Nuclear Magnetic Resonance as a Means of Assessing Structure *versus* Reactivity Relationships in Alicyclic Compounds

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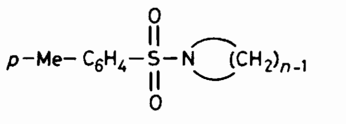
Proton–carbon-13 coupling constants ($J_{^{13}C,H}$) have been measured for three series of *N*-substituted azacycloalkanes. Structural features of the alicyclic compounds, as revealed by this and other n.m.r. techniques, reflect the strain present in the ring and can be used as a guide to predict ring-closure reactivity. Deviations from such structure *versus* reactivity relationships are found with highly strained small rings. Hence, it must be stressed that meaningful trends in the behaviour of ring compounds can only be revealed when large homologous series are examined. Literature *X*-ray structural studies are also exploited in order to comment on the situation in small rings and on their peculiar ring-closure tendency. It is suggested that, although some of the experimental features and behaviour can be accounted for in terms of strain, others, in the case of three-membered rings, are to be attributed to the presence of σ-aromaticity. Because of this, these three-membered ring compounds can efficiently gain stabilization by resonance interaction with exocyclic conjugative substituents: n.m.r. evidence is given on this point.

Examination of the behaviour of homologous series is of great significance in organic chemistry, because it often reveals interesting trends and features. For instance, this was the case when we reported on the mass spectra of a series of 1,1-bis(ethoxycarbonyl)cycloalkanes ranging from 4- to 21-membered rings.[1] Being involved for many years in ring-closure reactivity,[2] we are interested (*i*) in providing evidence, with the aid of several techniques, of structural factors that can be related to the strain affecting cyclic compounds and, consequently, (*ii*) in finding clues to explain their ring-closure tendency.

We describe here the results of an n.m.r. investigation carried out on *N*-substituted azacycloalkanes of different ring sizes.

Results and Discussion

The ^{13}C n.m.r. spectra of a series of *N*-tosylazacycloalkanes (I) including small- (3 and 4), common- (5 and 6), and medium (8, 10, and 13-membered) sized rings, were obtained in $CDCl_3$ along with the spectrum of a suitable non-cyclic compound taken as reference. In Table 1 the shielding of the heterocyclic methylene carbon (CH_2N) is reported. If one takes as reference the shielding in two practically strainless compounds, such as a six-membered ring and *N*,*N*-dibutyltosylamine, it appears that the larger the strain affecting the rings, the more pronounced are the resulting downfield shifts of the absorption of the chosen carbon. These strain values are derived from known heats of combustion of the parent unsubstituted cyclic amines.[3] In the absence of such data for the medium-sized cyclic amines, the values of the corresponding cycloalkanes were used.[3,4] Since heats of combustion of cycloalkanes and cyclic amines are extremely close, even for the small rings, such an approximation was considered satisfactory for the larger rings.



(I)

The data collected in Table 1 show a correlation between the strain of the ring and the shift of the CH_2N shielding, which we express in the form of relationship (1), where δ_n and δ_6 are,

$$(\delta_n - \delta_6) = \alpha \times \text{strain} \qquad (1)$$

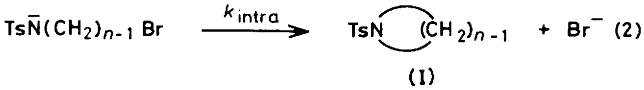
respectively, the carbon-shielding of a given ring and that of the six-membered ring taken as reference; the value α is 0.17 ± 0.01. The results closely follow the correlation, the only exception being the three-membered ring, which appears to behave in a non-comparable way to the larger cyclic homologues (Table 1).

Table 1. Strain, carbon shielding, and rate of formation of *N*-tosylazacycloalkanes (I)

		n^a							
		3	4	5	6^b	8	10	13	*N*,*N*-Dibutyltosylamine[b]
Strain energy	(kcal mol^{-1})	26.7	25.2	5.8	0	9.5	13.0	~7	0
Experimental	CH_2N δC^c	27.4	50.9	47.9	47.0	48.6	49.2	48.4	47.0
Predicted	CH_2N δC^d	51.5	51.3	48.0	47.0	48.6	49.2	48.2	
$k_{intra}/s^{-1\,e}$		88	0.027	630	13	5.7×10^{-4}	1×10^{-5}	4.5×10^{-4}	

[a] Dimension of the ring. [b] Taken as reference. [c] In p.p.m. from Me_4Si. [d] According to equation (1). [e] In Me_2SO at 25 °C. See equation (2) and reference 7.

