cluded as an important intermediate.

A final example of the photosynthetic potential inherent in the irradiation of semiconductor suspensions containing organic molecules is found in Bard's demonstration of amino acid synthesis. Irradiation of platinized TiO_2 suspensions in aqueous ammoniacal methane (eq 14)[62] lead to production of glycine, alanine,

$$NH_3 + 2CH_4 + 2H_2O \xrightarrow{TiO_2*} H_2NCH_2CO_2H + 5H_2 \qquad \Delta G = 55.4\ \text{kcal/mol} \quad (14)$$

serine, aspartic acid, and glutamic acid as well as products of intermediate functionality (methanol, ethanol, and methylamine). The relationship of this observation to chemical evolution is obvious, and the extension of this endothermic reaction[63] to other synthetic transformations remains a challenge.

Conclusions

Only recently has the concept of electron-transfer catalysis[64] been effectively applied in a mechanistic sense to organic reactions. We have shown how electron-transfer-mediated reactions can be initiated by long-wavelength ultraviolet or visible-light irradiation of semiconductor particles. The discovery and characterization of such organic transformations constitute a new area of organic photochemistry, a field replete with both synthetic applications and mechanistic delights. Since such reactions are also of great importance to the larger questions of heterogeneous catalysis, we anticipate that application of this research to many practical organic problems will be forthcoming.

Our research program on photoinduced electron transfer has been generously supported by the National Science Foundation and the Robert A. Welch Foundation. The use of semiconductors as sites for organic photooxidations has been supported by the Fundamental Interactions Branch, Office of Basic Energy Sciences, U.S. Department of Energy. The author is grateful to the Alfred P. Sloan Foundation for fellowship support and to the Camille and Henry Dreyfus Foundation for support as a Teacher–Scholar.

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Medium-Ring Bicyclic Compounds and Intrabridgehead Chemistry

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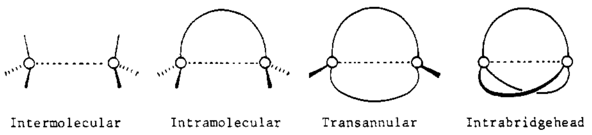
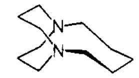
Two-center σ bonding is a cornerstone of chemistry, yet in some senses its limits have been less thoroughly probed than those of π bonding. For elements like carbon and nitrogen it can occur in four topological situations:



The intrabridgehead situation has important advantages if one wishes to look at weak and exotic σ bonding and antibonding interactions. The two bridgehead atoms can hardly escape from one another, and the structure and stability of the entire molecular species should be relatively independent of the σ interaction we want to examine. The most important point, however, is that close control on orbital alignment is easily achieved in the intrabridgehead situation. The compounds needed for these studies should have ~3–5 atoms[1] in each of the three bridges to permit close approach of the bridgehead atoms without strain; in other words medium-ring (8- to 11-membered) bicyclic compounds.

Organic chemists have put a lot of effort into the preparation of bicyclic compounds containing small (three- and 4-membered) rings in order to probe the limits of bond-angle strain.[2] Bicyclic compounds containing common-sized rings (5- to 7-membered) are indeed common and important, both as natural products and as "test-beds" for physical organic phenomena. Macrobicyclic compounds containing large (>12-membered) rings have rightly attracted attention recently because of their ability to encapsulate metal ions and other species.[3,4]



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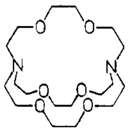

Roger Alder was born near Stow-on-the-Wold in 1937. His D.Phil. came from Oxford University where he worked on acidity functions in sulfolane with M. C. Whiting. After postdoctoral work with J. B. Hendrickson at UCLA and Brandeis University, he returned to Oxford as a NATO fellow. He moved to the University of Bristol in 1965, where he is now Reader in Organic Chemistry. Dr. Alder is coauthor, with R. Baker and J. M. Brown, of "Mechanism in Organic Chemistry". He has worked on strong amine bases (e.g., Proton Sponge, 1,8-bis(dimethylamino)naphthalene), on the use of methyl fluorosulfate as a powerful methylating agent, and on the mechanism of the thermal rearrangement of azulene to naphthalene.

