

Chemical Equilibrium between Five- and Six-Membered Nitrogen Heterocycles

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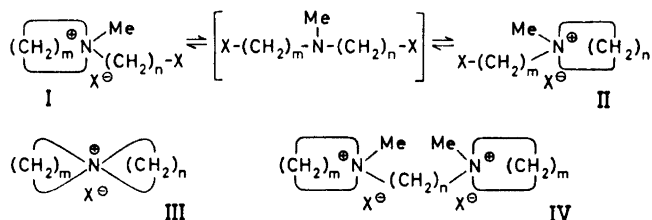
Whereas equilibria between quaternary azoniacycloalkane halides through intermediate ring-opened amines could not be established, azacycloalkanes could be equilibrated through intermediate quaternary salts when the anion was *p*-nitrophenolate. At 443 K *N*-methylpyrrolidine has a "ring-strain" of 5.0 ± 1.0 kcal/mol and a "ring-entropy" of 13 ± 3 e.u. as compared to *N*-methylpiperidine.

Thermodynamic data¹ for cycloalkanes show that standard enthalpy and absolute entropy do not increase regularly with the number of atoms as in the series of *n*-alkanes. Thus, cyclopentane has a relatively higher enthalpy than cyclohexane because of conformational strain and at the same time a relatively higher entropy due to pseudorotation.²

It was of interest to try to establish chemical equilibria between five- and six-membered rings at different temperatures to determine also in this way the enthalpy and entropy differences. One is then of course limited to heterocyclic compounds, the simplest of which should be conformationally similar to the cycloalkanes. Such equilibria are well known in carbohydrate chemistry, but the stability of furanose and pyranose rings is largely determined by their numerous substituents.³ This paper describes attempts to establish chemical equilibria between cyclic amines. The results have already been reported briefly,⁴ together with results obtained subsequently for the equilibration of simple cyclic ethers and formals having five-, six-, and seven-membered rings.

QUATERNARY AZONIACYCLOALKANE HALIDES

At high temperature the quaternization of an amine by an alkyl halide is partially reversed so as to give an equilibrium mixture containing salt, free amine, and alkyl halide.⁵ It was therefore considered possible that the quaternization product of *N*-methyl-azacycloalkanes with one mol of oligomethylene dihalide at high temperatures might set up an equilibrium between two monocyclic quaternized species (I and II).

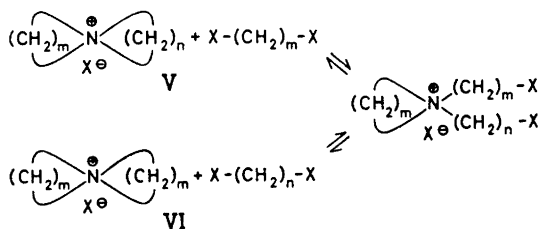


Scheme 1.

The methyl group was chosen as *N*-substituent for NMR-analytical purposes. Being uncoupled, it should give rise to a sharp NMR-line whose chemical shift would hopefully vary with ring size. Among other products to be expected, the spiro-compound III and a variety of bis-spiro-compounds, which might be formed after loss of methyl halide, would hardly be discernible by NMR-spectroscopy. On the other hand, bis-quaternary products of type IV, which could be formed if the halogenated side-chain is split off, would interfere in the NMR-analysis.

The starting materials (I, $m=4$, $n=5$; $m=5$, $n=4$) were prepared by alkylating the *N*-methyl-azacycloalkane with one mol of the dibromoalkane (or diiodoalkane). To minimize the formation of the bis-quaternary compounds of type IV, the amine was diluted with benzene (or ether) and dropped slowly into a small excess of the dihalide in benzene, from which the salts could precipitate. Nevertheless, the bis-quaternary compounds IV were formed to the extent of 5–10 % and had to be separated from the monocyclic compounds I by repeated crystallizations or by column chromatography on cellulose. Also the symmetrical compounds (I, $m=n=4$; $m=n=5$) were prepared, since they were needed for analytical identification in equilibrium mixtures, and again both with bromide and iodide as anion.

