Kinetics of *N*-Methylation Reactions and *X*-Ray Data of Quaternary Thiazolium Salts. The N ' Lone ' Pair Orientation in the Thiazole Ring.

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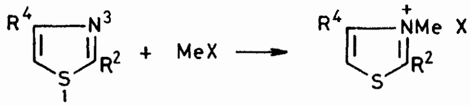
Kinetic measurements show that in 2- and 4-substituted thiazoles bulky 4-alkyl substituents have a stronger deactivating effect upon *N*-methylation than 2-alkyl isomers. This experimental result, corrected for electronic effects (pK_a) and conformational preference, suggests that the ' true ' steric hindrance of an alkyl substituent towards an electrophilic centre approaching nitrogen is greater for the 4-position ($\Delta\Delta\Delta\ G^{\ddagger}$ = 570 cal mol^{-1}). The geometries of thiazole [microwaves (12)] and thiazolium salt (*X*-rays) allow an interpretation of this difference of apparent bulkiness in terms of ' easier in plane bond distortion at C(2) in thiazole ' and ' unsymmetrical orientation of the lone pair '. Its axis, rather than lying along the $\widehat{C(2)NC(4)}$ bisectrix (15) seems to be ' nearer ' to the C(4) carbon.

ALTHOUGH the conformation of the lone pair in piperidine and other saturated heterocycles has been well examined,[1] almost nothing is known about the possible ' orientation ' of the unshared pair of electrons on a nitrogen atom in a dissymetrical heteroaromatic molecule. The aim of the present report is to give experimental evidence concerning this point for the thiazole ring.



(1)

The log values of rate constants (see Table) for reaction (1) when plotted against Taft's E_s [2] parameters give rise to a linear correlation.[3a,b,4] The slope of the line is greater for 4-R than for 2-R in all the solvents studied (MeCN, Me_2CO, $PhNO_2$, and CCl_4–MeCN).[3b] This difference may be evaluated in energetic terms:

$$\Delta\Delta\Delta\ G^{\ddagger} = 2.303\ RT \left(\frac{\log k^{25}2\text{-Bu}^t}{k^{25}2\text{-Me}} - \log\frac{k^{25}4\text{-Bu}^t}{k^{25}4\text{-Me}}\right) = 410 \text{ cal mol}^{-1}$$

What are the contributions to this 410 cal mol^{-1} value ?

RESULTS AND DISCUSSION

The origin of varying steric behaviour for a given alkyl group may arise for the following reasons. (1) A different electron-releasing ability for the substituent depending upon whether it occupies the *ortho* or the *ortho'* position of the ring. (2) A difference in conformational behaviour of the Bu^t group depending on whether it substitutes the 2 or the 4 carbon of the thiazole ring, *e.g.* $\widehat{R^2C(2)N}$ greater than $\widehat{R^4C(4)N}$. (3) A stronger bond-bending force constant for $\widehat{R^4C(4)N}$ than for $\widehat{R^2C(2)N}$. (4) Preferential orientation [or polarisability toward C(4)] of a nitrogen lone-pair.

Each of these factors may contribute either positively or negatively to the overall value of 410 cal mol^{-1}.

The ' hyperconjugative ' ability of the methyl group is approximately given by the pK_a values of thiazole, 2-methylthiazole, and 4-methylthiazole (see Table). The fact that these values provide indeed a good estimation of this contribution has been developed elsewhere.[5] The calculated difference (2.303 *RT* pK_a) for the ' hyperconjugative ' ability of the same methyl group which substitutes C(2) or C(4), amounts to 410 cal mol^{-1}. In fact, the charge development involved in the transition state of the quaternisation reaction is obviously less important than the one involved in the act of protonation. We tentatively estimate the extent of charge development at the nitrogen atom in the transition state to be 0.40.† This suggests an approximate value of *ca.* 160 cal mol^{-1} (±100) ‡ for the hyperconjugative contribution to the observed $\Delta\Delta\Delta\ G^{\ddagger}$. This contribution is a positive one: if the methyl group taken as a reference in the supposedly pure steric Taft relationship is actually exerting an electron donor effect, then the measured ' steric effect ' for the Bu^t group is underestimated.[7]