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(1) Leonard has discussed the use of trimethylene bridges as spacers for the detection of intramolecular interactions; N. J. Leonard, *Acc. Chem. Res.*, 12, 423 (1979). We think that our work has demonstrated that at least $(CH_2)_4$ may be an equally effective spacer.

(2) A. Greenberg and J. F. Liebman, "Strained Organic Molecules", Academic Press, New York, 1978.

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Bicyclic systems built from medium rings have been mainly remarkable for their rarity! There are just 10 basic bicyclic systems containing only 8- to 11-membered rings: bicyclo[3.3.3]undecane, bicyclo[4.4.2]dodecane, bicyclo[4.3.3]dodecane, bicyclo[5.4.2]tridecane, bicyclo[5.3.3]tridecane, bicyclo[4.4.3]tridecane, bicyclo[6.3.3]tetradecane, bicyclo[5.4.3]tetradecane, bicyclo[4.4.4]tetradecane, and bicyclo[5.4.4]pentadecane.

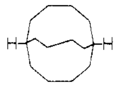
No simple derivatives or analogues of any of these systems have been isolated as natural products. Bicyclo[3.3.3]undecane (manxane) was prepared in 1970,[5] and a number of derivatives[6-8] and heterocyclic analogues[9-11] have been made. Some metal complexes of [4.4.2] and [5.4.2] tetraenes were reported in 1977 by Paquette et al.[12] The smallest "macrobicyclic" system known is 1,7-diaza-4,10,15-trioxabicyclo[5.5.5]heptadecane, Lehn's [1.1.1]cryptand.[13] The remaining systems were unknown in any shape or form when we began work in this area. The reason for this neglect has been synthetic problems, which, as we shall see, are conceptually overcome by the use of a ring-cleavage strategy. Using this approach, we have now prepared all the fundamental ring systems listed above in the form of bridgehead diamines such as 1,7-diazabicyclo[5.3.3]tridecane (1) (which we call the [5.3.3]diamine for convenience). This Account describes our exploration of the almost virgin territory of medium-ring bicyclic compounds. Prominent landmarks besides intrabridgehead chemistry are (i) high strain and unusual structures, (ii) inside–outside isomerism, and (iii) encapsulation of small species like H^+. Indeed it is hard to think of a set of simple compounds that can provide so many unique insights into current theory. Before describing our results, we should enquire further into the structure/strain situation in medium-ring bicyclic compounds.

Structure and Strain in Bridged Medium-Ring Bicyclics

The introduction of a new bridge so that two new medium rings are created is the most strain-enhancing trick one could play on a medium-ring monocycle, and the bicyclic systems are *much* more strained than their monocyclic counterparts, according to force-field (MM1) calculations.

	strain energy per carbon atom, kJ mol^{-1}	av C-C-C bond angle, deg
cyclodecane	5[14]	116.7[15]
bicyclo[4.4.4]tetradecane (out,out isomer)	17	119

In the bicyclic structure, none of the rings can adopt the BCB[15] or other low-energy[16] conformations of cyclodecane, and bond angles are opened up substantially to avoid intolerable H/H clashes between the bridges. In fact this out,out isomer **2**, ΔH_f = 41 kJ mol^{-1}, is less stable than an in,out isomer **3**, ΔH_f = 91 kJ mol^{-1}, and even the in,in isomer **4**, ΔH_f = 32 kJ mol^{-1}, is only marginally worse than **2**, despite a severe interaction between the inside hydrogens.



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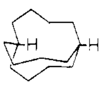

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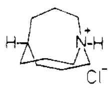

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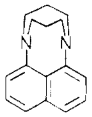

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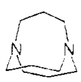