When either of the *N*-(ω -bromoalkyl)-*N*-methyl-azoniacycloalkane bromides or iodides (I) were heated in ethylene glycol in a sealed tube at 140°, the only new compound that was formed turned out to be the corresponding spiro-compound (III), as shown by the development of gas pressure (gas identified as methyl bromide), by near disappearance of the *N*-methyl line in the NMR spectrum of the worked-up products, and by final identification by synthesis. At 175° the spiro-compound was produced quantitatively. At



Scheme 2.

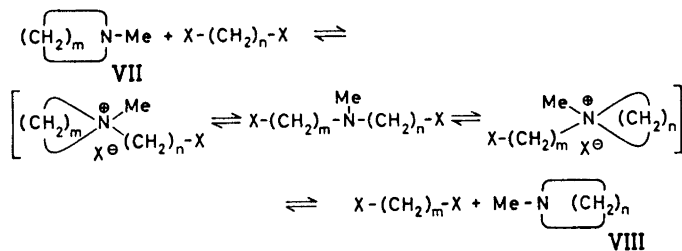
tempts to prevent its formation by addition of methyl iodide led to no different result in the temperature range 125–180°.

Accepting then the preference of the quaternary spiro-structure, it was attempted to effect the exchange of oligomethylene chain between such rings and a dibromoalkane so as to achieve equilibration of the type V \rightleftharpoons VI.

The various unsymmetric (V) or symmetric (VI) spiro-compounds were heated with the appropriate dibromo- or diiodo-alkane in ethylene glycol in sealed tubes. At temperatures from 130 to 180° the expected new spiro-compound was not formed. At 195°, when some exchange could indeed be demonstrated, extensive destruction of the dibromoalkanes took place. An additional reason why equilibration could not be achieved was that whenever isomerization to give a new spiro-compound occurred, it was invariably a five-membered ring that had been opened and replaced by a six-membered ring, never the opposite reaction. When both rings were five-membered, 1,5-dibromopentane replaced finally both of them with six-membered rings.

TERTIARY CYCLIC AMINES

The failure to achieve equilibration of stable quaternary azoniacycloalkane halides *via* intermediate tertiary amines, left us with the opposite possibility, the equilibration of cyclic tertiary amines (VII \rightleftharpoons VIII) through intermediate unstable quaternary ammonium salts.



Scheme 3.

Such a system has the analytical advantage that the amines VII and VIII, whose concentration is to be determined, are volatile. It is also a conformationally simpler system, since only monocyclic compounds are involved, and since nitrogen now carries only one substituent which by nitrogen inversion can always place itself in the least hindered ("equatorial") position.

The cyclic amines were *N*-methylpyrrolidine and *N*-methylpiperidine (VII, $m=4$ and 5). The corresponding *N*-phenyl derivatives were also examined, since they should give less stable salts, but the mesomeric modification of the amine function in anilines make them less interesting for the study of "saturated" rings. The anion X⁻ must correspond to a weak acid HX in order to destabilize the quaternary ammonium salt (whereby the halides are excluded) and should have well balanced nucleophilic and leaving-group properties to obtain a fast reaction. Phenolic compounds, whose properties can easily be

modified by substitution, were therefore tried out. Those used had pK_a values ⁶ ranging from 10 to 7 (phenol 9.9; thiophenol ~ 8; *p*-nitrophenol 7.2; 2,4,5-trichlorophenol ~ 7).

