Intramolecular Reactions. Part X.[1] Transition States in the Cyclisation of *N*-ω-Halogeno-alkylamines and -sulphonamides ‡

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Rates of cyclisation of a series of *N*-ω-halogenoalkylamines in dioxan–water and ethanol–water and of sulphonamides in alcohol–alkoxide media have been determined. Particular attention has been paid to the effect on rate of the ring-size formed, the leaving group, and the placement of aryl groups on nitrogen and on carbon adjacent to nitrogen. Five-membered rings are formed faster than three-, four-, or six-membered rings in each series. For amines (25°) the order is 6 > 3 > 4. For sulphonamides (55°) the order is 3 > 6 > 4. In three-membered ring formation, bromide : chloride ratios are 28 for the amines studied and 79 for the sulphonamides. Placement of a phenyl group on nitrogen or on carbon adjacent to nitrogen in the amines studied has very little effect on the rate or on the activation parameters. The results are discussed in terms of conjugative control of cyclisation reactions and it is concluded that there is little C–N bond formation in the transition state for these cyclisations.

In earlier papers,[2-4] formation of carbocyclic rings from ω-halogenoalkyl sulphones and malonates has been reported. Cyclopropyl derivatives were formed, in reactions of unambiguous mechanism, very much more rapidly than cyclopentyl, cyclobutyl, or cyclohexyl systems. Data on comparative cyclisation rates are extremely sparse [5] but the general view is that formation of three-membered rings is usually unfavourable because of the high enthalpy of formation.[6] Our own results, together with related information from other laboratories [7] led us to postulate [3] that attachment of an

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electron-accepting, conjugative group to the framework of an incipient three-membered ring reduces the unfavourable enthalpy term. This occurs because of a resonant interaction between the group and the σ bonds of the three-membered ring which have a high degree of *p* character.[8] Such a postulate has corollaries. Acceleration of ring closure by conjugative groups should be selectively observed for three-membered rings and the transition state for cyclisation must involve a considerable extent of bond formation, otherwise the effect of *p* orbital character in the ring bonds cannot come into play. Further, insertion of a conjugative group into a system otherwise lacking such a group, should selectively accelerate formation of three *versus* other ring sizes given that the transition state for the process is subject to the second condition above.

With these considerations in mind we have investigated cyclisation of a series of ω-halogenoalkylamines and ω-halogenoalkylsulphonamides. Formation of azacycloalkanes by cyclisation of simple primary ω-bromoalkylamines was the subject of Freundlich's [9,10] pioneering investigation of structure–reactivity relationships in intramolecular nucleophilic displacement. The striking differences found between rates of formation of the cyclic amines of various ring sizes has been widely interpreted [11] on the basis of the balance between entropy terms (favouring small rings) and enthalpy terms (favouring five- and six-membered rings especially). Activation parameters, however, have been determined for very few systems so as to allow assessment of these factors on the basis of the size of the ring being formed.