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These calculations bring out two points. (a) In,out isomerism should certainly be observable for these compounds; we can also expect to discover the encapsulation of at least the smallest ion, H^+. (b) Any process that allows outside pyramidalized bridgehead atoms to move toward planarity or pyramidalize inward brings considerable relief of strain. Thus 1-chlorobicyclo[3.3.3]undecane solvolyzes ca. 10^4 times faster than *t*-BuCl in aqueous alcohol,[6] corresponding to the relief of 28 kJ mol^{-1} of strain energy on formation of the bridgehead carbonium ion. In manxine hydrochloride (**5**), the C–N–C angles average 115.5°;[17] free manxine is believed to have an almost planar nitrogen on the basis of its unusual photoelectron spectrum.[18] In the naphtho[3.3.3]diamine **6**, the C–N–C angles average 118.6°.[19] An indication that nitrogen geometry is very flat in the [3.3.3]diamine itself (**7**) comes from comparison of the free energies of activation for bridge flipping in the diamine (29 kJ mol^{-1}) and its diprotonated and dimethylated ions (55 and 61 kJ mol^{-1}, respectively); outside pyramidalization of the bridgehead atoms increases the puckering of the bridges and the barrier to their inversion.[20] The strain relief from bridgehead flattening is greater in the larger [4.4.4] systems. It has been estimated[6] that 1-chlorobicyclo[4.4.4]tetradecane will solvolyze ca. 10^7 times faster than *t*-BuCl, with relief of 62 kJ mol^{-1} of strain. In these medium rings, it is *favorable* to introduce bridgehead double bonds[21]—poor old Bredt! The first "hyperstable" bridgehead alkene, bicyclo[4.4.2]dodec-

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(20) R. W. Alder and R. B. Sessions, unpublished results.

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Table I
Heats of Some Formal Dehydrogenations

hydrocarbon	dehydrogenation prod	ΔH, kJ mol^{-1}	ref for data
2 × propane	2,3-dimethylbutane	+29	14
cyclopentane	bicyclo[2.1.0]-pentane	+234	27
cyclodecane	*trans*-Decalin	−29	14
2 × 2-methylbutane	2,2,3,3-tetramethyl-butane	+46	14
bicyclo[1.1.1]-pentane	[1.1.1]propellane	+163	28
bicyclo[2.2.2]octane	[2.2.2]propellane	+280	29
bicyclo[3.3.3]-undecane	[3.3.3]propallane	−25	29
bicyclo[4.4.4]tetra-decane	[4.4.4]propellane	−163	30

1-ene, has recently been made.[22] Maier and Schleyer[21] calculate that the heat of hydrogenation of bicyclo[4.4.4]tetradec-1-ene to 2 will be only 50 kJ mol^{-1} compared with a normal figure of 109 kJ mol^{-1}. We have made amines 8[23] and 9[24]and calculate that the heat of hydrogenation of 8 to 9 is only 32 kJ mol^{-1}. Bridgehead alkene 8 is predicted to be more stable than its isomer 10 by 74 kJ mol^{-1}. As shown, 8 and 9 are believed to have inside lone pairs: for 9, which we call hiddenamine, this conformation is preferred to one with an outside lone pair by 77 kJ mol^{-1} (MM1). In agreement with expectations based on ^{1}H and ^{13}C NMR spectra and on its remarkable properties,[25] the [4.4.4]diamine 11 has recently been found[26] to have an in,in structure with D_3 symmetry and an N,N distance of 281 pm. MM2 calculations indicate this structure to be strongly preferred to in,out or out,out alternatives but perhaps underestimate the lone pair/lone pair repulsion in predicting an N,N distance of 264 pm. The transition from preferred out,out to in,in geometry for the diamines obviously comes somewhere within the set of 10 systems referred to in the introduction. Our "educated guess" is that the [3.3.3]diamine is (just) out,out; the [4.4.2]- and [4.3.3]diamines are in,out (or planar,planar?) and the remainder in,in.

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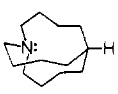

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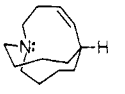

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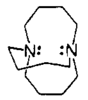

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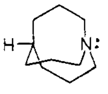

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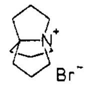