The necessary α,ω -disubstituted alkanes were synthesized, and attempts were made to equilibrate them with *N*-methyl-pyrrolidine and -piperidine. In the case of the bis(phenoxy)alkanes and the bis(phenylthio)alkanes, no reaction took place with the amines in diglyme at 160, 190 or 225°; the starting materials could be completely recovered. The derivatives of the most acidic phenol, the bis(2,4,5-trichlorophenoxy)alkanes, reacted on heating with the cyclic amines in triglyme at 120, 150, 180, and 220° to give a solid and a liquid phase. The liquid phase, as shown by gas chromatography, contained decreasing quantities of the original amine, but no new amine, and extensive destruction took place at the highest temperature. The solid formed at the lower temperatures contained the 2,4,5-trichlorophenolate anion, so that it is clear that irreversible salt-formation has taken place. Better results were obtained when the bis(*p*-nitrophenoxy)alkanes were heated with the amines in triglyme in sealed tubes. The expected new amines were now indeed formed at temperatures of 150° and higher, but the total quantity of amine decreased at, and above, 195°.

Although five-ring is thus formed from six-ring, and *vice versa*, no final common equilibrium could be reached. The reason for this was shown to be a relatively rapid thermal destruction of the bis(*p*-phenoxy)alkanes, which took place also in the absence of amines. Salt formation was not observed.

The only way to arrive at the equilibrium was then to start close to a guessed equilibrium composition, using mixtures containing both cyclic amines and both bis(*p*-nitrophenoxy)alkanes. When it is seen in which direction the change takes place, the equilibrium may be approached also from the other side, and the procedure repeated until a final constant value is reached. As

Table 1. Approach to the equilibrium composition at 180°. (Reaction time 24 h.)

Molar ratio (<i>k</i>) at start ^a		Molar ratio (<i>k</i>) at end ^b	
From six-ring side	From five-ring side	From six-ring side	From five-ring side
1.00		0.80	
	0.30		0.42
0.80		0.69	
	0.40		0.51
0.67		0.61	
	0.55		0.60
0.60		0.60	

$$^a k = \frac{[N\text{-methyl piperidine}]}{[N\text{-methyl pyrrolidine}]} = \frac{[1,4\text{-bis}(p\text{-nitrophenoxy})\text{butane}]}{[1,5\text{-bis}(p\text{-nitrophenoxy})\text{pentane}]}$$

^b Determined only on the cyclic amines.

an example, a series of runs at 180° are shown in Table 1. Similar runs at temperatures in the range 150–190° all gave equilibrium values slightly in favor of the five-membered ring (Table 2).

DISCUSSION OF THE THERMODYNAMIC DATA

When the obtained equilibrium constants (Table 2) are plotted against the inverse absolute temperature, a straight line can be fitted reasonably well so as to give the following enthalpy and entropy values:

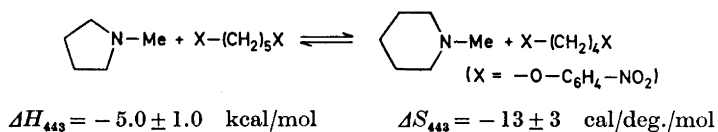


Table 2. Final equilibrium values at different temperatures.

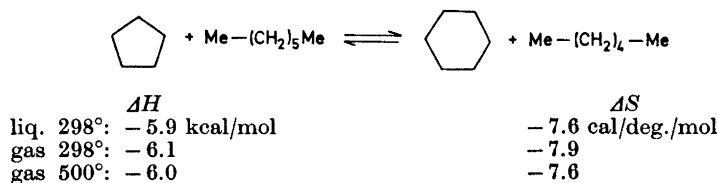
$t(^{\circ}\text{C})$	$T(\text{K})$	$1000/T$	k	$K^a = k^2$	$\ln K$
150	423	2.36	0.73	0.54	-0.61
162	435	2.30	0.68	0.47	-0.76
170	443	2.26	0.65	0.43	-0.84
180	453	2.21	0.60	0.36	-1.02
190	463	2.16	0.57	0.33	-1.10

$${}^a K = \frac{[\text{N-methylpiperidine}] [1,4\text{-bis}(p\text{-nitrophenoxy})\text{butane}]}{[\text{N-methylpyrrolidine}] [1,5\text{-bis}(p\text{-nitrophenoxy})\text{pentane}]}$$