TABLE 1

Cyclisation of ω-halogenoalkylamines

	Substrate	*t*/°C	k_{rel} at 25°	10^4k/s^{-1}	pK_a	$\Delta G_{25°}^{\ddagger}$/kcal mol^{-1}	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
	Medium: 50% dioxan–water							
(1)	$NH_2[CH_2]_2Cl$	39·0		0·85 ± 0·02				
(1)	$NH_2[CH_2]_2Cl$	50·0	5·3	2·43 ± 0·03		23·9 ± 0·7	19·3 ± 0·4	−15
(1)	$NH_2[CH_2]_2Cl$	59·9		5·80 ± 0·07				
(2)	$NH_2[CH_2]_4Cl$	14·5		20·0 ± 1·0	9·87			
(2)	$NH_2[CH_2]_4Cl$	25·0	1777	58·4 ± 2·0	9·58	20·4	16·5	−13
(2)	$NH_2[CH_2]_4Cl$	35·0		149 ± 6	9·30			
(3)	$PhNH[CH_2]_2Cl$	50·0		0·48 ± 0·01				
(3)	$PhNH[CH_2]_2Cl$	60·1	1	1·18 ± 0·01		24·8	19·8	−17
(3)	$PhNH[CH_2]_2Cl$	70·1		3·22 ± 0·06				
(4)	$PhNH[CH_2]_2Br$	40·0	28 *	7·46 ± 0·09				
(5)	$PhNH[CH_2]_4Cl$	20·0		16·5 ± 0·08	3·71			
(5)	$PhNH[CH_2]_4Cl$	30·0	833	43·7 ± 0·40	3·42	20·9	16·4	−15
(5)	$PhNH[CH_2]_4Cl$	39·9		108 ± 6	3·20			
(6)	$2,6\text{-}Me_2C_6H_3NH[CH_2]_2Cl$	50·0		0·92 ± 0·02				
(6)	$2,6\text{-}Me_2C_6H_3NH[CH_2]_2Cl$	59·9	1·7	2·44 ± 0·09		24·5	20·7	−13
(6)	$2,6\text{-}Me_2C_6H_3NH[CH_2]_2Cl$	69·9		6·39 ± 0·09				
(7)	$NH_2CHPhCH_2Cl$	40·1		1·15 ± 0·01				
(7)	$NH_2CHPhCH_2Cl$	50·1	5·5	3·48 ± 0·07		23·9	21·9	−7
(7)	$NH_2CHPhCH_2Cl$	60·1		10·2 ± 0·10				
(8)	$NH_2CHPh[CH_2]_3Cl$	9·9		10·8 ± 0·3				
(8)	$NH_2CHPh[CH_2]_3Cl$	15·0	1680	19·2 ± 0·1		20·5	17·5	−10
(8)	$NH_2CHPh[CH_2]_3Cl$	20·0		33·3 ± 0·6				
		25·0		54·4 ± 0·8	8·45			
	Medium: 60% EtOH–H_2O–K_2CO_3							
(4)	$PhNH[CH_2]_2Br$	25·6		1·37 ± 0·03 × 10^{-4}				
(4)	$PhNH[CH_2]_2Br$	40·0	1	7·15 ± 0·31 × 10^{-4}		22·7 ± 1·1	19·4 ± 0·7	−11 ± 1·2
(4)	$PhNH[CH_2]_2Br$	55·0		2·91 ± 0·18 × 10^{-3}				
(9)	$PhNH[CH_2]_3Br$	25·3		2·68 ± 0·05 × 10^{-6}				
(9)	$PhNH[CH_2]_3Br$	55·0	0·019	8·29 ± 0·06 × 10^{-5}		25·2 ± 0·7	21·7 ± 0·4	−11 ± 1·0
(9)	$PhNH[CH_2]_3Br$	74·0		5·08 × 10^{-4} †				
(10)	$PhNH[CH_2]_5Br$	25·0		1·33 ± 0·01 × 10^{-3}				
(10)	$PhNH[CH_2]_5Br$	10·4	9·55	3·07 ± 0·06 × 10^{-4}		21·3 ± 1·2	16·2 ± 0·8	−17 ± 1·3
(10)	$PhNH[CH_2]_5Br$	0·2		9·85 × 10^{-5} †				

* At 40° with value for $PhNH[CH_2]_2Cl$ at 40° from activation plot. † Single result.

The mechanisms of the cyclisation processes are clearly shown for reactions carried out at high pH. Under these conditions, reactions are first order in substrate and zero order in base for both amines and sulphonamides [12] indicating for amines, no associated protonation equilibrium of any significance, and for the sulphonamides, reaction by way of the anion. For the most reactive amines, reactions were run for convenience at lower pH values when protonation equilibria have to be taken into account. Analysis of the data (Experimental section) gives the rate *via* free amine for comparison with other data, together with the pK_a of the amine in the appropriate solvent system.

The substrates, examined in two different solvent

[8] R. Hoffmann, *Tetrahedron Letters*, 1965, 3819 and refs. cited.
[9] H. Freundlich and G. Salomon, *Z. Phys. Chem.*, 1933, **A166**, 161 and previous papers; 1936, **19**, 743.
[10] G. Salomon, *Helv. Chem. Acta*, 1933, **16**, 1361; 1934, **17**, 851.
[11] E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 198.
[12] F. L. Scott and E. Flynn, *Tetrahedron Letters*, 1964, 1675.

systems, were chosen (i) to evaluate the effect on cyclisation rate of the ring being formed; (ii) the effect of placing conjugative groups, phenyl, and toluene-*p*-sulphonyl, on nitrogen and on the carbon atom adjacent to nitrogen; and (iii) the effect of change of the leaving group from chloride to bromide.