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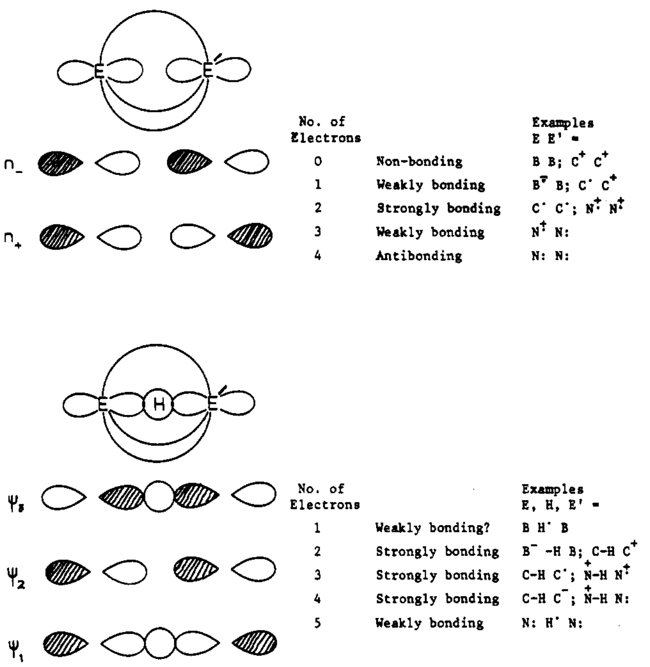
However the most efficient process for strain relief in these compounds is intrabridgehead bond formation, as can be gauged from the heats of the formal dehydrogenations in Table I. Intrabridgehead bond formation in medium-ring bicyclics is much more favorable than transannular bonding in medium-ring monocyclics, with a strain relief on bond *formation* that is comparable with that on bond *breakage* in small-ring compounds. The potential for harnessing this in the creation of novel chemistry is obvious. It can be seen that, in medium-ring bicyclic compounds, we not only have good control on orbital alignment in enforcing σ-type interactions between the two bridgehead atoms, but we have thermochemistry strongly on our side in the form of strain relief for the bridges. Medium-ring bicyclic compounds are therefore the perfect vehicles for looking at weak σ-bonding *and* anti-bonding interactions between a pair of atoms (see Figure 1). As we shall see, delicate situations like three-electron σ bonding can be realized in stable species inside medium-ring bicyclic compounds. More familiar weak σ interactions like hydrogen bonding can be set up in both linear and nonlinear geometries at will by adjustment of the sizes of the bridges.



No. of Electrons		Examples E E' =
0	Non-bonding	B B; C^+ C^+
1	Weakly bonding	$B^{\cdot-}$ B; $C^\cdot$ C^+
2	Strongly bonding	$C^\cdot$ $C^\cdot$; $N^{\cdot+}$ $N^{\cdot+}$
3	Weakly bonding	$N^{\cdot+}$ N:
4	Antibonding	N: N:

No. of Electrons		Examples E, H, E' =
1	Weakly bonding?	B $H^\cdot$ B
2	Strongly bonding	B^- -H B; C-H C^+
3	Strongly bonding	C-H $C^\cdot$; $\overset{+}{N}$-H $N^{\cdot+}$
4	Strongly bonding	C-H C^-; $\overset{+}{N}$-H N:
5	Weakly bonding	N: $H^\cdot$ N:

Figure 1. Simple MO picture of intrabridgehead interactions: (a) direct, E–E', (b) via hydrogen.

Synthesis

The key to the successful synthesis of medium-ring bicyclic compounds is a ring-cleavage strategy, as was first demonstrated by Leonard and his co-workers[9] who prepared manxine (12) by reductive cleavage of the propellane ammonium salt 13. The propellane precursor contains common-sized rings and is readily prepared. We have used this approach to synthesize the monoamines *out*-6*H*-1-azabicyclo[4.4.4]tetradecane (9)[24] and its unsaturated counterpart 8[23] (see Scheme I).

We have used various ring-cleavage strategies to make bridgehead diamines (Scheme II). The route[25,32,33] via

