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Influence of Ring Size on Properties and Reactivity of Cyclic Systems

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Results obtained during 1960-1979 on the effect of the size of a saturated or partly hydrogenated carbo- or hetero-cycle on the physicochemical (spectral, polarographic, ionisation) and chemical properties of cyclic compounds are summarised. Attention is paid mainly to the usual (C_5-C_7) cyclic systems. Results are interpreted in terms of classical strain theory, the *I*-strain concept, and the Finnegan-Streitwieser rehybridisation model. A list of 173 references is included.

CONTENTS

I.	Introduction	119
II.	Physicochemical properties of cyclic systems	119
III.	Ring size and reactivity	124
IV.	Ring size and equilibria	130

I. INTRODUCTION

The influence of the size of a saturated or partly hydrogenated ring on the properties and the reactivity of a cyclic system is now well known and continually subject to close attention by organic chemists. This problem is dealt with in some way or another in all the many monographs and reviews[1-10] concerned with aspects of the stereochemistry of cyclic compounds. However, the ever increasing information on this topic has not been subjected to detailed analysis since publication of the 1960 review[9]. The present survey is intended in some measure to fill this gap. Nevertheless, it is not possible to cover all aspects of the problem, and this Review will be confined mainly to the "usual" (C_5-C_7) and to a less extent small (C_3, C_4) rings. Information on rings larger than seven-membered has not been specially systematised (reviews have appeared[11,12]), and is considered only when necessary to ensure completeness of exposition.

Although the data given below are largely determined by the strain in the rings, it seems useful to include appropriate thermodynamic parameters, which have been summarised in detail in the above monographs and reviews[1-3,9]. Results published during recent years[13-15] do not change fundamentally existing information on the relative stabilities of cyclic systems. It must be noted only that the strain sequence known for carbocyclic derivatives is on the whole maintained in saturated heterocyclic compounds[15].

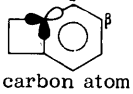
The premises on which experimental results obtained to establish a correlation between properties and ring size can be interpreted have now been quite well developed. They involve primarily the types of strain inherent in the systems† and the changes they undergo on passing from the ground to the transition state (or final state in the case of equilibrium).

† These comprise mainly Baeyer or angular strain involving distortion of bond angles; Pitzer or torsional strain, due to the "striving" of substitutents attached to adjacent atoms to avoid an unfavourable eclipsed conformation and to occupy the energetically most favourable relative positions; transannular interaction (across the ring); *F*-strain, i.e. increase in steric strain on formation of a bond between two atoms, due to spatial interaction of substituents attached to these atoms; and finally *I*-strain—change in the internal strain of the cyclic system due to changes in angles and conformation accompanying change in the coordination number of a ring atom during reaction[9].

An important supplement to such a treatment, especially in connection with the concept of *I*-strain, is that differences in reactivity between compounds depending on ring size are determined, under otherwise similar conditions, also by how far along the reaction coordinate the transition state was formed (i.e. whether the latter was "initial-like" or "final-like"). If achievement of the transition state involves rehybridisation of a ring atom, the influence of ring size will be considerably less marked in the former than in the latter case[16].

Even the most rigorous examination possible of all types of strain and their variation during a reaction in no way exhausts all aspects of the problem and relates mostly to reactions involving a ring atom. Simple angular strain clearly cannot provide an interpretation of the overall effect of a fused ring on the reactive behaviour of a molecule, e.g. the Mills-Nixon effect. Results on effects of this type were generalised[17,18] with an explanation that has now been confirmed by many spectral and kinetic investigations[19,20].

According to this generalisation aryl positions attached to a strained fused ring (α-positions) exhibit diminished reactivity towards electrophilic reagents. The reason is enhancement of the *p*-character of those orbitals (shown solid)



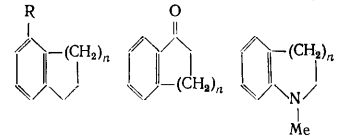
that are directed from a carbon atom of the benzene ring towards the strained ring with consequent enhancement of the *s*-character of the orbitals (shown open) directed towards the α-position of the benzene ring. Such increase in *s*-character clearly improves the electron-accepting properties of the orbital and hence lowers the reactivity of the α-position towards electrophilic reagents with greater acidity of the corresponding carbon-hydrogen bonds. These conditions provide a good explanation of the Mills-Nixon effect[21], i.e. why in indane derivatives (which contain a strained five-membered ring), in contrast to tetrahydronaphthalene derivatives, electrophilic substitution is oriented predominantly at a β-position.

II. PHYSICOCHEMICAL PROPERTIES OF CYCLIC SYSTEMS

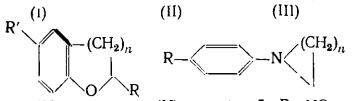
1. Spectral Properties

Spectral methods, in particular electron spectroscopy, have been widely used to elucidate reasons for the differences in reactivity between cyclic systems varying in ring

size. Mention must first be made of several early papers on bicyclic derivatives, not covered in existing reviews. Examination of the ultraviolet spectra of benzocycloalkanes (I),[22] benzocycloalkanones (II),[23] and heterobicyclic compounds (III) and (IV)[24–26] indicated that maximum conjugation was present in the almost planar five-membered ring:



(I) (II) (III)



(IV)

(V): $n = 1-5$, R=NO_2;
(VI): $n = 1-4$, R=H.

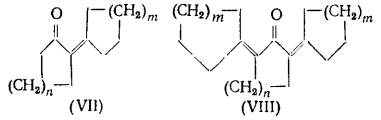
Study of the ultraviolet spectra of the *N*-arylazacycloalkanes (V) and (VI) has revealed[27] for the aziridine derivative (V: $n = 1$) a strong hypsochromic displacement of the absorption maximum and a decrease in the extinction coefficient relative to the other compounds of this series. Some fall in intensity and shift in the absorption maximum to shorter wavelengths is observed also with the *N*-arylpiperidine (V: $n = 4$). The conclusion[27] that sp^3-hybridisation of the nitrogen atom occurs in the former compound and inhibition of conjugation in the latter, six-membered compound is confirmed by the nuclear magnetic resonance spectra (down-field shift in the signals from *ortho*-protons of the benzene ring) and by measurements of the ionisation constants (subsection 2).

Other workers[28] who studied the ultraviolet spectra of *N*-phenylazacycloalkanes (VI: $n = 1-4$) assumed that the nitrogen atom has an sp^3-configuration in all the compounds, but the degree of conjugation decreases according to ring size in the sequence

$$C_5 > C_4 > NN\text{-dimethylaniline} > C_6 > C_3$$

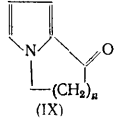
which is consistent with the exaltation of molecular refraction. In this case the degree of conjugation is determined by the angle ϕ between the direction of the orbital bearing the lone pair of electrons of the nitrogen atom and the normal to the plane of the benzene ring, with increase in ϕ leading to a weakening of absorption. From an analysis of molecular models it was concluded[28] that for a five-membered ring $\phi = 0$, whereas for a six-membered ring $\phi > 0$ owing to interaction of α-protons of the piperidine ring with *ortho*-protons of the benzene ring.

A study[29] of the electronic spectra of the cycloalkylidene ketones



(VII) (VIII)

also showed that five-membered compounds absorb in the ultraviolet at longer wavelengths than do six-membered compounds. Analysis of the spectra of the fused pyrroles



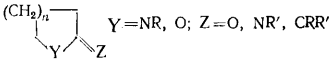
(IX)

($n = 1-3$) also indicated[30] that conjugation of the carbonyl with the pyrrole ring is best in the five-membered compound ($n = 1$). The infrared spectra of the pyrroles (IX) were also examined, and found to be closely similar for the six- and seven-membered compounds (ν_{CO} respectively 1650 and 1645 cm^{-1}) but appreciably different for five-membered compounds (1700 cm^{-1}). The increase in the carbonyl frequency in the spectrum of (IX: $n = 1$) was attributed[30] to enhancement of the *s*-character of the orbital directed towards the oxygen atom.

Analogous results were obtained from the infrared spectra of cycloalkanones, lactams, lactones, cyclic ureas, imides, urethanes, and other compounds of similar type[31]. The carbonyl frequencies were regarded[31] in all cases as indicating not ring-strain by hybridisation of the orbital directed towards the oxygen atom: enchancement of the *s*-character of this orbital, which increases on passing from seven- and six-membered to five- and four-membered rings, is the reason for the higher ν_{CO} frequency in compounds having strained rings.

Hypotheses of this type are consistent with a very good correlation[32] between the acetolysis rate constants of toluene-*p*-sulphonates $RR'CHOSO_2Ar$ and the carbonyl frequencies of the corresponding ketones. From this it can be concluded that the two parameters are equally sensitive to angular strain and to hybridisation. The correlation does not apply to compounds whose hydrolysis is sterically accelerated, as e.g. the pair cyclopentyl toluene-*p*-sulphonate and cyclopentanone.

The above views on the correlation between carbonyl frequency and the *s*-character of the hybride orbital are apparently quite valid for non-conjugated systems[33]. For systems in which the carbonyl is conjugated with other groups Y, as in lactams, lactones, etc.