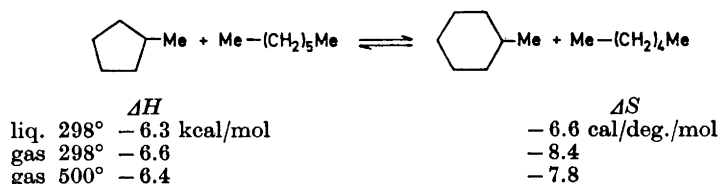
The uncertainties are based on an assumed maximum error of 3 % in the gaschromatographic determination of the cyclic amines. The destruction of the bis(*p*-nitro-phenoxy)alkanes may influence the equilibrium to an unknown degree, but is assumed unimportant for the final values, as these were obtained using starting mixtures very close to the equilibrium composition.

The data for this specific equilibrium express that the right-hand side is favoured by a lower enthalpy and the left-hand side by a higher entropy. However, no direct information can be extracted for the enthalpy and entropy differences between the two cyclic amines alone, since their equilibrium is coupled with the equilibrium between the two alkane derivatives. At any rate, such knowledge would tell little about the relative conformational stability of the two rings, since they contain a different number of atoms. The total equation, on the other hand, has exactly the same number of atoms on both sides, so if it is assumed that the effect of the *N*-methyl group on each ring, as well as the effect of the *p*-nitrophenoxy group on each open-chain compound, cancels, then the data for the total equilibrium can be taken as a direct and better measure of conformational differences between the two rings, since a correction for the difference in number of atoms is built in. This involves of course the further assumption that in the open-chain compounds each extra CH₂-group contributes constant increments to the molar enthalpy and entropy (which is known to be true for alkanes)⁷ and that these are considered the "normal" increments also for cycloalkanes.

Our obtained values may therefore be compared with values calculated from enthalpies of formation and absolute entropies^{1,8} for the imagined equilibrium between the simplest corresponding hydrocarbons:



As the higher symmetry of cyclopentane and cyclohexane must be reflected in the entropy value, an even better comparison may be made with the imagined equilibrium involving methylcyclopentane and methylcyclohexane, for which the following values are similarly calculated:



As can be seen, the entropy change is surprisingly little modified by substitution. This must mean that the increase in rotational entropy, which no doubt is greatest for substitution on the highly symmetric cyclohexane chair, is counterbalanced by an increased entropy of mixing of the new possible conformers, whose number is no doubt greatest for substituted cyclopentane. Whichever is the preferred ring conformation of methylcyclopentane,² all six different positions on the envelope, or all five different positions on the twist-envelope (half-chair), are able to accept the methyl group, whereas on the cyclohexane chair there are only two different positions, of which the equatorial is largely preferred.²

It is remarkable how little all these thermodynamic values change not only with substitution, but also with change of state and with temperature, and we propose on this basis that an enthalpy value of 6–6.5 kcal/mol be taken as a measure of ring-strain in cyclopentanes and an entropy value of 7–8 cal/deg./mol be attributed to pseudorotation and reduced symmetry in cyclopentanes.

The enthalpy change observed in our aza-cycloalkane equilibrium is somewhat lower, but not sufficient to warrant comment. The entropy change is on the other hand substantially larger. Since little difference is expected² between *N*-methylpiperidine and methylcyclohexane, both having well defined rigid chair conformations of the same symmetry and with the methyl group equatorial, one explanation may be that *N*-methylpyrrolidine is higher in

entropy than methylcyclopentane due to a more even population of all possible conformations. This implies that pseudorotation is not substantially impeded in *N*-methylpyrrolidine as compared with cyclopentane, but that it is impeded in methylcyclopentane. As it is inconceivable that the pseudorotational entropy is greater for any substituted derivative than for cyclopentane itself the loss in pseudorotational entropy in both cases must have been more than compensated by the variety of possible positions for the methyl group.

Many other factors may be important, notably the solvation of the amine function, but it is hard to see in which direction this should work.

