 (2:1)	64 ± 2	142 ± 4	245 ± 1	49.5 ± 0.2
(17)	^1H	CD_3OD	17.3 ± 0.5	38.5 ± 1	236.0 ± 0.5	50.2 ± 0.1
	^{13}C	CD_3OD	10.4 ± 0.5	23 ± 1	233 ± 1	50.5 ± 0.3
(19a)	^1H	$CDCl_3$–CH_2Cl_2 (2:1)	15.8 ± 0.5	35 ± 1	182 ± 1	38.5 ± 0.2

[a] Difference between the chemical shifts of the two methyl groups at the coalescence temperature, extrapolated from data obtained in the absence of exchange. [b] Rate constant at the coalescence temperature calculated with method A. The error is estimated from that on $\Delta\nu_\infty$ (see text). [c] Error in $\Delta G^\ddagger$ determined from those in temperature and rate constant [equation (3)]. [d] Value evaluated at 152 K with $\Delta\nu_\infty$ (**15**) value. [e] Data previously reported (ref. 1).

Table 2. N.m.r. and thermodynamic parameters for the hindered internal rotation of the dimethylamino group in 2-(*N*,*N*-dimethylamino)pyrimidines

Compd.	Nucleus	Solvent (v/v)	$\Delta\nu_\infty(T_c)$[a]/Hz	$k(T_c)$[b]/s^{-1}	T_c/K	$\Delta H^{\ddagger}$[c]/kJ mol^{-1}	$\Delta S^{\ddagger}$[c]/J mol^{-1} K^{-1}	$\Delta G_2^{\ddagger}(T_c)$[d]/kJ mol^{-1}
(4b)	^{1}H	CD_3OD	17.6 ± 0.5	39 ± 1(A)	213 ± 1			45.1 ± 0.2
				39 ± 5(B)				45.1 ± 0.3
(8b)	^{1}H	$CDCl_3$–CH_2Cl_2 (2:1)	3.2 ± 0.5	7 ± 1(C)	236 ± 1	54 ± 2	2 ± 6	53.8 ± 0.3 (0.05)
(9b)	^{1}H	$CDCl_3$	8.4 ± 0.2	18.6 ± 0.5(A)	232 ± 1			50.7 ± 0.2
				17.5 ± 2(B)				50.8 ± 0.3
(10b)	^{13}C	$CDCl_3$–CH_2Cl_2 (2:1)	4.8 ± 0.5	11 ± 1(C)	240 ± 1	54.2 ± 0.8	2 ± 3	53.7 ± 0.2 (0.04)
(11b)	^{13}C	$CDCl_3$–CH_2Cl_2 (2:1)	3.5 ± 0.5	23 ± 8(B)	229 ± 2			49.6 ± 0.8
	^{1}H	$CDCl_3$–CH_2Cl_2 (2:1)	10.9 ± 0.2	24.1 ± 0.5(B)	232 ± 2			50.2 ± 0.5
(13)	^{1}H	CD_3OD	8.2 ± 0.5	15.5 ± 1(C)	200 ± 2	42.9 ± 0.7	−4 ± 3	43.7 ± 0.5 (0.07)
(14)	^{13}C	CD_3OD	7.8 ± 0.5	17 ± 1(A)	196 ± 1			42.7 ± 0.3
				11 ± 3(B)				43.4 ± 0.5
				14 ± 2(C)		41.3 ± 0.4	−9 ± 2	43.1 ± 0.3 (0.06)
(16)	^{13}C	$CDCl_3$–CH_2Cl_2 (2:1)	7.0 ± 0.2	15.6 ± 0.5(A)	288 ± 1			63.9 ± 0.2
				13 ± 2(B)				64.3 ± 0.4
				14.8 ± 0.5(C)		61 ± 2	−11 ± 5	63.8 ± 0.2 (0.09)
(17)	^{1}H	CD_3OD	3.0 ± 0.5	8 ± 4(B)	208 ± 1			46.7 ± 0.9
	^{13}C	CD_3OD	6.2 ± 0.5	15 ± 4(B)	216 ± 2			47.5 ± 0.8
(20b)	^{1}H	CD_3OD	9.7 ± 0.5	22 ± 1(C)	198 ± 1	43.5 ± 1.5	3 ± 7	42.9 ± 0.2 (0.04)
	^{13}C	$CDCl_3$–CH_2Cl_2 (2:1)	14.2 ± 0.2	30.5 ± 1(C)	215 ± 2	44.0 ± 0.9	−9 ± 5	46.0 ± 0.5 (0.04)

[a] Difference between the chemical shifts of the two methyl groups at the coalescence temperature, extrapolated from data obtained in the absence of exchange. [b] Rate constant at coalescence temperature. The *k* values are determined by the method indicated in parentheses (see text). For errors see text. [c] The errors are the standard deviations from a least-squares fit of the Eyring equation. [d] Free energy of activation at coalescence temperature. All errors were calculated according to equation (3). Furthermore, when method C was used, equation (2) leads to errors in parentheses.