TABLE 2

Cyclisation of *N*-ω-halogenoalkyltoluene-*p*-sulphonamides

Substrate	*t*/°C	k_{rel}	k/s^{-1}
Medium: ethanolic sodium ethoxide			
(11) *p*-TolylSO$_2$NH[CH$_2$]$_2$Cl	25	1	$4{\cdot}8 \pm 0{\cdot}5 \times 10^{-4}$
(12) *p*-TolylSO$_2$NH[CH$_2$]$_3$Cl	55	2	$10{\cdot}9 \pm 0{\cdot}7 \times 10^{-6}$
(13) *p*-TolylSO$_2$NH[CH$_2$]$_5$Cl	25	0·06	$3{\cdot}0 \pm 0{\cdot}08 \times 10^{-5}$
(13) *p*-TolylSO$_2$NH[CH$_2$]$_5$Cl	55	79	$8{\cdot}6 \pm 0{\cdot}3 \times 10^{-4}$
Medium: Bu^{t}OK–Bu^{t}OH			
(11) *p*-TolylSO$_2$NH[CH$_2$]$_2$Cl	29·9	1	$5{\cdot}08 \pm 0{\cdot}32 \times 10^{-4}$
(14) *p*-TolylSO$_2$NH[CH$_2$]$_2$Br	29·9	79	$3{\cdot}96 \pm 0{\cdot}08 \times 10^{-2}$

TABLE 3

Products from intramolecular displacement reactions

Substrate	Product	Yield (%)
(1)	Aziridine	86 [a]
(2)	Pyrrolidine	92 [b]
(3)	*N*-Phenylaziridine	96,[a] 50 [c]
(4)	*N*-Phenylaziridine	91 [a]
(5)	*N*-Phenylpyrrolidine	92 [d]
(6)	*N*-2,6-Xylylaziridine	86 [e]
(7)	2-Phenylaziridine	91 [f]
(8)	2-Phenylpyrrolidine	95 [g]
(9)	*N*-Phenylaziridine	91 [a]
(9)	*N*-Phenylazetidine	98 [h]
(10)	*N*-Phenylpiperidine	100 [j]
(11)	*N*-*p*-Tolylsulphonylaziridine	94,[k] 94 [l,m]
(12)	*N*-*p*-Tolylsulphonylazetidine	86 [n]
(13)	*N*-*p*-Tolylsulphonylpiperidine	100 [p]
(14)	*N*-*p*-Tolylsulphonylaziridine	92 [l,m]

[a] G.l.c.; anisole as internal standard calibrated against authentic specimen. [b] As benzoyl derivative, m.p. and mixed m.p. 47°. [c] B.p. 80° at 13 mmHg, n_D^{29} 1·5485. A. H. Filbey and L. R. Buzbee, B.P. 772,988 (*Chem. Abs.*, 1957, **51**, 15,568) give b.p. 73° at 18 mmHg, n_D^{20} 1·5515. [d] B.p. 126° at 9 mmHg, n_D^{20} 1·5824 (lit.,[31] b.p. 100° at 6 mmHg, n_D^{25} 1·5796). [e] B.p. 112° at 13 mmHg, n_D^{23} 1·5488 (Found: C, 81·9; H, 9·0. $C_{10}H_{13}N$ requires C, 81·6; H, 8·9%). [f] B.p. 94° at 10 mmHg, n_D^{25} 1·5562. S. J. Brois, *J. Org. Chem.*, 1962, **27**. 3532, gives b.p. 94° at 15 mmHg, n_D^{20} 1·5588. [g] n_D^{25} 1·5390, J. H. Burckhalter and J. H. Short, *J. Org. Chem.*, 1958, **23**, 1281, give picrate, m.p. 149°. [h] B.p. 104° at 11 mmHg, n_D^{25} 1·5706 (Found: C, 81·1; H, 8·1. Calc. for $C_9H_{11}N$: C, 81·2; H, 8·3%) (lit.,[17] n_D^{24} 1·5695). [j] B.p. 122° at 10 mmHg, n_D^{22} 1·5608 (lit.,[18] b.p. 93° at 3 mmHg, n_D^{22} 1·5593. [k] t-Butyl alcohol medium; m.p. 64° (lit.,[12] m.p. 63—64°). [l] t-Butyl alcohol medium. [m] M.p. and mixed m.p. 64°. R. P. Mariella and R. R. Raube, *J. Amer. Chem. Soc.*, 1952, **74**, 521, give m.p. 63—64°. [n] M.p. and mixed m.p. 119—120°. R. P. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, 1960, **26**, 138, give m.p. 119—120°. [p] M.p. and mixed m.p. 99°.