Rate constants and activation parameters of 2-alkyl- and 4-alkyl-thiazoles

R^2 or R^4	pK_a (±2%) [a]	$k_{25°} \times 10^6$ (±2%) [b]	$\Delta H^{\ddagger}$ (±0.25) [c]	$\Delta S_{\ddagger}$ (±1.2) [c]
H	2.52	9.4		
2-Me	3.42	11.8	15.1	−30.2
2-Et	3.37	9.2	15.0	−31.0
2-Pr^i	3.28	4.3	15.6	−30.7
2-Bu^t	3.15	0.29	16.9	−31.7
4-Me	3.12	9.8	14.4	−33.1
4-Et	3.17	7.8	14.4	−33.8
4-Pr^i-4	3.00	2.58	15.5	−32.2
4-Bu^t	2.87	0.12	17.1	−33.4

[a] From the following sources: R. Phan Tan Luu, J. M. Surzur, J. Metzger, J. P. Aune, and C. Dupuy, *Bull. Soc. chim. France*, 1967, 3274, and M. Carrega, Thesis, Marseille, 1959. [b] In l mol^{-1} s^{-1} for the reaction between the considered thiazole and MeI in nitrobenzene. [c] $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ in kcal mol^{-1}, $\Delta S^{\ddagger}$ in cal K^{-1} mol^{-1}; the given values for $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ result from the *k* determined over a range of 30 °C.[3,18] It has been checked [3] that the above products quaternise without appreciable reversibility of the reaction: solutions of quaternary salts keep a constant conductivity during several days.

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† This is the value of the Brönsted parameter determined in quaternisation of aza-aromatic amines.[6]

‡ The difference of electronic effect associated with Bu^t substituents which substituent C(2) and C(4) are far less important (see ΔpK_a values in the Table when Me is replaced by Bu^t). Thus this difference is included in the rather large error (±100 cal associated to the estimation of the hyperconjugative contribution).

This increases the original 410 cal mol^{-1} difference in the 'steric behaviour' for the Bu^t substituent to 570 cal mol^{-1} in terms of 'true steric' hindrance.*

If the Bu^t group had a preferentially more hindering conformation in the 4-position than in the 2-position, part of the difference in 'steric behaviour' could be rationalised. In such systems, the Pitzer strain favours the conformer where one of the three geminal methyl group eclipses the carbon–carbon double bond.[8] Thus, the 2-Bu^t group, in which one methyl group points toward nitrogen, should be 'bulkier' than the 4-Bu^t one. In any case, this effect is very slight; if strong conformational preference were induced in the alkyl substituents the plot log k_R/k_{Me} *vs.* E_s would no longer provide a linear correlation.[9] The 2,5-dimethyl-4-alkylthiazole quaternisation rates (methyl tosylate, nitrobenzene, 25°) clearly illustrate such a situation (Figure 1) and give us information about the higher possible conformational contribution to $\Delta\Delta\Delta\ G^{\ddagger}$. The (25 °C) values of 2-methyl-4-t-butylthiazole,[10] 2,5-dimethyl-4-t-butylthiazole,[9] 2-methylthiazole,[4] and 2,5-dimethylthiazole [11] are respectively 0.005, 0.0076, 4.54, and 10.5 × 10^{-6} l mol^{-1} s^{-1}. The rate constants of the third and fourth compounds allow an estimate of the rate constant ratio between a 4-t-butylthiazole in its more and least hindering conformations:

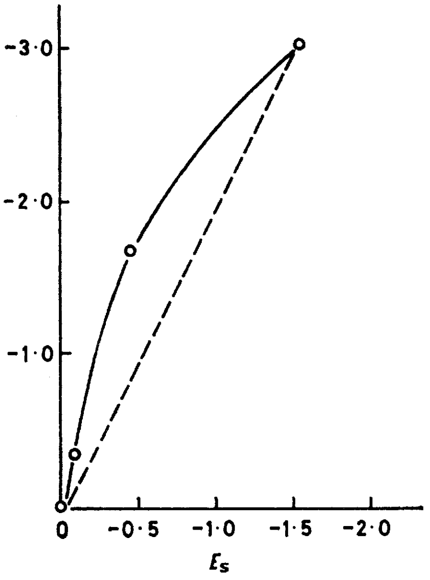

FIGURE 1 Plot of logk/k_0 for quaternisation of 2,5-dimethyl-4-R-thiazoles (R = Me, Et, Pr^i, or Bu^t) *vs.* Taft's E_s parameters

$$r = \frac{0.0076}{0.005} \times \frac{4.54}{10.5}$$

Thus, the higher possible difference between an almost free 4-Bu^t group and a blocked one amounts to 240 cal mol^{-1} (2.3 RT log r). This value is, however, far more important than the one associated with both the almost freely rotating 2- and 4-Bu^t groups. The very good E_s parameters–rate constants linear relationship displayed by both the 2- and 4-alkylthiazole series (slopes 0.96 and 0.81, correlation coefficients 0.9987 and 0.999) compared with the curvature shown in Figure 1 suggests that conformational differences between 2- and 4-t-butylthiazole contribute only very slightly if at all to $\Delta\Delta\Delta\ G^{\ddagger}$. This may be a result of the very weak energetic preferences exhibited by these conformational systems.[8] Thus, no account is taken of a conformational contribution to the measured 410 cal mol^{-1}.

Three contributions could participate in the remaining 570 cal mol^{-1}. An examination of the geometry of the thiazole ring determined by Bak [12] (Figure 2) shows that the bond distances H(2)–N and H(4)–N are identical. Thus for weakly perturbing substituents such as alkyl groups, the above result will also be true, and the contribution of difference in geometrical parameters to $\Delta\Delta\Delta^{\ddagger}$ more than likely vanishingly small.

An *X*-ray analysis [13] of 3-methyl-2-t-butylthiazolium bromide and 3-methyl-4-t-butylthiazolium iodide (Figure 3) establishes that the angle $\widehat{\mathrm{CBu^tC(2)N}}$ is more easily widened than the angle $\widehat{\mathrm{CBu^tC(4)N}}$. This is well illustrated by the following values for substituted thiazolium bromides:[14]

2,3,4-Me$_3$	$\widehat{C_{exo}C(4)N}$	121°;	$\widehat{C_{exo}C(2)N}$	123°
3-Me,2-Bu^t			$\widehat{C_{exo}C(2)N}$	128°
3-Me, 4-Bu^t	$\widehat{C_{exo}C(4)N}$	124°,2		
·2,3,4-Me$_3$	$\widehat{C_{Me}NC(4)}$	120°;	$\widehat{C_{Me}NC(2)}$	124°
3-Me,2-Bu^t			$\widehat{C_{Me}NC(2)}$	127°
3-Me,4-Bu^t	$\widehat{C_{Me}NC(4)}$	128° 1		

Furthermore, none of these three structures displays out-of-plane bending for the alkyl substituents; this result indicates that the steric strain in the quaternisation reaction is essentially minimised by in-plane deformations.

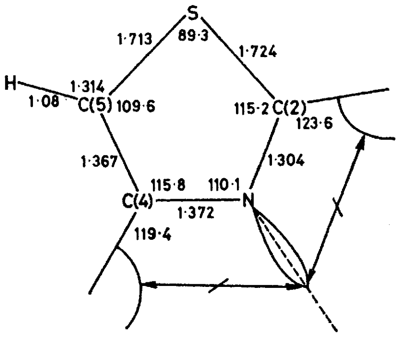

FIGURE 2 Steric interactions between the 2-methyl (or 4-methyl) group and the approaching electrophilic centre. The geometry adopted is that given by microwave measurement [12,15]

A 5° deviation of a C–C–C angle leads [1] to an energy increase of 500 cal mol^{-1}. Since differences of angular deviation between C(2) and C(4) substituents are being discussed this 500 cal mol^{-1} is more likely to be divided at least by a factor of 2. Thus the difference of force