(i) 4-*Dimethylamino group.* In addition to compounds (**1a**), (**2a**), (**5a**), (**13**), and (**15**) previously reported[1] we have extended our studies to compounds (**6a**), (**7a**), (**8a**), and (**17**) in order to increase the reliability of the correlation. Those pyrimidines which possess substituents in both the 4- and 5-positions (**14**), (**16**), and (**19a**) could not be considered in this correlation, since a large decrease in the $\Delta G_4^{\ddagger}$ value is observed, probably due to steric interaction between the substituents. Such an interaction causes the substituents to twist out of plane of the pyrimidine ring,[9,10] decreasing their conjugation with the ring.[1,10]

A conventional unweighted linear least-squares analysis as well as a weighted analysis, which takes into account the errors in both *x* and *y*,[11] have been carried out. The mean values of the slope and the intercept calculated from the two treatments were used for all the linear correlations. For the latter method, the standard errors were replaced by the experimental ones, which is undoubtly an overestimation. Therefore errors recorded herein are the average of the errors obtained from the two treatments.

Since the errors in ^1J(C,H) with respect to the range of the experimental values were larger than those of the corresponding $\Delta G^{\ddagger}$ data, the ^1J(C,H) values were plotted *vs.* the $\Delta G^{\ddagger}$ values. The regression analysis of the data for the nine 4-dimethylamino-pyrimidines reported in Table 3 gives the following relationship (4) [correlation coefficient (*r*): 0.98 and *F* value: 176]:

$$^1J(NMe_2\text{-}4) = 128.8\,(\pm 0.6) + 0.17\,(\pm 0.01)\,\Delta G_4^{\ddagger} \quad (4)$$

$^1J(NMe_2\text{-}4)$ being in Hz and $\Delta G_4^{\ddagger}$ in kJ mol^{-1}.

This equation allows one to estimate the $\Delta G_4^{\ddagger}$ values within ±4 kJ mol^{-1}, with a 95% confidence level, for ^1J(C,H) values in the range 136—139 Hz (error ±0.2 Hz). For pyrimidine (**11b**) [$^1J(NMe_2\text{-}4') = 138.0 \pm 0.1$ Hz] determination of the coalescence temperature for the 4′-dimethylamino group is difficult due to a severe overlapping of the methyl proton lines. It appears to occur at 265 ± 4 K and the $\Delta\nu_\infty$ extrapolated at this temperature is 24.8 ± 0.2 Hz. These results lead to a $\Delta G_4^{\ddagger}$ value of 55.8 ± 0.9 kJ mol^{-1} which is in agreement with the value of 54 ± 2 kJ mol^{-1} estimated from equation (4). For (**12b**), where lines overlap both in the ^{1}H and ^{13}C spectra, a $\Delta G_4^{\ddagger}$ value of 48 ± 2 kJ mol^{-1} corresponds to the ^1J(C,H) value of 137.00 ± 0.05 Hz. The rotational barrier in compound (**18**) cannot be determined because the coalescence temperature for the 4-dimethylamino group is too low (T_c < 195 K).[1] The estimated value of $\Delta G_4^{\ddagger}$ for this group is 44 ± 3 kJ mol^{-1} [$^1J(NMe_2\text{-}4) = 136.2 \pm 0.1$ Hz].

(ii) 2-*Dimethylamino group.* For the 2-(*N*,*N*-dimethylamino)-pyrimidines, only six of the ten compounds, for which the $\Delta G_2^{\ddagger}$ value has been determined, can be considered to form a relation-

Table 3. Free energies of activation $\Delta G_4^{\ddagger}(T_c)$ and ^1J(C,H) coupling constants for the dimethylamino group in 4-(*N*,*N*-dimethylamino)-pyrimidines[a]

Compd.	$\Delta G_4^{\ddagger}(T_c)$/kJ mol^{-1}	$^1J(NMe_2\text{-}4)$/Hz
(1a)[b]	53.8 ± 0.3	137.9 ± 0.1
(2a)[b]	58.6 ± 0.1	138.80 ± 0.05
(5a)[b]	51.4 ± 0.2	137.9 ± 0.1
(6a)	57.7 ± 0.3	138.5 ± 0.1
(7a)	60.3 ± 0.2	139.0 ± 0.2
(8a)	56.0 ± 0.3	138.2 ± 0.2
(13)[b]	49.4 ± 0.4	137.1 ± 0.2
(15)[b]	47.6 ± 0.5	136.95 ± 0.05
(16)[c]	49.5 ± 0.2	139.0 ± 0.2
(17)	50.4 ± 0.3	137.30 ± 0.05

