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INTRABRIDGEHEAD CHEMISTRY

ROGER W. ALDER
School of Chemistry, University of Bristol, Bristol BS8 1TS, England

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CONTENTS

1. Introduction 683
2. Bridgehead Chemistry 685
  2.1. Nitrogen at a bridgehead position 685
3. Geometry and Strain in Medium-ring Bicyclic Compounds 686
4. Intrabridgehead Interactions 689
  4.1. Direct interactions 690
    4.1.1. Four electrons in the intrabridgehead orbitals 690
    4.1.2. Three electrons in the intrabridgehead orbitals 694
      4.1.2.1. Three-electron σ-bonding 694
      4.1.2.2. Intrabridgehead three-electron $N\ldots N^{\cdot}$ cations 695
      4.1.2.3. An intrabridgehead $C^{\cdot}$:N interaction—evidence for very weak bonding 698
      4.1.2.4. Three-electron σ-bonding between phosphorus and nitrogen? 699
    4.1.3. Two electrons in the intrabridgehead orbitals 699
      4.1.3.1. Donor/acceptor intrabridgehead bonding 699
      4.1.3.2. Intrabridgehead bonds between atoms with like charges 699
    4.1.4. One electron in the intrabridgehead orbitals 701
    4.1.5. No electrons in the intrabridgehead orbitals 701
  4.2. Indirect interactions via hydrogen 701
    4.2.1. Five electrons in the intrabridgehead orbitals 701
    4.2.2. Four electrons in the intrabridgehead orbitals 702
      4.2.2.1. Mechanisms for inside protonation 702
      4.2.2.2. Equilibria for inside protonation 704
      4.2.2.3. Intrabridgehead hydrogen bonds: structure and properties 705
    4.2.3. Three electrons in the intrabridgehead orbitals 707
    4.2.4. Two electrons in the intrabridgehead orbitals: μ-hydrido-bridged carbocations 708
  4.3. Indirect interactions via elements other than hydrogen 709
5. Strain in Medium-Ring Bicyclic Systems—Effects at Non-bridgehead Atoms 709
6. Conclusions 710

1. INTRODUCTION

The subject of this review is the study of interactions and chemical reactions between two bridgehead atoms in a bicyclic system.[1] These interactions can be direct or occur via an intervening atom, as in hydrogen bonding. Intrabridgehead interactions can be seen as the fourth stage in the sequence: intermolecular, intramolecular and transannular interactions, illustrated for hydrogen bonding between amino nitrogen atoms in Fig. 1. Figure 1 shows the most favourable chain length and ring sizes for hydrogen bond formation;[2] for other interactions the optimum chain length/ring sizes will vary, but are likely to be always within the range of 3 to 5 atoms for each 'bridge' between the interacting atoms. Thus transannular reactions are most important for 8- to 11-membered rings (the classic medium rings).[3-7] By analogy then, we should look to bicyclic compounds built entirely from medium rings to provide the best vehicles for intrabridgehead interactions.

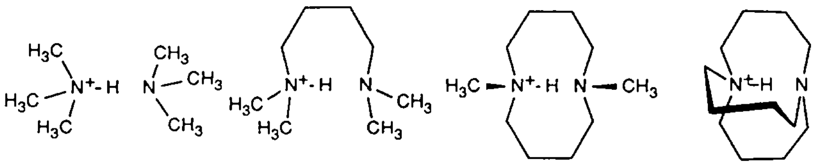

Intermolecular Intramolecular Transannular Intrabridgehead

Figure 1

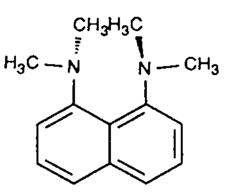
The 27 ring systems which only contain rings between 7- to 12-membered are listed in Table 1. The best choice from these for a particular interaction will be discussed later, but an important preliminary question must be answered first. The synthesis of medium ring bicyclic compounds is not a trivial matter—why bother? As one progresses from left to right across Fig. 1, there is a trade-off between increasing control over molecular geometry and increasing synthetic difficulty.

Table 1

Bicyclic Ring Systems Containing only 7- to 12-membered Rings

No. of Ring Atoms						
10						[3.3.2]
11				[4.4.1]	[4.3.2]	[3.3.3]
12			[5.4.1]	[5.3.2]	[4.4.2]	[4.3.3]
13	[6.4.1]	[5.5.1]	[6.3.2]	[5.4.2]	[5.3.3]	[4.4.3]
14	[7.3.2]	[6.4.2]	[5.5.2]	[6.3.3]	[5.4.3]	[4.4.4]
15			[7.3.3]	[6.4.3]	[5.5.3]	[5.4.4]
16					[6.4.4]	[5.5.4]
17						[5.5.5]

Moreover, molecular geometry can be controlled in other ways, e.g. by introducing rigid elements. Thus simple acyclic diamines are not unusually basic in solution,[8] but enhanced basicity can be achieved in 'proton sponges' such as **1**[9] and **2**.[10] To understand the special advantages of the intrabridgehead case, we need to remember the unique properties associated with bridgehead atoms in general and the special molecular mechanics of bicyclic medium-ring compounds; these are briefly reviewed next. However, two simple advantages of the intrabridgehead situation should always be borne in mind. First, the two bridgehead atoms cannot escape far from one another even if there is repulsion between them. Thus the transannular situation has provided important examples of weak attractive interactions such as those between amines and carbonyl groups.[4–7] However it is fundamentally unsuitable for looking at repulsive interactions. Secondly, only in the fourth (intrabridgehead) situation in Fig. 1 is the direction of the important orbitals and bonds controllable (e.g. the lone pair and the N–H bond).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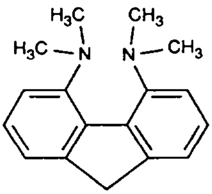
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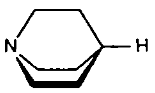
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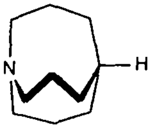

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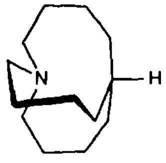

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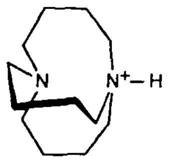

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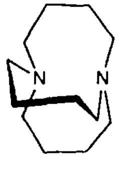

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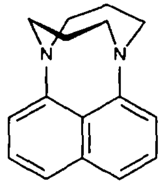

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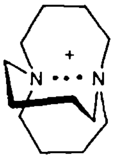

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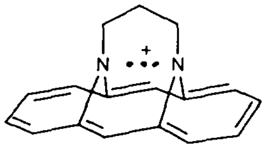

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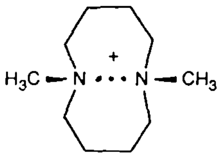

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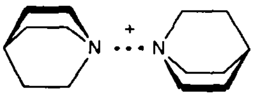

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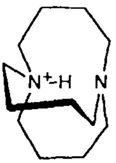

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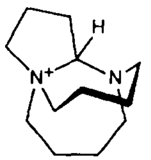

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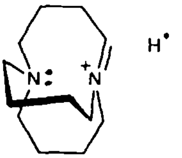


15

2. BRIDGEHEAD CHEMISTRY

The investigation of the chemical reactions and properties of bridgehead atoms has a long and distinguished history, going back to the early investigations of bridgehead alkenes.[11,12] Our understanding of the properties and structures of carbonium ions,[13,14] and to a lesser extent radicals and carbanions has been advanced significantly by studies of the effects of generating these at bridgehead sites. A review of this work would be out of place here, although reference to selected aspects will be made later. The effects of siting a centre of interest at a bridgehead can of course be studied with any atom which is at least three-coordinate. The properties of bridgehead nitrogen atoms will be briefly discussed here since they are particularly relevant to the N . . . N intrabridgehead chemistry which forms a major part of this review.

2.1. *Nitrogen at a bridgehead position*

The effects of the geometrical constraints imposed at bridgeheads can be nicely seen in the properties (Table 2) of the three amines 1-azabicyclo[2.2.2]octane (quinuclidine) **3**, 1-azabicyclo[3.3.3]undecane (manxine) **4**,[15-17] and 1-azabicyclo[4.4.4]tetradecane **5**[18] (which we christened hiddenamine because of its apparently hidden lone pair). Quinuclidine **3** behaves as a normal, unhindered, tertiary amine in its reactions as a base and nucleophile, since for an amine which is already pyramidal, there is little geometrical change involved in these reactions. However

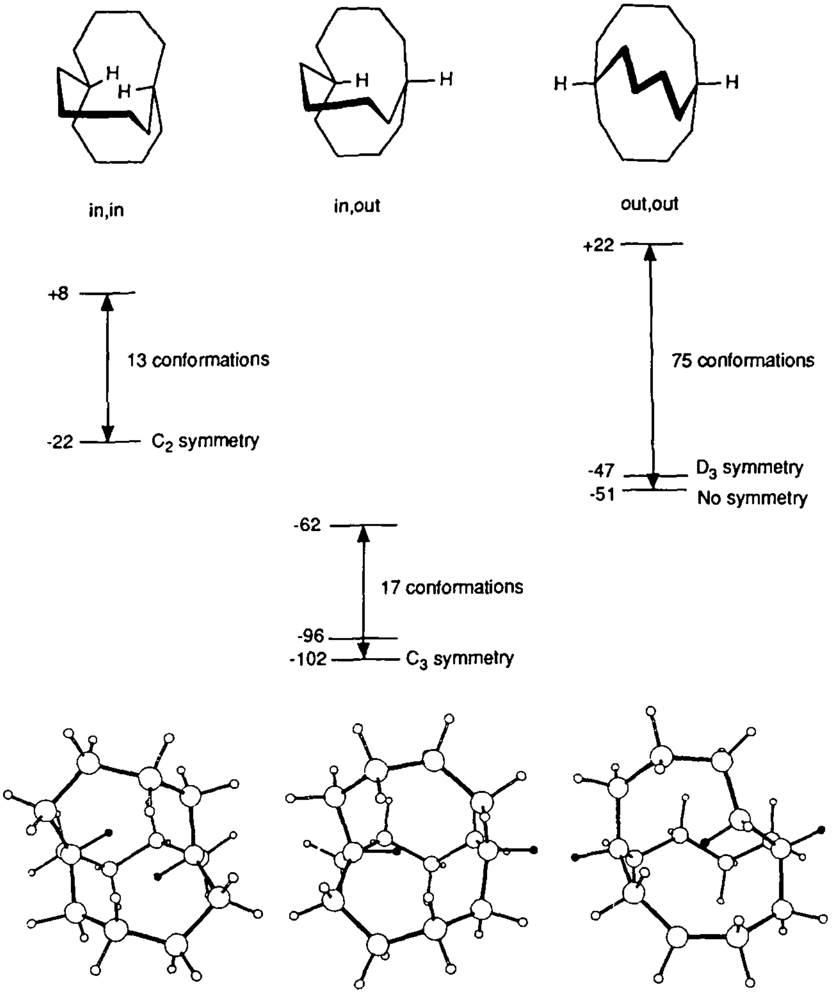
Table 2
Properties of Bridgehead Monoamines

	Quinuclidine (3)	Manxine (4)	Hiddenamine (5)
pK_a	10.95	9.9	0.6
Proton Affinity (PA) in kJ/mol	977	977	908
PA of acyclic model	979 (Et_3N)	988 ($n\text{-}Pr_3N$)	994 ($n\text{-}Bu_3N$)
Ionisation Energy, eV	8.06	7.13	7.84
UV spectrum			220 nm (Σ 4800) in $EtOH/H_2O$ or isooctane
Hydrogen bonding (with PhOH in CCl_4)	Yes	Yes	No
Solubility in H_2O			$<10^{-6}$ M
Reaction with CH_3I	Yes	Yes	No
Reaction with CH_3OSO_2F	Violent	Violent	Half-life 94 h in CH_2Cl_2 at 25°

3 shows an unusually high ionisation potential;[19] this can be rationalised because amine radical cations are normally planar, but that geometry is impossible in this case. Although the precise geometry of manxine **4** is unknown, this amine behaves as if the nitrogen atom was practically planar. It is a somewhat weaker base than normal, but shows an unusually low oxidation potential. In the photoelectron spectrum, the first ionisation band is sharp, unlike typical amines, and this is due to the fact that the amine is already in the geometry of the radical cation, so that the transition between the lowest vibrational levels is strong.[19] Hiddenamine **5**, is an exceptionally weak base both in the gas phase[20] and in solution;[18] it is also very unreactive as a nucleophile reacting only very slowly with methyl fluorosulphate, a reagent which reacts almost explosively with typical amines.[21] On the other hand its photoelectron spectrum is rather normal.[20] We explained these properties by postulating that the nitrogen was pyramidalised inwards, and that there was a large penalty to pay in the form of increased strain when the nitrogen inverted to have an outside lone pair. This is supported by molecular mechanics calculations (see Section 3 below).