Empirical correlations such as (1) have sometimes been exploited to predict the relative reactivity of cyclic compounds of different ring size, such as, for instance, in solvolytic processes.[4,5] It must be stressed, however, that such extrapolations may only be correct for ring sizes larger than six. In the small-ring region strong deviations from the predictions are likely, since the cyclic compounds (and their structural features) are no longer good models for the transition state.[6] This can be exemplified in Table 1, where the intramolecular rates of process (2) in Me_2SO at 25 °C are also given;[7] Ts = tosyl. While

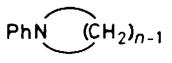


(2)

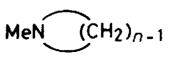
(I)

the results for the ring-closure tendency of the strained medium-sized rings are lower, as expected,[2] than that of the six-membered ring, in agreement with the trend of equation (1), the three- and four-membered rings form much more easily than their strains[4] would have predicted. Similar discrepancies have been well documented elsewhere.[6a,7]

A deeper insight into the anomalous behaviour of the small rings can be found by examining the $^1H-^{13}C$ coupling constant ($J_{^{13}\mathrm{C,H}}$) values obtained for *N*-tosylazacycloalkanes (I), *N*-phenylazacycloalkanes (II), and *N*-methylazacycloalkanes (III),



(II)



(III)

along with literature data for other cyclic compounds (Table 2). It is now accepted[4,8] that both open-chain aliphatic and alicyclic strainless compounds, presenting only sp^3 carbon atoms, display $J_{^{13}\mathrm{C,H}}$ values of *ca.* 125 Hz. The $J_{^{13}\mathrm{C,H}}$ values for compounds presenting sp^2 aromatic or vinylic carbon hybrids are, however, in the range 160—170 Hz. Introduction of electronegative atoms such as nitrogen or oxygen accounts for an increase in the $J_{^{13}\mathrm{C,H}}$ values of *ca.* 10 Hz.[9] It would appear therefore, from the widely accepted notion, that small strained alicyclic compounds, which present severe bond-angle distortions (from 109.5 to 90 or 60°), would cope with this geometric constraint by adjusting their sp^3 carbon hybrids so as to have a higher *p* character in the ring atom bonds.[10] This allows longer C–C bonds and smaller bond angles in the ring, which is a favourable consequence, but means that the remaining C–H bonds will have higher *s* character. The increasing $J_{^{13}\mathrm{C,H}}$ values (up to sp^2) of the four- and three-membered rings (Table 2) have been rationalized in this way.[4,8]

We do not want to question the general sense of this explanation, which, in our opinion, gives at least a partial account of the extraordinarily high reactivity of formation of small rings.[7] However, we feel that some comments and distinctions are necessary. For instance, Foote[11] reported evidence that medium-sized cycloalkanes, distorted as an effect of their strain, present $J_{^{13}\mathrm{C,H}}$ constants of less than 125 Hz, which implies CCC angles larger than tetrahedral (up to 116°). This characterization of medium-sized rings appears to be regarded as satisfactory and is quoted in the literature.[4] Our observations, resulting from the study of three series of compounds (Table 2), do not seem to strengthen these findings, in that the strained medium-sized rings display $J_{^{13}\mathrm{C,H}}$ values very close to those of their strainless homologues. Moreover, Foote pointed to some experimental difficulties arising from broadening of the signals, which we do not find with our heterocyclic compounds. Hence, whether the medium-sized rings present smaller $J_{^{13}\mathrm{C,H}}$ constants or not, the effect at play appears to be decidedly small on the basis of the larger number of compounds investigated by us, and in our view supports the opinion[12] that the major source of strain in the medium-sized rings is due to transannular 1,3- or 1,4-axial interactions or to eclipsing interactions, rather than to bond-angle deformations.[13]

Next, we want to point out a distinction between the three- and the four-membered rings. The structural parameters of the latter appear to be consistent with an extension to those of the larger homologues, as indicated (Table 1) by the agreement between the experimental ^{13}C-shielding (CH_2N) and the calculated one [from equation (1)]. In addition, on the grounds of the gradual increase in the $J_{^{13}\mathrm{C,H}}$ coupling constants from the common- to small-sized rings reported in Table 2, one also estimates that the *p* character of the intra-ring bonds becomes increasingly higher. The notion that this is accompanied by a lengthening of intra-ring bonds is confirmed by existing determinations[8,14,15] of interatomic distances, reported in Table 3, showing that the bonds of the four-membered rings are indeed longer than the standard ones. However, the bonds of the three-membered rings are not particularly long, in contrast with the trend of the $J_{^{13}\mathrm{C,H}}$ values and with the general explanation given previously. To overcome such a discrepancy, it had been assumed that the ring bonds in cyclopropane and its analogues are 'bent' and that consequently the resulting internuclear distances are shorter.[8,10]