[a] Solvent CD_3OD, except for compound (**16**) in $CDCl_3$–CH_2Cl_2. [b] Data previously reported (ref. 1). $\Delta G_4^{\ddagger}$ Errors calculated from equation (2). [c] Compound with 5-substituent, therefore not considered for the correlation $\Delta G_4^{\ddagger}$ *vs.* $^1J(NMe_2\text{-}4)$ (see text).

ship between $\Delta G_2^{\ddagger}$ and ^1J(C,H). As for the 4-dimethylamino series, it was necessary to eliminate compounds with a non-planar 4-substituent, *i.e.* piperidine in (**9b**) and the 4-dimethyl-*amino* group in (**14**) and (**16**), the latter group twisted out of the ring plane as a result of the 5-substituent. The rotational barrier of the 4-dimethylamino group in the latter pyrimidines is lowered while that of the 2-dimethylamino group is increased probably by destabilization of the transition state [see below; discussion of (**9b**) data].

The correlation obtained is not as precise as the former one since the range of ^1J(C,H) values is slightly smaller in the series, whereas the range of $\Delta G^{\ddagger}$ values is larger. The linear regression [see equation (5)] was derived from the data of the six compounds (see Table 4) using the two previously described analyses (*r*: 0.97 and *F* value: 61.5): where $^1J(NMe_2\text{-}2)$ is in Hz and $\Delta G_2^{\ddagger}$ in kJ mol^{-1}.

$$^1J(NMe_2\text{-}2) = 134.2(\pm 0.4) + 0.065(\pm 0.008)\ \Delta G_2^{\ddagger} \quad (5)$$

This correlation may be used to estimate the $\Delta G_2^{\ddagger}$ values within ± 16 kJ mol^{-1}, which corresponds to a 95% confidence level, when the ^1J(C,H) value is in the range 136—139 Hz (error ± 0.1 Hz). For symmetric compounds [(**1b**), (**7b**), and (**19b**)], and compounds for which the coalescence temperature cannot be reached [(**2b**), (**3b**), (**6b**), (**15**), and (**18**)] or determined [(**12b**)] evaluation of $\Delta G_2^{\ddagger}$ was achieved using the linear correlation (see Table 5). The small estimated value of 37 kJ mol^{-1} for $\Delta G_2^{\ddagger}$ (**15**) is in good agreement with the experimental data since an evaluation of this parameter by method A [$\Delta\nu_{\infty}$ *ca.* 7.8 Hz by analogy with (**14**) data] leads to a maximum value of 38 kJ mol^{-1}.

(iii) *Conditions required to use these correlations.* Methanol and chloroform–dichloromethane were chosen as solvents because of their large temperature ranges and the ease of solubility of the pyrimidines. However it was important to check if the relationships of equations (4) and (5) were suitable for other solvents. Therefore, the coupling constants ^1J(C,H) of 2,4-bis(*N*,*N*-dimethylamino)pyrimidine have been studied *vs.* solvent, concentration, and temperature (see Table 6). For the 4-dimethylamino group, there is no significant variation, indicating that equation (4) seems valid for all solvents. However, for the 2-dimethylamino group, there is a noticeable solvent effect according to the proton-donating or -accepting properties of the solvent. Consequently, the use of equation (5) should be restricted to solutions of pyrimidines in methanol or chloroform–dichloromethane.

Furthermore substituents which greatly modify the aromatic character of the 2- or(and) 4-dimethylamino ring [see (**20b**) data] should be avoided.

Substituent Effects on the Conjugation of the Dimethylamino Group with the Ring.—(i) 4-*Dimethylamino group.* The substituent effects observed in the 4-dimethylamino series confirm those reported.[1] The 2- (or 6-) substituents decrease or increase the barrier height according to their electron-donating or electron-withdrawing abilities respectively (see Table 7). As expected, a dimethylamino group has a larger effect than an amino group, as shown by the $\Delta G^{\ddagger}$ values of (**17**) (50.4 kJ mol^{-1}, see Table 1) and 2-amino-6-chloro-4-dimethylamino-pyrimidine (52.8 kJ mol^{-1}).[12] It is important to note that the substituent effect of a Cl atom is larger through a ring nitrogen than a carbon atom (Table 7). Finally, a 5-substituent influences the $\Delta G_4^{\ddagger}$ value by both its steric and electronic effects. The steric effect always decreases the $\Delta G_4^{\ddagger}$ value (see above and ref. 1) whereas the contribution of the electronic effect depends upon the type of substituent. The decrease due to a 5-methyl group is larger than 18 [(**14**) *vs.* (**13**)] or 26 kJ mol^{-1} [2-chloro-4-dimethylamino-5-methylpyrimidine,[1] *vs.* (**2a**)]; for a methylthio group it amounts to 22 kJ mol^{-1} [(**19a**) *vs.* (**7a**)]. For a nitro substituent, the steric effect nearly balances the electronic one so that the residual effect is zero [(**16**) *vs.* (**13**)] or a decrease of only 7 kJ mol^{-1} [2-chloro-4-dimethylamino-5-nitropyrimidine[1] *vs.* (**2a**)].