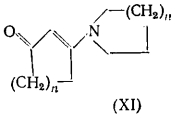


Y=NR, O; Z=O, NR', CRR'

(this applies also to other types of compounds having a conjugated exocyclic double bond—enamines and amidines), however, it must also be borne in mind that such conjugation is best realised in a six-membered ring[34,35], and the increase in the carbonyl (or C:C or C:N) frequency for five-membered compounds must be partly attributed to inhibition of conjugation in them#.

Enhancement of the *s*-character of the C–O orbital in strained cycloalkanones affects also their capacity for hydrogen bonding (determined from the infrared spectra). Depending on ring size the strength of the hydrogen bond diminishes in the sequence $C_5 < C_6 < C_7$.[37] For cyclic imines[38] and ethers[39] it has been shown earlier that hydrogen bonding is stronger in five- than in six-membered compounds. For lactones[39], on the other hand, the situation is similar to that observed for cyclic ketones, and valerolactone forms a stronger hydrogen bond with methanol than does butyrolactone. Comparison of the behaviour of lactones and cyclic ethers indicated[30] that in the former the carbonyl oxygen is involved in hydrogen bonding.

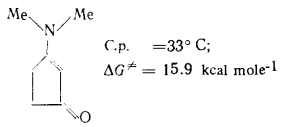
Several comparisons have been made of ^1H n.m.r. spectra as a function of ring size[40–42]. The chemical shifts of signals from vinyl protons of enamines, e.g. of type



(XI)

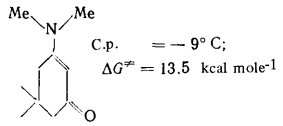
The increase in carbonyl frequency in five-membered rings in a series of benzolactams has been explained in terms of diminished conjugation between carbonyl and imino-groups[36].

indicate that delocalisation of the electron pair of the nitrogen atom is more strongly marked in five- than in six-membered compounds[40,41]. These results are confirmed by infrared and ultraviolet spectra and also by the greater restriction of rotation about the carbon–nitrogen bond in the five-membered enamino-ketone (XII) than in its six-membered analogue (XIII)§:



C.p. =33° C;
$\Delta G^{\neq} = 15.9$ kcal mole^{-1}

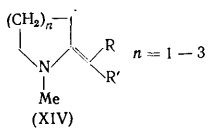
(XII)



C.p. = — 9° C;
$\Delta G^{\neq} = 13.5$ kcal mole^{-1}

(XIII)

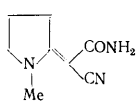
In a detailed analysis of the influence of ring size on the barrier to rotation about the carbon–carbon double bond in enamines of the type



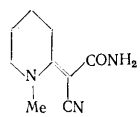
$n = 1 - 3$

(XIV)

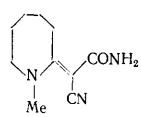
it was established[42] by ^{1}H n.m.r. spectroscopy that restricted rotation occurs with a comparatively low energy barrier, with activation free energies of *cis–trans* isomerisation lowest for six-membered and highest for five-membered compounds. A characteristic example is[42]



C.p. °C 71°
$\Delta G^{\neq}$ kcal mole^{-1} 19.1; 17.4



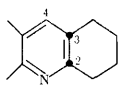
—14°
13.1; 13.7



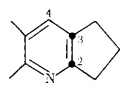
45°
16.0; 16.3

Interpretation of these results was based on the conclusion that the energy of the transition state is significantly higher for five- than for six-membered compounds owing to the unsuitability for the former of transformation of the exocyclic into an endocyclic double bond.

Annelated pyridines have recently been studied[20] by ^{13}C n.m.r. spectroscopy. On passing from six-membered (XV) to five-membered (XVI) analogues



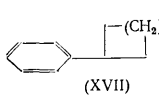
(XV)



(XVI)

the signals from carbon atoms 2 and 3 undergo down-field shifts of ~8–9 and 4.8–5 ppm respectively, which agrees well with the stronger electron-accepting effect of a strained five-membered ring (Section I). Thus annelation with a strained ring enhances the electronegativity of the nitrogen atom and carbon atom 4, with consequent deshielding of the carbon atoms at positions 2 and 3.

Study of the fragmentation under electron bombardment of the compounds



(XVII)

n	1	2	3
E_a, kcal mole^{-1}	34.5±4.8	53.5±4.8	62.5±4.8

has established[43] a parallelism between stability of the ring and resistance to electron impact: i.e. the activation energy of fragmentation E_a increases on passing from the strained cyclobutane and cyclopentane rings to the unstrained cyclohexane ring.

2. Ionisation Constants

Most research on the dependence of physicochemical properties on ring size has been based on the measurement of ionisation constants and interpretation of the results[44–73]. Firstly we must note that the kinetic acidity of cycloalkanes varies[44] in the sequence¶

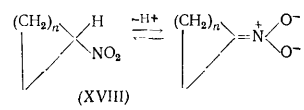
$$C_3 \gg C_4 > C_5 > C_6 \approx C_9 > C_7 \approx C_{10} > C_8 \approx C_{11} > C_{12} > C_{14}.$$

The divergence of these results from those for the rates of solvolysis of the corresponding toluene-*p*-sulphonates led to the conclusion[44] that the conformations of initial and final states (cycloalkane and cycloalkyl anion) are closely similar, and the differences in acidity are determined solely by the degree of *s*-character of the C–H orbital. These workers[44] regarded this conclusion as supported by the good correlation of kinetic acidities with the $J(^{13}C–H)$ values characterising hybridisation.

The action of n-butylsodium on mixtures of cyclopentene and cyclohexene showed[46] that the carbon–hydrogen bond in the former cycloalkene possesses the more acidic properties. On the other hand, measurement of the basicity of unsaturated ketones —cyclopent-2-enone and cyclohex-2-enone—revealed no effect of ring size[47]. The acidity of a series of nitrocycloalkanes

$$C_8 > C_7 > C_5 > C_6 > C_4 \gg C_3$$

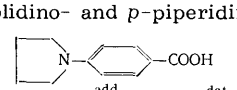
diminishes with ring size in the sequence[48]



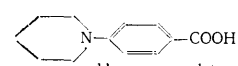
(XVIII)

The greater acidity of seven- and five-membered than of six-membered compounds agrees well with the change from sp^3 to sp^2 hybridisation of the cyclic carbon atom accompanying formation of an anion, i.e. with the concept of *I*-strain.

Considerably more research in this field has been done on heterocyclic compounds. It has been shown[27] for *N*-aryl-azacycloalkanes that five-membered compounds are least basic, which is due to steric inhibition of conjugation of the nitrogen lone pair with the benzene ring (subsection 1)†. Basicity and acidity constants had been determined[50] for *p*-pyrrolidino- and *p*-piperidino-benzoic acids:



(XIX), $pK_a^{add} = 0.39$; $pK_a^{det} = 6.07$



(XX), $pK_a^{add} = 2.67$; $pK_a^{det} = 5.75$

where pK_a^{add} and pK_a^{det} correspond to addition and detachment of a proton respectively. Comparison with the acidity constants of corresponding acyclic compounds (e.g. for *p*-dimethylaminobenzoic acid (XXI) $pK_a^{det} = 6.0$) shows[50] that (XX) is characterised by considerable steric inhibition

§ Here and subsequently C.p. = coalescence temperature (point).

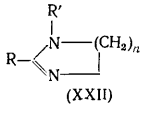
¶ Different relations apparently occur among chlorofluoroalkenes[45].

† Similar results had been obtained earlier for *N*-phenylpyrrolidine and -piperidine[49].

of resonance interaction, due to overlapping of the orbitals of α-protons of the piperidine ring with those of *o*-protons of the benzene ring.

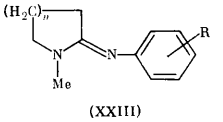
The very low basicity of (XIX) in comparison with not only (XX) but also (XXI) ($pK_a^{det} = 1.40$) was attributed[50] to non-bonded interactions occurring on protonation of the pyrrolidine nitrogen atom, accompanied by a change in its configuration from sp^2 to sp^3. The Reviewer regards such an explanation as entirely logical; from these results the hypothesis of an sp^3 configuration for the nitrogen atom in all *N*-phenylazacycloalkanes (subsection 1) can be considered improbable. Basicity measurements on oxacycloalkanes[51] gave the same sequence depending on ring size $C_5 > C_7 > C_6$ as for cyclic imines#. The effect of *F*-strain during protonation was regarded as insignificant (application of this concept would have given the different sequence $C_5 > C_6 > C_7$), and the results were explained in terms of the so called electronic correlation effect. This explanation presupposes that repulsion of the lone pair of the oxygen atom from the α–C–H group accompanying protonation at the oxygen would be more greatly diminished for five- and seven-membered rings (where shielding is present) than for a six-membered ring. It was supposed that this would relieve a certain proportion of the strain on the protonation of oxygen in a five-membered (and to a less extent seven-membered) ring. Since shielding is absent from a six-membered ring, this effect plays no part; hence an additional gain in energy accompanies protonation of five- and seven-membered compounds, so that they are more basic than the pyran derivative.