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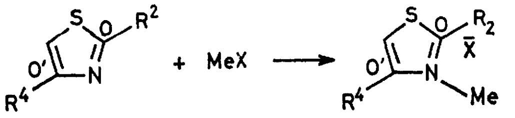
* It has been shown in ref. 7*b* that the word 'steric hindrance' covers, in fact, several intricated factors and particularly steric and electronic factors. The present work demonstrates that even 'true steric' terms result in at least three different subterms if the analysis is done by application of the Westheimer model to intermolecular transition states (see F. M. Westheimer, 'Steric Effects in Organic Chemistry,' M. S. Newman, Wiley, New York, 1965, p. 523.

constants for bond distortions in position C(2) and C(4) is insufficient to explain the value of 690 cal mol^{-1}. A contribution from the N electron-pair orientation must be considered. ^{14}N Quadrupolar coupling constants of thiazole obtained from microwave studies,[15] suggest that the axis of the unshared pair of electrons bisects $\widehat{C(2)NC(4)}$. This interpretation depends upon the quality of the wave functions used to describe the electric field gradient.[16] The *X*-ray structure of 2,3,4-trimethylthiazolium bromide (Figure 4) shows that the N–Me bond is nearer to the C(4) substituent than to the C(2).



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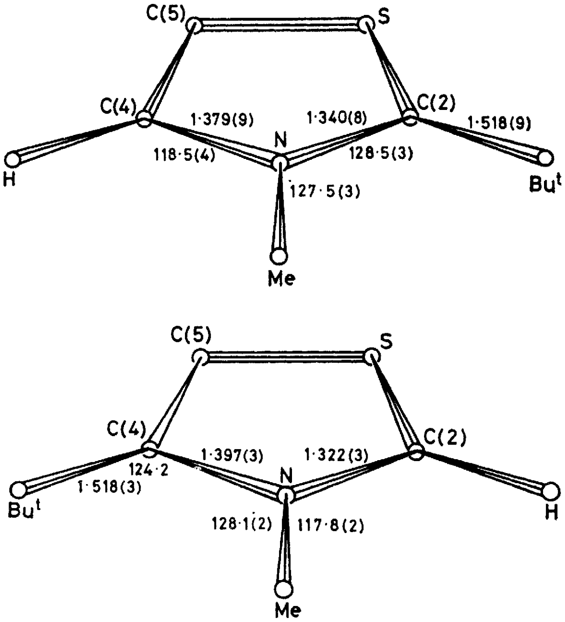

FIGURE 3 Geometries of 3-methyl-2-t-butylthiazolium bromide and 3-methyl-4-t-butylthiazole iodide around the nitrogen[13]

This result indicates that the 'lone pair' is dissymmetrically oriented, its axis being nearer to C(4) than to C(2). The final orientation of N–Me indeed results from two opposing factors; the first is the necessity for maximum overlap between the lone pair and the LUMO of methyl bromide, the second is the necessity of minimising the non-bonded van der Waals interactions by in-plane angular distortion. Since a C(2) alkyl substituent is more easily distorted than a C(4) one (Figure 3) it is improbable that the lone pair axis lies along the bisectrix of $\widehat{C(2)NC(4)}$ because such an orientation would lead to a CH_3–N bond nearer to C(2) than to C(4), the reverse of the observed geometry (Figure 4).

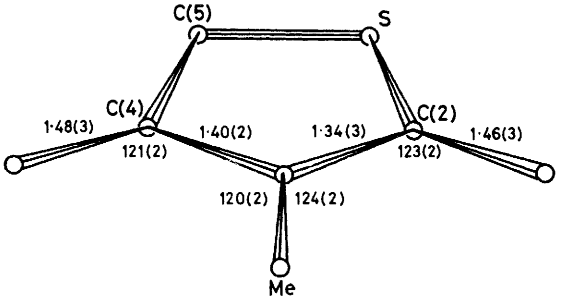

FIGURE 4 Geometry of 2,3,4-trimethylthiazolium bromide around the nitrogen[14]

[7/1954 *Received*, 7*th November*, 1977]

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