(ii) 2-*Dimethylamino group.* For planar substituents in the 4- and/or 6-position, the main effect is electronic, which leads to a decrease or an increase of $\Delta G_2^{\ddagger}$ depending on their electron-donating or -withdrawing abilities, respectively (see Table 7). This same effect was observed for $\Delta G_4^{\ddagger}$.

When the substituent in the 4-position is a pyrimidine, its electronic effect depends on the nature of its own substituents. For two electron-withdrawing groups, the pyrimidine substituent behaves as an electron-withdrawing group [$\Delta G_2^{\ddagger}$ increases *ca.* 5 kJ mol^{-1}, (**10b**) *vs.* (**1b**)]. In the case of an electron-donating (NMe_2) and an electron-withdrawing (Cl) group

Table 4. Free energies of activation $\Delta G_2^{\ddagger}(T_c)$ and ^1J(C,H) coupling constants for the dimethylamino group in 2-(*N*,*N*-dimethylamino)-pyrimidines

Compd.	Solvent[a]	$\Delta G_2^{\ddagger}(T_c)$/kJ mol^{-1}	$^1J(NMe_2\text{-}2)$/Hz
(**4b**)	A	45.1 ± 0.3	137.1 ± 0.1
(**8b**)	B	53.8 ± 0.3	137.8 ± 0.2
(**9b**)[b]	B	50.8 ± 0.3	137.00 ± 0.05
(**10b**)	B	53.7 ± 0.2	137.60 ± 0.05
(**11b**)	B	49.9 ± 0.8	137.4 ± 0.1
(**13**)	A	43.7 ± 0.5	136.9 ± 0.2
(**14**)[b]	A	43.1 ± 0.3	136.6 ± 0.1
(**16**)[b]	B	63.8 ± 0.2	138.3 ± 0.2
(**17**)	A	47 ± 1	137.30 ± 0.05

[a] A: CD_3OD; B: $CDCl_3$–CH_2Cl_2 (2:1 v/v). [b] Compound with 4-substitutent twisted out of the plane of the pyrimidine ring, therefore not considered for the correlation $\Delta G_2^{\ddagger}$ *vs.* $^1J(NMe_2\text{-}2)$ (see text).

Table 5. ^1J(C,H) Coupling constants for dimethylamino group and corresponding estimated free energies of activation $\Delta G_2^{\ddagger}$ in 2-(*N*,*N*-dimethylamino)pyrimidines

Compd.	Solvent (v/v)	$^1J(NMe_2\text{-}2)$/Hz	$\Delta G_2^{\ddagger}$[a]/kJ mol^{-1}
(**1b**)	CD_3OD	137.4 ± 0.1	49 ± 4
(**2b**)	CD_3OD	138.00 ± 0.05	59 ± 7
(**3b**)	$CDCl_3$–CH_2Cl_2 (2:1)	138.1 ± 0.1	60 ± 10
(**6b**)	CD_3OD	137.75 ± 0.05	54 ± 4
(**7b**)	CD_3OD	138.5 ± 0.1	66 ± 14
(**12b**)	$CDCl_3$–CH_2Cl_2 (2:1)	137.00 ± 0.05	43 ± 5
(**15**)	CD_3OD	136.60 ± 0.05	37 ± 10
(**18**)	CD_3OD	136.0 ± 0.1	28 ± 16
(**19b**)	CD_3OD	138.60 ± 0.05	68 ± 14

[a] $\Delta G_2^{\ddagger}$ is estimated from the correlation between $^1J(NMe_2\text{-}2)$ and $\Delta G_2^{\ddagger}$, within the 95% confidence level limits.

Table 6. ^1J(C,H) Coupling constants for the dimethylamino groups in 2,4-bis-(*N*,*N*-dimethylamino)pyrimidines

Solvent	mol l^{-1}	*T*/°C	$^1J(NMe_2\text{-}2)$/Hz	^1J(NMe -4)/Hz
CD_3OD	0.5	28	136.8 ± 0.1	137.1 ± 0.1
CD_3OD	0.8	28	136.9 ± 0.2	137.1 ± 0.2
CD_3OD	1.05	28	136.7 ± 0.1	137.1 ± 0.1
CD_3OD	1.05	40	136.7 ± 0.1	137.1 ± 0.1
$CDCl_3$–CH_2Cl_2 (2:1)	1.88	28	136.7 ± 0.1	136.9 ± 0.1
$(CD_3)_2SO$	1.04	28	136.4 ± 0.1	136.9 ± 0.1
$(CD_3)_2CO$	1.57	28	136.1 ± 0.1	136.9 ± 0.1
$(CD_3)_2CO$	1.57	40	136.2 ± 0.1	136.8 ± 0.1

being present in the same substituent compensation occurs and $\Delta G_2^{\ddagger}$ does not vary [(**11b**) *vs.* (**1b**)]. For two electron-donating groups [NMe_2 and $NH(CH_2)_2NMe_2$], the pyrimidine substituent behaves as a donor, since a decrease of $\Delta G_2^{\ddagger}$ [*ca.* −6 kJ mol^{-1}, (**12b**) *vs.* (**1b**)] is observed. These results indicate that the electronic effects of substituents are efficiently transmitted from one ring to the other in bipyrimidine compounds.

