Tetrahedron, 1967, Vol. 23, pp. 813 to 816. Pergamon Press Ltd. Printed in Northern Ireland

NUCLEOPHILIC HETEROAROMATIC SUBSTITUTION—XXIV[1]

KINETICS OF PIPERIDINODECHLORINATION OF 2- AND 6-ALKYL-4-CHLOROPYRIMIDINES IN ETHANOL AND TOLUENE—EVIDENCE FOR A STERIC HINDRANCE TO SOLVATION OF THE *AZA*-GROUP

M. CALLIGARIS, P. LINDA and G. MARINO
Istituto Chimico-Universita di Trieste, Trieste, Italy

(*Received* 26 *April* 1966)

Abstract -The rate constants for the reaction of 2- and 6-alkyl-4-chloropyrimidines with piperidine in toluene and ethanol have been determined at 30·0°.

The reactivity ratio $k_{Me}/k_{t\text{-}Bu}$ increases considerably in passing from the reaction of 6-alkyl-4-chloropyrimidines in toluene (1·62) to the reaction of 2-alkyl-4-chloropyrimidines in ethanol (17·3). This remarkable increase (over a factor of ten) is ascribed to a steric hindrance to solvation of the *aza*-groups caused by the bulkier substituent.

THE generally observed absence of steric interactions between the activating moiety and an adjacent substituent represents one of the main advantages of *aza*-activated with respect to nitro-activated systems in the study of aromatic nucleophilic substitutions.[2] The steric requirements of a nitrogen lone-pair are smaller than those of a nitro group although not completely negligible. Aroney and Le Fevre[3] suggested, on the basis of Kerr constant measurements in benzene, that the space-filling ability of a lone electron pair exceeds that of a covalently bonded hydrogen atom and compares with that of a methyl group. These conclusions have been criticized[4] and more recent work based on dipole moment measurements[5,6] and spectroscopical data[7,8] of various N-heterocycles indicates that a free electron pair is slightly smaller than an hydrogen atom and of the same order of magnitude. Van der Waals and quanto-mechanical calculations[9] support these conclusions.

In solvents of high polarity and capable of hydrogen bonding with the spare pair, the situation is modified and the effective size of a "solvated" lone-pair (piperidine in methanol) is larger than that of an hydrogen atom.[10]

In protic solvents, steric interactions between neighbouring bulky substituents

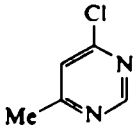
[1] Part XXIII: G. Illuminati and G. Marino, *Ricerca Sci.* 35, (II-A), 449 (1965).
[2] G. Illuminati, *Advances in Heterocyclic Chemistry* Vol. 3; pp. 319–321. Academic Press, New York (1964).
[3] M. Aroney and R. J. W. Le Fevre, *Proc. Chem. Soc.* 82 (1958); *J. Chem. Soc.* 3002 (1958).
[4] E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* p. 245. Interscience, New York (1965).
[5] N. L. Allinger, J. G. D. Carpenter and F. M. Karkowski, *Tetrahedron Letters* 3345 (1964); *J. Amer. Chem. Soc.* 87, 1232 (1965).
[6] R. J. Bishop, L. E. Sutton, D. Dinean, R. A. Y. Jones and A. R. Katritzky, *Proc. Chem. Soc.* 257 (1964).
[7] T. M. Moynehan, K. Schofield, R. A. Y. Jones and A. R. Katritzky, *J. Chem. Soc.* 2637 (1962).
[8] N. W. S. Pumphrey and M. J. Y. Robinson, *Chem. & Ind.* 1903 (1963).
[9] N. L. Allinger and J. C. Tai, *J. Amer. Chem. Soc.* 87, 1227 (1965),
[10] K. Brown, A. R. Katritzky and A. J. Waring, *Proc. Chem. Soc.* 257 (1964).

and the solvation sphere of the *aza* group could be therefore expected. These interactions should be even larger in the transition states of nucleophilic substitutions due to the increased negative charge of the nitrogen atom.

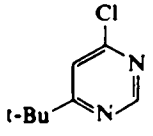
The hypothetic influence of such steric interactions upon the rate of heteroaromatic nucleophilic substitutions has been considered by Shepherd and Fedrick[11] and a first experimental evidence reported concerns the velocity of methoxydechlorination of 2-chloroquinolines[12] having a substituent at position 8 (i.e. *peri* to the *aza* group).

If the substituent is *ortho* instead of *peri* to the *aza* group, the steric interactions are expected to be smaller,[13] although they could be still appreciable if sufficiently bulky substituents are involved.

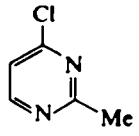
In order to verify this point, the rates of piperidinodechlorination of 4-chloropyrimidines I-IV in toluene and ethanol have been compared.