3. GEOMETRY AND STRAIN IN MEDIUM-RING BICYCLIC COMPOUNDS

The familiar bicyclic ring systems built from common-sized rings (5- and 6-membered) are mostly rigid, and only relatively simple conformational problems arise, such as the question of chair–chair vs. chair–boat conformations for bicyclo[3.3.1]nonanes. In contrast, medium-ring bicyclic compounds are conformationally very complex. Although the introduction of a bridge into a monocyclic medium-ring system must reduce the number of possible conformations, prediction and understanding of the possibilities is a difficult matter. This was forcibly brought home to us when we tried to find the best structures for the various isomers (*out,out*-, *out,in*- and *in,in*-) of bicyclo[4.4.4]tetradecane using MM2 calculations.[22-25] We accidentally located a completely unsymmetrical conformation for the *out,out*-isomer which was more stable than any symmetrical structure we could devise. It was obvious that there were potentially many other unsymmetrical conformations, and virtually impossible to be sure we had found the best. Saunders' stochastic search procedure[26] provides an ideal answer to this problem and it has now been applied to many of the basic medium-ring bicyclic ring systems. The results for the bicyclo[4.4.4]tetradecane ring system are summarised in Fig. 2.[27] In fact, our intuitive guesses for the *out,in-* and *in,in*-isomers and our lucky accident for the *out,out*-isomers were the best structures, but the number of conformational energy minima found dramatically illustrates the complexity of the situation. Similar calculations have been performed for many of the other bicyclic medium-ring systems and the strain energies of the global minima are given in Table 3.[28] As the sizes of the rings increase, the strain energy of the *out,out*-isomer increases rapidly, reaching a maximum at the [4.4.4] system. *Out,out*-bicyclo[4.4.4]tetradecane, built entirely from ten-membered rings, has a strain energy which is more than three times that of cyclodecane[29] on a per-carbon-atom basis. Because of this high strain energy, *in,out*-isomers become preferred to *out,out* in surprisingly small ring systems. As it happens, the maximum strain energy among the *in,out*-isomers also occurs in the [4.4.4] system. Even *in,in*-[4.4.4] is only a little less strained than the *out,out*-isomer, and the *in,in*-isomer becomes preferred



in, in -37 kJ/mol   in, out -102 kJ/mol   out, out -51 kJ/mol

Figure 2 Molecular mechanics calculations for bicyclo[4.4.4]tetradecane. Calculated heats of formation are in kJ/mol. In the structural diagrams, the bridgehead hydrogen atoms are shown black, and the hydrogen which is tipped inside in the *out,out*-isomer is shaded.

Table 3

Strain Energy of Bicyclo[k.l.m]alkanes

Bicyclo[k.l.m]alkane	MM2 Strain Energy for the Global Minimum Structure (kJ/mol) *out,out*	*out,in*	*in,in*
Bicyclo[3.2.2]nonane	76.6	315.8	
Bicyclo[3.3.2]decane	97.7	251.8	517.0
Bicyclo[3.3.3]undecane	125.6		469.9
Bicyclo[4.3.3]dodecane	170.2	200.3	357.9
Bicyclo[4.4.3]tridecane	208.2	193.4	309.0
Bicyclo[4.4.4]tetradecane	248.7	197.6	262.3
Bicyclo[5.4.4]pentadecane	223.0	188.9	224.8
Bicyclo[5.5.4]hexadecane	222.8	185.0	194.7
Bicyclo[5.5.5]heptadecane	207.7	179.7	161.4

in the [5.5.5] system. One conclusion which can be drawn from these calculations is that the symmetrical [4.4.4] ring system can be regarded as the archetypal bicyclic medium-ring system; fortunately, we had earlier guessed this and concentrated our efforts on this system.

Of course, the changeover from preference for *out,out*- to *in,out*- to *in,in*-structures will be a function of the size of the groups on the bridgehead atoms. In particular, lone pairs are 'smaller' than hydrogen atoms, so that the changeover will occur earlier for bridgehead amines than for the corresponding hydrocarbons. Thus *out*-6H-1-azabicyclo[4.4.4]tetradecane (hiddenamine) **5** is calculated[20,27] to strongly prefer to have its lone pair inside, and this is supported by the X-ray structure[27] of the isoelectronic outside monoprotonated ion **6** from 1,6-diazabicyclo[4.4.4]decane **7**. Even the (unknown) *in*-6H-isomer of hiddenamine should prefer to have an inside lone pair. The calculated heats of formation (in kJ/mol) of the four structures are:

out-6H, *out*-N	232
out-6H, *in*-N	309
in-6H, *out*-N	242
in-6H, *in*-N	273

The diamine, 1,6-diazabicyclo[4.4.4]tetradecane, which will be referred to as the [4.4.4]diamine, prefers an *in,in* geometry,[30] despite the lone pair–lone pair repulsion this entails. Nitrogen can, in principle, be forced into a continuum of geometries from *out,out* to *in,in*. The naphtho[3.3.3]diamine **8**, has almost planar nitrogen atoms[31] and this is probably also the case for the [3.3.3]amine itself. In less symmetrical ring systems such as [6.3.1], *in,out* geometries are preferred.[32]

The structure/strain situation in medium-ring bicyclic compounds forces inverting atoms like nitrogen to have inside lone pairs, with interesting consequences, but the most effective strain-relieving process is intrabridgehead bond formation. We have tried to assess the thermodynamics for this process by calculating the energetics of the hypothetical dehydrogenation reaction which removes the bridgehead hydrogen atoms from a bicyclic ring system and forms a propellane. The results are shown in Table 4;[1,33] similar calculations for related dehydrogenations provide a yardstick and serve to show that the [4.4.4] system is once again the peak performer. In fact the strain relief on *bond formation* in this case is comparable with the strain relief from the *bond-breaking* hydrogenation in the most strained small ring systems (the reverse reaction). It is also important to understand that intrabridgehead bond formation is much more strain-relieving than alternative transannular dehydrogenations in the [4.4.4] system (Fig. 3). The unique properties of medium-ring bicyclic compounds are certainly intimately connected with these special structure/strain relationships.

Table 4

Heats of Some Formal Dehydrogenations[a]

Hydrocarbon	Dehydrogenation Product	Heat of Dehydrogenation (kJ/mol)
2 x Propane	2,3-Dimethylbutane	+29
Cyclopentane	Bicyclo[2.1.0]pentane	+234
Cyclodecane	*trans*-Decalin	-29
2 x 2-Methylpropane	2,2,3,3-Tetramethylbutane	+46
Bicyclo[1.1.1]pentane	[1.1.1]Propellane	+163
Bicyclo[2.2.2]octane	[2.2.2]Propellane	+280
Bicyclo[3.3.3]undecane	[3.3.3]Propellane	-22
Bicyclo[4.3.3]dodecane	[4.3.3]Propellane	-54
Bicyclo[4.4.3]tridecane	[4.4.3]Propellane	-103
Bicyclo[4.4.4]tetradecane	[4.4.4]Propellane	-151
Bicyclo[5.4.4]pentadecane	[5.4.4]Propellane	-90
Bicyclo[5.5.4]hexadecane	[5.5.4]Propellane	-41
Bicyclo[5.5.5]heptadecane	[5.5.5]Propellane	+2

[a] Only *out,out*-isomers considered.

4. INTRABRIDGEHEAD INTERACTIONS

Intrabridgehead interactions will be divided into direct ones and those via an intervening atom. It is also useful to classify each by the number of electrons involved in the interaction, as illustrated in Fig. 4. The discussion which follows will be ordered by decreasing electron count, since more is known about the electron-rich cases.

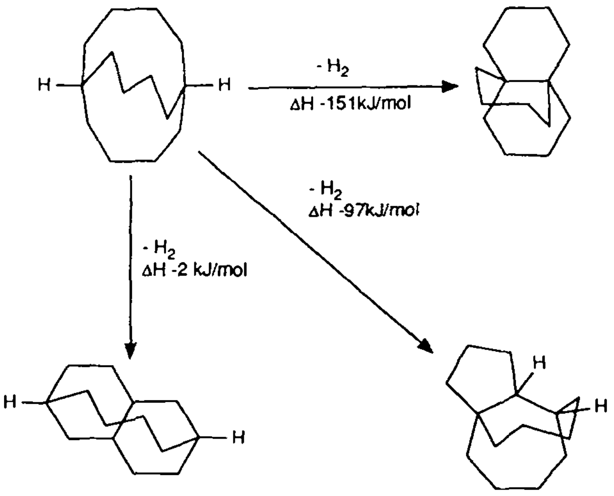
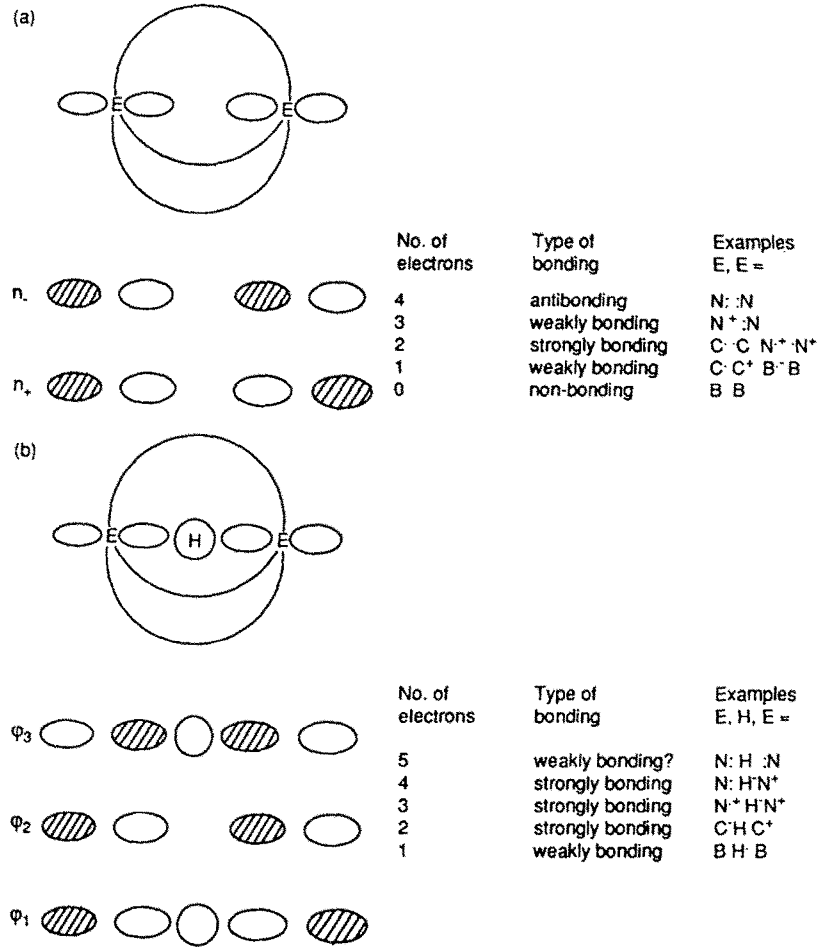


Figure 3 Alternative formal transannular dehydrogenations of *out,out*-bicyclo[4.4.4]tetradecane. The 2,6-bridged decalin can be formed in *cis* or *trans* form, but the energetics are approximately the same.