Among cyclic amidines



(XXII)

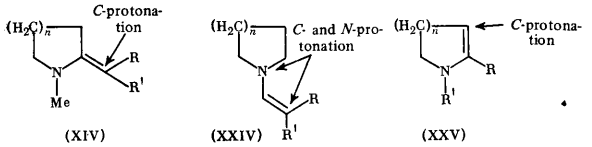
the most basic are hydrogenated pyrimidine derivatives, which are followed by seven- and eight-membered compounds, the least basic being imidazolines (XXII: $n = 1$).[53] The same sequence $C_6 > C_7 > C_5$ is maintained[35] in amidines of the different type



(XXIII)

The explanation of such variation in basicity is that the best conditions for conjugation of the lone pair of the cyclic nitrogen atom with the exocyclic double bond occur in the six-membered ring§. Correlation analysis showed[35] that rotation of the benzene ring relative to the plane of the C : N bond depends little on ring size.

Several studies have been made of the basicity of tertiary enamines

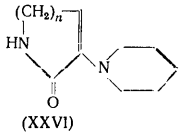


(XIV) (XXIV) (XXV)

The same sequence had previously been obtained[52] for cyclic ethers, but a different sequence for lactones ($C_6 > C_5 > C_4$) and cycloalkanones ($C_7 > C_6 > C_5 > C_4$), which indicates a change in the site of protonation (at the carbonyl oxygen) for these compounds.

§ Such an explanation had earlier been advanced[34] in connection with the basicity of lactams.

For the compounds of type (XIV) the sequence $C_6 > C_7 > C_5$ has been established[54–56] for the variation of basicity with ring size¶. Study of restricted rotation about ethylenic bonds in these enamines (subsection 1) indicates[56] that migration of such a bond from an exocyclic to an endocyclic position (on protonation at the β-carbon atom) is energetically most favourable for six-membered and unfavourable for five-membered rings. For enamines of type (XXIV) it is assumed[57] that, in contrast to (XIV), they are protonated not at the β-carbon atom but mainly at the nitrogen atom, owing to steric hindrance to conjugation. From the concept of *I*-strain it would be expected that the six-membered compound would be more basic. Actually, however, the opposite situation is observed[57]: pK_a is respectively 8.71 and 8.34 according as n has the value 1 or 2 in (XXIV)†. A possible reason is that in the former case steric hindrance to conjugation is smaller and the contribution of *C*-protonation to the effective ionisation constant larger: hence the enhanced basicity of the five-membered enamine. The above view is confirmed by study of the protonation of enamines of this type[58]. Five-membered are more basic than six-membered enamines of type (XXV) also[59], apparently owing to diminished angular stress accompanying *C*-protonation of the former. A marked change in basicity with ring size is observed[60] also for enamines of a fourth type:

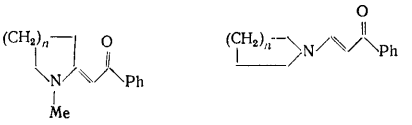


(XXVI)

$n=2$, $\Delta pK_a(MeNO_2) = 3.93$;
$n=3$, $\Delta pK_a(MeNO_2) = 1.6$

The lower the basicity of the six- than of the seven-membered enamine is due to a smaller contribution of *C*-protonation to the ionisation constant of the former compound.

Unusual results have been obtained[61] in a study of the basicity of the enamino-ketones (XXVII) and (XXVIII):



(XXVII): a) $n=1$, pK_a 3.24; b) $n=2$, pK_a 5.22; c) $n=3$, pK_a 4.3

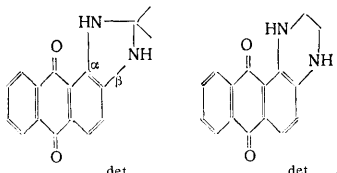
(XXVIII): $n=1$, $pK_a = 2.08$; $n=2$, $pK_a = 2.11$; $n=3$, $pK_a = 1.83$

The dependence on ring size in the series (XXVII) is the same as for the enamines (XIV), but that in (XXVIII) is considerably smaller. These facts, as well as the sharp fall in basicity on passing from (XXVII) to (XXVIII), have been explained by studying the protonation of these compounds: the former undergo *C*-protonation, but the latter *N*- and *O*-protonation[61].

We have been considering research on heteromonocyclic compounds, but several studies have been made of the ionisation constants of fused heterocycles. An interesting investigation of the properties of tetracyclic derivatives containing an anthraquinone fragment has revealed[62] a considerable difference in acidity between the compounds

¶ The same sequence is maintained for other compounds (amidines, lactams[34,35]) which, like the enamines (XIV), are protonated at an exocyclic atom.

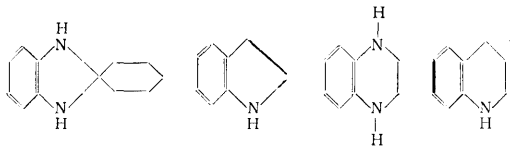
† These differences were not discussed[57].



(XXIX), $pK_a^{det} = 14.7$ (XXX), $pK_a^{det} = 18.9$

the former, containing a strained five-membered ring, is a stronger acid than its six-membered analogue (XXX) by a factor of ~10^4. This is explained[62] in terms of the enhanced *p*-character[17,18] of the orbitals of atoms α and β forming the strained ring: hence the N : H orbital of (XXIX) has an enhanced *s*-character, which is responsible for the increased acidity of this compound.

Among other examples of nitrogen heterocycles the five-membered compounds (XXXI) and (XXXII) are stronger acids than their six-membered analogues (XXXIII) and (XXXIV) [63]:

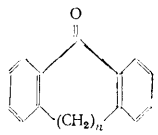


(XXXI) (XXXII) (XXXIII) (XXXIV),

pK_a^{det} 29.3 30.5 32.1 32.1

In explaining such effects we must also bear in mind that the better conditions of solvation of the anion of a five-membered ring may play an important part.

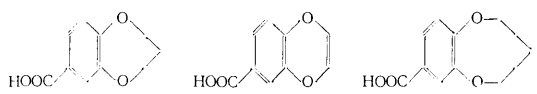
In contrast to basicity measurements on unsaturated[47] (above) and saturated ketones, in which the influence of ring size is insignificant, the fused cycloalkanones



(XXXV)

show a decrease in basicity with ring size[64] in the sequence $C_6 > C_7 \cong C_8 > C_5$.

Measurements on a series of oxygen-containing bicyclic compounds showed[65] that the seven-membered is the strongest acid, and the five-membered the weakest:

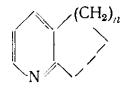


(XXXVI) (XXXVII) (XXXVIII),

pK_a 4.50 4.35 4.23

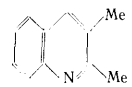
This was attributed to two effects—conjugation of the lone pair of the oxygen atom *para* to the carboxyl and the negative inductive effect of the second oxygen atom on the first—both of which are largest for the five-membered ring and smallest for the seven-membered ring. The former effect produces a decrease in acidity with ring size in the sequence $C_7 > C_8 > C_5$, and the latter effect in the sequence $C_5 > C_6 > C_7$. Superposition of these effects gave[65] the experimental situation $C_7 > C_6 > C_5$, with a relatively small influence of ring size on acidity (the need to consider both effects follows from results for hydrolysis of the ethers (XXXVI)–(XXXVIII), which will be discussed in section III, 3).

The greater electron-accepting influence of a small, strained ring on an adjacent position in a fused aromatic ring agrees well with basicity data for annelated pyridines (XXXIX) [66] and quinolines (XL) [67]:

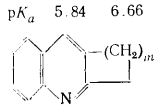


(XXXIX)

n	1	2	3	4
pK_a	5.84	6.66	5.40	5.42



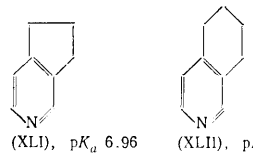
pK_a 5.90



(XL)

m	1	2
pK_a	4.55	5.45

Comparison of similar data with ^{13}C n.m.r. spectra reveals[20] the interesting fact that, when the fused ring is attached at positions 3 and 4 instead of 2 and 3 of the pyridine ring, the five-membered are more basic than the six-membered compounds:



(XLI), pK_a 6.96 (XLII), pK_a 6.83.

It is suggested[20] that atoms located β to the strained ring are enriched with electrons. In other words, the *p*-character of orbitals in this position is assumed to be enhanced (this is not mentioned in Ref. 20). Although these considerations seem to be consistent with the ^{13}C n.m.r. data, considerably more experimental results will be required to confirm them.

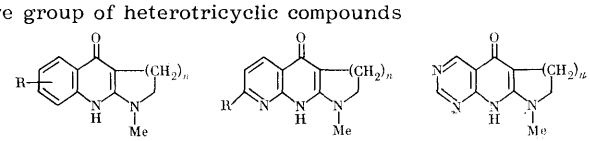
Measurement of the ionisation constants of series of hydrogenated furo- and pyrano-[2,3-*b*]pyridine derivatives has shown[68] that for the *N*-unsubstituted compounds (XLIII) and (XLIV) the five-membered system is much more strongly acid than the six-membered, but they are equally basic:



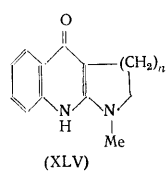
(XLIII), pK_a^{det} 8.92; pK_a^{add} 1.95 (XLIV), pK_a^{det} 10.17; pK_a^{add} 1.94,

The former effect is apparently due to the influence of the strained five-membered ring on the adjacent position (NH) of the aromatic ring, and the latter to protonation at the exocyclic oxygen atom. The same explanation applies to the closely similar basicities of the *N*-methyl derivatives contrasted with the less basic five-membered than six-membered methoxy-derivative (pK_a respectively 1.84 and 3.04).