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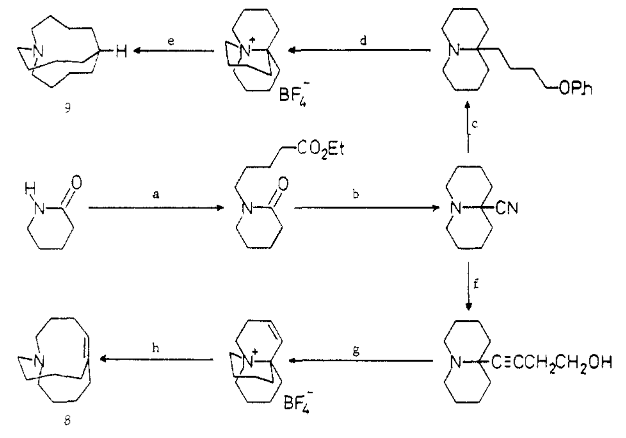
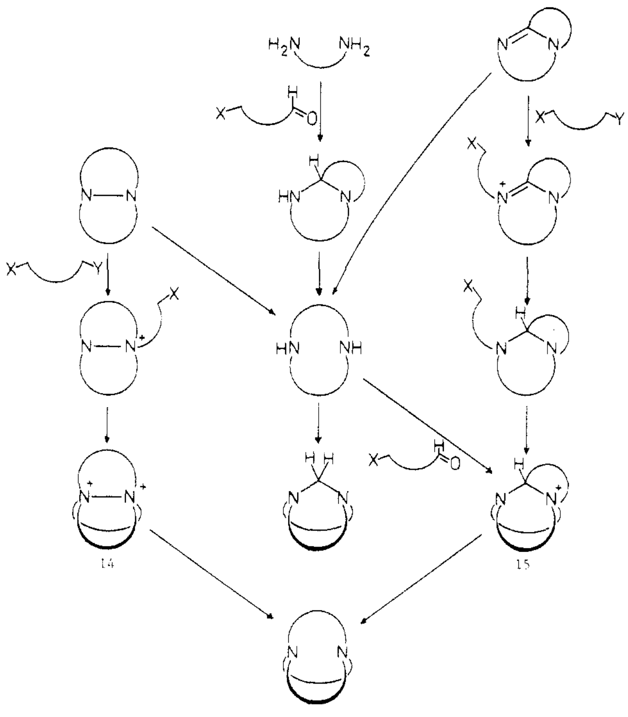
Scheme I



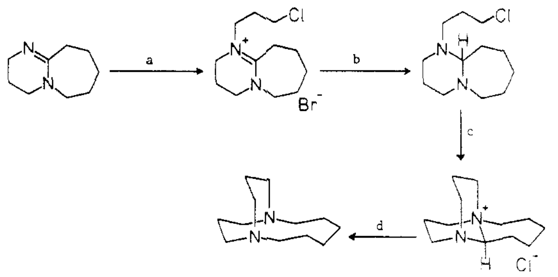
[a] i, KH, DME; ii, $Br(CH_2)_4CO_2Et$, 71%. [b] i, soda lime distillation; ii, $HBF_4{\cdot}Et_2O$; iii, aqueous KCN, 67%. [c] $PhO(CH_2)_4MgBr$, 93%. [d] i, 60% HBr; ii, Ag_2O,H_2O; iii, aqueous HBF_4, 42%. [e] Na, NH_3, 83%. [f] i, [4-(2-tetrahydropyranyloxy)butynyl]magnesium bromide, 81%. [g] i, H_2, Pd/C, MeOH; ii, TsCl, Et_3N; iii, aqueous HBF_4, 50%. [h] Na, NH_3, *t*-BuOH, 58%.

Scheme II



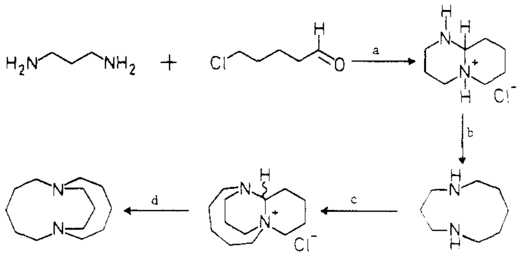
propellane hydrazinium dications **14** is particularly interesting in that this functionality was previously unknown. Pentaalkyl hydrazinium monocations are, not surprisingly, weak nucleophiles and while the final cycloalkylation works well for the construction of a five- or six-membered ring, closing a seven-membered ring was not practical. Using this approach we have made the [3.3.2]-, [3.3.3]-, [4.3.3]-, [4.4.3]-, and [4.4.4]diamines from the bicyclic hydrazines 1,5-diazabicyclo[3.3.0]octane and 1,6-diazabicyclo[4.4.0]decane.

Scheme III



[a] $Br(CH_2)_3Cl/Et_2O$, 97%. [b] $LiAlH_4$/THF, 49%. [c] CH_3CN, reflux, 68%. [d] $LiAlH_4$/DME, 80%.

Scheme IV



[a] $MgSO_4$, CH_2Cl_2, 86%. [b] i, NaOH, ii, Dibal, $PhCH_3$, 70%. [c] $Cl(CH_2)_4CHO$, $MgSO_4$, CH_2Cl_2, 65%. [d] $LiAlH_4$/DME, 67%.