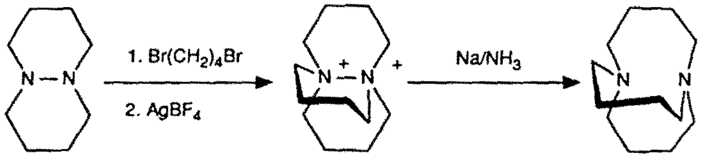
No. of electrons	Type of bonding	Examples E, E =
4	antibonding	$\mathrm{N{:}\ {:}N}$
3	weakly bonding	$\mathrm{N^{+}\ {:}N}$
2	strongly bonding	$\mathrm{C\cdot\ \cdot C\quad N^{\cdot+}\ \cdot N^{+}}$
1	weakly bonding	$\mathrm{C\cdot\ C^{+}\quad B^{\cdot-}\ B}$
0	non-bonding	B B

No. of electrons	Type of bonding	Examples E, H, E =
5	weakly bonding?	$\mathrm{N{:}\ H\ \ {:}N}$
4	strongly bonding	$\mathrm{N{:}\ H^{-}N^{+}}$
3	strongly bonding	$\mathrm{N^{\cdot+}\ H^{-}N^{+}}$
2	strongly bonding	$\mathrm{C^{-}H\ C^{+}}$
1	weakly bonding	$\mathrm{B\ H\cdot\ B}$

Figure 4 Simple orbital picture for intrabridgehead interactions (a) direct interactions (b) indirect interactions via hydrogen.

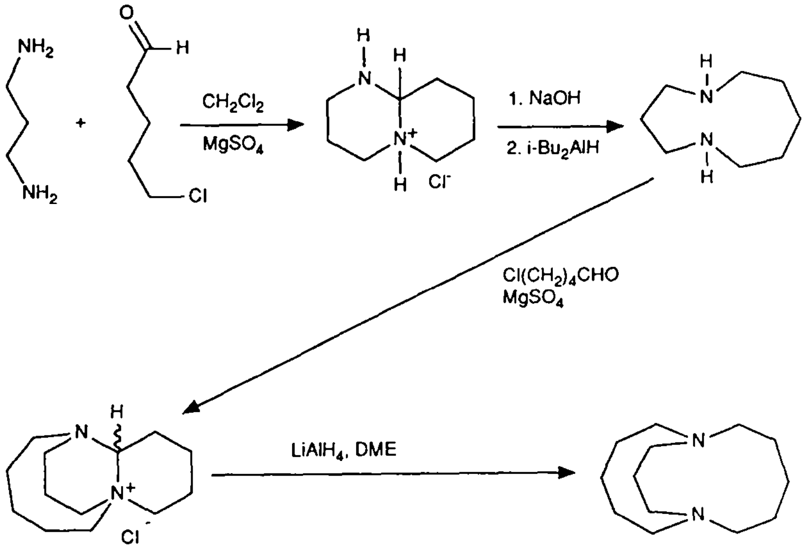
4.1. *Direct interactions*

4.1.1. *Four electrons in the intrabridgehead orbitals.* The only case which has been studied in any detail involves two nitrogen atoms. Of the 27 ring systems in Table 1, 21 have been prepared at Bristol in the form of bicyclic bridgehead diamines. Two main synthetic routes were developed, both using ring cleavage as the principal strategy. The first uses reductive cleavage of propellane hydrazinium dications[34–36] and is illustrated by the preparation of the [4.4.4]diamine shown in Scheme 1. The chief limitation of this route is in the cycloalkylation to make the hydrazinium



Scheme 1

dications; hydrazinium monocations are, not surprisingly, weak nucleophiles, so that using halides and silver tetrafluoroborate, only five- and six-membered rings could be closed efficiently. Nelsen *et al.*[36b] have used this route to make some diamines with one bridgehead and one non-bridgehead nitrogen atom, such as 6-methyl-1,6-diazabicyclo[6.2.2]dodecane. The second, and more versatile, route involves hydride cleavage of α-aminoammonium ions[37,38] and is illustrated by the synthesis of the [5.5.3]diamine, Scheme 2.



Scheme 2

The chemical properties of these diamines vary according to the sizes of the bridges they contain, but many of them are quite unstable in the air, being rapidly oxidised to sticky, insoluble materials. It seems that this behaviour is due to the repulsive four-electron interaction in the diamines which is converted into a weakly bonding interaction in the radical cation produced on oxidation. When the oxidation of these diamines is examined in solution by cyclic voltammetry, it is found that many of them are oxidised exceptionally easily.[34,35,39] Thus the [4.4.4]diamine is oxidised at a more negative potential than N,N,N′,N′-tetramethylphenylenediamine, the diamine which produces the well-known and indefinitely stable Wurster's blue radical cation. Further oxidation with loss of a second electron occurs *much* more easily for the [4.4.4]diamine than for the aromatic diamine; a new strong two-electron σ-bond is formed.

The ease of electron loss from these diamines can also be examined in the gas phase by photoelectron spectroscopy (PES).[20,31,32,34,40] Two ionisation bands are seen (Table 5) in the region corresponding to loss of lone pair electrons and, in terms of Koopmans' theorem, these can be seen as arising from removal of electrons from the antibonding and bonding molecular orbitals derived from the lone pair orbitals. The splitting is a measure of the interaction of the lone pair orbitals. For diamines containing only bridges of three or more methylene groups, we believe that the interactions are almost entirely direct (through-space). Historically, the first bridgehead diamine to be examined by PES was 1,4-diazabicyclo[2.2.2]octane,[41] (DABCO) and in this case the interaction is predominantly through-bond.[42–45] The remnants of through-bond interaction can be seen in other diamines with one or two two-carbon bridges.

Table 5

Lone Pair Ionisation Energies for Bicyclic Diamines

Bicyclic Diamine	Ionisation Energy (eV)[a] I_1	I_2	I_2-I_1	$(I_1+I_2)/2$
[3.2.1]	8.90	9.65	0.75	9.30
[3.3.1]	7.75	8.80	1.05	8.30
[4.3.1]	7.45	8.45	1.00	7.95
[4.4.1]	7.40	8.50	1.10	7.95
[5.3.1]	7.40	8.55	1.15	8.00
[6.3.1]	8.00	8.00	0.0	8.0
[2.2.2]	7.60	9.70	2.10	8.60
[3.2.2]	7.45	8.65	1.20	8.05
[3.3.2]	7.55	7.80	0.25	7.70
[4.3.2]	7.35	7.60	0.25	7.50
[4.4.2]	7.30	7.60	0.30	7.45
[5.3.2]	7.30	7.30	0.0	7.30
[5.4.2]	7.15	7.65	0.50	7.40
[6.3.2]	7.35	7.70	0.35	7.55
[5.5.2]	7.15	7.65	0.50	7.40
[3.3.3]	6.85	7.90	1.05	7.40
[4.3.3]	6.75	7.80	1.05	7.30
[4.4.3]	6.65	7.75	1.10	7.20
[5.3.3]	6.60	7.90	1.30	7.25
[5.4.3]	6.75	8.05	1.30	7.40
[6.3.3]	6.80	8.00	1.20	7.40
[5.5.3]	7.00	8.15	1.15	7.60
[6.4.3]	7.00	8.05	1.05	7.50
[6.5.3]	7.15	8.10	0.95	7.65
[4.4.4]	6.75	7.85	1.10	7.30
[5.4.4]	6.95	8.00	1.05	7.50
[5.5.4]	7.25	8.10	0.85	7.70

[a] Allvalues rounded to ±0.05 eV

Figure 5 shows that there is only a rough correlation of ionisation energies from PES with the electrochemical oxidation potentials.[34,35,39,46] A major reason for this is that electron removal in PES is a vertical process, so the radical cation is formed in the geometry of the diamine, whereas oxidation in solution is adiabatic, so there is genuine chemical equilibrium. As we shall see, there are likely to be large differences in structure between the diamine and its radical cation.

Unfortunately, there is only meagre structural data available for these diamines. Many of them give apparently well-formed, waxy crystals, but these give no diffraction patterns at all. We assume that these almost spherical molecules are rotating in the solid state. The structures of naphtho-fused [3.3.3]diamine **8**[31] and of the [4.4.4]diamine **7**[30] have been determined. In the latter, the nitrogen atoms are 2.81 Å apart (see Fig. 6) and it is apparent from an examination of the bond and torsion angles within the four-carbon bridges that there is considerable strain. In fact we calculated using MM2 that the strain energy within the bridges would decrease by 22 kJ/mol if the N...N distance were to decrease to 2.53 Å (which is the N...N distance in the inside protonated ion). It should be noted that MM2 somewhat underestimates the effects of the lone pair-lone pair repulsion; it calculates the N...N distance in [4.4.4]diamine to be 2.65 Å. It is of course a moot point whether a molecular mechanics program should be able to deal with such an electronic interaction.

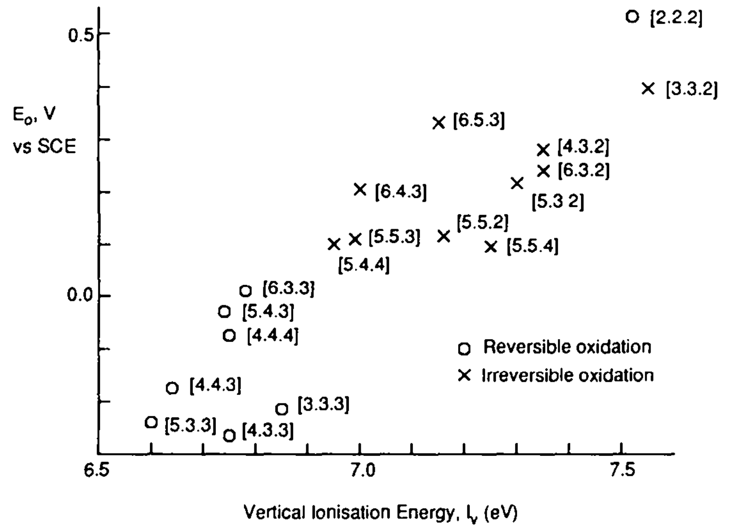


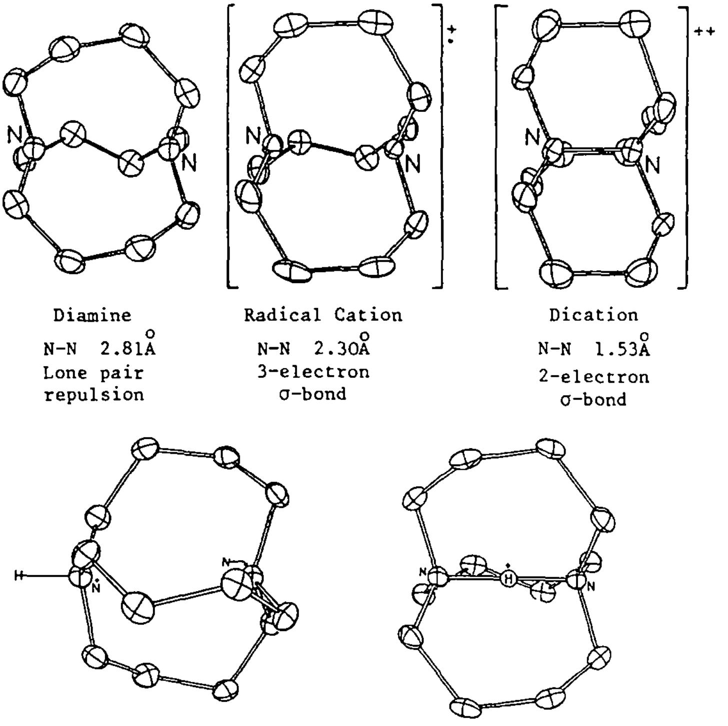
Figure 5 Correlation of electrochemical oxidation potentials in acetonitrile solution with first ionisation energies from photoelectron spectra for bicyclic diamines. Diamines which show irreversible oxidation give radical cations with lifetimes of less than 1 sec at room temperature.