EXPERIMENTAL

N-Methyl-*N*-(ω -haloalkyl)-azoniacycloalkane halides (I) and oligomethylene- α,ω -bis(*N*-methylazoniacycloalkane halides)(IV). General procedure: A solution of the α,ω -dihaloalkane (0.100 mol) in dry benzene was heated to boiling under nitrogen in a 1 l flask. Into the refluxing solution was dropped a solution of *N*-methyl-azacycloalkane (0.102 mol) in dry benzene or dry ether (100 ml) over a period of 3 h, and refluxing continued for 9 h. The precipitated salt mixture was filtered off and washed with ether under nitrogen, then dried in vacuum. The yield of crude product was about 80 %.

Paper chromatography (Whatman No. 1) with water-saturated 1-butanol showed two spots after development with AgNO₃ and fluorescein in ethanol, the major spot at R_F 0.87, the minor at R_F 0.09. Preparative separation of the two compounds was carried out in a column packed with cellulose powder (Whatman Column Chromedia CF II) using a dispersion in water-saturated 1-butanol. The same solvent was used for elution of the mono-quaternary salt, the bis-quaternary salt being retained on the column. After evaporation in vacuum, the mono-salt was recrystallized from abs. ethanol/ethyl acetate.

Separation could also be achieved by fractional precipitation from boiling abs. ethanol with warm ethyl acetate, whereby the bis-salt precipitates first. The process had to be repeated three times.

These quaternary salts are so hygroscopic that it was impossible to get correct combustion analyses. However, they are homogeneous in two chromatographic systems, and have NMR-spectra revealing no impurities.

The following mono-salts (I) and accompanying bis-salts (IV) were made: *N*-methyl-*N*(4-bromobutyl)pyrrolidinium bromide and corresp. iodobutyl iodide ($m=4$, $n=4$), *N*-methyl-*N*(5-bromopentyl)pyrrolidinium bromide and corresp. iodopentyl iodide ($m=4$, $n=5$), *N*-methyl-*N*(4-bromobutyl)piperidinium bromide and corresp. iodobutyl iodide ($m=5$, $n=4$), and *N*-methyl-*N*(5-bromopentyl)piperidinium bromide and corresp. iodopentyl iodide ($m=5$, $n=5$).

Azonia-spiroalkane halides (III). General procedure: Into a stirred refluxing mixture of the α,ω -dihaloalkane (0.1 mol), sodium hydroxide (0.1 mol), and water (100 ml), the liquid azacycloalkane (0.1 mol) was dropped over a period of 30 min. The solution was then cooled in a freezing mixture of ice and sodium chloride, and shaken with an ice-cold aqueous 40 % solution of sodium hydroxide (50 ml). An oily layer was formed which was taken up in chloroform. To the concentrated chloroform extracts was added some ether until the quaternary salt crystallized. The crude solid was filtered off, washed with ether, dried, and recrystallized either from isopropanol or by precipitation from warm methanol with ether.

The following spiro-compounds (III) were made: 5-azonia-spiro[4,4]nonane bromide and corresp. iodide ($m=4$, $n=4$) in yields of 51 and 55 %, 5-azonia-spiro[4,5]decane bromide and corresp. iodide ($m=4$, $n=5$) in yields of 87 and 72 %, and 6-azonia-spiro[5,5]undecane bromide and corresp. iodide ($m=5$, $n=5$) in yields of 90 and 86 %.

1,5-Bis(phenoxy)pentane. A vigorously stirred mixture of phenol (18.8 g = 0.2 mol), 1,5-diiodopentane (32.4 g = 0.1 mol), finely powdered potassium carbonate (19.8 g = 0.2 mol), and acetone (200 ml) was refluxed for 8 h. After cooling, extraction with ether and removal of the solvents, the residue was distilled at 1 mm to give two fractions; a liquid, b.p. 120–124° (3 g), and a solid, b.p. 180–182° (13.3 g). Recrystallization of the main

fraction from 96 % ethanol gave *1,5-bis(phenoxy)pentane*, m.p. 50–52°. (Found: C 79.71; H 7.74. Calc. for $C_{17}H_{20}O_2$: C 79.68; H 7.81.)