It is noteworthy that, when a hydroxy function is at the 4-position (**20b**) of the pyrimidine ring, the $\Delta G_2^{\ddagger}$ decreases significantly as compared to that of the parent compound, (**1b**). We believe that this decrease reflects the change in aromatic character of the pyrimidine ring. In addition, the $\Delta G_2^{\ddagger}$ value of (**20b**) exhibits a noticeable solvent effect: the $\Delta G_2^{\ddagger}$ value is about 3 kJ mol^{-1} smaller in CD_3OD than in $CDCl_3$–CH_2Cl_2.

Comparison of results for compounds (**9b**) and (**17**) shows an increase of the $\Delta G_2^{\ddagger}$ value (*ca.* 4 kJ mol^{-1}). Since these compounds are substituted in the 4-position by groups (piperidin-1′-yl and dimethylamino, respectively) with similar electron-donating abilities, this increase may be explained by a destabilization of the transition state of the rotational process, induced by a steric effect of the non-planar piperidine ring.

As stated, substitution in both the 4- and 5-position induces a steric effect which twists the 4-dimethylamino out of the plane of the pyrimidine ring. This effect seems to increase the $\Delta G_2^{\ddagger}$ value in 2,4-bis(dimethylamino)pyrimidines. A 5-methyl group reduces the $\Delta G_2^{\ddagger}$ by only 0.6 kJ mol^{-1} [(**14**) *vs.* (**13**)] while a 6-methyl group decreases it by *ca.* 7 kJ mol^{-1} [(**15**) *vs.* (**13**)]. In contrast the barrier height is considerably raised by a 5-nitro group [20 kJ mol^{-1}, (**16**) *vs.* (**13**)] partially due to its strong electronic effect. Finally, a 5-methylthio group (Hammett constant $\sigma_p = 0$), when flanked by two chlorine atoms, has a negligible effect [compare (**19b**) and (**7b**)].

(iii) *Comparison of* $\Delta G_2^{\ddagger}$ vs. $\Delta G_4^{\ddagger}$. For the parent compounds, the dimethylamino group is conjugated to a greater extent with the ring when it is at the 4- rather than at the 2-position [$\Delta G_4^{\ddagger} - \Delta G_2^{\ddagger}$ *ca.* 5 kJ mol^{-1}, (**1a**) *vs.* (**1b**)]. This difference, however, depends on the nature of the substituents. If we disregard the 5-substituted pyrimidine data in order to avoid the influence of steric interactions, comparison of the data reported in Tables 1, 2, and 5 shows that this difference $\Delta G_4^{\ddagger} - \Delta G_2^{\ddagger}$ increases with electron-donating substituents and decreases with electron-withdrawing ones [for two chlorine atoms this difference becomes even more negative, *ca.* −6 kJ mol^{-1}, (**7a**) *vs.* (**7b**)]. A trend exists, without any ambiguity, between the two parameters $\Delta G_2^{\ddagger}$ and $\Delta G_4^{\ddagger}$ (see Figure 1). Although the large errors, especially on the $\Delta G_2^{\ddagger}$ values, prevent any serious statistical analysis, the least-squares line is nevertheless plotted to illustrate this trend. This line is given by equation (6) where

$$\Delta G_2^{\ddagger} = -42 + 1.7\,\Delta G_4^{\ddagger} \qquad (6)$$

$\Delta G^{\ddagger}$ are in kJ mol^{-1}. Such a diagram may be useful to give a rough estimate of $\Delta G^{\ddagger}$ values for 2- or 4-dimethylamino-pyrimidines having similar electronic structure.

The influence of the various substituents on the barrier heights is larger through a ring nitrogen than a carbon atom in the pyrimidine series. This is clearly shown in Table 7 where the effects of Me, NMe_2, OCH_2Ph, and Cl substituents are summarized.