Evidence of lone pair–lone pair repulsion can also be seen in the electronic spectrum of these diamines. For example, the [3.3.3]diamine shows a maximum at 217 nm (Σ 5700) with a shoulder at 278 nm (Σ 700);[34] the bands for the [4.4.4]diamine are at 233 nm (Σ 8100), with a shoulder at 261 nm (Σ 3800).[35] However, it is difficult to disentangle the effects of geometry of the individual nitrogen atoms from that of the nitrogen–nitrogen interaction. The monoamine manxine **4** also shows unusually long wavelength absorption.[16,47]

The lack of structural information on the diamines also prevents more thorough interpretation of the photoelectron spectra, where both nitrogen geometry and the lone pair–lone pair repulsion will affect the band position. Here, however, it is likely that the separation of the two bands will mainly reflect the lone pair- lone pair repulsion, whereas the mean position of the two bands will reflect the hybridisation and thus geometry at the nitrogen atoms. In practice, the separation between the two bands reaches a maximum (about 1.3 eV) and the average of the two ionisation energies reaches a minimum (at about 7.3 eV) with diazabicyclotridecanes (13 heavy atoms). This is indeed near the point where we believe that the switchover from outside to inside lone pairs is occurring (i.e. the nitrogen atoms are likely to be nearly planar). It is also close to the point where the strain energy in these systems reaches a maximum (see Section 3), and so is presumably the region where strain will force the lone pairs into closest proximity.

4.1.2. *Three electrons in the intrabridgehead orbitals*

4.1.2.1. *Three-electron σ-bonding.* Three-electron σ-bonding dates back to the recognition of the [Cl... Cl] ion as the cause of one type of 'colour centre' in alkali metal chloride crystals in 1959,[48] and it has now been observed in a wide variety of chemical 'contexts' ranging from simple gas-phase ionic species like [He... He]$^+$,[49] observed spectroscopically, to the use of pyridine... Cl adducts as reagents for remote functionalisation.[50] However, the great majority of cases concern species which would have a very short lifetime (if they existed at all) in fluid solution or the solid state at ambient temperature.[51-53] By making the three-electron σ-bond an intrabridgehead bond, we can attain this convenient level of persistence.



Diamine
N-N 2.81Å
Lone pair repulsion

Radical Cation
N-N 2.30Å
3-electron σ-bond

Dication
N-N 1.53Å
2-electron σ-bond

Outside protonated
N-N 3.11Å
Unprotonated lone pair inside

Inside protonated
N-N 2.53Å
Linear H-bond

Figure 6 Structure of 1,6-diazabicyclo[4.4.4]tetradecane ([4.4.4]diamine) and of ions derived from it. C-H hydrogen atoms have been omitted for clarity. The N-H hydrogen atom on the outside protonated ion was not located in the X-ray structure.

Three-electron σ-bonding has been the subject of high-level (MP2/6-31G* or better) *ab initio* calculations by Radom and co-workers[54,55] and by Clark.[56,57] Clark has studied all the possible species which can be derived from combinations of the hydrides from lithium to argon. For homonuclear dimers, the calculated bond dissociation energies range up to 200 kJ/mol for $[HF\ldots FH]^+$, so that some of these bonds are calculated to be quite strong. Quite a range of homonuclear three-electron σ-bonded species are now known. An interesting outcome of the calculations is that for heteronuclear three-electron bonds, Clark finds a good correlation between the calculated dissociation energies and the difference in the ionisation energies of the partners. Thus Clark finds that a methyl radical does not bind to ammonia according to a UHF/6-31G calculation, even though the calculated bond energy for $[H_3N\ldots NH_3]^+$ is 150 kJ/mol. A simple valence bond explanation of this dramatic result is the effectiveness of the charge-sharing no-bond resonance for $[H_3N\ldots NH_3]^+$ compared with the ineffectiveness of the charge separating resonance for $[H_3C^{\cdot}:NH_3]$ (Scheme 3).

We shall see some experimental evidence for this in an intrabridgehead situation later, but it is indeed true that most of the known heteronuclear[52] three-electron bonds are between atoms or groups which have similar electronegativities.

$$H_3N^{\cdot+}\ :NH_3 \leftrightarrow H_3N:\ ^{\cdot}NH_3^{+}$$
$$H_3C^{\cdot}\ :NH_3 \leftrightarrow H_3C:^{-}\ ^{\cdot}NH_3^{+}$$

Scheme 3

4.1.2.2. *Intrabridgehead three-electron N . . . N^+ cations.* We had hoped twenty years ago, in studying 1,8-bis(dimethylamino)naphthalene (Proton Sponge),[9] that the interaction between the two lone pairs would lead to easy oxidation to a stable radical cation; this was shortly after the observation that the radical cation of 1,4-diazabicyclo[2.2.2]octane (DABCO) persisted for about one second at room temperature.[58] Although 'Proton Sponge' is indeed easily oxidised, we were unable to see a persistent radical cation, and pulse radiolysis experiments subsequently indicated[59] a lifetime of no longer than a microsecond. It has been claimed recently[60] that the radical of 'Proton Sponge' can be generated electrochemically, however the reported ESR spectrum was featureless, quite unlike those discussed below, and we believe that the simple three-electron species has not been observed.

It was not until we made the naphtho[3.3.3]diamine **8** that we found a long-lived radical cation. Acidic aqueous solutions of this diamine turn red over a period of weeks—not uncommon behaviour for an aromatic amine; we paid no attention to this for some months, but eventually the unusual structure of this diamine and its very low first ionisation energy persuaded us to look at the solution oxidation, and we found that the simple three-electron radical cation is formed and lasts for months in polar organic (CH_3CN) and acidic aqueous solution.[31,39]

We subsequently oxidised a wide range of bicyclic medium-ring diamines electrochemically,[34,35,39,46] and found that only the following gave radical cations with lifetimes of more than one second at room temperature in acetonitrile: [3.3.3], [4.3.3], [4.4.3], [5.3.3], [4.4.4], [5.4.3] and [6.3.3.] (see Fig. 5). In terms of simple bench experience, we find that 'stability' (really, persistence) increases along the series [3.3.3] < [4.3.3] = naphtho[3.3.3] < [4.4.3] < [4.4.4]. The [4.3.3] survives evaporation of the solvent and immediate redissolution, the [4.4.3] can be kept as a solid for a few hours, while the [4.4.4]diamine radical cation **9** is indefinitely stable as a crystalline solid.[61,62] Vogel *et al.*[63] have prepared **10**, which can be regarded as a modified [3.3.3] structure and this is also stable as a solid. It really is remarkable that the [5.4.4]diamine, for example, gives a radical cation with a lifetime of less than one second, but contains only one extra methylene than the [4.4.4], and has very similar ionisation and oxidation potentials.

The two most important parameters of a bond are its strength and its length. Theoretical calculations give a bond length of 2.16 Å for the simplest species $[H_3N\ldots NH_3]^+$;[54–57] the calculated H—N—H bond angle is 112.8°. The bond length in **9** is 2.295 Å, while **10** has an appreciably shorter N . . . N bond of 2.160 Å. In broad terms the agreement with theory can be regarded as excellent. There is also a substantial difference between the two crystal structures with regard to the angles at the nitrogen atoms, 114.0° in the former and an average of 119.1° in the latter. Undoubtedly, this reflects the different demands of the two cage structures. Indeed it may be that the three-electron σ-bond, being inherently weak, is also inherently easily distorted. Nevertheless it is curious that it is the [4.4.4] structure which shows the longer bond because it is undoubtedly true that this ring system has the shorter N . . . N distance when the bridges are strain-free. It is therefore worth noting that theoretical treatments show that three-electron σ-bonds, unlike normal two-electron bonds, are not dependent on overlap and are in fact destroyed by too much.[64] In **10** the three-electron σ-bond is formed from nearly pure p orbitals, whereas in **9** the appropriate orbitals will have appreciable s character. At a given distance, p orbitals will overlap less than inwardly-pointing sp^x orbitals, so that the actual structures may be adjusted to ensure that overlap is similar in the two cases.

The strength of the three-electron σ-bond cannot be easily obtained in these cage structures. It is possible to make an estimate of an upper limit based on the PE spectrum of the diamine or, better, on the electronic spectrum of the radical cation. The argument runs the following way. The transition responsible for the red-brown colour of the radical cations (the maximum is at 480 nm for the [4.4.4] radical cation) is undoubtedly due to the promotion of an electron from the S (symmetrical, through-space bonding) to the A (antisymmetrical, through-space antibonding) orbital, so that the excited state has the electronic structure $S(\uparrow)A(\uparrow\downarrow)$. In effect, the three-electron σ-bond has been replaced by an anti-bond and half a bond. Therefore the transition energy should be twice the three-electron σ-bond energy, which leads to an estimate of 130 kJ/mol for the bond energy. This is an upper limit, since orbital overlap means that the antibonding A level is always raised above the non-bonding level by more than the bonding S level is stabilised.

We suggested that another estimate of the bond strength of a three-electron σ-bond could be made from the activation energy (61 kJ/mol) for the decomposition of the radical cation **11**.[65] This radical cation can be generated by pulse radiolysis but has a lifetime of only 5 ms at room temperature. The contrast in the lifetimes between **9** and **11** is dramatic proof of the effectiveness of the intrabridgehead situation for producing persistence in these delicate species, since we can expect that the structure of **11** is very similar to that of **9**; we know that the corresponding $N \ldots H—N^+$ ions are of very similar structure (see later) and three-electron σ-bonds and hydrogen bonds have rather strengths and lengths. The assumption in this estimate of bond strength is of course that succeeding reactions are fast. The very short lifetimes of simple amine radical cations makes this likely. It is worth noting in passing that this estimate of the strength of a three-electron σ-bond makes it somewhat weaker than the three-electron π-bond in the radical cations of hydrazines,[66] which is surprising, since with normal two-electron bonds σ-bonds are always more stable than similar π-bonds. It is also well below the theoretical estimate for $[H_3N \ldots NH_3]^+$ (150 kJ/mol); a major reason for this must be the hexaalkyl substitution in our examples—the hydrocarbon analogy would be of the bond strengths of ethane and hexamethylethane.

Recently, Dinnocenzo and Banach[67a] prepared the first unsupported three-electron σ-bond between nitrogen atoms in the dimer ion **12** in a very elegant experiment involving oxidation of quinuclidine with an O_2^+ salt. They were unable to generate similar dimer ions from any other amines and they therefore suggested that **12** was unique in having a three-electron σ-bond between nitrogen atoms with a positive bond energy because the nitrogen atoms of quinuclidine radical cation are necessarily pyramidal; no reorganisation energy is therefore required to form the dimer radical ion. They suggested that other $N \ldots N$ three-electron σ-bonds would have negative bond energies, due to the reorganisation energy required. They pointed out that the $[H_3N \ldots NH_3]^+$ ion formed on γ-radiolysis of $[H_3NNH_3]^{2+}$ disappears irreversibly on warming the solid matrix,[51a] so it may not be a bound species. However $[H_3NNH_3]^{2+}$ is a strong acid ($pK_a < -1$), so that the NH_3 formed on dissociation would be rapidly protonated. In fact protonation would be exothermic by at least 55 kJ/mol. It really seems unlikely that the high-level theoretical calculations can be out by so much. We believe that the uniqueness of the observation of **12** is due to kinetic rather than thermodynamic factors. The remarkable difference in persistence between the [4.4.4]- and [5.4.4]-diamine radical cation mentioned earlier must be due to kinetic factors (rapid follow-up reactions when the weak bond dissociates). In the present case, the monomeric quinuclidine radical cation should have a longer than normal lifetime due to the bridgehead nature of the nitrogen, the loss of α-hydrogens being prevented.[67b]