Synthetic routes via the α-amino ammonium ions **15** are versatile since these intermediates can be assembled in several ways. Alkylation of bicyclic amidines, followed by reduction and cyclization, is successful[34] provided the halide is $X(CH_2)_2Y$ or $X(CH_2)_3Y$, as in the preparation of the [6.3.3]diamine from DBU (Scheme III). Alkylation of an amidine with $X(CH_2)_4Y$ can lead to an alternative spirocyclic product. Fortunately C_4 and C_5 units are readily introduced by a reaction of a monocyclic diamine with an ω-halo aldehyde[35] as in the preparation of the [5.5.3]diamine in Scheme IV. The necessary monocyclic diamines are available by a variety of routes. At the time of writing we have made the following diamines by this route: [4.3.2], [4.3.3], [4.4.2], [5.3.2], [4.4.3], [5.3.3], [5.4.2], [6.3.2], [5.4.3], [5.5.2], [6.4.2], [5.4.4], [5.5.3], [6.4.3], [5.5.4], and [6.5.3]. Finally C_1 bridges can be introduced by reaction of a monocyclic diamine with formaldehyde, and we have made [4.4.1] and [5.4.1], for example, this way.

Nitrogen as a Bridgehead Atom: the Unique Properties of Medium-Ring Amines and Diamines[36]

As a probe of the properties of bridgehead atoms in these systems, nitrogen is the ideal atom. It readily inverts and it can be protonated, alkylated, and oxidized. In the remainder of this Account, I shall describe the special chemistry of medium-ring bicyclic amines and diamines. The rich array of ionic species that can be generated from the [4.4.4]diamine **11** by oxidation and protonation[25,37] are shown in Scheme V.

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(30) R. W. Alder and A. Casson, unpublished results; see also ref 23, 24, and 29.

(31) R. W. Alder, R. J. Arrowsmith, A. Casson, R. B. Sessions, E. Heilbronner, B. Kovac, H. Huber, and M. Taagepera, *J. Am. Chem. Soc.*, **103**, 6137 (1981).

(32) R. W. Alder, R. B. Sessions, J. M. Mellor, and M. F. Rawlins, *J. Chem. Soc., Chem. Commun.*, 747 (1977).

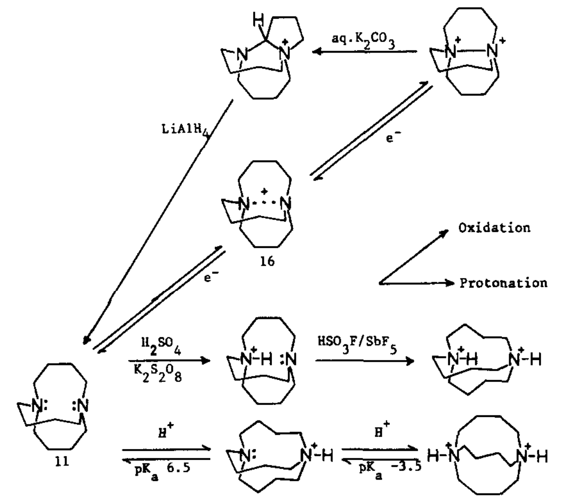
(33) R. W. Alder, R. B. Sessions, A. J. Bennet, and R. E. Moss, *J. Chem. Soc., Perkin Trans. 1*, 603 (1982).

(34) R. W. Alder and R. B. Sessions, *Tetrahedron Lett.*, **23**, 1121 (1982).

(35) R. W. Alder, P. Eastment, R. E. Moss, R. B. Sessions, and M. A. Stringfellow, *Tetrahedron Lett.*, **23**, 4181 (1982).

(36) For a review of the special properties of diamines, see R. W. Alder and R. B. Sessions in "The Chemistry of Amino, Nitoso, and Nitro Compounds and Their Derivatives", S. Patai, Ed., Wiley, Chichester, 1982, Chapter 18.