Finally, a recent study of the ionisation constants of a large group of heterotricyclic compounds



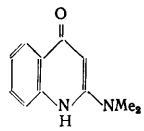
has shown fairly weak basic and acidic properties with protonation occurring at the oxygen atom[69,70]. An example is provided by the data obtained[69] for the quinoline derivatives



(XLV)

n	1	2	3
pK_a^{add}	5.60	5.31	4.97
pK_a^{det}	12.55	12.65	12.70

which fit well into the above schemes: the basicity is maximal, since electrons of the nitrogen atom in the five-membered ring are conjugated best, while the maximum acidity of the compound containing a five-membered ring is explained by Streitwieser rehybridisation of the orbitals, as has already been discussed several times. However, comparison of these data with pK_a measurements for 2-dimethylaminoquinol-4-one



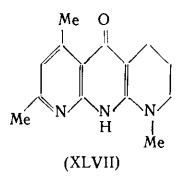
(XLVI)

pK_a^{add} 5.60;
pK_a^{det} 11.92,

reveals that the results cannot be explained in terms of the Finnegan-Streitwieser concept (the pattern is preserved for compounds containing a substituent such as chloro or nitro at position 6 in the benzene ring). Indeed, on this view compounds containing a fused five-membered ring should be far stronger acids than bicyclic compounds of type (XLVI). With regard to basicity, too, the ultraviolet spectra would suggest that the six-membered compound (XLVI) would be more basic, whereas for compounds of type (XLV) (and their chloro-derivatives) and (XLVI) the opposite pattern is in fact observed.

In order to interpret these results it was suggested[69,70] that an important (if not leading) role is played by the ability of the solvent to solvate cations and anions on protonation and deprotonation respectively. On this hypothesis acid and basic strengths in this series of compounds are determined by steric hindrance to solvation, such hindrance being least for five-membered rings on protonation, but on deprotonation for compounds devoid of a third, fused ring (XLVI).

To confirm these views, basicity and acidity measurements were made[70] on the 1,8-naphthyridine derivative

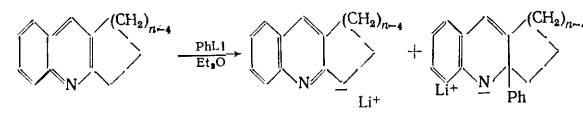


(XLVII)

pK_a^{det} 12.86; pK_a^{add} 4.61

containing methyl groups at positions 2 and 4 of the pyridine ring. As was to be expected, this compound proved to be less basic than the benzene analogue (XLV: $n = 2$) (pK_a 5.31), owing to the stronger electron-accepting influence of the annelated dimethylpyridine than of the benzene ring. Introduction of methyl groups at α and γ positions of the pyridine ring does not affect solvation of the protonated form, where the chief role belongs to solvation of the positive charge concentrated mainly on the nitrogen atom of the middle pyridone ring. On the other hand, solvation of the negative charge on the pyridone oxygen atom is the main factor for the anion, and the vicinity of a bulky methyl group should have an appreciable effect. These conclusions and hypotheses agree well with experimental results: the acidity of (XLVII) is even lower (despite the electron-accepting effect of the pyridine ring) than that of the benzene analogue (XLV: $n = 2$) (pK_a 12.65).

In concluding this subsection we consider the reaction of fused quinolines (XLVIII) with phenyl-lithium, which indicates the acidity of the corresponding α-methylene groups[71]:



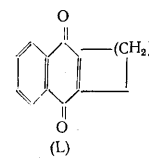
(XLVIII) (XLIX)

n	Yield, %	
1	97	< 1
2	96	< 1
3	61	31
4	33	48

It is assumed[70] that the acidity of the methylene groups is much lower for seven- and eight-membered rings, owing to steric inhibition of resonance in the resulting anion. A competitive process involving formation of the compounds (XLIX) is therefore observed with these rings.

3. Polargraphy

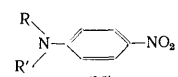
The polarographic reduction of C_5–C_{16} bromocycloalkanes gives a curve[74] similar to that obtained earlier for S_N2 solvolytic reactions. The five-membered compound is reduced most readily, and the six-membered compound with greatest difficulty (bromocycloheptanone occupies an intermediate position)[74], in good agreement with the concept of *I*-strain. For the fused cyclic compounds



(L)

n	1	2	3
$-E_{1/2}$, V	0.695	0.748	0.854

the variation in ease of polarographic reduction agrees well[75] with the Finnegan–Streitwieser concept. In the case of nitrobenzenes containing *p*-diethylamino, *p*-pyrrolidino, or *p*-piperidino



(LI)

a) R = R′ = Et, $E_{1/2}$ = −0.625 V;
b) RR′ = $(CH_2)_4$, $E_{1/2}$ = −0.619 V;
c) RR′ = $(CH_2)_5$, $E_{1/2}$ = −0.599 V.

on the other hand, the six-membered compound is reduced more readily, since the pyrrolidine ring conjugates better with the benzene ring, i.e. is a stronger electron donor[50].

The polarographic behaviour of enamines (XIV: $n = 1$–3) shows[76] small but definite differences in half-wave potentials depending on ring size, with six-membered most readily reduced, and five-membered enamines with the greatest difficulty. This is explained[76] in terms of *I*-strain on the hypothesis that reduction to the radical-anion involves enhancement of the *p*-character of the radical centre. It was shown in the same and a subsequent paper[77] that this is apparently a general rule and can be used to indicate the site of reduction of an enamine (i.e. whether a ring atom or a side-chain is attacked by the electron) and the structure of the radical-anion.

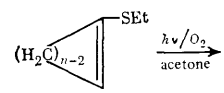
III. RING SIZE AND REACTIVITY

1. Oxidation and Reduction

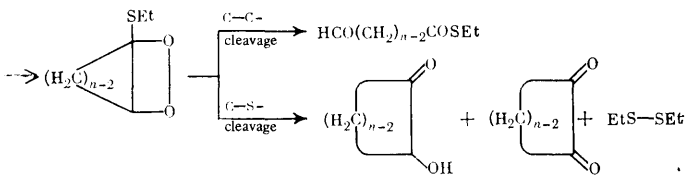
Rates of oxidation of cycloalkanes[78] and their derivatives by various reagents decrease with ring size in the sequence $C_8 > C_7 > C_5 > C_6$, which on the whole is consistent with the concept of *I*-strain[79]. However, the differences in rates of oxidation are far smaller than those in rates of solvolysis,

from which it was concluded that oxidation involves not formation of a carbonium ion but homolytic fission of a carbon-carbon bond[78].

Among cycloalkenes cyclohexene undergoes more rapid autoxidation than does cycloheptene, while cyclopentene is the most difficult to oxidise[80]. In contrast, rates of ozonolysis of cycloalkenes diminish in the sequence cyclopentene > cycloheptene > cyclohexene[81]: i.e. on the assumption that the reaction involves an $sp^2 \rightarrow sp^3$ change in configuration of the cyclic carbon atoms, this sequence is the opposite to that to be expected on the basis of *I*-strain. The direction of the photo-oxidation of cyclic vinyl sulphides (LII) depends considerably on ring size[82]:

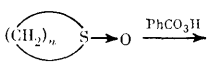


(LII)

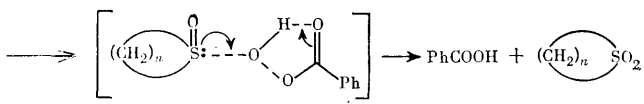


Carbon–carbon cleavage takes place almost quantitatively in unstrained six-membered and little strained twelve-membered rings[82].

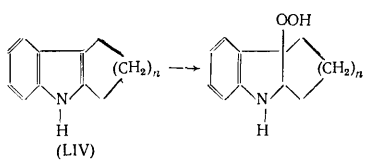
The rate of oxidation of cyclic tertiary amines, with slow intermediate formation of a planar radical-cation, decreases[83] in the sequence *N*-methylhexamethyleneimine > *N*-methylpyrrolidine > *N*-methylpiperidine. The oxidation of cyclic sulphoxides in acid and alkaline media



(LIII), $n = 3$–5



diminishes with ring size[84] in the sequences $C_6 > C_4 > C_5$ (pH 3.2–3.6) and $C_6 \cong C_4 > C_5$ (pH 11.85), the differences in rate being small. Finally, the dependence of rate of oxidation of polymethyleneindoles



(LIV)

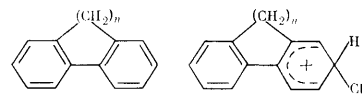
on ring size agrees well with the concept of *I*-strain[85].

Several studies have been made of the dependence of rate of reduction on ring size. Reduction of cycloalkenes by various methods gives a sequence of variation in rate (cycloheptene > cyclopentene > cyclohexene) the direct reverse of what might be expected on the basis of *I*-strain. It was supposed[86] that the main factor here is not change in hybridisation of the cyclic atoms but change in torsional and angular strains and the effect of α-substitutents. The dependence of rate of hydrogenation of cycloalkanones on ring size ($C_6 > C_5 > C_7$) suggests[87] change in hybridisation $sp^2 \rightarrow sp^3$ of the carbonyl carbon atom at slow stage. Other workers[88,89] have obtained similar results for the hydrogenation of cycloalkanones.