Activation parameters have been obtained for most systems studied and in all cases the products have been quantitatively determined. Rate data are in Tables 1 and 2 and details of products are in Table 3.

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[15] R. S. Tipson, *J. Org. Chem.*, 1962, **27**, 1449.
[16] W. M. Pearlman, *J. Amer. Chem. Soc.*, 1948, **70**, 871.
[17] L. W. Deady, G. J. Leary, R. D. Topsom, and J. Vaughan, *J. Org. Chem.*, 1963, **28**, 511.

EXPERIMENTAL

General.—Extractions were with dichloromethane and extracts were dried over Na_2SO_4.

Preparation of Substrates.—Amines. 2-Chloroethylamine hydrochloride had m.p. 142—144° (from ethanol–ether) (lit.,[13] m.p. 144°). 4-Aminobutanol was treated with hydrogen chloride in ether and the resulting hydrochloride, on being refluxed with an excess of thionyl chloride for 30 min, gave 1-amino-4-chlorobutane hydrochloride (64%), m.p. 166—168° (from acetone–ethyl acetate) (lit.,[14] m.p. 161—163°). *N*-2-Chloroethylaniline hydrochloride (48%) was obtained from *N*-2-hydroxethylaniline hydrochloride and phosphorus oxychloride in chloroform, m.p. 156—157° (from ethanol) (lit.,[15] m.p. 159—160°). Treatment of *N*-2-hydroxyethylaniline with 48% aqueous hydrobromic acid at 0° gave 2-bromoethylaniline hydrobromide (70%), m.p. 137° (from methanol–ether) (lit.,[16] m.p. 137—138°).

Similar treatment of *N*-3-hydroxypropylaniline hydrobromide gave *N*-3-bromopropylaniline hydrobromide (75%), m.p. 131° (from ethanol) (lit.,[17] m.p. 131—132°), and of *N*-5-hydroxypentylaniline gave [18] N-5-*bromopentylaniline hydrobromide* (39%), m.p. 59° (from ethanol–ether) (Found: C, 41·4; H, 5·3; ionic Br, 24·3. $C_{11}H_{17}Br_2N$ requires C, 40·9; H, 5·3; ionic Br, 24·7%). Repeated attempts to convert *N*-4-hydroxybutylaniline to the bromide by similar procedures failed.

N-4-*Chlorobutylaniline hydrochloride.* Aniline and 4-chlorobutanol (0·5 mol) were kept at 100° for 48 h. The mixture was made alkaline and extraction gave *N*-4-hydroxybutylaniline, b.p. 138° at 1 mmHg, n_D^{25} 1·5626 (lit.,[19] b.p. 138° at 1 mmHg, n_D^{25} 1·5596). The alcohol (0·02 mol) was treated with hydrogen chloride in ether and the crude hydrochloride was treated portionwise with an excess of phosphorus oxychloride in chloroform at 25°. The *amine salt* (62%), obtained by evaporation and recrystallisation of the residue from ethyl acetate–ether, had m.p. 134—136° (Found: C, 54·6; H, 6·9. $C_{10}H_{15}Cl_2N$ requires C, 54·6; H, 6·9%).

N-2-*Chloroethyl*-2,6-*xylidine.* 2,6-Xylidine (1·2 mol) and 2-chloroethanol (0·36 mol) were kept at 100° for 48 h. Extraction as above gives N-2-*hydroxyethyl*-2,6-*xylidine* (73%), b.p. 149° at 9 mmHg, n_D^{16} 1·5516 (Found: C, 72·7; H, 9·1. $C_{10}H_{15}NO$ requires C, 72·7; H, 9·1%). The alcohol was converted as above into the *amine salt* (68%), m.p. 199—204° (from ethanol) (Found: C, 54·5; H, 6·7. $C_{10}H_{15}Cl_2N$ requires C, 54·6; H, 6·9%).

2-*Chloro*-1-*phenylethylamine.* Ethyl α-aminophenylacetate was obtained by the Fischer–Spier procedure from the acid. Reduction with lithium aluminium hydride in ether gave 2-amino-2-phenylethanol (70%), b.p. 106° at 0·05 mmHg, m.p. 47—49° (lit.,[20] b.p. 125° at 3 mmHg). The hydrochloride, m.p. 137—138° (lit.,[21] 137—138°), was prepared as before and the phosphorus oxychloride procedure gave the amine hydrochloride (54%), m.p. 176—177° (from propan-1-ol–ether) (lit.,[21] m.p. 190°).

