# Barriers to Rotation of the Dimethylamino Group in Some 2-Amino-4-(N,Ndimethylamino)pyrimidines

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The free energy of activation for rotation about the exocyclic C—N bond of the dimethylamino group of some 6-substituted 2-amino-4-(N,N-dimethylamino)pyrimidines has been determined using <sup>1</sup>H NMR line shape analysis. The results are discussed in terms of the relative electron-withdrawing and electron-releasing effects of the substituents.

## **INTRODUCTION**

Hindered internal rotation about partial double bonds has been the subject of a great deal of research. The partial double bond character of exocyclic C-N bonds has been of particular interest, and a number of reports have appeared on the barriers to rotation of the C-N bond in N,N-dimethylamino-substituted benzenes, pyrimidines and related compounds.<sup>1-5</sup> The thermodynamic parameters  $\Delta H^{\neq}$ ,  $\Delta S^{\neq}$ ,  $\Delta G^{\neq}$  relating to rotation about the C-N bond can be determined by line shape analysis of the variable temperature <sup>1</sup>H NMR spectra of the N,N-dimethylamino group. This method has now been applied to the spectra of the 6-substituted 2-amino-4-(N,N-dimethylamino)pyrimidines 1-6 in order to investigate the effect of meta substitution on rotation around the C-N bond of the dimethylamino group.

$$R = CH_{3} \qquad 2 R = (CH_{3})_{2}CH \qquad 3 R = CI R = OH \qquad 5 R = NH_{2} \qquad 6 R = (CH_{4})_{3}N$$

#### **RESULTS AND DISCUSSION**

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The thermodynamic parameters for hindered rotation about the exocyclic C—N bond of the N,Ndimethylamino group in compounds **1–6** are given in Table 1, together with the temperatures,  $T_c$ , at which the peaks for the methyl resonances of the N,Ndimethylamino group coalesce. The coalescence temperatures for **1–5** span a range of about 100 K and, as expected, the enthalpy of activation,  $\Delta H^{\neq}$ , decreases as the coalescence temperature falls. Barriers to rotation are best discussed, however, in relation to  $\Delta G^{\neq}$ rather than to  $\Delta H^{\neq}$  values.<sup>6–9</sup> The values for the free energy of activation at the coalescence temperature,  $\Delta G_{T_c}^{\neq}$ , (Table 1) are similar in magnitude to those reported<sup>5</sup> for rotation about the exocyclic C—N bond

Fable 1.	Thermodynamic	parameters <sup>a</sup>	for	the	ba	urrier	to
	rotation of the	dimethylamino	) gr	oup	in	4-(N,	N-
	dimethylamino)p						

Compound	Solvent	т <sub>с</sub> (К)	ΔH <sup>≠</sup> (kJ mol <sup>−1</sup> )	ΔS <sup>≠</sup> (J mol <sup>-1</sup> K <sup>1</sup> )	ΔG <sup>≠</sup> (kJ mol <sup>−1</sup> )			
1	CDCl <sub>3</sub>	$276\pm0.5$	$75.2 \pm 3.5$	$50\pm6$	61.4			
2	CDCl <sub>3</sub>	$283\pm0.5$	$\textbf{78.0} \pm \textbf{3.9}$	$55\pm7$	62.5			
3	CDCI <sub>3</sub>	$243 \pm 1$	$44.8 \pm 1.8$	$-33\pm3$	52.8			
4	CDCl <sub>3</sub>	$230\pm2$	$41.6\pm2.6$	$-48\pm5$	52.7			
	$CD_3OD$	231±1	$43.5\pm1.9$	$-42 \pm 5$	53.1			
5	$CD_3OD$	$190 \pm 3$	$23.3\pm0.9$	$-153\pm16$	52.3			
6	CD₃OD	<183						
Errors are the standard devictions from the least errors alot								

\* Errors are the standard deviations from the least-squares plot.

in 2-substituted 4-(*N*,*N*-dimethylamino)pyrimidines. The results given in Table 1 for **4** show that there is no significant solvent influence on  $\Delta G_{T_c}^{\neq}$ , in accord with previous findings.<sup>5</sup>

The most notable feature of the results is that the values of  $\Delta G_{T_c}^{\neq}$  for **3–5** are constant at approximately 52 kJ mol<sup>-1</sup>. These compounds have substituents at the 6-position which possess lone-pair electrons, and the values for  $\Delta G_{T}^{\neq}$  are significantly lower than those for 1 and 2, in which the substituents at the 6-position do not have lone-pair electrons. The Hammett substituent constants,  $\sigma_m$ , for the Cl, OH and NH<sub>2</sub> groups in 3-5 cover a wide range, being 0.37, 0.12 and -0.016, respectively, and if the bond order of the exocyclic C-N bond at the 4-position was affected by the electron-withdrawing power of the substituent, as has been found for substituents at the 2-position in other 4-(N,N-dimethylamino)pyrimidines,<sup>5</sup> then a variation in the  $\Delta G_{T_c}^{\neq}$  values for **3–5** would probably have been observable. The relative constancy of the  $\Delta G_{T_c}^{\neq}$  values for **3–5** thus suggests that the mesomeric effect of the lone-pair electrons on the substituents outweighs their electron-withdrawing effect.

The canonical forms contributing to the resonance interaction of the N,N-dimethylamino group with the ring system can be represented by structures A–C.

The 4- and 6-positions in A-C are equivalent in that both are *ortho* and *para* to the ring nitrogen atoms. When both the substituent, R, at the 6-position and that at the 4-position possess lone-pair electrons, there

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will be 'competition' between the two substituents in relation to the placement of negative charge at the ring nitrogen atoms. The net result would be that the contribution to the resonance hybrid from structures B and C would be reduced, with a consequent decrease in the bond order of the exocyclic C—N bond at the 4-position. This would be manifested by lower  $\Delta G_{T_c}^{\dagger}$  values for compounds having substituents with lone-pair electrons at the 6-position compared with compounds having substituents without lone-pair electrons at the 6-position. Thus, it would be expected that **1** and **2**, with alkyl groups at the 6-position, would have higher  $\Delta G_{T_c}^{\dagger}$  values for rotation about the C—N bond at the 4-position.

The rotational barrier in 6 could not be measured because the coalescence temperature is too low. This

was also found for the related compound 2,4,6-tri(N,N-dimethylamino)pyrimidine.<sup>5</sup>

#### EXPERIMENTAL

Compounds **1–6** were prepared by refluxing the appropriate 6-substituted derivative of 2-amino-4chloropyrimidine with a 20 fold molar excess of dimethylamine in propan-1-ol for 2–3 h, evaporating the reaction mixture to dryness under reduced pressure and recrystallizing the residual solid from either toluene, toluene–ethanol (95:5) or benzene–toluene (95:5). The compounds were characterized by NMR and mass spectral data.

The NMR spectra were recorded on a Perkin–Elmer R32 90 MHz spectrometer. The rate constants for rotation about the C—N bond of the N,N-dimethyl-amino group were determined by the standard method of line shape analysis using the equations of Gutowsky and Holm and assuming equal population of sites.<sup>10</sup> The values of  $\Delta H^{\neq}$  and  $\Delta S^{\neq}$  were obtained using absolute rate theory.

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