The large differences in $N \ldots N$ bond length and in hybridisation at nitrogen between **9** and **10** have already been mentioned, showing that the $N \ldots N$ bond is easily distorted by other influences (polarisable). This also emerges from the spectroscopic properties of these ions. In the electronic spectrum the absorption band is extraordinarily broad. Thus the ion **9** shows a maximum at 480 nm (Σ 4500) with a width at half height is 8100 cm^{-1}, which means that the band spans the whole of the visible spectrum.[61] This must be due to the wide amplitude of the soft $N \ldots N$ bond stretch, and the large difference in $N \ldots N$ bond lengths between ground and excited states (see Fig. 7). In the ESR spectra, the hyperfine coupling to nitrogen is very sensitive to the hybridisation, being small if the odd electron is in a p orbital, but increasing strongly as s character is introduced. For this reason **10** has a_N 14 G,[62] but this rises to almost 36 G in **9**; the very large value for **9** led to the first observation of second order splittings in an ENDOR spectrum.[68] The persistence of **9** has enabled us to do some unusual experiments with these radical ions. Heating the dark red solid salt **9**. BF_4 leads to its becoming almost colourless at 130°C, with the clean formation of an equimolar mixture of salts of **13** and **14**.[61] A likely mechanism is shown in Scheme 4, with the hydrogen being

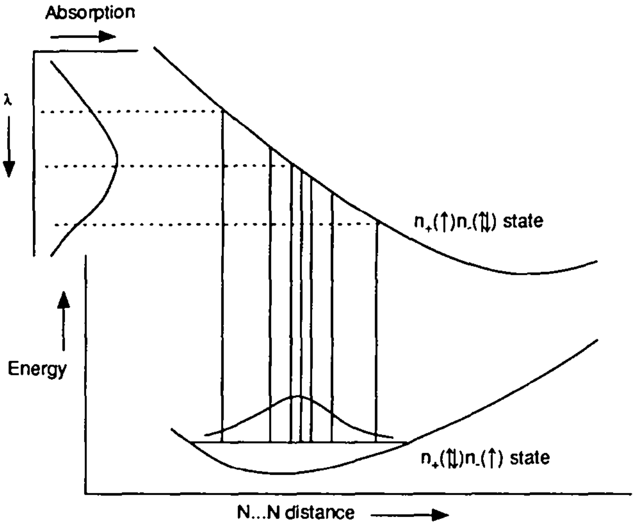
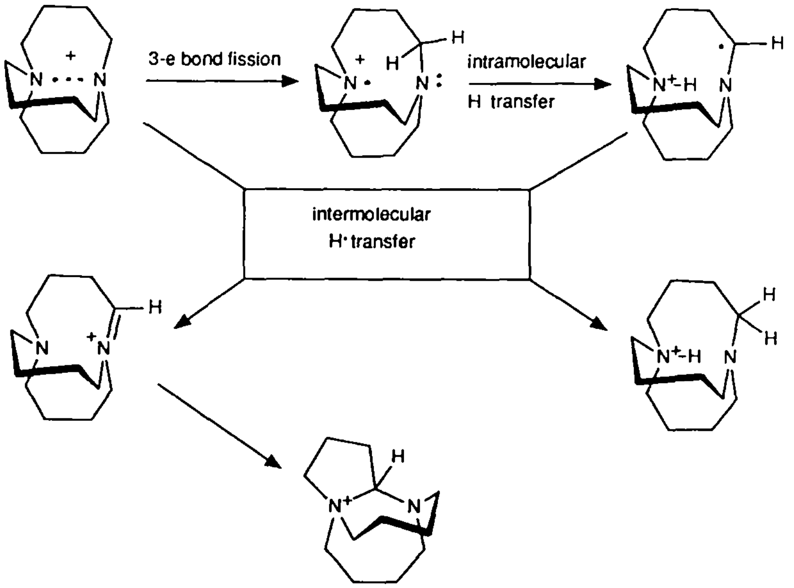


Figure 7 Schematic energy level diagram for a three-electron σ-bonded radical cation showing how shallow potential energy functions and a large displacement of equilibrium N...N distance leads to very broad electronic absorption.

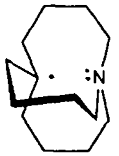
transferred inside by a Hofmann Loeffler–Freytag reaction. The second hydrogen atom transfer in the mechanism in Scheme 4 shows **9** acting as a hydrogen atom donor. We obtained further evidence for the ease of hydrogen atom abstraction from the α-C H bonds of **9** (almost certainly those antiperiplanar to the N ... N bond) when we looked at the reactions of stable **9** with a range of short-lived radicals generated by pulse radiolysis.[69] We were surprised to find that hydrogen atom transfers seems to compete effectively in many cases with electron transfer reactions leading to the



Scheme 4

oxidation and reduction of **9**. Even the normally unreactive t-BuS$^{\cdot}$ radical abstracted hydrogen at 3.2×10^{9} mol^{-1} dm^{3} s^{-1}, nearly the diffusion-controlled rate. This must mean that these α–C–H bonds are extraordinarily weak, which can be seen as arising from contributions to the structure from canonical forms such as **15**.

4.1.2.3. *An intrabridgehead C : N interaction —evidence for very weak bonding.* It has recently been possible to generate the neutral radical **16** by γ-radiolysis of the BF_4^- salt of the cation **17**.[70] The ESR spectrum shows the expected hyperfine coupling to three hydrogens but the nitrogen hyperfine coupling is small (<8 G), in stark contrast with the large coupling seen in **9**, indicating very little spin density on the nitrogen atom, and therefore a very weak three-electron σ-bond, in excellent agreement with Clark's predictions (see Section 4.1.2.1 above).[57]



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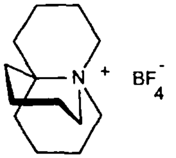

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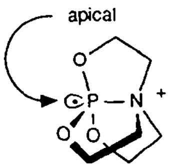

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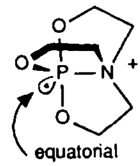

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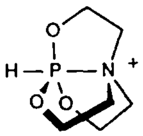

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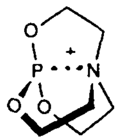

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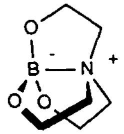

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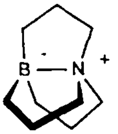

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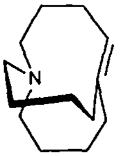

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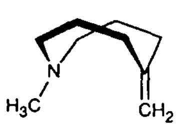

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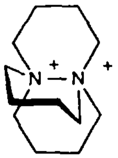

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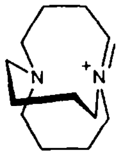

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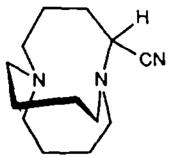

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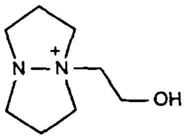

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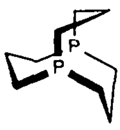

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4.1.2.4. *Three-electron σ-bonding between phosphorus and nitrogen?* In a solid state ESR study, Hamerlinck *et al.*[71] generated radicals to which they ascribed the structures **18** and **19** by different irradiation procedures from the interesting phosphoranium ion **20**.[72] Phosphoranyl radicals with the odd electron in an apical orbital were previously unknown and the assignment of this structure has been disputed;[73,74] it is certainly true that the differences between this structure and the three-electron σ-bonded structure **21** is very subtle. The magnitude of the hyperfine coupling to nitrogen (21 G) is very close to what we would expect for **21** by comparison with the N . . . N species; on the other hand, this hyperfine coupling was reported to be isotropic, which would hardly be expected for **21**. Whatever the solution to this particular problem, it is certain that the investigation of other examples of intrabridgehead three-electron σ-bonding should be worthwhile; an example of a three-electron σ-bond between carbon atoms would be of especial interest to organic chemists.

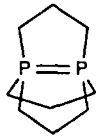
4.1.3. *Two electrons in the intrabridgehead orbitals.* The chemistry of propellanes, which have two electron central bonds, has been very well reviewed.[75] Most two-electron σ-bonds are strong anyway, so their examination in an intrabridgehead situation is only revealing where strain *weakens* the bond, the reverse of the situation which has been discussed so far. This is the case in the small ring propellanes, especially [1.1.1]propellane.[76] The carbons involved in the central bond are 'inverted', forming all their bonds within one hemisphere. *Ab initio* calculations on [1.1.1]propellane[77] show none of the normal accumulation of electron density in the 'bonding' region between the two carbons, and experimental evidence has been produced for a similar lack of bonding electron density in a derivative of [3.1.1]propellane.[78] These results raise intriguing questions about the definition of a covalent bond, and this is the subject of debate at present.

Several propellanes with C—N^+ central bonds have been prepared, and subjected to reductive cleavage, presumably via $C^{\cdot}$:N and $C:^{-}$:N species, to provide convenient synthetic access to medium-ring bicyclic amines such as manxine **4**,[16] and hiddenamine **5**.[18] No propellanes with a central C—B bond are yet known. Some more unusual propellanes with heteroatom-heteroatom intrabridgehead bonds will now be discussed.

4.1.3.1. *Donor/acceptor intrabridgehead bonding.* Triethanolamine borate is really a propellane, **22**, while hydroboration of triallylamine leads to **23**.[79] The reactions of these simple donor/acceptor bonded propellanes have not been extensively investigated, but the B—N bond seems to be quite normal. If we move to second row elements, the most thoroughly investigated compounds are the silatranes, with a Si—N bond and pentacoordinate silicon; their chemistry has been extensively reviewed.[80]

The properties and reactions of 1-azabicyclo[4.4.4]tetradec-5-ene, **24**,[81] can be seen as arising from donation of the nitrogen lone pair into the antibonding π* orbital of the double bond. The two lowest energy bands in the photoelectron spectrum arise from mixing of these orbitals to give a bonding and an antibonding combination; the splitting of 1.3 eV is larger than that seen in related transannular interactions, such as **25**,[82] as befits the tighter geometry imposed by the intrabridgehead case. The reactions of **24** are rather like an enamine, for example protonation occurs at the alkene with participation by the nitrogen lone pair, leading to formation of the propellane ion **17**; this reaction even occurs in ethanol to give the ethoxide of **17**— the reverse of a Hofmann elimination reaction.

4.1.3.2. *Intrabridgehead bonds between atoms with like charges.* We prepared the first hexa-alkylhydrazinium dications in the form of propellanes with a central N^+—N^+ bond,[34–36] and were able to examine their reactions.[83] Diprotonated hydrazines had been known for many years, but their reactions were confined to deprotonation (and the benzidine rearrangement in the case of some aromatic hydrazines). The N^+—N^- bond length of 1.532 Å in **26** is surprisingly normal (see Fig. 6).[62] As might be expected, these dications are reduced by many reagents with cleavage of the N^+—N^+ bond to diamines (see Scheme 1, Section 4.1.1 above). Reaction with weak bases usually occurs by deprotonation at the α-carbon atoms, with concomitant cleavage of the N^+—N^+ bond (an E2 reaction) to give products derived from iminium ions with a bridgehead $C{=}N^+$ bond, e.g. **27**. Trapping by the transannular amino nitrogen atom leads to α-aminoammonium ions, e.g. **14**, while external nucleophiles give products like **28**. One propellane hydrazinium dication, the 1,5-diazoniatricyclo[3.3.2.0]decane ion behaved differently, giving **29** with hydroxide ion, presumably due to relief of ring strain in the four-membered ring. No propellanes with central B^-—B bonds are known; if they could be constructed, oxidative cleavage might be an attractive route to medium-ring compounds with boron bridgeheads. Compounds with a central P^+—P^+ bond are still unknown but Diel and Norman[84] have reported the preparation of 1,5-diphosphabicyclo[3.3.3]undecane, **30**, by reaction of allylphosphine with a radical initiator (AIBN) in refluxing benzene. In simple terms, this would be expected to be a very strained compound, whether the phosphorus atoms are *in* or *out*—they are unlikely to tolerate being planar as easily as the nitrogens do in **8** or 1,5-diazabicyclo[3.3.3]undecane. Could it be that there is a novel type of P(III)—P(III) ↔ P(V)=P(V) resonance, see **31**?