4-*Chloro*-1-*phenylbutylamine.* Methyl 3-benzoylpropionate [22] was converted to the ethylene acetal by treatment with ethylene glycol and toluene-*p*-sulphonic acid in benzene under reflux. The acetal ester was reduced with

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[20] M. T. Leffler and R. Adams, *J. Amer. Chem. Soc.*, 1937, **59**, 2252.
[21] S. Gabriel and J. Colman, *Ber.*, 1914, **41**, 1866.
[22] W. G. Dauben and H. Tilles, *J. Org. Chem.*, 1950, **15**, 785.

lithium aluminium hydride in ether and the crude hydroxy-acetal was hydrolysed by treatment with toluene-*p*-sulphonic acid in methanol–water to yield 3-benzoylpropan-1-ol (74%), b.p. 121° at 3 mmHg, n_D^{25} 1·5530 (lit.,[23] m.p. 32—33°). The alcohol (0·1 mol), ammonium chloride (10 g), and ammonia solution (*d* 0·88; 20 ml) were shaken under hydrogen with Adams platinum catalyst (0·24 g). After an induction period of 24 h, absorption of hydrogen (2035 ml) continued over 3 days. The catalyst was filtered off and the acidified filtrate was extracted with ether. Basification and extraction of the aqueous layer gave 1-*amino*-1-*phenylbutan*-4-*ol* (80%), b.p. 126° at 0·1 mmHg, m.p. 66·5—68° (from di-isopropyl ether) (Found: C, 72·3; H, 8·9. $C_{10}H_{15}NO$ requires C, 72·7; H, 9·1%). Treatment of the amino-alcohol successively with hydrogen chloride and thionyl chloride gave 4-chlorobutylamine hydrochloride (64%), m.p. 201—205° (sealed tube) (lit.,[24] m.p. 200—205°) (Found: C, 54·8; H, 7·3. Calc. for $C_{10}H_{15}Cl_2N$: C, 54·6; H, 6·9%).

Sulphonamides.— *N*-2-Chloroethyltoluene-*p*-sulphonamide, m.p. 100° (from di-isopropyl ether), was obtained (50%) by treatment of 2-chloroethylamine hydrochloride with a suspension of toluene-*p*-sulphonyl chloride in ether in aqueous sodium carbonate at 0° (lit.,[25] m.p. 100°). The *N*-2-bromo-analogue prepared (72%) similarly had m.p. 93—94° (from di-isopropyl ether) (lit.,[26] m.p. 93°). The sodium salt of toluene-*p*-sulphonamide was treated with 3-chloropropanol (1·1 mol. equiv.) in dimethyl sulphoxide at 100°. After 12 h, the solvent was distilled off and water was added to the residue. Extraction gave the hydroxy-sulphonamide (96%), m.p. 120° (from methanol) (lit.,[27] 120—121°), which, on treatment with thionyl chloride and pyridine at <40° gave *N*-3-chloropropyltoluene-*p*-sulphonamide (86%), m.p. 53° (from di-isopropyl ether) (lit.,[28] m.p. 53°).

N-5-Chloropentyltoluene-*p*-sulphonamide had m.p. 64° (from methanol) (lit.,[29] 61—62°). Repeated attempts to convert *N*-4-chlorobutylbenzamide [30] to *N*-4-chlorobutyltoluene-*p*-sulphonamide *via* 4-chlorobutylamine hydrochloride as above failed. The sole product isolated was *N*-*p*-tolylsulphonylpyrrolidine.

Product Analyses.—Amines. Reactions with halogenoamines were carried out on a *ca.* 5 mmolar scale for direct isolation or a *ca.* 0·5 mmolar scale for g.l.c. analysis (Carbowax 1540). Details are given in Table 3 together with evidence of product authenticity in addition to comparisons where appropriate by n.m.r. and i.r. spectra and g.l.c. with authentic specimens (below).