Among the compounds (LIa–c) the six-membered derivative is reduced far more rapidly[50], because of the difference in conjugation of pyrrolidine and piperidine rings with the benzene ring (Section II,3). The reduction of cyclic sulphoxides[90], which probably has an S_N2 mechanism, gives the expected dependence $C_5 > C_7 > C_6$ of rate on ring size. The negative entropy of activation increases as the ring becomes larger[90], because small and five-membered rings are quite rigid in the ground state, and the degree of order in the activated complex does not increase so substantially as in six- and seven-membered rings.

2. Reactions with Electrophilic Reagents

Bromination[91], nitration[91,92], and isotope exchange[93] in indane and tetralin show that, when a strained fused ring is present, electrophilic substitution occurs to a considerably greater extent at a β- than at an α-position, in good agreement with the above Finnegan–Streitwieser concept. This effect does not operate[94] in the chlorination of tricyclic compounds (LV)



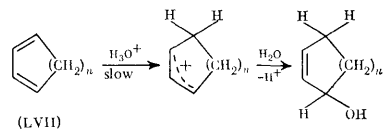
(LV) (LVI)

where the ability of the second benzene ring to stabilise a transition state of type (LVI) is the most important factor. Values for (LV) of the angle θ of the twisting of the second benzene ring from the plane of the first and the relative rates of chlorination

n	1	2	3	4
θ	0	16	49	67
k_{rel}	300	26.6	1.3	0.84

demonstrate[94] the importance of coplanarity of the two aromatic rings in reactions of this type.

Protodesilylation of benzocyclobutane, indane, and tetralin derivatives also gives the expected results[95]: the presence of a strained fused ring directs electrophilic addition of a proton (the rate-determining stage) mainly at a β-position (Section I). The main factor in the addition of various reagents at the double bond in cycloalkenes is apparently (as in reduction) not the change in hybridisation but the overall change in strain in the rings: in such cases addition to cyclopentene is more rapid than that to cyclohexene[96]. On the other hand, the highest rate of hydration of dienes in acid medium is observed with the six-membered compound[97]:



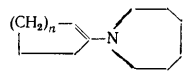
(LVII)

n	1	2	3	4
k_{rel}	200	2000	4	1

These workers remark[97] that a model of *I*-strain fits nucleophilic substitution better than electrophilic substitution: differences in the dependence on ring size are substantially smaller in the latter case. This is attributed[97] to a smaller

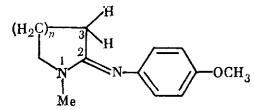
degree of rehybridisation in the transition state involved in electrophilic substitution.

Several studies[98-100] of the alkylation of cyclic enamines have shown in all cases that attack at a cyclic carbon atom (*C*-alkylation) occurs more readily with five-membered compounds, owing to the stronger conjugation of the lone pair of the pyrrolidine nitrogen atom with the enamine double bond. The rate of deuterium exchange K^D_{rel} of a vinyl proton in enamines also depends on ring size[101]:



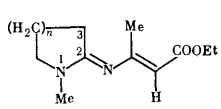
n	1	3
k^D_{rel}	5.95	1.98

Dependence of rate of deuterium exchange of protons in perdeuteromethanol at position 3 on the size of a saturated nitrogen heterocycle has been observed also in series of amidines and enamidines[102,103]:



(LVIII)

n	1	2	3
10^5k, s^{-1}	13.02	51.69	6.48

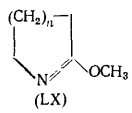


(LIX)

n	1	2	3
10^5k, s^{-1}	1.44	3.77	0,25

On the assumption that the reaction involves tautomeric enamines with the double bond at position 2 or 3, rehybridisation of carbon atom 3 takes place in the rate-determining stage, and the resulting series corresponds to the variation in *I*-strain.

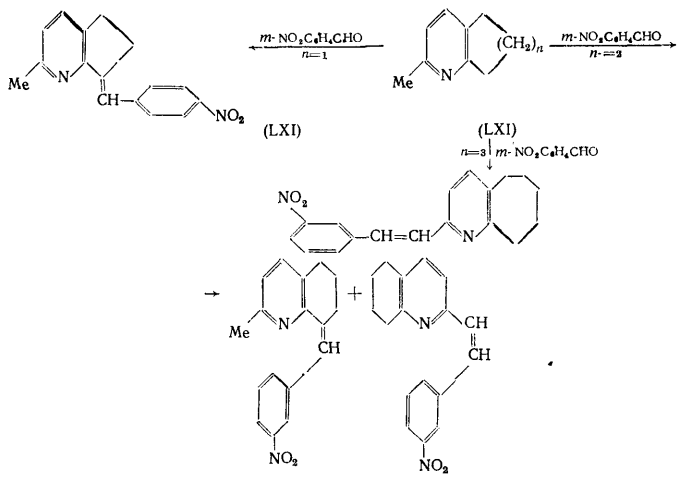
Small but definite differences have been observed[104] in the alkylation of lactim ethers with dimethyl sulphate:



(LX)

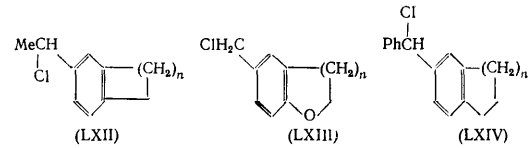
n	1	2	3
k_{rel}	1.36	1.13	1

Rehybridisation does not occur, and *F*-strain is apparently responsible for the variation in rate. The action of aldehydes on 2,3-polymethylenepyridines (LXI) depends[105,106] on the length of the polymethylene chain:



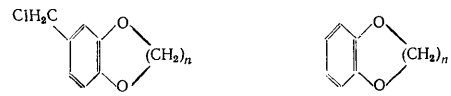
3. Reactions with Nucleophilic Reagents

Most of the work concerned with the problem covered in this Review has been devoted to reactions of cyclic compounds with nucleophilic reagents[107-131], and most of these investigations have studied various types of solvolytic reactions. Thus the rate of solvolysis of the chlorine atom in (LXII)



(LXII) (LXIII) (LXIV)

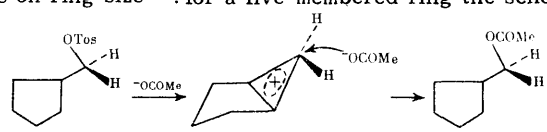
decreases in the sequence $C_5 > C_4 > C_6$.[92] The same rules for five- and six-membered rings had been observed earlier in oxygen-containing bicycles (LXIII)[25] and the compounds (LXIV)[107]; in the latter case the effect was explained in terms of hyperconjugation. For the bicyclic compounds (LXVa-c)



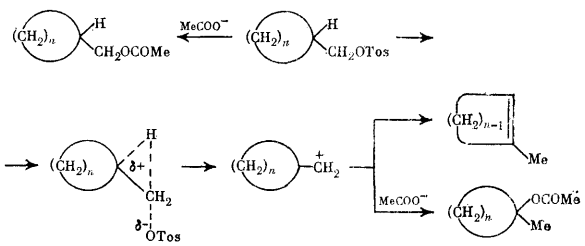
(LXV): a) $n = 1$; b) $n = 2$; c) $n = 3$ (LXVI)

the relative rates of solvolysis were 10 : 6 : 1.[108] What these workers[108] regarded as the two main effects in this system (conjugation of the lone pair of the oxygen atom with the cationic centre and the inductive effect of the second oxygen atom) have already been discussed in detail (Section II,2). These same effects determine the relative rates of hydrolysis of the complex ethers (LXVI).[65] The solvolysis of cycloalkyl bromides (as well as their reaction with the iodide anion) is fully consistent with the concept of *I*-strain[109].

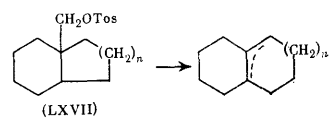
The solvolysis of cycloalkylmethyl toluene-*p*-sulphonates depends on ring size[110]: for a five-membered ring the scheme



has been suggested; and for larger rings



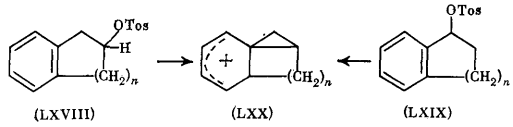
It is evident that in all cases a planar configuration of the cyclic carbon atom should arise at an intermediate stage, so that the rate of solvolysis varies with the *I*-strain: $C_5 > C_7 > C_6$. The solvolysis of toluene-*p*-sulphonates (or *p*-nitrobenzoates) in the different type of system (LXVII) is also appreciably more rapid in the five-membered compound[111]:



(LXVII)

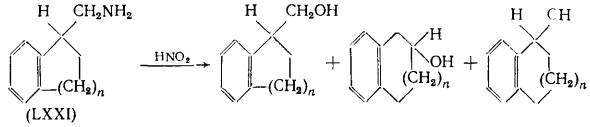
n	1	2
k_{rel}	1500	3.9

An interesting comparison has been made of the solvolysis of the toluene-p-sulphonates (LXVIII) and (LXIX), in which the same mechanism with intermediate formation of a phenonium ion (LXX) is involved[112]:



(LXVIII) (LXX) (LXIX)

