

QUATERNISATION OF HINDERED AMINES : CORRELATION
BETWEEN GEOMETRY AND STERIC PARAMETERS.

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The recent report by Swain of the effect of steric hindrance on the structure of transition states(1) has prompted us to publish results obtained in this field(2).

The mechanism of the Menshutkin reaction is SN₂, and it has already been studied with respect to solvent effects(3), and the structure of amines and electrophiles(4). Heterocyclic azaaromatic amines are interesting models from the point of view of steric effects: they are planar molecules in which substituents and the lone pair of electrons of the nitrogen lie in the plane of the ring.

The transition state of a quaternisation reaction has a geometry between that of the amine and that of the quaternary salt formed. Geometries of amines and quaternary salts have been determined using microwave(5-7) and X-Ray analysis(8).


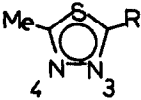

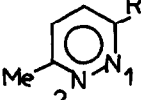
It is possible to separate steric and electronic effects in quaternisation reactions: an alkyl substituent ortho to the nitrogen has little effect on the basicity (referred to the methyl isomer)(9) although pK_a measurements when compared to calorimetric data show a second order variation of basicity due to steric hindrance to solvation(2). For such alkylated amines the reaction rates for quaternisation depend on the size of the substituents so that the ratio $\log k/k_0$ (k_0 refers to the methyl isomer) provides a measure of the steric effect of the alkyl group.

According to an Hammett-type approach(15), comparison of results with several heterocycles by an equation $\log k/k_0 = \delta \log(k/k_0)'$ should show the parameter δ to depend upon the structure of the transition state which itself depends on the geometry

of the heterocycle, nature of quaternizing agent, solvent and temperature. Thus keeping the last three variables constant should provide a relation between δ and the geometry of the heterocycle.

TABLE I

Data for quaternisation reactions of heterocycles with methyl iodide

								
	solvent nitrobenzene(b)		solvent acetonitrile(b)		solvent nitrobenzene(10)		solvent acetonitrile	
R =	$k \cdot 10^6$ l.mole ⁻¹ .sec ⁻¹	logk/k _o	% quat at N-4	logk/k _o	$k \cdot 10^6$ l.mole ⁻¹ .sec ⁻¹	logk/k _o	% quat at N-2	logk/k _o
Me	11.8	0.	50	0.	162	0.	50	0.
Et	9.2	-0.11	57	-0.12	76.4	-0.32	65	-0.27
i-Pr	4.3	-0.43	74.5	-0.45	24.5	-0.82	81.5	-0.64
t-Bu	0.29	-1.61	97.5	-1.60	0.08	-3.30	>99.5 (a)	>-2.30 (a)
n-Pr	9.1	-0.11	58	-0.14				
i-Bu	8.5	-0.14	61	-0.19				
neopent	6.0	-0.29	67	-0.30				

(a)calculated from the results of 3-methyl-6-isopropyl- and 3-isopropyl-6-tertiobutyl-pyridazines

(b)log k/k_o was shown to be the same for these two polar aprotic solvents

Results of correlations with the equation $\log(k/k_o)_y = \delta \log(k/k_o)_x$

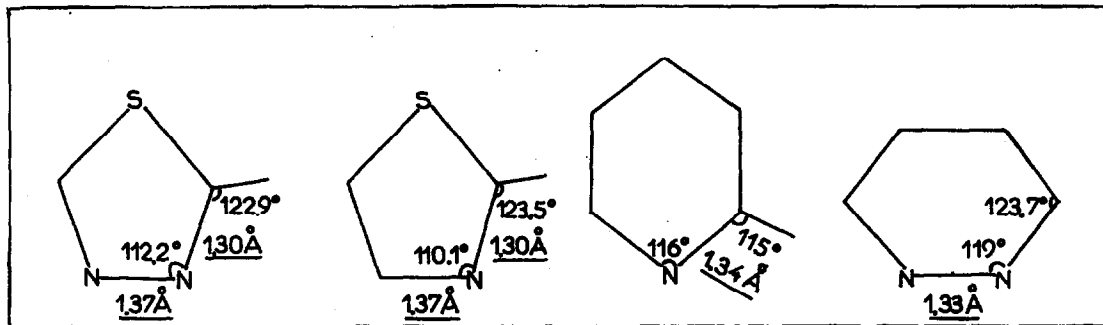
y =	x =	δ	R = correlation coefficient	T = Student's test
2-alkyl-pyridines	2-alkyl-thiazoles	2.03	0.9988	29.5
5-methyl-2-alkyl-thiadiazoles	2-alkyl-thiazoles	0.98	0.9995	75.9
3-methyl-6-alkyl-pyridazines	2-alkyl-thiazoles	1.39	0.9989	30.4

Data reported have been obtained from direct kinetic measurements with thiazole (2) and pyridine (10) by conductimetry and titration. For the thiadiazole and the pyridazine rings the ratio of the isomeric quaternary salts was determined directly by N.M.R., the reaction having run to completion (11).