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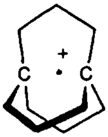

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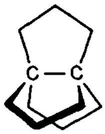

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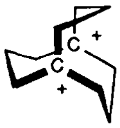

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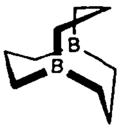

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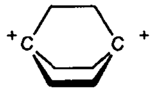

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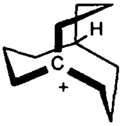

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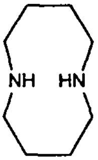

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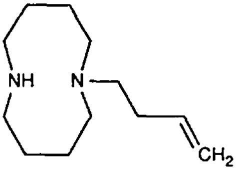

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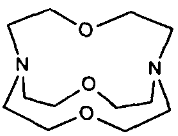

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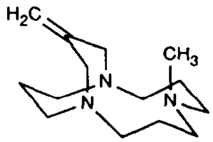

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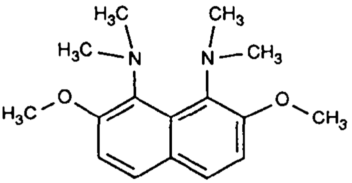

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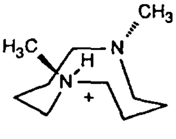

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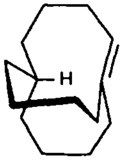

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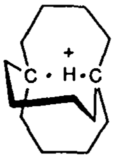

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4.1.4. *One electron in the intrabridgehead orbitals.* Here the most significant cases should be those involving $[\mathrm{B^{\cdot}B}]$, $[\mathrm{C^{\cdot}B}]$, and $[\mathrm{C^{\cdot}C}]^{+}$ one electron bonds, but very little is known. Non-intrabridgehead [B . B] species are known, e.g. $[\mathrm{B_2H_6}]^{\cdot}$ [85] and $[(\mathrm{MeO})_3\mathrm{BB(OMe)_3}]^{\cdot-}$,[86] but these are not persistent in solution at room temperature. It would certainly be interesting to examine intrabridgehead examples. One-electron bonding between boron and carbon would be expected to be very weak, for the same reasons give for the three-electron $\mathrm{C^{\cdot}{:}N}$ bonds, but no examples are known. The radical ion **32** has been generated by γ-radiolysis of [3.3.3]propellane, **33**, in a $\mathrm{CCl_4}$ matrix at 77 K.[87] The ESR spectrum shows only one major hyperfine coupling (17 G) to six equivalent hydrogens. This indicates that the spin density is largely confined to the central carbons, and it is thus appropriate to describe the species as having a one-electron bond. Radical cations have been generated from many saturated hydrocarbons in solid matrices but, in most other cases, the spin is extensively delocalised.[88] It may be that **32** would be persistent in solution, at least at low temperatures, but we have so far been unable to generate it under these conditions. As discussed below, the corresponding dication **34** is known,[89] thus forming a set of redox species involving only the removal of C—C σ-bonding electrons.

4.1.5. *No electrons in the intrabridgehead orbitals.* The most important first row cases in this category are [B B], $[\mathrm{B\ C^{+}}]$, and $[\mathrm{C^{+}\ C^{+}}]$. 1,5-Diborabicyclo[3.3.3]undecane **35** was prepared in 1964 by Greenwood, Morris and Wright[79] who obtained it by thermolysis of the polymeric product from the hydroboration of triallylboron, but there is little information on its properties and reactions. A study of electron addition to it would be very interesting but my research group has been unable to reproduce the preparation; it seems likely that the conditions for the thermolysis are rather critical.

The generation of both dications **34**[89] and **36** has been reported, but the claim to the generation of **36** has now been withdrawn; apparently only monocationic species are formed.[90] Comparison of the NMR spectra of **34** with those of the manxyl monocation **37** reveals two surprising features (i) the chemical shift of the carbocationic carbons in **34** (346.2 ppm) is upfield of that in the monocation **37** (356.3 ppm) and (ii) the barrier to ring flipping in the dication is comparable to that in manxane itself, whereas the barrier for the monocation is either much higher or (more likely) much lower. If one also considers the barrier to ring flipping in other [3.3.3] species, there is a general trend to higher barriers as the two bridgehead atoms move apart, and monocation **37** appears out of line. One intriguing possibility is that the carbocationic carbon in **37** is slightly pyramidalised inwards, possibly interacting weakly with the σ-bond orbital of the bridgehead C—H (see Section 4.2.4 below for evidence of related interactions in other carbocations). However, the NMR chemical shifts of the C—H group are apparently normal.

4.2. *Indirect interactions via hydrogen*

All of the observed indirect interactions across medium-ring bicyclic compounds involve hydrogen. In macrocyclic compounds, interactions via other atoms (or ions) are possible; these have been well-reviewed elsewhere, but are discussed briefly at the end of this review. As with direct interactions, the discussion is ordered in terms of the number of electrons involved in the intrabridgehead orbitals.

4.2.1. *Five electrons in the intrabridgehead orbitals.* Addition of an electron to an ion with an intrabridgehead $\mathrm{N^{+}{—}H{:}N}$ might be expected to generate a trapped hydrogen atom, $\mathrm{N{:}H^{\cdot}{:}N}$. How would such a species behave? At the moment this is just an amusing speculation. Reaction of the inside-protonated [4.4.4]diamine ion **13** with lithium in ethylenediamine led to the monocyclic diamine **38** as the main product (none of the [4.4.4]diamine **7** was produced). However, the same product was obtained from reaction with lithium 2-aminoethylamide, a base, and it seems likely that the initial step was E2 elimination to give 1-(3-butenyl)-1,6-diazacyclodecane **39**, which was perhaps isomerised to the 1-butenyl isomer and this enamine then hydrolysed in the course of the workup.[91] Lehn[92,93] has reported that the [1.1.1]cryptand **40** cannot be produced by deprotonation of its inside monoprotonated ion, but that it can be prepared by reaction of the doubly inside

Table 6

Medium-ring Bicyclic Diamines which form Inside Protonated Ions

(P = Protonation by a normal proton transfer mechanism)
(R = Inside protonated ion formed by a redox mechanism)

No. of Ring Atoms	$H_2N(CH_2)_2NH_2$ Derivatives	$H_2N(CH_2)_3NH_2$ Derivatives	$H_2N(CH_2)_4NH_2$ Derivatives
13	[6.3.2](P)[a] [5.4.2](P)	[4.4.3](R)[b]	
14	[6.4.2](P) [5.5.2](P)	[6.3.3](P)(R) [5.4.3](R)	[4.4.4](R)
15		[6.4.3](P) [5.5.3](P)	[5.4.4](R)
16		[6.5.3](P)	[5.5.4](P)(R)

[a] Equilibrium mixture of outside and inside protonated ions formed in $CHCl_3$.

[b] This inside protonated ion is only obtained (in low yield) through thermal decomposition of the corresponding radical cation salt.

protonated dication with sodium in liquid ammonia. Is this last reaction one in which a hydrogen molecule is formed inside the cage and then escapes?

4.2.2. *Four electrons in the intrabridgehead orbitals.* We have been able to convert 13 medium-ring bicyclic diamines to inside protonated monocations,[94] see Table 6, all of which have intrabridgehead hydrogen bonds. Inside mono- and di-protonated ions have also been prepared from macrobicyclic diamines and cryptands but, in general, there are not strong hydrogen bonds in the mono-protonated ions derived from these larger diamines. The kinetics, mechanism, and thermodynamics of the inside protonation process itself are considered next before examining the properties of intrabridgehead hydrogen bonds.

4.2.2.1. *Mechanisms for inside protonation.* Thermodynamically-favourable protonation of simple amines normally occurs at close to the diffusion-controlled rate, and NMR spectra of solutions containing comparable quantities of amines and their protonated ions normally show averaged spectra. Many years ago, we observed that Proton Sponge **1**, when present in solutions with its protonated ion, showed separate spectra for the diamine and its ion, an indication of much slower proton transfer. This was examined much more thoroughly by Hibbert and his co-workers,[95,96] who established that protonation/deprotonation was a two-step process, involving the formation of low equilibrium concentrations of a non-hydrogen bonded species which then underwent rapid proton transfer with external base. In the case of 2,7-dimethoxy-1,8-bis(dimethylamino)naphthalene **42**, the reactions were slow enough that they could be followed by conventional spectroscopic methods (not stopped flow).[97] Simmons and Park[98–101] found that inside protonation of their macrobicyclic diamines was quite slow, and similar results have been observed with cryptands. The most interesting case is the [1.1.1]cryptand **40**, where detailed kinetic study[102] showed (Fig. 8) very slow rates for inside protonation and deprotonation; in fact the inside monoprotonated ion could not be deprotonated to the free base. This led to the estimation of a very high $pK_a(>17.8)$ for the inside protonation.

In the case of the [4.4.4]diamine and several others,[61,94] it is apparently impossible to put a proton inside the molecular cage or to remove one once it is there by conventional proton transfer reactions. The formation of the inside protonated ion was discovered accidentally while measuring the very low pK_a for the second outside protonation of the [4.4.4]diamine, which only occurs in 50% sulphuric acid. Checking the NMR spectrum of solutions after several days showed conversion

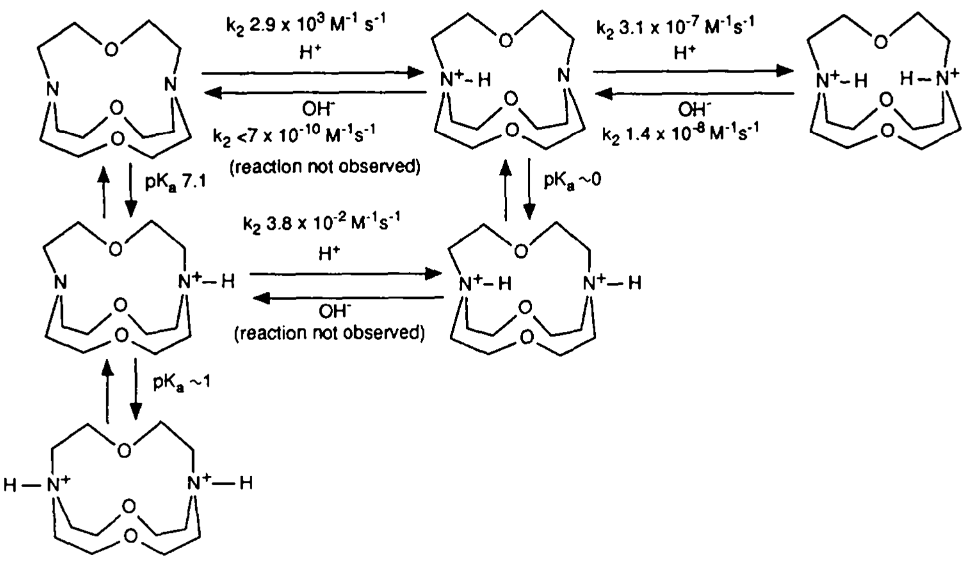
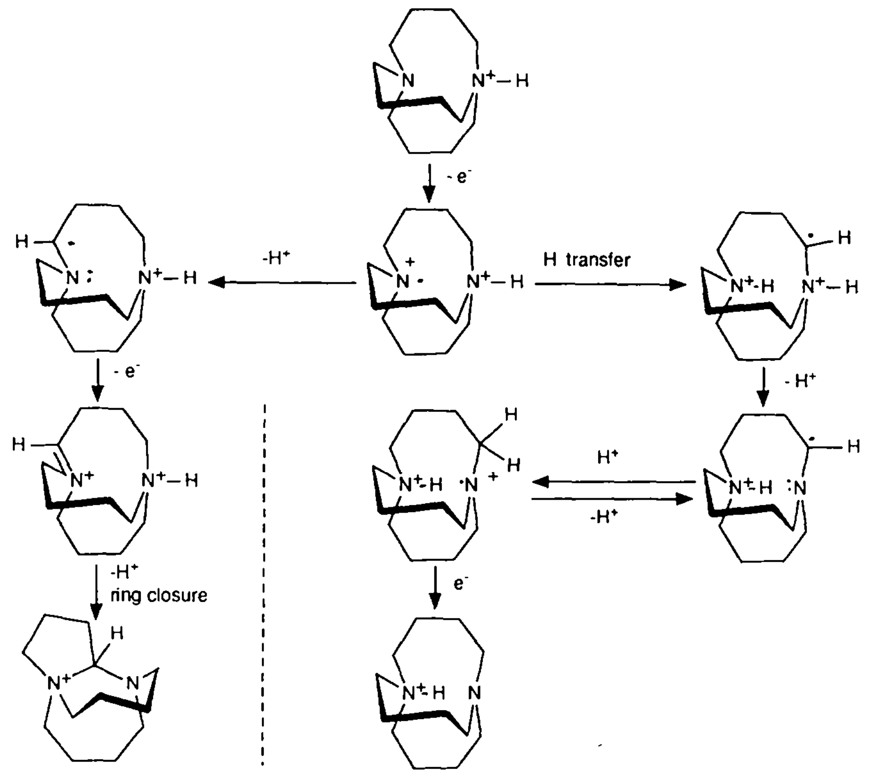