For 5-substituted pyrimidines, since the steric effect decreases $\Delta G_4^{\ddagger}$ and increases $\Delta G_2^{\ddagger}$ (see above), the difference between $\Delta G_4^{\ddagger} - \Delta G_2^{\ddagger}$ is negative for compound (**15**; R^5 = Me) as well as for compound (**16**; $R^5 = NO_2$). The same result has been observed for the 6,8-bis(dimethylamino)pyrimido[5,4-*d*]-1,2,3-triazines.[13]

Relationship between Free Energies of Activation and Hammett Substituent Constants.—Relationships[14,15] between different spectroscopic properties and σ-Hammett constants allow a better understanding of the perturbations induced by substituents in the electronic structure of aromatic systems. Some attempts have been successful in correlating the $\Delta G^{\ddagger}$ parameter with σ-Hammett constants.[16,17] Therefore, such a correlation has been investigated for pyrimidines with substituents of different inductive and resonance effects within a large range of σ-values. For this purpose, only pyrimidines with substituents in the *meta*-position with respect to the 2- and 4-dimethylamino groups were considered. It was assumed that the electronic effect of the 2- or 4-substituent was transmitted to the reaction centre, in the 2- or 4-position respectively, analogous to the situation that occurs in the benzene series. Furthermore, the

Table 7. Effect of substituents on the barrier heights[a] of 2- and 4-(*N*,*N*-dimethylamino)pyrimidines

Substituent	Effect through a ring carbon atom	Effect through a ring nitrogen atom
Me	−0.9 [(**6a**) − (**2a**)]	−5 [(**6b**) − (**2b**)]
	−1.8 [(**15**) − (**13**)][b]	−7 [(**15**) − (**13**)][c]
NMe_2		−4.4 [(**13**) − (**1a**)]
		−5 [(**13**) − (**1b**)]
	−5 [(**18**) − (**13**)][b]	−16 [(**18**) − (**13**)][c]
OCH_2Ph	−2.6 [(**8a**) − (**2a**)]	−5 [(**8b**) − (**2b**)]
Cl		4.8 [(**2a**) − (**1a**)]
		10 [(**2b**) − (**1b**)]
	1.7 [(**7a**) − (**2a**)]	7 [(**7b**) − (**2b**)]
	1.0 [(**17**) − (**13**)][b]	3 [(**17**) − (**13**)][c]

[a] Difference between the $\Delta G^{\ddagger}$ values of the molecules reported in parentheses. [b] Refers to $\Delta G_4^{\ddagger}$ values. [c] Refers to $\Delta G_2^{\ddagger}$ values.

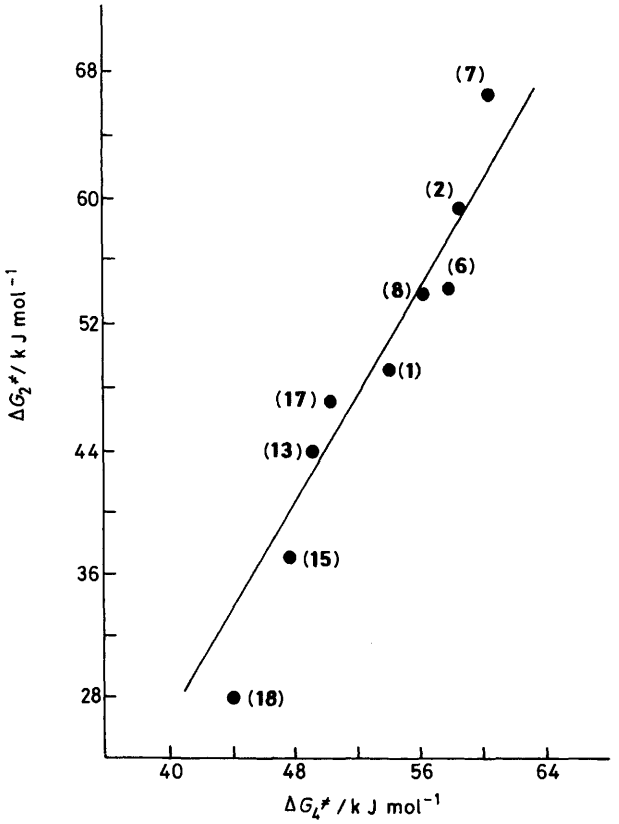


Figure 1. Relationship between the free energies of activation $\Delta G_2^{\ddagger}$ and $\Delta G_4^{\ddagger}$

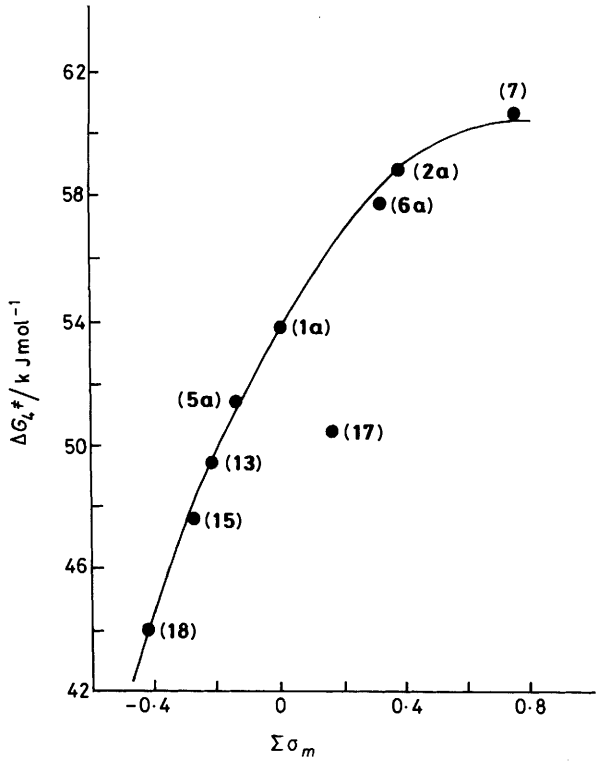


Figure 2. Relationship between the free energies of activation $\Delta G_4^{\ddagger}$ and Hammett constants $\Sigma\sigma_m$ [(**17**) data were not considered in the regression]