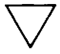
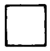
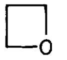
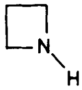
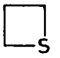
We feel that this and other anomalies and singularities of three-membered rings can be better explained according to the concept of σ-aromaticity, as reported recently by Dewar.[16] For example, an aromatic ring current can account for the peculiar CH_2N shift of (I, *n* = 3) reported in Table 1, which eludes

Table 2. $J_{^{13}\mathrm{C,H}}$ coupling constants (Hz) for some cyclic compounds[a]

	n^b											
	3	4	5	6	7	8	9	10	11	12	13	Open chain
N-Tosylazacycloalkanes, (I)[c]	175	149		138		136		134			135	*N,N*-Dibutyltosylamine, 136
N-Phenylazacycloalkanes, (II)[c]	171	144	138	133	133							*N,N*-Dioctylaniline, 134
N-Methylazacycloalkanes, (III)[c]	165		136	130	131				128		130	Trimethylamine,[d] 132
Cycloalkanes[e]	161	135	128	124	123	122		118		123		Ethane, 125
Cyclic ethers[d]	176	148	145	139								Dimethyl ether,[d] 140

[a] Average accuracy ± 0.5 Hz. [b] Dimension of the ring. [c] This work, determined on the heterocyclic methylene (CH_2N) signals from gated decoupled experiments. [d] Data from reference 9. [e] Data from reference 11.

Table 3. Interatomic distances (Å) of small-sized cyclic compounds[a]

	C–C = 1.524		C–C = 1.577	Me–Me	C–C = 1.535
	C–O = 1.436 C–C = 1.470		C–O = 1.46 C–C = 1.55	Me–OH	C–O = 1.427
	C–N = 1.488 C–C = 1.480		C–N = 1.46 C–C = 1.54	$HNMe_2$	C–N = 1.46
	C–S = 1.819 C–C = 1.492		C–S = 1.85 C–C = 1.55	Me–SH	C–S = 1.817

[a] Data from references 8, 14, and 15.

Table 4. Coalescence temperatures (T_c) for nitrogen inversion in *N*-substituted aziridines

N-substituent	T_c/ °C	Reference
Et	108	20
Ph	−77 to −40	20
Ph	−40	This work
$p\text{-}MeC_6H_4SO_2$	−30	20
$p\text{-}MeC_6H_4SO_2$	−25	This work
CF_3	−50	20
$\underset{\mathrm{O}}{\underset{\|}{\mathrm{MeC}}}$	< −160	20

prediction by equation (1). Moreover, σ-aromaticity may justify why the strain energy of cyclopropane is close to that of cyclobutane, and give a partial account of why some three-membered rings are so easily formed.[13]

Hence, the three-membered ring appears to have a peculiar nature and features not homogeneous with those of the higher homologues. As a direct consequence of its aromatic nature, resonance interaction with exocyclic conjugative group(s) becomes effective. This factor had been theoretically accounted for by Hoffmann and Davidson[17] and has been proposed by Stirling[18] to be responsible for the remarkably high ring-closure tendency of some three-membered rings. We suggest that a favourable result of such an orbital interaction would be represented by a lengthening of intra-ring bonds with a consequent relief of the strain. Indeed, the first experimental evidence for this point has appeared recently.[19] Our data (Table 2) offer further indications of lengthening of intra-ring bonds due to the same factor, since the $J_{^{13}\mathrm{C,H}}$ constant appears to increase, although slightly, on passing from *N*-methyl-aziridine (**III**, $n = 3$) to *N*-tosyl- (**I**, $n = 3$) or *N*-phenyl-aziridine (**II**, $n = 3$). This would reflect higher *p* character of the intra-ring bonds in the latter compounds, and could effectively reduce the strain in the transition state of the parent cyclization processes [such as in equation (2)].[7]

In addition to previous evidence, further proof of exocyclic conjugation in *N*-substituted aziridines is to be found in the rate of nitrogen inversion. N.m.r. spectrometry is a suitable tool for such studies.[20] Table 4 shows that, while the coalescence of the signals of the ring-methylene protons occurs for *N*-alkyl-aziridine at rather high temperatures, the presence of conjugative *N*-substituents dramatically reduces the coalescence temperature (T_c). In fact, conjugation lowers the nitrogen inversion barrier in (**II**, $n = 3$) by *ca.* 8 kcal mol^{-1} with respect to that of *N*-ethylaziridine, that for (**I**, $n = 3$) being some 6.5 kcal mol^{-1} lower.[21] This stabilizing factor in the cyclic compound can influence the transition state of the intramolecular reaction leading to it [such as in reaction (2)]. However, only a fraction of this conjugative interaction can play a role in the transition state. Thus, it is likely that at least part of the origin of the ring-closure tendency of (**I**, $n = 3$), being some two orders of magnitude higher than that of the unsubstituted aziridine, can be associated with the resonance interaction between the substituent and the three-membered ring.[7]

Conclusions

Experimental n.m.r. evidence has been collected on the peculiar nature and structure of three-membered rings with respect to the larger cyclic homologues. It is stressed that structural parameters of cyclic compounds, as assessed by several instrumental techniques, can be used to reflect the relative reactivity in ring-closure reactions, with the obvious exception of the small rings, where other factors are responsible for the unusual experimental behaviour. To account for the high ring-closure tendency of compounds such as (**I**, $n = 3$), resonance interaction with the exocyclic conjugative groups is suggested to be operating and this factor could be linked to the σ-aromatic nature of the three-membered rings.