Figure 8 Rates and equilibria for protonation of 1,7-diaza-4,10,15-trioxabicyclo[5.5.5]heptadecane (or [1.1.1]cryptand).[102]

to a new species with a broad one proton singlet at δ 17.4. This proton was not exchangeable with D_2O, and it was soon recognised that we had made the inside protonated ion **13**. It subsequently emerged that the inside proton did not come from the solvent or acid but from one of the CH_2 groups adjacent to the nitrogen atoms. Further, it was found that the reaction was strongly promoted by one-electron oxidising agents, such as potassium persulphate. Most remarkable of all, under carefully chosen conditions (D_2SO_4/D_2O, 85% acid, and traces of potassium persulphate at 100°C) there was almost complete exchange of all the α-CH_2 protons for deuterium, although the hydrogen between the nitrogen atoms was a proton! As described earlier (Section 4.1.2.2), the inside protonated ion is also one product of the thermal decomposition of the radical ion **9** and the crucial step in the acid-catalysed reaction is also presumably a Hofmann–Loeffler–Freytag hydrogen atom transfer. Scheme 5 shows a mechanism which incorporates this and which accounts for the extensive proton exchange at the α-CH_2 groups by reversible protonation of an α-amino radical. I know of no precedent for the protonation step (aminium cation radicals certainly undergo deprotonation), but it is hard to think of any satisfactory mechanistic alternatives. This part of the mechanism amounts to an electron-transfer catalysed proton exchange α to an amine (an $S_{OE}1$ reaction).[103]

We found that this redox-promoted formation of the inside protonated ion occurred in several other diamines ([5.4.3], [6.3.3], [5.4.4] and [5.5.4]) where protonation by a normal mechanism was clearly very difficult (both [6.3.3] and [5.5.4] do protonate to some extent by a classical mechanism).[94] The preparation of selectively deuterated diamines showed that the intramolecular hydrogen atom transfer step was regioselective and stereoselective (normally only occurring in the longest, i.e. most flexible bridge—presumably because the transferring hydrogen has to be tipped inside the cage). In addition to the evidence already reported, we have found that inside protonation of the [5.4.3]diamine in D_2SO_4 gave an inside protonated ion in which one α-CHD group (in the $(CH_2)_5$ bridge) was formed stereospecifically.[104] Finally, we found that although we were unable to form the inside protonated ion of the [4.4.3]diamine in solution at all, small amounts of this ion were produced in the thermal decomposition of the [4.4.3] radical cation.

As shown in Table 6, several bridgehead diamines can be converted to their inside-protonated



Scheme 5

ions by classical proton transfer mechanisms, as shown by the formation of the inside deuterated ion in deuterated acids.[94] In all cases, the reactions were quite slow, the fastest reactions being with diamines like [5.5.2] which have one large (e.g. 12-membered) ring and one short bridge. Steric accessibility of the lone pairs is obviously the key factor, and it seems quite reasonable that this is apparently better for the derivatives of ethylenediamine than for those of 1,3-diaminopropane and 1,4-diaminobutane. Some preliminary results[105] suggest that the pH/rate profile for these reactions may be quite varied; [5.5.3]- and [6.5.3]-diamine showed quite different behaviour in dioxan/water mixtures (the diamines are far too insoluble to be studied in pure water unfortunately). We intend examining this aspect further; it is also interesting to ask what type of acid is most effective at inserting protons into a small, very hydrophobic site—could there by such a thing as a slim acid?

If an additional donor atom were present in one of the bridges of a bicyclic medium-ring diamine, would it act as a relay for transferring the proton inside? Bell[106] has prepared the triamine **41** and shown that it inside protonates by a classical mechanism easily. Unfortunately, the [7.3.3]diamine is still unknown, but the [6.3.3]diamine only protonates by a classical mechanism very slowly.

4.2.2.2. *Equilibria for inside protonation.* So far, the kinetics of inside protonation have been discussed without considering the thermodynamics. What are the pK_a values for inside protonation of these diamines? Where is the dividing line between preferred inside and outside protonation? Clearly, it is not possible to establish equilibrium in the case of the [4.4.4]diamine, although we have estimated[27] the pK_a for inside protonation as 25, compared with a measured value of 6.5 for outside protonation.[61] The [4.4.4]diamine is undoubtedly the optimum case, since the hydrogen bond is linear and the relief of strain resulting from inside protonation is probably nearly maximal. In other

Table 7

Relative Basicities of 1,k+2-Diazabicyclo[k.l.m]alkanes with respect to 2,7-Dimethoxy-1,8-bis(dimethylamino)naphthalene.[a,b]

[k.l.m] diamine	ΔpK in d_6-DMSO	ΔpK in CD_2Cl_2
[6.3.2]	-2.43 ± 0.13[c]	
[5.4.2]	-1.46 ± 0.04	
[6.4.2]	-0.80 ± 0.04	
[5.5.2]	+0.67 ± 0.04	-0.34 ± 0.05
[6.5.3]	+0.78 ± 0.04	+1.27 ± 0.05
[5.5.3]	+1.71 ± 0.08	+2.19 ± 0.09
[6.4.3]	+1.60 ± 0.08	

[a] pK_a 16.1 in 35% aqueous DMSO.

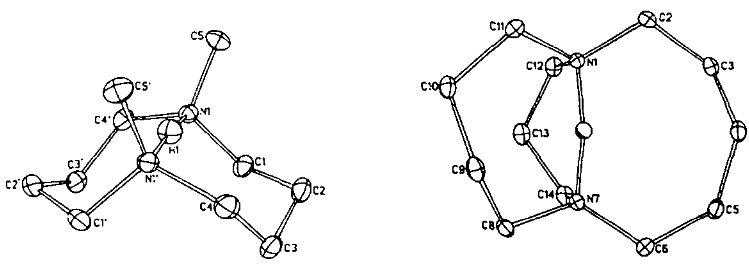
[b] Alder, R. W.; Eastment, P., unpublished results.

[c] outside protonation only. All other diamines listed give only inside protonated ions.

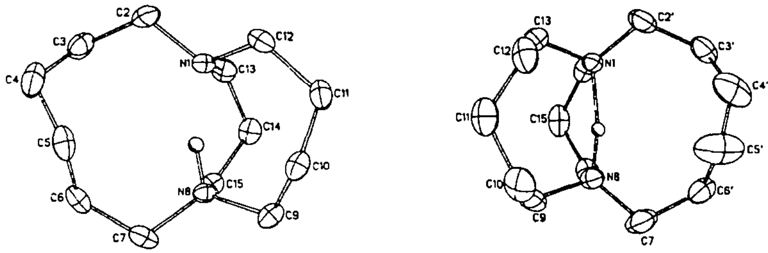
cases, we can establish equilibrium, and several compounds are indeed very strong bases for inside protonation (Table 7).[107] The basicities are too high to be measured in aqueous solution, so we resorted to comparison with **42** one of the most powerful proton sponges. It is not easy to separate the effects of the relief of strain[108] and of the strength of the hydrogen bond, but qualitatively it seems that the more linear the hydrogen bond, the stronger it is and the higher the basicity. We found one diamine, 1,8-bicyclo[6.3.2]tridecane, which gave a mixture of inside and outside protonation in $CDCl_3$ solution ;[94] when we tried to measure the pK_a in DMSO, we found that only the outside protonated ion was formed. It is quite reasonable that the outside protonated ion should be favoured relative to the inside ion in DMSO since it can partake of a hydrogen bond to the solvent ($CDCl_3$ is not a significant hydrogen bond acceptor).

4.2.2.3. *Intrabridgehead hydrogen bonds : structure and properties.* Why study hydrogen bonding in the intrabridgehead situation (see Fig. 1)? After all, hydrogen bonding is now a very well-studied phenomenon so the focus must be very different from the three-electron σ-bonding discussed earlier, although the strength of the two interactions is probably very similar. In the intrabridgehead situation, there can be substantial variation in the geometry of the hydrogen bond while preserving the same interacting atoms and a fairly constant molecular environment. We have therefore concentrated on the correlation of the chemical and spectroscopic properties of the inside protonated ions with their detailed geometry, as revealed by X-ray and neutron diffraction studies.

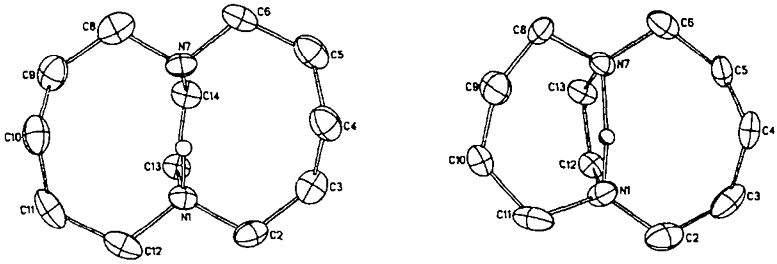
We have been able to obtain X-ray structures for seven inside-protonated ions,[30,109–114] and for the transannularly hydrogen-bonded monoprotonated cation, **43**,[115] from 1,6-dimethyl-1,6-diazacyclodecane (Fig. 9). The structural parameters for the N : H—N bonds in these ions together with infra-red and NMR data for all the inside-protonated ions[116] are given in Table 8. The constraints of the intrabridgehead situation have produced N . . . N bond lengths varying from 2.47 to 2.69 Å, and N—H—N angles ranging from 180° (linear) to 132°. This is a much wider range for a chemically-similar series of hydrogen bonds than has been seen before. In general terms, the ^1H NMR chemical shift increases and the i.r. frequency decreases as the hydrogen bond becomes more linear and shorter, but even with the structural data we now have, it is not easy to disentangle the effects of bond length and bond angle changes.



in[4.4.Me$_2$]H$^+$ iodide in[5.4.3]H$^+$ triflate



in[6.4.3]H$^+$ picrate in[6.5.3]H$^+$ picrate



in[5.5.2]H$^+$ picrate in[5.4.2]H$^+$ picrate

Figure 9 Structures of some inside protonated ions. Hydrogen atoms on carbon have been omitted for clarity. For the inside protonated ion from the [4.4.4]diamine, see Figure 6.