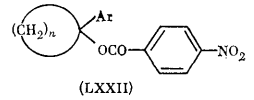
The rate constants (10^5k, s^{-1}) of formolysis of (LXVIII) are 27.3 (6), 152 (7), 2250 (8) (ring size in parentheses). Such successive increase in rates was attributed[112] to decrease in the angular strain in the cation (LXX). However, a different variation in rate applies to the process (LXIX) → (LXX): 2.51 (5), 6.80 (6), 1.80 (7), 0.18 (8). These results were interpreted[112] on the basis of molecular models: only axial isomers can be converted into (LXX), but because of conformational factors the existence of such isomers is unfavourable for seven- and especially eight-membered compounds. The same conformational effects determine the composition of the products in the deamination of amines (LXXI)[113]:



(LXXI)

n		Yield, %	
1	—	85	15
2	38	62	—
3	—	45	53
4	—	<5	54

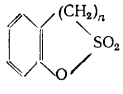
A closely related investigation of the hydrolysis of *p*-nitrobenzoates (LXXII)[114] has given results agreeing well with the concept of *I*-strain:



(LXXII)

n	3	4	5	6	7
k_{rel}	0.426	178	1	51.5	515

An attempt has been made[115] to relate rates of hydrolysis of lactones and cyclic toluene-*p*-sulphonates with the strain in the rings. However, a correlation has been observed only for the pair

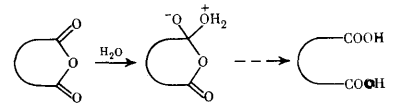


(LXXIII), $n = 1$
(LXXIV), $n = 2$

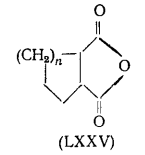
the five-membered ring is more stressed by ~100 kJ mole^{-1}, and is hydrolysed more rapidly by a factor of 10^4.

In aqueous ethanol five-membered anhydrides are hydrolysed rather more rapidly than the six-membered compounds, whereas in an alkaline medium glutaric anhydride is hydrolysed slightly more rapidly[116]. In contrast to this closeness of the rates of hydrolysis of anhydrides the differences for lactams and especially lactones and thiolactones are incomparably larger[116], and agreement with Brown's views (*I*-strain) is better. Various degrees of change in hybridisation in the transition state were assumed[116] to be possible, and these changes determined the relative rate constants of six- and five-membered compounds. The rate of the reverse reaction—cyclisation of acid esters into anhydrides—is much higher for the five-membered ring, apparently because of the entropy factor, consisting in better steric conditions for closure of such a ring[116].

Rates of hydrolysis of succinic and glutaric anhydrides at pH 5.2 and 20 °C are almost equal[117]. This is interpreted in terms of *I*-strain, with respect to which the situation in the transition state is more favourable of the six-membered ring:



On the other hand, succinic anhydride is characterised by an extremely strained ground state (three sp^2-carbon atoms), which facilitates addition of water. The superposition of these effects gives almost the same rate constants for the five- and six-membered rings. Results in the same paper[117] for the effect of the size of the fused ring on the rate of hydrolysis of anhydrides

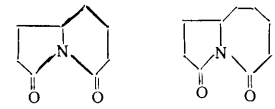


(LXXV)

n	1	2	3
k, min^{-1}	1.13	0.381	0.185

show that the effect is due to steric hindrance (by the methylene groups) to attach by water in seven- and six-membered in comparison with five-membered anhydrides.

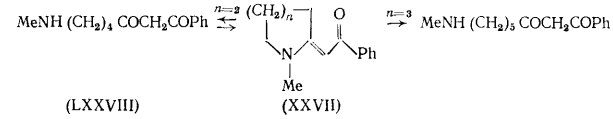
For *N*-methyl-succinimide, -glutarimide, and -adipimide rates of hydrolysis fall in the sequence $C_6 > C_7 > C_5$, with not very large differences ($k_6 : k_7 : k_5 = 2.6 : 1.5 : 1$).[118] Hydrolysis of the bicyclic imides



(LXXVI); 85.7% (LXXVII); 66.1%

in an alkaline medium occurs preferentially at the six- and seven-membered rings (degrees of hydrolysis given for 20 °C).[118]

Among enamines, compounds containing a six-membered ring are hydrolysed appreciably more rapidly in the pH range in which addition of water ($sp^2 \rightarrow sp^3$ transition for the β-carbon atom) limits the rate[119,120]. Rates of hydrolysis of the enamines (XXVI) depend significantly on ring size[60, 121], owing to the difference in the site of their protonation in strongly acid media. Detailed polarographic study[122] of the hydrolysis of the enamino-ketones (XXVII) has established that in 0.1*N* hydrochloric acid only the seven-membered (XXVIIc) is hydrolysed quantitatively, the equilibrium (XXVIIb) ⇋ (LXXVIII) being established for the six-membered compound:

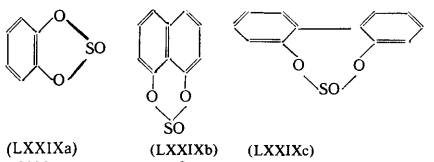


(LXXVIII) (XXVII)

the five-membered (XXVIIa) is not hydrolysed. Such differences are explained by acceleration of the reverse reaction on passing from the seven- to the six- and then the five-membered ring as a consequence of the entropy factor. The rate constant of the forward reaction (hydrolysis) for the six-membered ring (9×10^{-4} s^{-1}) is about double that for the seven-membered ring. Heating (XXVIIa and b) in an acetate buffer results in acid cleavage (with formation of benzoic acid), the rate of which is lower for the five- than for the six-membered ring (10^4k respectively 1.63 ± 0.37 and 6.2 ± 1.9 s^{-1}). Heating (XXVIIa–c) in 0.1*N* sodium hydroxide yields acetophenone, the rate decreasing in the sequence $C_6 > C_7 > C_5$.

The kinetics of the alkaline hydrolysis of amidines[53] is not consistent with the concept of *I*-strain: the rate of hydrolysis falls in the sequence $C_5 > C_6 \gg C_7 > C_8$. In the

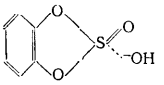
alkaline hydrolysis of cyclic sulphites the five-membered compound is hydrolysed most rapidly, and the seven-membered compound most slowly[123]:



(LXXIXa) (LXXIXb) (LXXIXc)

$10^6\ k,\ s^{-1}$	2000	16	2.9

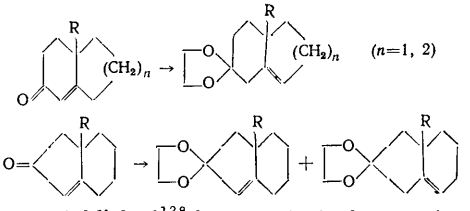
The explanation given[53] for these results is that attainment of a transition state of type



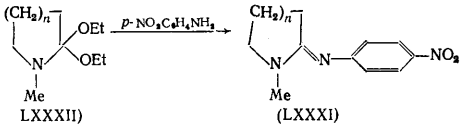
(LXXX)

is more favourbale for the planar five-membered ring. An alternative explanation can be based on repulsion of the hydroxide anion and the lone pair of the oxygen atom (as already discussed for lactones)[124], which diminishes in the sequence $C_7 > C_6 > C_5$.

Results[125,126] on the formation of hemiacetals and acetals of cyclic ketones agree well with concept of *I*-strain. An extremely interesting investigation[127] on migration of a double bond during acetalisation as a function of ring size has shown that, if the carbonyl group is present in a six-membered ring, 100% migration into the other ring takes place, whereas in a five-membered ring a mixture is formed:



It has been established[128] by a method of competing reactions that the rate of formation of amidines (LXXXI) by the action of primary amines on lactam acetals (LXXXII) depends on ring size, varying in the sequence $C_5 > C_7 > C_6$:

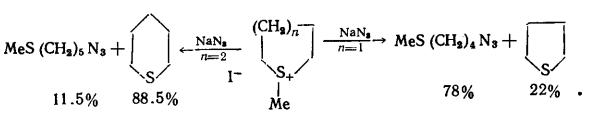


LXXXII) (LXXXI)

n	1	2	3
k_{rel}	28	1	8.3

The reaction mechanism was not studied specially, but the above relation corresponds to a change in hybridisation of the cyclic carbon from sp^3 to sp^2.

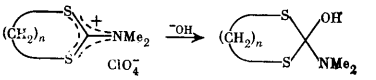
In the action of sodium azide on onium salts, e.g. (LXXXIII), the five-membered ring undergoes cleavage, wheras a six-membered ring is preserved:



(LXXXIII)

It was assumed[129] that the cleavage of an unstrained five-membered ring is more favourable than that of an unstrained six-membered ring, and that attack on the unshielded carbon atom 2 in the saturated ring is more favourable for the five-membered ring. Six-membered compounds are characterised by attack at the exocyclic methyl group.

Maximum and minimum rates of reaction of dithiolonium salts

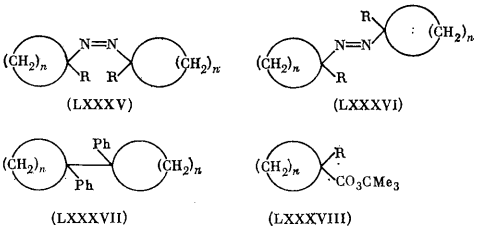


(LXXXIV), $n = 2-4$

are exhibited by seven- and five-membered compounds respectively, which is regarded[130], as corresponding to an increase in stability of the ground state in this sequence ($C_5 > C_6 > C_7$).