Formation of N-phenylazetidine. *N*-3-Bromopropylaniline (2·95 g) in 60% aqueous ethanol (100 ml) was treated with aqueous 2M-potassium carbonate (12 ml) at 55°. After 12 h, saturated brine (200 ml) was added and extraction gave *N*-phenylazetidine, b.p. 104° at 11 mmHg, n_D^{25} 1·5706 (Found: C, 81·1; H, 8·1. Calc. for $C_9H_{11}N$: C, 81·2; H, 8·3%) (lit.,[17] $n_D^{23·5}$ 1·5695). The yield was raised to 98% when [bromoalkylaniline] = 0·03M and $[K_2CO_3]$ = 0·07M. This procedure is typical of the direct isolation product analyses.

Sulphonamides. Reactions were carried out in the media employed for kinetic determinations at *ca.* 5 times the kinetic concentrations. Acidification and extraction of the reaction mixture when reaction was complete yielded the *N*-*p*-tolylsulphonylazacycloalkane. Details are in Table 3.

Authentic Specimens.—*N*-Phenylpyrrolidine, b.p. 124° at 10 mmHg, $n_D^{21·5}$ 1·5813 (lit.,[31] b.p. 101° at 6 mmHg, n_D^{25} 1·4796), and *N*-phenylpiperidine, b.p. 122° at 10 mmHg, n_D^{22} 1·5608 (lit.,[32] b.p. 95° at 4 mmHg, n_D^{22} 1·5593), were prepared by successive treatment of pyrrolidine and piperidine with sodamide and bromobenzene. *N*-Allylaniline was obtained by treatment of aniline with allyl bromide and aqueous sodium carbonate at 100° for 12 h, b.p. 105° at 8 mmHg, n_D^{22} 1·5625 (lit., 106° at 15 mmHg,[33] n_D^{20} 1·564 [34]). *N*-But-3-enylaniline, b.p. 120° at 13 mmHg, $n_D^{22·5}$ 1·5510 (Found: C, 81·4; H, 9·25. Calc. for $C_{10}H_{13}N$: C, 81·6; H, 8·9%) (lit.,[35] b.p. 133 at 3 mmHg, n_D^{20} 1·5538), and N-*pent*-4-*enylaniline*, b.p. 130° at 10 mmHg, n_D^{21} 1·5448 (Found: C, 82·0; H, 9·35. $C_{11}H_{15}N$ requires C, 81·9; H, 9·4%), were obtained similarly.

Kinetics.—Amine reactions. For slower reactions ($t_{\frac{1}{2}} \geqslant 3$ min), estimation of halogenoamine reacted was by potentiometric titration of halide ion in aliquot parts of the reaction mixtures which were withdrawn at intervals and quenched in an excess of nitric acid. Addition of azacycloalkanes or *N*-alkenylanilines to the reaction mixtures did not affect the estimations.

For more rapid reactions, the pH-stat technique was used [36] with a combined glass and calomel electrode in conjunction with a Metrohm pH meter E300 and an Impulsomat E373 controlling a motor-driven burette and recorder. The glass electrode was aged in 50% aqueous dioxan for at least 24 h and the pH meter was calibrated with acetate buffers in dioxan–water of known pH values.[37] pH-Stat runs were conducted under nitrogen, and concentrated sodium hydroxide solutions were used so as to avoid undue concentration changes during reaction.

For pH-stat runs, values at different pH values were obtained from a plot of log $(v - v_t/v)$ where v is the total volume of sodium hydroxide added at $t = \infty$. As $k_{obs} = k_1K_a/([H_3O^+] + K_a)$, where k_1 is the rate constant for cyclisation of free base, and K_a the dissociation constant for protonated base, $\log k_{obs} - \log k_1 = -\log(1 + 10^{pK_a - pH})$. This equation was solved graphically for the unknowns k_1 and pK_a by curve fitting from a plot of $y = -\log(1 + 10^x)$. An example of the determination of k_1 and pK_a for *N*-4-chlorobutylaniline is in the Figure.

Sulphonamides. Reactions were followed by potentiometric titration of halide ion in aliquot parts of reaction mixtures removed at appropriate intervals and quenched in acetate buffer (pH 4·7). For the sulphonamido-bromide

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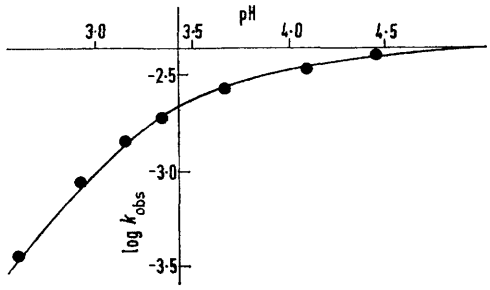
(14), this procedure was inapplicable because potassium bromide precipitated soon after the start of the reaction. Portions of stock solutions of the bromide were treated with small volumes of concentrated butoxide solution (syringe) and the entire mixtures were subsequently



Determination of solvolysis rate k_2 and pK_a for *N*-4-chlorobutylaniline

quenched. Addition of *N*-*p*-tolylsulphonylazacycloalkanes to the reaction mixtures did not interfere with the estimations of halide ion.