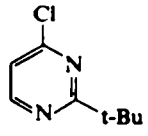
I



II



III



IV

A direct comparison between the methyl and t-butyl groups is particularly valuable, since these substituents have similar electronic effects and very different steric requirements.[14]

Whereas in 6-substituted-4-chloropyrimidines (I and II) only one *aza* group is shielded from solvation by the alkyl substituent, in the 2-substituted isomers both *aza* groups are shielded. Therefore, the possible deactivating effects will be larger in the latter system.

RESULTS AND DISCUSSION

The reactions of pyrimidines (I–IV) with piperidine have been followed by titrating the liberated chloride ions. Linear 2nd order kinetic plots were obtained throughout the reaction range examined (up to 70%).

The lack of autocatalysis for reaction in both ethanol and toluene must be due to the very weak basicity of these substrates compared with that of the nucleophile. Although the pK_a's of the examined chloroalkylpyrimidines are not known, it is possible to deduce, on the basis of the relative effect of chloro and alkyl groups upon the basicity,[15] that they are considerably smaller than the pK_a of unsubstituted pyrimidine (1·30).[16]

The kinetic data are summarized in Table 1. The rate constants for the reactions of pyrimidines (I, II and III) in methanol previously determined by Chapman *et al.*[17,18]

[11] R. G. Shepherd and J. L. Fedrick, Ref, 2, Vol. 4; p. 186.
[12] G. Illuminati, P. Linda and G. Marino, *Rend. Acc. Naz. Lincei* VIII **38**, 389 (1965).
[13] G. Illuminati and F. Tarli, *Ricerca Sci.* **28**, 1464 (1958).
[14] K. Le Nelson and H. C. Brown, *J. Amer. Chem. Soc.* **73**, 5605 (1951).
[15] H. C. Brown and D. H. McDaniell, *J. Amer. Chem. Soc.* **77**, 3756 (1956).
[16] A. Albert, R. Goldacre and J. Philips, *J. Chem. Soc.* 2240 (1948).
[17] S. Capon and N. B. Chapman, *J. Chem. Soc.* 600 (1957).
[18] N. B. Chapman and C. W. Rees, *J. Chem. Soc.* 1190 (1954).

are also reported. The measurement for 2-methyl-4-chloropyrimidine was checked and the result reported by Chapman confirmed.

Table 1 shows that, in both solvents, the methyl derivatives are more reactive than the corresponding t-butyl which is in keeping with the inductive effect of the teo groups.[19] It may be interesting to observe, in this connection, that, if direct conjugative interactions between the activating *aza* group and the electron-releasing substituent were important, then the reverse order of reactivity, t-Bu — Me would be observed. The above results, therefore, confirm the view that such conjugative interactions are, in the case of the alkyl groups, negligible.[20]

The minimum value for the reactivity ratio $k_{Me}/k_{t\text{-}Bu}$, (observed for the reaction of 4-chloro-6-alkyl-pyrimidines in toluene) is probably due to the difference in inductive effect between the two alkyl groups. This value (1·62) is not very different from that (1·33) observed in the piperidinodechlorination of 1-chloro-2-nitro-5-alkylbenzenes[17] in which secondary steric effects are not present. An approximate calculation based on the Hammett equation ($\sigma_{m\text{-}t\text{-}Bu} - \sigma_{m\text{-}Me} = 0{\cdot}03$)[21] assuming the reaction constant rho in the range 3–5·5 (as for the most of nucleophilic aromatic substitutions), gives for the above ratio a value between 1·3 and 1·5.

The reactivity ratio $k_{Me}/k_{t\text{-}Bu}$ increases in passing either from the less to the more polar solvent or from the 6-alkyl to the 2-alkyl substituted isomers (in which the alkyl group is flanked by two *aza* groups) and reaches the maximum value (17·3) for the piperidinodechlorination of 4-chloro-2-alkylpyrimidines in ethanol.

The remarkable increase in this reactivity ratio (over a factor of ten) can be explained by taking into account the steric hindrance to solvation of the nitrogen atom caused by the *ortho* substituent.

The effect is particularly large for the reactions in ethanol; in this solvent, a reversible formation of strong hydrogen bonds between the *aza* group and the solvent takes place and provokes an increase of the reactivity towards the nucleophiles through a lowering of the electron density at the reaction center. The presence of the bulky t-butyl group in *ortho* position will decrease strongly the reactivity of the substrate by hindering the formation of such activating hydrogen bonds and consequently the value of the ratio $k_{Me}/k_{t\text{-}Bu}$ will become greater.

This work shows that, also in *aza*-activated systems, the reactivity can be affected by the intervention of secondary steric effects caused by substituents *ortho* to the activating group, However, unlike the nitro-activated systems, these effects become important only in the case of very bulky groups and for reactions carried out in polar solvents. In most other cases the interactions are small and the substituents *meta* and *para* to the reaction center concur to establish the reactivity mainly through their electronic effects.