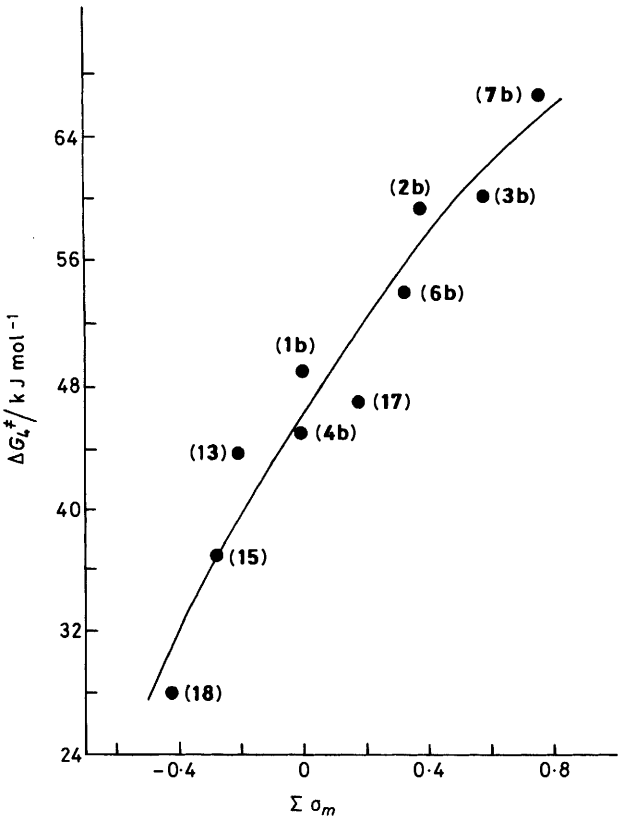


Figure 3. Relationship between the free energies of activation $\Delta G_2^{\ddagger}$ and Hammett constants $\Sigma\sigma_m$

Table 8. Hammett constants $\Sigma\sigma_m$[a] used for the (*N*,*N*-dimethylamino)-pyrimidines

Compds.		$\Sigma\sigma_m$
(**1a**)	(**1b**)	0
(**2a**)	(**2b**)	0.373
	(**3b**)	0.560
	(**4b**)	−0.020
(**5a**)		−0.138
(**6a**)	(**6b**)	0.304
(**7a**)	(**7b**)	0.746
(**13**)		−0.211
(**15**)		−0.280
(**17**)		0.162
(**18**)		−0.422

[a] *cf.* references 14 and 18.

Table 9. Experimental data for some 2-(*N*,*N*-dimethylamino)-pyrimidines

Compds.	Solvent (v/v)	$\Delta\nu_\infty(T_c)$[a]/Hz	$W(T_c)$[b]/Hz	$W_0(T_c)$[c]/Hz
(**6b**)	CD_3OD	17.6 ± 0.5	18.5 ± 1	0.82 ± 0.05
(**9b**)	$CDCl_3$	8.4 ± 0.2	10.1 ± 0.1	1.6 ± 0.1
(**11b**)	$CDCl_3$–CH_2Cl_2 (2:1)	3.5 ± 0.5	3.50 ± 0.05	1.30 ± 0.05
(**14**)	CD_3OD	7.8 ± 0.5	11.0 ± 0.2	2.2 ± 0.1
(**16**)	$CDCl_3$–CH_2Cl_2 (2:1)	7.0 ± 0.2	9.2 ± 0.1	2.1 ± 0.1
(**17**)	CD_3OD (^1H)	3.0 ± 0.5	3.2 ± 0.1	0.6 ± 0.1
	CD_3OD (^{13}C)	6.2 ± 0.5	7.0 ± 0.5	1.4 ± 0.2

[a] Difference between the chemical shifts of the two methyl groups at coalescence temperature, extrapolated from data obtained in the absence of exchange. [b] Linewidth at coalescence temperature. [c] Linewidth in the absence of exchange, *i.e.* the sum of the natural linewidth (extrapolated from data obtained at low temperatures) and the instrumental broadening.

effect of several substituents was expected to be the sum of the effect of each one.[18,19] Plots of $\Delta G^{\ddagger}$ *vs.* $\Sigma\sigma_m$ values (*cf.* Table 8) are given in Figures 2 and 3. A trend clearly exists between the variation of these two parameters. The curves obtained by a curvilinear (quadratic equation) regression have been drawn to illustrate these trends. As suggested by one of the referees, the observed curvatures are thought to be the results of a saturation effect which is brought about by the decreased efficiency of the electron-withdrawing substituent on an already electron-deficient ring. These empirical curves allow a rough estimation of $\Delta G^{\ddagger}$ values.