Results in Tables 1 and 2 are the mean of at least four and usually six runs at each temperature.

DISCUSSION

Cyclisation rates of the simple halogenoalkylamines (1) and (2) directly confirm the earlier work [9,10] in terms of the very small $k_{3\text{-ring}} : k_{5\text{-ring}}$ ratio. Activation parameters for these substrates show that it is a less favourable enthalpy of activation for three-membered ring closure that is almost entirely responsible for the low ratio. There is little compensation by the entropy term as would be expected according to the Allinger–Zalkow [38] theory of small ring formation.

The simplest direct test of the effect of a conjugative substituent was to place a phenyl group on nitrogen [substrates (3) and (5)] and compare formation of three- and five-membered rings. The $k_3 : k_5$ ratio remains small and the enthalpy of activation for cyclisation is somewhat *greater* in the *N*-phenyl pair. It is clear that the presence of a conjugative group has little role in this type of intramolecular displacement. Two further points must, however, be considered. Is there any structural feature of the transition state that would prevent interaction between the phenyl group and the three-membered ring? For *unprotonated N*-phenylaziridine it is clear that the most favourable conformation is that in which p(N)–π interaction is possible. In this conformation, the planes of the benzene ring and of the aziridine ring are quasi-coplanar, a conformation in which p(C–C) and π orbitals are orthogonal and without overlap. This would prevent an *N*-phenyl group from having any lowering effect on the enthalpy of activation for the formation of the aziridine. It seems certain, however, that at the transition state, the proton(s) on the partly positive nitrogen remain to be removed in a subsequent (rapid) step. In support of this conclusion, reactions in media sufficiently basic to ensure essentially no concentration of protonated acyclic amine, show no second order component in the kinetics of cyclisation. Removal of an *N*-proton concertedly with cyclisation may, therefore, be disregarded. We suggest that p(N)–π interaction cannot in any event be involved and that the opportunity for p(C–C)–π interaction is available but not accepted.

The hypothesis was further tested in two ways: in substrate (6), the bulky *o*-substituents *should* encourage the incipient aziridine ring to adopt an orientation quasi-orthogonal to the plane of the benzene ring, and hence promote p(C–C)–π interaction. The data of Table 1 show that a negligible degree of acceleration of ring closure is produced and the activation parameters show small but mutually compensating changes in the respective enthalpies and entropies of activation.

Examination of substrates (7) and (8) was prompted as these are free of any of the complications associated with placement of the conjugative group on the nucleophilic atom. Comparison of substrates (7) and (8) (Table 1) shows an extraordinarily close correspondence with the simple chloroamines (1) and (2). Clearly there is no special effect of the conjugative phenyl group.

Ring closures are accelerated by substituents on the chain connecting nucleophilic atom and leaving group. This (Thorpe–Ingold) effect has been accounted for in a number of different ways [38,39] but little assessment of the effect according to the size of the ring being formed has been made. There is no evidence, however, to suggest that the effect operates more strongly when a three-membered ring rather than, for example, a five-membered ring is involved and we therefore have no reservations about comparing this system with the other systems reported in this paper. It seems clear that either the transition state for these reactions is not amenable to the operation of the effect of small ring conjugation or that the hypothesis is of restricted application and value.

The structure of the transition state is crucial, of course, to the operation of conjugation with the developing three-membered ring. Diagnosis of transition state structure in displacements has rested rather little on the effect of change of leaving group because of the limited range of groups studied. Comparison of chloride : bromide ratios has, however, been applied to a number of systems [40,41] with the implicit assumption that the higher the value of the ratio, the greater the degree of leaving-group bond cleavage in the displacement. While we do not accept this generalisation,[42] it is nevertheless clear that a typical value for a simple displacement is in the range 30—100. An abnormally large degree of cleavage of the bond to the leaving group, associated with a large degree of C–C bond-making,

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would be expected to result in a significant deviation from this value.