4. Radical Reactions

Capture of a hydrogen atom by various radicals (butoxy, bromine, chlorine, phenyl, etc.) on reaction with cycloalkanes gives a sequence of diminishing reaction velocity $C_5 \cong C_7 > C_6 > C_8 > C_9$ corresponding well to formation of a planar (sp^2) radical centre[132]. Similar results have been obtained for the detachment of a bromine radical from cycloalkyl bromides[133]. A series of studies[134,135] of the formation of radicals by the thermolysis or photolysis of *cis*- and *trans*-azo-compounds (LXXXV) and (LXXXVI), biscycloalkanes (LXXXVII), and peroxides (LXXXVIII)



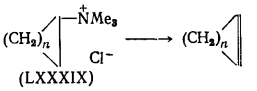
(LXXXV) (LXXXVI)

(LXXXVII) (LXXXVIII)

has established that, although the concept of *I*-strain applies well to (LXXXVI) and (LXXXVII), with (LXXXVIII) the dependence of rate on ring size is quite insignificant, but for (LXXXV) the rate increases monotonically. The explanation is that the variation in rate depends on the extent to which hybridisation of the reaction centre has changed in the transition state, i.e. whether the latter resembles the initial or the final state. It is necessary[135] to take into account *F*-strain as well as *I*-strain.

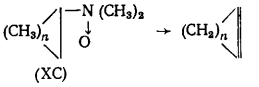
5. Elimination Reactions

Relatively few investigations have been made on the influence of ring size on rate of elimination. In that of trimethylamine from salts



(LXXXIX)

the rate varies in the sequences $C_5 > C_7 > C_6$ and $C_7 > C_5 > C_6$ in the presence of potassium t-butoxide and ethoxide respectively[136,137]. The suggested reaction mechanism involves formation of a planar activated complex, which is energetically unfavourable for six-membered and favourable for five- and seven-membered compounds. Similar results (with the same interpretation) have been obtained for the formation of cycloalkenes from *N*-oxides[138]

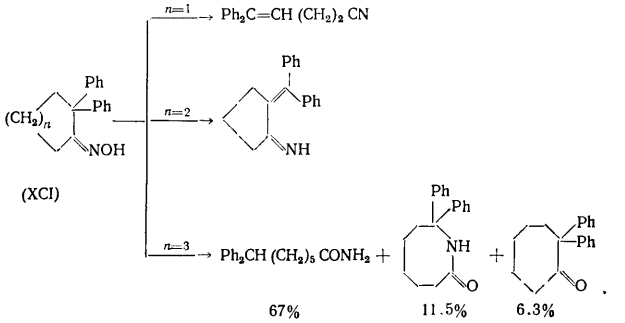


(XC)

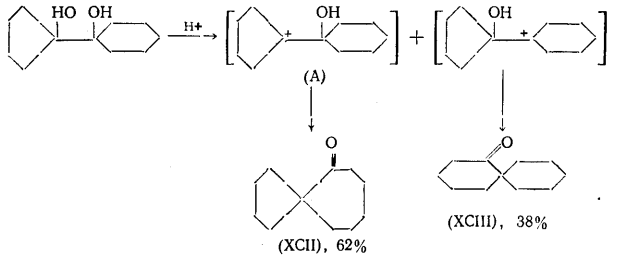
and also in the dehydration of cycloalkanols and the dehydrochlorination of cycloalkyl chlorides[139].

6. Rearrangements

It was shown in several studies[140-143] that the rate of the Beckmann rearrangement falls in the aqueous cyclohexanone > cycloheptanone > cyclo-octanone > cyclopentanone. If the rate determining stage is assumed to involve conversion of an exocyclic into an endocyclic carbon-nitrogen double bond, these results are consistent with Brown's generalisation that five-membered rings are especially likely to retain double bonds in an exocyclic position[42]. When oximes (XCI) are heated under the conditions of the rearrangement, considerable differences are observed[144] in the dependence on ring size, with preferential opening of strained five- and seven-membered rings:

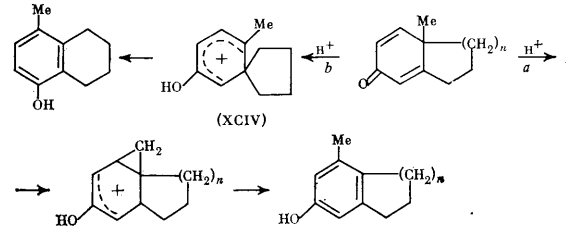


Important results have been obtained for the pinacoline rearrangement, clearly showing[145] that the first direction predominates when the carbonium centre is located in a five- or six-membered ring:



From our point of view formation of the cation (A) is still more favourable than would follow from the relative yields of reaction products (XCII) and (XCIII), since the entropy factor promotes closure of a six-membered (XCIII), not a seven-membered (XCII), ring. This factor must be taken into account in other cases as well (e.g. in the rearrangement of a compound containing five- and seven-membered rings), but the conclusion from the above work seems to be valid—that a carbocation centre is more readily localised on cyclic atoms of five- and seven-membered than of a six-membered ring.

The dienone–phenol rearrangement also depends on ring size:

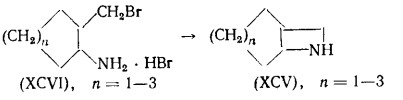


Only reaction path (*a*) is followed by the five-membered ring, since a four-membered spiro-compound of type (XCIV) is apparently unstable[146].

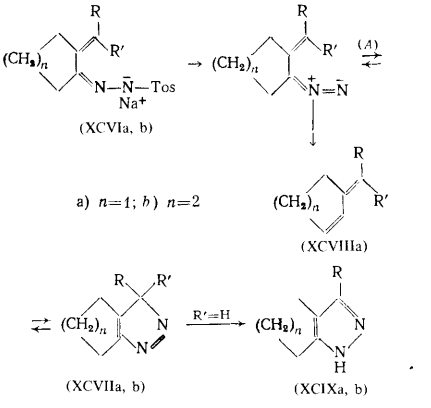
The rate of rearrangement of toluene-*p*-sulphonates of 1-hydroxymethyl-1-phenylcycloalkanes (into benzylcycloalkenes and benzylidenecycloalkanes) accompanying acetolysis decreases in the sequence $C_6 > C_5 > C_3 > C_4$.[147] The rate of isomerisation of methylenecycloalkanes into cycloalkenes[148, 149] diminishes with ring size in the sequence $C_4 > C_5 >$ acylic cpd. $> C_6$. The slow stage is apparently formation of an anion with rehybridisation of the corresponding orbital.

7. Heterocyclisation

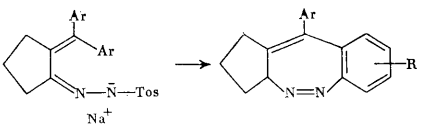
Formation of fused azetidines



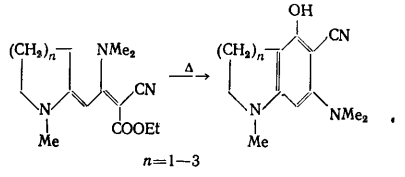
is most rapid for the seven-membered and slowest for the six-membered compound[150]. The increased rate of closure of (XCVI: $n = 3$) is attributed to greater conformational mobility of the seven-membered ring. Distinct differences are observed[151] in the cyclisation of toluene-*p*-sulphonylhydrazones (XCVIa, b):



If R, R′ ≠ H, cyclisation of (XCVIa) yields only dienes, but that of (XCVIb) gives pyrazoles, since (XCVIIa) is then unstable, equilibrium (*A*) is displaced to the left, and stabilisation is achieved with formation of the dienes (XCVIIIa). When R′ = H, stable pyrazoles (XCIXa, b) are formed. With R = R′ = Ar the direction of reaction is unchanged for six-membered compounds, but fused diazepines are formed from five-membered rings:

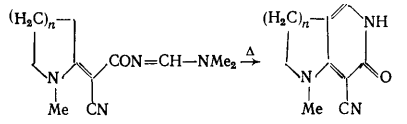


It has been established polarographically that in the formation of fused phenols from dienediamines six-membered compounds are cyclised most rapidly, and five-membered least rapidly[152]:

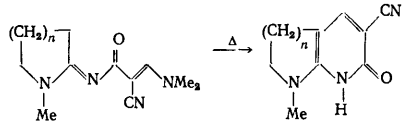


n=1–3

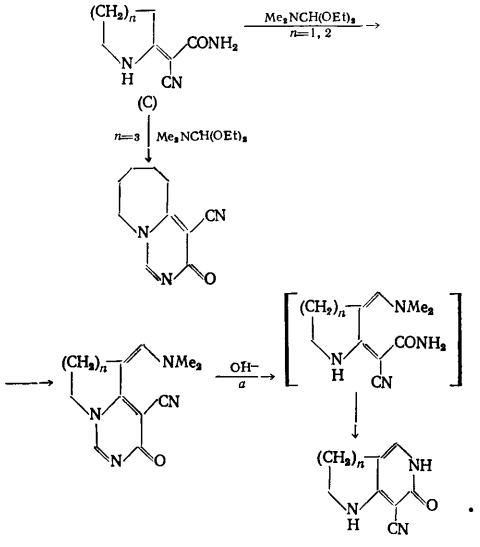
It has been shown by the same method that the rate of formation of fused pyrid-2-ones diminishes in the sequence $C_6 > C_7 > C_5$ [77]:



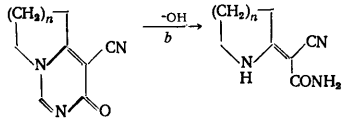
n	1	2	3
k_{rel}	1	249	28.6



Such variation in rate is due to rehybridisation of cyclic carbon from sp^2 to sp^3 on formation of the transition state (it is supposed that tautomers having a $C_{(2)}:C_{(3)}$ endocyclic double bond undergo cyclisation). In the reaction between enaminoamides (C) and dimethylformamide acetal different compounds are formed depending on ring size[153–155]:



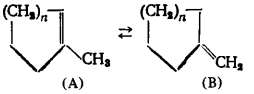
The ready cleavage of the pyrimidine ring observed in alkaline medium, with or without subsequent recyclisation (path *a* or *b*)



also depends on ring size, the rate varying in the sequence $C_5 \cong C_6 > C_7$.