For example, the $\Sigma\sigma$-value for 2-amino-6-chloro-4-dimethylaminopyrimidine (0.213) leads to an estimated $\Delta G_4^{\ddagger}$ value (*ca.* 56 kJ mol^{-1}) in reasonable agreement with the experimental value (53 kJ mol^{-1}) reported recently.[12]

Experimental

The following compounds were prepared according to literature methods: (**1b**),[20] (**2b**),[20] (**3b**),[21] (**6b**),[22] (**7a**),[23] (**7b**),[24] (**8b**),[23] (**10b**),[21] (**11b**),[21] (**12b**),[21] (**16**),[25] (**17**),[26] (**19a**),[27] (**19b**),[27] and (**20b**).[20] Compound (**4b**) (m.p. 106 °C) was prepared from (**2b**) and hydrazine hydrate (85% in water), by a procedure described for an analogous pyrimidine.[25] Compound (**6a**) was prepared by reaction of an alcoholic solution of dimethylamine with 2,4-dichloro-6-methylpyrimidine at 20 °C. Compound (**8a**) was synthesized from a toluene solution of (**7a**) and sodium benzyloxide heated at 100 °C, as for compound (**8b**);[23] isolation in the usual way gave a solid residue from which the

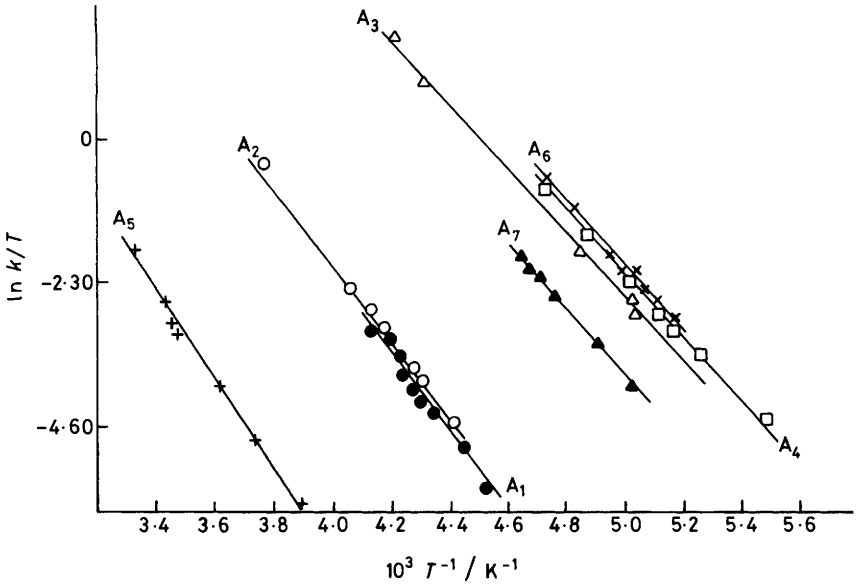


Figure 4. Eyring plots for hindered rotation of the dimethylamino group in 2-(*N*,*N*-dimethylamino)pyrimidines: A_1, (**8b**) (*r* 0.997); A_2, (**10b**) (*r* 0.9995); A_3, (**13**) (*r* 0.999); A_4, (**14**) (*r* 0.9998); A_5, (**16**) (*r* 0.999); A_6, (**20b**) in CD_3OD (*r* 0.997); A_7, (**20b**) in $CDCl_3$–CH_2Cl_2 (*r* 0.999)

monobenzyloxy compound was extracted. Compound (**9b**) was obtained by reaction of piperidine with (**7b**) in acetone at 25 °C in a way similar to that already described for 4-chloro-6-piperidinopyrimidine.[28] Compound (**14**) (m.p. 47 °C) was prepared by reaction of dimethylamine in an ether solution of 2-chloro-4-dimethylamino-5-methylpyrimidine as for pyrimidine (**16**).[25]

The experimental conditions used for the ^1H and ^{13}C n.m.r. experiments have been previously reported.[1] The theoretical line-shapes were calculated with a DNMR program of Binsch and Kleier,[29] modified as previously described,[1,2] and based on the Gutowsky–Holm theory.[6] Experimental data of some 2-dimethylaminopyrimidines are given in Table 9 with the values of $\Delta\nu_\infty(T_c)$, $W(T_c)$, and $W_0(T_c)$. The Eyring plots for compounds (**8b**), (**10b**), (**13**), (**14**), (**16**), and (**20b**) are shown in Figure 4.

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