Experimental

Preparation of *N*-tosylazacycloalkanes[7,22] and of *N*-methylazacycloalkanes[23] has been reported previously. *N*-Phenylazacycloalkanes were synthesized by standard procedures.[24]

^{13}C N.m.r. spectra were recorded at 308 K on a Bruker Spectrospin WP 80 SY spectrometer operating at 20.15 MHz, with a digital resolution of 0.488 Hz per point, 16K data points, 4 000 Hz sweep width. For the acquisition of broad-band proton-decoupled spectra, a 15—25° flip angle and a 1—2 s relaxation delay were used. Gated decoupled spectra were obtained using a 3—5 s saturation delay and a 60—80° flip angle. Solutions were 5—10% v/v. Deuteriochloroform was used as the solvent for both internal ^2H lock and internal reference (central peak 77 p.p.m. downfield from Me_4Si). Determinations of the coalescence temperature were carried out at 80.13 MHz, employing the variable temperature unit of the Bruker instrument.

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References

1 M. A. Casadei and C. Galli, *Org. Mass Spectrom.*, 1981, **16**, 551

2 G. Illuminati and L. Mandolini, *Acc. Chem. Res.*, 1981, **14**, 95.

3 J. D. Cox and G. Pilcher, 'Thermochemistry of Organic and Organometallic Compounds,' Academic Press, New York, 1970.

4 L. N. Ferguson, *J. Chem. Educ.*, 1970, **47**, 46.

5 P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1964, **86**, 1854.

6 (*a*) M. A. Casadei, C. Galli, and L. Mandolini, *J. Am. Chem. Soc.*, 1984, **106**, 1051; (*b*) D. F. DeTar and N. P. Luthra, *ibid.*, 1980, **102**, 4505.

7 A. Di Martino, C. Galli, P. Gargano, and L. Mandolini, *J. Chem. Soc., Perkin Trans. 2*, in the press, and unpublished work.

8 H. A. Bent, *Chem. Rev.*, 1961, **61**, 275; V. G. Granik, *Russ. Chem. Rev.* (*Engl. Transl.*), 1982, **51**, 119.

9 J. B. Stothers, 'Carbon-13 NMR Spectroscopy,' Academic Press, New York, 1972.

10 M. Yu. Lukina, *Russ. Chem. Rev.* (*Engl. Transl.*), 1962, **31**, 419.

11 C. S. Foote, *Tetrahedron Lett.*, 1963, 579.

12 N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Am. Chem. Soc.*, 1971, **93**, 1637.

13 L. Mandolini, personal communication.

14 E. Goldish, *J. Chem. Educ.*, 1959, **36**, 408; A. Almenningen, O. Bastiansen, and P. N. Skancke, *Acta Chem. Scand.*, 1961, **15**, 711.

15 For azetidine see P. D. Mollere and K. N. Houk, *J. Am. Chem. Soc.*, 1977, **99**, 3226 (note 28).

16 M. J. S. Dewar, *J. Am. Chem. Soc.*, 1984, **106**, 669.

17 R. Hoffmann and R. B. Davidson, *J. Am. Chem. Soc.*, 1971, **93**, 5699.

18 C. J. M. Stirling, *J. Chem. Educ.*, 1973, **50**, 844.

19 E. Osawa, P. M. Ivanov, and C. Jaime, *J. Org. Chem.*, 1983, **48**, 3990.

20 F. A. L. Anet, R. D. Trepka, and D. J. Cram, *J. Am. Chem. Soc.*, 1967, **89**, 357 and references cited therein.

21 P. Sohár, 'Nuclear Magnetic Resonance Spectroscopy,' CRC Press Inc., Boca Raton, FL, 1984, vol. 2, p. 94.

22 P. Gargano and L. Mandolini, *Gazz. Chim. Ital.*, 1982, **112**, 31.

23 G. Cerichelli, G. Illuminati, and C. Lillocci, *J. Org. Chem.*, 1980, **45**, 3952.

24 R. Bird, A. C. Knipe, and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1215; H. W. Heine, B. L. Kapur, and C. S. Mitch, *J. Am. Chem. Soc.*, 1954, **76**, 1173; C. Horning and F. W. Bergstrom, *ibid.*, 1945, **67**, 2110.

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