Results for substrates (3) and (4) show bromide : chloride ratio of 28, at the lower end of the range for a simple displacement. This suggests a transition state typical of a simple intermolecular displacement and excludes the special features which would be *sine qua non* for operation of the small ring conjugative effect. Further, a low degree of charge development in the transition state is indicated by solvent dependence for the cyclisation of 5-chloropentylamine. Transfer of the substrate from water to methanol results [43] in a decrease of the rate constant by a factor of 16. For the solvolysis of t-butyl chloride, the rate constant decreases [44] by a factor of 3×10^4.

A further indication of the low degree of N–C bond formation is the comparison of the pairs of substrates (1) and (3) and (2) and (5). Attachment of a phenyl group to nitrogen reduces proton basicity by a factor of 10^6 (pK_a $NH_2CH_2CH_2Cl = 9{\cdot}57$; $PhNHCH_2CH_2Cl = 3{\cdot}58$) but cyclisation rate by factors of less than 10, *irrespective* of whether the ring size produced is of three or five members. Such a high nucleophilicity : basicity ratio for arylamines has been recorded for intermolecular displacements,[45] but in addition reactions, either at carbonyl centres [46] or to electrophilic alkenes,[47] much greater sensitivity to the basicity of the nucleophilic atom (high β value) is observed. This is consistent with a much higher degree of bond formation in the transition states for these latter reactions as reflected in, for example, values of entropy of activation and the importance of steric effects.[48]

Formation of three-membered rings has mainly been compared with that of five-membered rings because of availability of data. Comparison with four- and six-membered ring formation has, however, been made for the bromoalkylamines (Table 1) in ethanol–water mixtures. It is striking that, in view of the assumptions made [38] about factors which control intramolecular nucleophilic displacement, the slower rate of cyclisation of the four- compared with the three-membered ring is entirely due to a less favourable *enthalpy* term for the former process.

The entropy of activation for two of the three-membered ring reactions is more negative than for the five-membered ring system. These results do not conform with the postulate that the smaller the ring formed the smaller should be the entropy of activation because of the lesser extent of restriction of bond rotamers in the transition state. Solvation of an aziridine-like transition state is, however, probably more favourable than for a pyrrolidine-like transition state and hence solvent restriction may be responsible for the decrease in entropy. Entropies of activation more negative for reactions with a three-membered ring transition state than for larger sizes have also been reported for solvolyses of ω-alkoxyalkylsulphonates [49] and ω-chloroalkyl ketones.[50] Earlier conclusions are clearly not generally valid. Comparison of three- with six-membered ring formation *does*, however, show a more favourable enthalpy term and a less favourable entropy term.

A synthetic point worth mentioning is that formation of *N*-phenylazetidine occurs in very high yield provided that reactions are run in dilute solution. This method is decidedly more convenient than other procedures.[17,51]

The results of a similar investigation of the corresponding sulphonamides are in Table 2. Numerous attempts to prepare *N*-4-bromobutyltoluene-*p*-sulphonamide so as to allow comparison of five- with three-membered ring formation failed. Even in preparations conducted under strongly acidic conditions, the required product was always contaminated with cyclic sulphonamide and it must be concluded that cyclisation is very rapid by comparison with the other substrates.

The rate differential with ring-size formed is considerably larger than for the amines, and the three-membered ring is formed substantially faster than the six-membered ring under the same conditions. As found for the amines, the four-membered ring is formed much the most slowly. Relative rates derived using Scott and Flynn's [12] activation parameters for substrate (11), are $3 : 4 : 6 = 1 : 0{\cdot}0074 : 0{\cdot}044$. Solvent effects are small [*cf.* substrate (11) in ethanol and t-butyl alcohol] and a higher bromide : chloride ratio [substrates (11) and (14)] is obtained for the three-membered ring closure. The poorer the solvent for halide ion solvation, the greater is likely to be [42] the chloride : bromide ratio (following paper) and no comparison should thus be made between the amines and the sulphonamides in this respect except that the value is not consistent with a very high degree of C–N bond formation in the transition state.

Conclusions.—The present results show that conjugative control of the formation of three-membered rings is not observed when the nucleophilic atom is nitrogen. The transition state for intramolecular displacement appears to resemble those for intermolecular displacements as judged by chloride : bromide ratios, and solvent effects suggest a rather low degree of C–N bond formation. These factors account for the lack of conjugative control.

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