One interesting question is whether these hydrogen bonds have double or single minima potential functions; in other words, does the hydrogen shuttle back and forth between the nitrogen atoms, or does the minimum energy occur when it is centrally placed? Obviously, the overall symmetry of the system needs to be considered. Thus in principle the [4.4.4] system can have a perfectly symmetrical hydrogen bond, but in the [6.4.3]diamine, for example, the two nitrogen atoms are unlikely to be equivalent even in the free diamine, so a perfectly symmetrical hydrogen bond is not possible in that case. In addition, in the solid state, the space group symmetry must be taken into account. Hydrogen atoms are not located with high precision by X-ray data, so this does not yield an unequivocal answer in many cases. Neutron diffraction is a better technique and we have applied this to the inside protonated [4.4.4]diamine; the hydrogen atom seems to be central even at 20 K.[117] In spite of these qualifications about deductions from X-ray structures, it is interesting to note from Table

Table 8

Structural and Spectroscopic Properties of Inside Protonated Ions

Bicyclic Diamine	Distance N..N	N-H	Angle N-H-N	δ_{NH}	$\Delta\delta$ (^{1}H,^{2}H)	ν_{NH}, cm^{-1}
[4.4.4][a]	2.53	1.26	180	17.40	0.06	1400-1900
[5.5.4]	2.69	0.96	172	15.30	0.92	1500-2300
cis-[4.4]Me$_2$[b]	2.60	1.30	169	15.71	0.54	1500-2300
[5.4.3]	2.55	1.29	160	17.48	0.53	1400-1900
[6.4.3]	2.65	1.04	155	14.62	0.65	2150
[6.5.3]	2.61	1.16	154	13.78	0.58	2200
[5.5.2]	2.56	1.09	134	12.35		2475
[5.4.2]	2.47	1.35	132	13.5		2450
[6.3.3]				17.35	0.76	2200
[5.5.3]				17.20	0.87	2100
[5.4.4]				16.19	0.43	1500-2300
[6.4.2]				10.7		2450

[a] With bridgehead nitrogens, i.e. 1,6-diazabicyclo[4.4.4]tetradecane

[b] 1,6-Dimethyl-1,6-diazacyclodecane

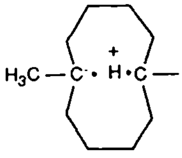
8 which ions have hydrogens apparently centrally placed and which have the hydrogen clearly associated with one nitrogen atom. For those species with nearly linear hydrogen bonds, *in*[4.4.4]H$^+$, with an N ... N distance of 2.53 Å, is single minimum, while *in*[5.5.4]H$^+$, N ... N 2.69 Å, is a double minimum case; the monocyclic ion **43**, with an intermediate N ... N distance is apparently finely balanced (see below). In the two cases with the most strongly bent hydrogen bonds, *in*[5.4.2]H$^+$, with N ... N 2.47 Å, seems to have the hydrogen atom centrally placed, while for *in*[5.5.2]H$^+$, with a longer N ... N distance, the hydrogen is sited on one nitrogen atom. Superficially, it seems that one needs a shorter N ... N distance to get a single minimum for a bent hydrogen bond. This is exactly what theory predicts.[118,119]

The rate of shuttling of the hydrogen atom is aways likely to result in an averaged NMR spectrum even at the lowest attainable temperatures. Nevertheless, there are several NMR techniques which can be applied to this question of single vs double minima. The easiest to apply experimentally is the $\delta\Delta$ (^{1}H, ^{2}H) test.[120] Most deuterium chemical shifts are the same as the corresponding proton shifts, when measured on a p.p.m. basis (differences of no more than 0.05 p.p.m.), but this is not the case for hydrogen atoms involved in strong, double minima hydrogen bonds, as can be seen from Table 8. This effect has been ascribed to the differences in average N—H, N—D (and N—T) bond lengths due to differences in zero point energies. On the basis of this test, all our inside-protonated ions have double minima structures except the *in*[4.4.4]H$^+$ ion. Ion **43** seems to be a double minima case on this basis, although the X-ray structure shows the hydrogen atom centrally placed. We prepared the ^{15}N$_2$-labelled versions of **13** and **43** and looked for a difference between the ^{15}N chemical shift of these species and their ^{14}N, ^{15}N counterparts, present in natural abundance material added to the same solution in great excess; no chemical shift difference could be detected (<0.2 p.p.m.) in either case. If either were double minima, a difference might have been detected (the Saunders isotopic perturbation method).[121] It looks as if the ion **43** is near the critical point where the central maximum in the potential energy curve disappears below the zero point energy levels.

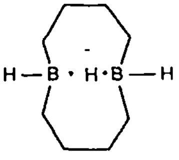
4.2.3. *Three electrons in the intrabridgehead orbitals.* The mechanism discussed earlier (Section

4.1.2) for the formation of the inside-protonated ion of the [4.4.4]diamine (Fig. 10) shows an dication radical with an inside hydrogen atom. This species might have a symmetrical three-electron N—H—N bond. In the molecular orbitals for a normal four-electron hydrogen bond, the HOMO is formally non-bonding, so it might be expected that a three-electron N—H—N bond would not be too different in strength. However, we have not succeeded in observing this dication by spectroscopic methods.

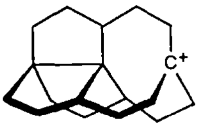
4.2.4. *Two electrons in the intrabridgehead orbitals: μ-hydrido-bridged carbocations.* McMurry and Hodge[122] made *in*-CH-bicyclo[4.4.4]dec-5-ene **44**, and protonated it in $CDCl_3$ containing trifluoroacetic acid to produce the ion **45**, which shows a chemical shift of δ-3.5 for the inside hydrogen, a strong indication that there is a μ-hydrido bridge in the carbocation. Application of the Saunders isotopic perturbation method[121] indicated that the hydrogen atom was in a single minimum potential. This ion is therefore the two-electron counterpart of the four-electron hydrogen-bonded ion **13**. The extremely shielded chemical shift for the inside hydrogen atom in **45** contrasts with the extreme deshielding in **13**, despite the presence of two extra electrons. These μ-hydrido-bridged cations apparently have a substantial contribution from the canonical form $C^+H^-C^+$. The most striking thing about **45**, however, is its thermodynamic stability—it is formed in a quite weakly acidic medium; in fact, ion **45** is half-formed from **44** in glacial acetic acid, and probably has $pK_{R^+} > 0$. The monocyclic analogues such as **46** prepared earlier by Sorensen and co-workers[123] were not persistent above −50°C in 'magic' acid. The dramatic difference between **45** and **46** is unlikely to be purely thermodynamic; it is more likely that the relatively weak μ-hydrido-bridge in these ions does dissociate, but in the intrabridgehead situation, follow-up reactions which are normally very fast are prevented. Thus the situation is very similar to the three-electron σ-bonded cations described earlier (Section 4.1.2.2). There is a general important point here; intrabridgehead hydrogen bonds are probably not much stronger in terms of bond dissociation energy than three-electron σ-bonds or μ-hydrido-bridges, but when they dissociate, there are no rapid follow-up reactions apart from reformation of the hydrogen bond. Hydrogen bonded species can therefore persist in situations where three-electron σ-bonded ions and μ-hydrido cations disappear rapidly. Nevertheless, the advantages of studying delicate types of σ-bonding in the intrabridgehead situation is shown up once again.



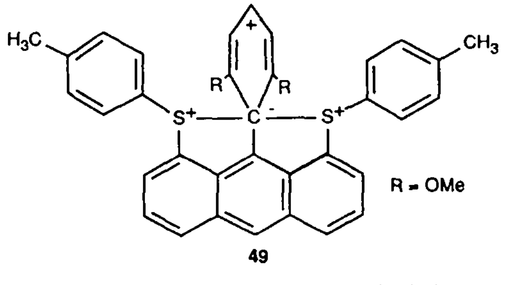
46



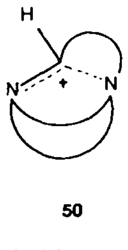
47



48



49



50

The ion **45** presumably has a linear μ-hydrido bridge and **46** is probably not far from linear. However μ-hydrido bridges, unlike hydrogen bonds, can be strongly bent according to theory, becoming three-centre two-electron bonds with hypervalent carbons.[124] So far, no simple three-centre two-electron triangular bonds between two carbons and a hydrogen unsupported by other bonds have been observed spectroscopically (well-known non-classical cations have a normal C—C bond in addition). It would appear that the intrabridgehead situation would be an ideal place to seek them, for example in the [4.4.2] ring system.

In principle, the empty orbitals of a carbocation could gain electron density from the back lobe of a C—H bond, forming a delocalised [H—C C^{+}] system. The possibility of this occurring in the manxyl monocation **37** has been mentioned earlier (Section 4.1.5). It appears that the same phenomenon is responsible for the rapid rates of solvolysis of bridgehead halides in the [1.1.1],[125] [2.1.1],[126] and [3.1.1][127] bicyclic ring systems. Thus 1-bromobicyclo[3.1.1]heptane solvolyses faster than *t*-butyl bromide, in spite of the fact that the carbonium ion must be very far from planar, and it suggested that backside interaction of the empty orbital with the backside of the C—H bond at the other bridgehead is responsible for extra stability of the carbonium ion. The interaction seems to occur in the examples given due to the short 1,3-distance across a cyclobutane ring.

Two-electron X—H X intrabridgehead interactions involving other elements than carbon are unknown, although their observation would be intersting. A transannular [B H—B]$^{-}$ bond is found in the ion **47**, whose crystal structure has been reported;[128] it is interesting that the B—H—B angle of 140° is considerably lower than the N—H—N angle of 169° in **43**.

4.3. *Indirect interactions via elements other than hydrogen*

Medium-ring bicyclic compounds are normally too small to accommodate anything larger than a hydrogen atom, although the [1.1.1]cryptand **40**, which is a [5.5.5] system, can hold two hydrogen atoms or one lithium cation.[92,93,102] In terms of the classification adopted in this review, the lithium cryptate would be treated as a four-electron case like a hydrogen bond. However it is certain that interactions between the lithium and the oxygen atoms are comparable in importance to the intrabridgehead N—Li—N bonding: metal ions normally seek higher coordination numbers than two as offered by the bridgehead atoms. We have sought in vain for evidence of lithium complexation by the [5.5.2]diamine, which is nothing more than a cyclic version of N,N,N′,N′-tetramethylethylenediamine, often used as a lithium ligand. Presumably, the $(CH_2)_5$ bridges inhibit coordination of other ligands which may be necessary for stability. We can also find no eivdence for a lithium analogue of the transannular protonated ion **43**. In this case, the ligand requires a nearly linear N—Li—N geometry, which is probably unfavourable; even when we make analogues of this ligand with suitably placed oxygen atoms in side chains (e.g. the N,N′-bis(2-methoxyethyl) derivative), there is no sign of lithium coordination. Simmons and co-workers reported no metal ion complexation with their macrobicyclic diamines,[98–101] presumably because additional coordination sites are required, as provided by the cryptands.

The mechanisms for insertion of metal ions into cryptands also bear only a superficial resemblance to the mechanisms for inside protonation.[129,130] The extra ligand sites play an important role in transferring the metal ion inside the cage.

Simmons and Park[100] demonstrated the encapsulation of chloride ions in the inside diprotonated[10.10.10]diamine; in terms of intrabridgehead interactions, this is eight-electron five-centre bonding. In the present context, this serves to draw attention to the many more complex intrabridgehead bonding schemes which might be realised. Two prime candidates for organic chemists are the two-electron σ-allyl cation[131] which might be realised in a double bicycle such as **48**, and the corresponding four-electron σ-allyl anion or heteroanalogues, where one might seek to pin down a S$_N$2 transition state. Such an objective has not been realised in an intrabridgehead situation, but the ion **49** comes close to this.[132,133]

5. STRAIN IN MEDIUM-RING BICYCLIC SYSTEMS—EFFECTS AT NON-BRIDGEHEAD ATOMS

As discussed in Section 3, intrabridgehead bond formation relieves more strain than alternative transannular bonding processes. At least in the [4.4.4] system, the next best process is 1,5-bonding (see Fig. 3). We encountered bonding of this type in the α-aminoammonium ions which are formed by deprotonation of propellane hydrazinium dications (Section 4.1.3.2)[83] and which we also used as synthetic intermediates (Scheme 2, Section 4.1.1).[37,38] The ^{13}C and ^{1}H NMR chemical shifts of the C—H group between the two nitrogen atoms in these ions varied widely, and it was suggested that partial bond breaking as in **50** was responsible. X-Ray structure determination of several of the α-aminoammonium ions has shown[134] that this does indeed occur, with the N—CH bond varying from 1.447 Å down to 1.404 Å as the CH—H^{+} bond varies from 1.549 Å to 1.635 Å. Moreover, the degree of iminium ion character in the ion seems to correlate with calculated strain energy changes.

6. CONCLUSION

The purpose of this article was to review present knowledge of intrabridgehead chemistry and to demonstrate the potential of the intrabridgehead situation for providing good opportunities for the careful examination of fundamental questions of structure and bonding. I believe there are still many interesting opportunities for further work in this area.

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