IV. RING SIZE AND EQUILIBRIA

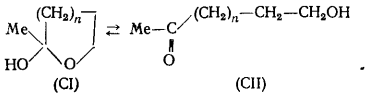
Investigation of the equilibrium between methylenecycloalkanes and methylcycloalkenes indicated that, in contrast to Brown's conclusion[5], the *endo/exo* ratio was higher for five- than for six-membered rings. The earlier assumption[158] was adopted[156,157] that the "greater substitution" of the double bond in tautomer (A) than in (B) is important:



(A) (B)

It is significant that the position of equilibrium is very largely determined by solvation, and in the gas phase the above ratio is close to unity.

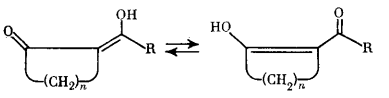
The leading role in the ring–chain equilibrium aminoketone ⇋ aminomethanol belongs to the entropy factor, and the cyclic form is observed only on formation of a five-membered ring[159]. When on cyclisation a larger number eclipsed interactions arise (in five-membered compounds), the situation levels off even for the equilibrium[160]



(CI) (CII)

Extremely contradictory results have been obtained for keto–enol tautomerism. Thus comparison of 2-benzoylindan-1-one with tetrahydronaphthalen-1-one reveals a much higher enol content in the five-membered compound[161], whereas in cycloalkanones and in acyl-lactones, -thiolactones, and -lactams[162–164] the quantity of the enolic tautomer diminishes on passing from the six- to the five-membered compounds. In 2-benzoylcycloalkanones[165], in contrast, the enol content decreases in the sequence $C_5 > C_7 > C_6$; in the enolic form the benzene ring is completely conjugated with carbonyl only in the five-membered compound.

Examination of the influence of ring size on the equilibrium



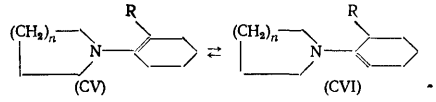
(CIII) (CIV)

shows[166,167] that tautomers having an endocylic double bond predominate in the six-membered compounds, followed by derivatives of cycloheptanone and cyclopentanone#.

The sequence $C_6 > C_8 > C_5 > C_7 > C_4$ in the rate of acid enolisation was explained[162] by the energetic advantage of formation of an endocylic double bond. However, the rate of basic enolisation of cycloalkanones varies in the different sequence $C_4 > C_5 > C_6 > C_7$, and it was correctly stated[162] that neither the advantage or disadvantage of formation of such a bond nor the concept of *I*-strain would explain such a sequence of decrease in rate of basic enoslisation. The explanation advanced[162] was that on passing from a seven- to a four-membered ring the s-character of the C–H orbital increases and ionisation of the C–H bond is facilitated, the latter being the rate-determining process in enolisation.

Similar relations have been observed[168] for the tautomerism of 2-acylcycloalkanethiones and 2-thioacylcycloalkanones.

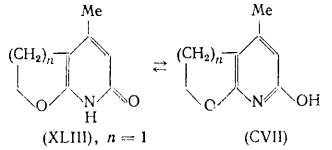
On the whole the view that exocyclic double bonds predominate with five-membered rings, and endocylic double bonds with six-membered rings[5], has now become fundamental in the interpretation of results for enamine–enamine tautomerism of the type[169,170]



(CV) (CVI)

With a substituent R capable of conjugation (COOAlK, $COCH_3$, COC_6H_5, etc.) the tautometer (CV) predominates with the five-membered ring, whereas the ratio of tautomers for the six-membered ring is close to unity. This was attributed[169, 170] to a greater degree of conjugation of the former ring (associated with greater favourability of the resonance structure having an exocyclic N : C bond) and less steric hindrance to such conjugation (involving steric interaction of methylene protons of the pyrrolidine or piperidine ring with R). However, as has already been pointed out repeatedly[9], Brown's "exo–endo" generalisation[5] is not rigorous and is by no means always observed. For hydrazone–enehydrazine tautomerism in *NN*-dimethylhydrazones of ethyl 2-oxocycloalkanecarboxylates[171] the quantity of the latter tautomer (having an endocyclic double bond) increases in the sequence $C_7 < C_6 < C_5$, perhaps because conditions for intramolecular hydrogen bonding are best in a cyclopentenylhydrazine derivative.

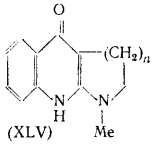
Lactim–lactam tautomerism



(XLIII), $n = 1$ (CVII)
(XLIV), $n = 2$

is another type exhibiting a distinct dependence of the position of equilibrium on ring size. Replacement of a dihydrofuran by a tetrahydropyran ring, both fused to a pyridone, leads to an appreciable decrease in the content of the lactim tautomer: the ratio of lactim to lactam decreases by factors of 15–20.[68] This was explained[68] by the Mills-Nixon-Brown effect (in the pyridone tautomer the double bond is localised in greater measure between the rings, which creates a more unfavourable situation for the five-membered ring: i.e. an endocyclic double bond is present) and by the electron-accepting influence of the strained ring, which increases the acidity of the nitrogen–hydrogen bond in (XLIII). Some uncertainty arises concerning the electron-accepting influence of five-membered compounds in the case of fused oxa- and aza-rings, since the degree of conjugation of the lone pair, in such case with the pyridone ring (electron-donor effect), is apparently highest also for these rings.

In another approach to the dependence of the position of lactim–lactam equilibrium the decrease in the content of lactim tautomers of the tricycles



(XLV)

n	1	2	3
Lactim, %	89	49	31

in the sequence $C_5 > C_6 > C_7$ has been attributed[172] to an accompanying diminution in the solvation of this tautomer, since hypothetical rehybridisation does not explain the differences between the six- and seven-membered rings. We can also try on this view to explain results for the equilibrium (XLIII), (XLIV) ⇆ (CVII). The orbital of the second pair of electrons of the oxygen atom (that of the first pair is perpendicular to the plane of the pyridine ring) is parallel to the nitrogen–hydrogen bond, and unfavourable shielding occurs with increase in the bulk of the substituent attached to the nitrogen atom (i.e. on solvation). For a six-membered ring, for which conjugation is less, the degree of shielding is also smaller, the lactam tautomer is better solvated, and the lactim content is appreciably diminished.

Finally, yet another equilibrium also characterised by dependence on ring size is the intermolecular association of lactams in non-polar solvents[173]: depending on the solvent the degree of association of lactams varies in the sequence $C_7 > C_5 > C_6$ (in tetrachloromethane, cyclohexane) or $C_5 > C_7 > C_6$ (benzene).

---oOo---

From the above survey several considerations arise of which, in the Reviewer's opinion, insufficient account is taken in interpreting experimental results, especially when the concept of *I*-strain is used. Thus in processes involving $sp^2 \rightarrow sp^3$ rehybridisation very much depends on the size of α-substitutents in the ring and that of the attacking species. Steric hindrance to attack at a ring atom increases in the sequence $C_5 < C_6 < C_7$, which differs from the rate sequence $C_5 < C_7 < C_6$ to be expected from a model based on *I*-strain: i.e. inversion of rates for five- and seven-, six- and seven-, and even five- and six-membered compounds is by no means excluded. In reactions of the reverse type (change in hybridisation $sp^3 \rightarrow sp^2$), in which the sequence $C_5 > C_7 > C_6$ is to be expected, the presence of bulky substituents at the reaction centre may lead to unexpected acceleration of reactions with six- and especially seven-membered compounds.

It must also be stressed that the tendency of a reaction centre to be solvated has likewise only occasionally been discussed as a function of ring size, although in several cases solvation may exert an appreciable (and perhaps decisive) influence on the relative rates of processes. It is clearly an extremely complicated task to separate these effects.

In conclusion it must be noted that, despite the complexity of the questions and the hitherto inadequate predictive power of existing theoretical approaches, efforts aimed at solving the problem of the relation between ring size and the properties and reactivity of compounds have proved extremely fruitful and have enriched significantly both theoretical and synthetic organic chemistry.

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