The liquid fraction crystallized on cooling and proved to be *1-phenoxy-5-iodopentane*, m.p. –10°. (Found: C 45.01; H 5.19. Calc. for $C_{11}H_{15}OI$: C 45.12; H 5.13.) The quantity of this by-product could be kept lower by using methyl ethyl ketone instead of acetone and a small excess of phenol and potassium carbonate.

1,4-Bis(phenoxy)butane. The preparative procedure was as above but using 1,4-diiodobutane, and methyl ethyl ketone as solvent. Recrystallization from 96 % ethanol gave *1,4-bis(phenoxy)butane* (80 %), m.p. 115–116°. (Found: C 79.24; H 7.52. Calc. for $C_{16}H_{18}O_2$: C 79.35; H 7.40.)

1,5-Bis(2,4,5-trichlorophenoxy)pentane. The procedure was analogous to that described above for 1,5-bis(phenoxy)pentane, but using 2,4,5-trichlorophenol. The crude product was recrystallized from a mixture of chloroform and methanol. Yield 65 %, m.p. 72–73°. (Found: C 44.36; H 2.95. Calc. for $C_{17}H_{14}O_2Cl_6$: C 44.06; H 3.02.)

1,4-Bis(2,4,5-trichlorophenoxy)butane. The procedure was as above but using 1,4-diiodobutane. Yield 73 %, m.p. 136–137°. (Found: C 42.65; H 2.61. Calc. for $C_{16}H_{12}O_2Cl_6$: C 42.60; H 2.67.)

1,5-Bis(p-nitrophenoxy)pentane. A vigorously stirred mixture of *p*-nitrophenol (27.8 g = 0.2 mol), 1,5-diiodopentane (32.4 g = 0.1 mol), finely powdered potassium carbonate (19.8 g = 0.2 mol), and methyl ethyl ketone (100 ml) was refluxed for 20 h. After cooling, aqueous sodium hydroxide solution (5 N) was added until basic reaction. Addition of ether precipitated a solid which was filtered off. Recrystallization by addition of warm methanol to a warm chloroform solution gave long white needles (63 %), m.p. 98–99°. (Found: C 58.80; H 5.24. Calc. for $C_{17}H_{18}N_2O_6$: C 58.95; H 5.20.)

1,4-Bis(p-nitrophenoxy)butane. The procedure was as described above but using 1,4-diiodobutane. Recrystallization of the precipitated product twice from benzene gave the expected compound (69 %), m.p. 145–146°. (Found: C 57.90; H 4.76. Calc. for $C_{16}H_{16}N_2O_6$: C 57.85; H 4.82.)

1,5-Bis(phenylthio)pentane. Into a dry-ice/acetone cooled mixture of thiophenol (11.0 g = 0.1 mol) and 1,5-dibromopentane (11.5 g = 0.05 mol) was condensed liquid ammonia (25 ml), then metallic sodium (2.3 g = 0.1 mol) added under vigorous stirring.⁹ The blue mixture turned clear after all the sodium had been added. After further stirring for 20 h, the ammonia was evaporated, and the white residue taken up in ether and worked up. Recrystallization from methanol/chloroform gave the bis-thioether (73 %), m.p. 42–44°. (Found: C 70.93; H 6.85. Calc. for $C_{17}H_{20}S_2$: C 70.83; H 6.95.)

1,4-Bis(phenylthio)butane. The procedure was as described above, but using 1,4-dibromobutane. The crude product was recrystallized by adding chloroform to a warm methanol solution and gave on cooling long white crystals (11.8 g = 86 %), m.p. 56–57°. (Found: C 69.76; H 6.73. Calc. for $C_{16}H_{18}S_2$: C 70.01; H 6.57.)

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