The kinetic data reported in Table 1 enable another interesting comparison between the effects of the substituents in positions 2 and 6. These positions are both *meta* to the substitution center but differ in the following point: whereas from position 6 inductive effects are transmitted by a polarization of carbon–carbon bonds alone, from position 2 they are necessarily transmitted also through a polarization of

[19] See for instance A. R. Remick, *Electronic Interpretations of Organic Chemistry* 2nd Edition) p. 67. Wiley, New York (1949).

[20] M. L. Belli, G. Illuminati and G. Marino, *Tetrahedron* **19**, 345 (1963).

[21] D. H. McDaniell and H. C. Brown. *J. Org. Chem.* **23**, 420 (1958).

carbon–nitrogen bonds. As regards the methyl derivatives (for which the steric effects are negligible) the 2-substituted isomer is more reactive in both solvents by a factor of about 1½. This indicates a weaker transmission of the deactivation through the *aza* group. In the case of the t-butyl derivatives, the steric effects tend to reverse the reactivity order determined by the electronic effects: in toluene the two isomers react at about the same rate and in ethanol the 6-t-butyl isomer is five times more reactive.

TABLE 1. KINETIC DATA OF PIPERIDINODECHLORINATION OF 4-CHLORO-2-ALKYL- AND 4-CHLORO-6-ALKYLPYRIMIDINES IN TOLUENE AND ETHANOL

	In Toluene		In Ethanol	
Pyrimidine	$k_2 \times 10^4$, [a] at 30°	$\frac{k_{Me}}{k_{t\text{-}Bu}}$	$k_2 \times 10^4$, [a] at 30°	$\frac{k_{Me}}{k_{t\text{-}Bu}}$
4-Cl-6-Me	0·42		21·4[b]	
		1·62		2·57
4-Cl-6-t-Bu	0·26		8·33[c]	
4-Cl-2-Me	0·66		30·0[b]	
		2·36		17·34
4-Cl-2-t-Bu	0·28		1·73	

[a] l × moles^{-1} × sec^{-1}
[b] Ref. 18
[c] Ref. 17

EXPERIMENTAL

Materials. Toluene (C. Erba), dried over $CaSO_4$ and Na, was fractionated in a Todd column using a reflux ratio of about 10. The middle fraction boiling at 110° was used for the kinetic measurements.

Abs EtOH was purified by refluxing with Mg and I[23] and subsequently fractionated at atm. press.

The following pyrimidine derivatives were prepared according to previously described procedures and purified by fractionation at red. press. (original Refs and m.ps are given): 2-methyl-4-chloro,[25] 55–56°; 4-chloro-6-methyl,[18] 34–35° and 4-chloro-6-t-butyl,[17] 38–39°. The synthesis of 2-t-butyl-4-chloropyrimidine, not described in the literature, is reported in the following paragraph.

2-t-Butyl-4-chloropyrimidine. Pivalamidine hydrochloride (5 g, 0·036 moles) was added to a soln of 5 g (0·036 moles) sodium formylacetate[24] in 25 ml water; the resulting soln was allowed to stand at room temp for 2 days, then evaporated. The residue (7 g), crude 4-hydroxy-2-t-butylpyrimidine, after two crystallizations from water melted at 147–148°. (Found: C, 63·4; H, 8·3; N, 18·4; $C_8H_{12}N_2O$ requires: C, 63·1; H, 8·0; N, 18·4%.)

The crude hydroxypyrimidine (7 g) was heated at 130° for 1 hr with 20 ml $POCl_3$. The crude 4-chloro-2-t-butylpyrimidine was purified by steam distillation and subsequent distillation at red press, b.p. 80–81° (15 mm) g 1·6; yield from pivalamidine, 26%. (Found: C, 56·8; H, 6·6; Cl, 20·3; $C_8H_{11}N_2Cl$ requires: C, 56·3; H, 6·5; Cl, 20·8%.)

Kinetic measurements. The kinetics were followed by determining the increase of the chloride ion concentration.[26] Since in some cases, a continuation of the displacement reaction was taking place in the acidic quenching soln, we preferred to accomplish the quenching in water.

After extraction of the unreacted chloropyrimidine with two portions benzene, the aqueous layer was acidified with HNO_3 and analysed for the chloride ions by the Volhard method.

Acknowledgements—The authors are grateful to Prof. Illuminati for encouragement and discussion and to the National Research Council (C.N.R.) for a financial support which made this research possible

[23] A. I. Vogel, *Practical Organic Chemistry* (3rd Edition) p. 167. Longmans, London (1959).
[24] S. Gabriel, *Ber. Dtsch. Chem. Ges* 37, 3638 (1904).
[25] Houben-Weyl, *Methoden der organischen Chemie* Vol. 7/1; p. 48. G.T. Verlag, Stuttgart (1954)
[26] D. J. Brown and R. F. Evans, *J. Chem. Soc.* 4039 (1962).
[26] G. Illuminati and G. Marino, *J. Amer. Chem. Soc.* **80**, 1421 (1958).