Because of the symmetry of the thiadiazole ring, both nitrogens have the same basicity but they suffer different steric strains depending upon the nature of the substituents in the 2- and 5-positions. For the 5-methyl-2-alkylthiadiazole series the ratio of 3- and 4-isomers leads directly to the quaternization rate ratios i.e. $k_3/k_4 = k/k_0$. For the same reason, with the 3-methyl-6-alkyl-pyridazine series the ratio of 1- and 2-isomers leads to $k_1/k_2 = k/k_0$.

As the carbon-nitrogen bond length between the reactants in the transition state is unknown, geometries are reported with particular emphasis upon bond lengths and bond angles around the nitrogen atoms in the reactants. The relation between the geometry and δ parameter is striking and quite in line with early results obtained from electrophilic substitution reactions which compared primary steric effects in benzene and thiophene ring (12). The δ parameter for the five membered rings are equal but different from those of the six membered ones. Correlation coefficients for the two cases are excellent: $R = 0.999$ and they allow us to develop the theory of quaternization reactions.

GEOMETRIES OF HETEROCYCLES



1, 3, 4-thiadiazole (5)

thiazole (6)

pyridine (7)

pyridazine (16)

By keeping constant the geometrical parameters which determine the sensitivity towards steric effects and by varying the energy of reactants by means of factors which are not directly involved in such potential repulsions (e.g. nature of leaving group, basicity of amine or solvent) one should induce geometrical changes in the transition state in accord with the Hammond postulate (13) or with more recent qualitative considerations (14). This effect in turn should alter the δ parameter.

In conclusion, this model reaction is an interesting example of the experimental measurement of geometrical variations in transition states.

REFERENCES

1. a. C.G. SWAIN and N.D. HERSHEY, *J Amer Chem Soc*, 94 1901 (1972).
 b. T.M. BARE, N.D. HERSHEY, H.O. HOUSE and C.G. SWAIN, *J Org Chem*, 37 997 (1972).
2. R. GALLO, Thesis, Universite de Provence, 1971.
3. a. P. HABERFIELD, A. NUDELMAN, A. BLOOM, R. ROMM and H. GINSBERG, *J. Org. Chem*, 36 1792 (1971).
 b. T. MATSUI and N. TOKURA, *J Chem Soc Japan*, 1751 (1970).
 c. M. ABRAHAM, *Chem Comm*, 1307 (1969).
 d. C. LASSAU and J.C. JUNGERS, *Bull Soc chim France*, 2678 (1968).
 e. K. KALLIORINE and E. TOMMILA, *Suomen Kemistilehti*, 209 (1967).
 f. H. VOROBIEV and G. TITOV, *Khim i Khim Teknol*, 218 (1966).
4. a. H.C. BROWN, *J Chem Ed*, 36 424 (1959).
 b. K. CLARKE and K. ROTHWELL, *J Chem Soc*, 1885 (1960).
 c. K. OKAMOTO, S. FUKUI and H. SHINGU, *J Chem Soc Japan*, 1920 (1967).
 d. A. JONES, A.R. KATRITZKY and P.G. MENTE, *J Chem Soc (B)*, 1210 (1970).
 e. J. LENOBLE and Y. OGO, *Tetrahedron*, 4119 (1970).
 f. K. UNDHEIM and T. GRÖNNEBERG, *Acta Chem Scand*, 18 (1971).
5. L. NYGAARD, E. ASMUSSEN and J. HØG, *J Mol Structure*, 225 (1971).
6. B. BAK, L. NYGAARD, E.J. PEDERSEN and J. RASTRUP-ANDERSEN, *J Mol Spect*, 19 283 (1966).
7. A. ALMENNINGEN, O. BASTANSEN and L. HANSEN, *Acta Chem Scand*, 9, 1306 (1955).
8. G. PEPE, M. PIERROT and M. CHANON, *Tetrahedron letters*, 590 (1972).
 G. PEPE and M. PIERROT, *Acta Crystallographica* to be published June 1972.
9. H.C. BROWN and X. MIHM, *J Amer Chem Soc*, 77 1723 (1955).
 R. PHAN TAN LUU, J.M. SURZUR, J. METZGER, J.P. AUNE and C. DUPUY, *Bull Soc Chim France* 3274 (1967).
10. H.C. BROWN and A. CAHN, *J Amer Chem Soc*, 77 1715 (1955).
11. H. LUND and P. LUNDE, *Acta Chem Scand*, 1067 (1967).
12. S. CLEMENTI, P. LINDA and M. VERGONI, *Tetrahedron Letters*, 611 (1971).
13. G.S. HAMMOND, *J Amer Chem Soc*, 77 334 (1955).
14. J. HARRIS and J. KURZ, *J Amer Chem Soc*, 92 349 (1970).
 E.R. THORNTON, *J Amer Chem Soc*, 89 2915 (1967).
15. R.W. TAFT Jr, *Steric effects in organic chemistry*, M.S. NEWMAN, J. WILEY, Ed. New York, 1956.
16. K.K. INNES and R.M. LUCAS, *J Mol Spect*, 24 247 (1967).