Scheme V



Amine Oxidation and Persistent Radical Cations

Diamines like 7 and 11 are among the most easily oxidized of all saturated compounds: they decompose on being exposed to air for a few minutes. Oxidation in solution produces dications via radical cations of astonishing persistence. The two-step redox system is particularly interesting because it is σ-type, actually σ^*, electrons that are being removed in the oxidation. Most[38] organic redox systems involve the removal of π electrons,[39] while most inorganic systems involve d electrons. In the case of 11 all three oxidation states are stable for long periods at room temperature. Cyclic voltammetry shows two waves at −0.1 and +0.2 V vs. SCE, although the waves are not ideal due to slow electron transfers; for comparison, oxidation of *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine to the famous Würster's blue radical cation occurs at −0.01 V. The salt 16·BF_4 can be prepared by mixing CH_3CN solutions of the amine and dication and isolated as a dark red solid. The absorption band λ_{max} 480 nm (ϵ 4500) is remarkably broad (width at half-height 8100 cm^{-1}). Similar bands are observed for the long-lived radical ions derived from the [3.3.3]-, [4.3.3]-, [4.4.3]-, and [5.4.3]diamines. The transition is a simple one, $n_+(\uparrow\downarrow)n_-(\uparrow) \rightarrow n_+(\uparrow)n_-(\uparrow\downarrow)$ in the language of Figure 1, the enormous band width reflecting the large difference in relaxed N,N distance between ground and excited state. ESR spectra for 16 and related ions show hyperfine coupling to two nitrogens. This coupling varies from 14.7 G for the radical cation from the [3.3.3]diamine[32] to 34.4 G for 16.[25] We believe the nitrogens are close to planar for the [3.3.3] radical ion but strongly pyramidal (inwards) for the [4.4.4] ion 16.

σ^* radicals like 16, containing a three-electron σ bond, are known in a wide range of structures. Most examples are, however, unstable outside the glassy or solid state.[40] The transannular $S\cdot\overset{+}{\cdot}S$ radical ions generated from medium-ring disulfides like 1,5-dithiacyclooctane[38b] are an exception, although these are not stable to water, unlike 16.

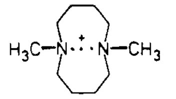
There are two primary questions to ask about a novel type of bond: (i) how strong is it and (ii) how long is it? The ion 17 can be generated by pulse radiolysis, but unlike 16, its half-life is only 5 ms.[41] Fission of the three-electron σ bond in 17 is probably the rate-limiting step in its decomposition; the free energy of activation is 61 kJ mol^{-1} and this is a fair estimate of the three-electron bond strength. Alternative estimates of the bond strength ($\geqslant$46 kJ mol^{-1}) come from gas-phase proton affinity and ionization energy for 11.[31] Theoretical calculations on $N_2H_6^{+}\cdot$ predict a bond length of 216 pm.[42] So far attempts to grow satisfactory crystals of a salt of 16 have failed. The best that can be said at present is that this bond length would fit well in the [3.3.3] and [4.4.4] cages with the nitrogen geometries discussed above.

Although most of the medium-ring diamines are easily oxidized, radical cations with lifetimes of more than a second at room temperature are only obtained from the [3.3.3]-, [4.3.3]-, [4.4.3]-, [4.4.4]-, and [5.4.3]-diamines. Nelsen and Gannett[43] found that the radical ion from 18 is not long lived, despite its structural similarity to 11. A good explanation of the persistence of these ions must await more work, but we believe that tight constraint on the nitrogens is vital for persistence, in particular, prevention of easy intramolecular hydrogen transfers (see below).

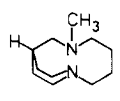
Photoelectron Spectra

Medium-ring diamines built with three-, four-, and five-carbon bridges show two photoelectron bands separated by ~1 eV. We have argued[19,31,32] that this is due to "through-space" splitting with n_+ more stable than n_- (see Figure 1). First ionization energies are very low indeed, e.g., [3.3.3], 6.85; [4.3.3], 6.75; [4.4.3], 6.64; [4.4.4], 6.75; [6.3.3], 6.78 eV.

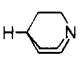
The photoelectron spectra of the monoamines quinuclidine (19), manxine (12), and hiddenamine (9) are also interesting.[18,31] Quinuclidine and hiddenamine have broad first ionization bands typical for normal tertiary amines, whereas that for manxine is sharp and at lower energy. The data fit the sequence (19) pyramidal (out), (12) flat, (9) pyramidal (in). In the unsaturated amine 8 the large splitting (1.3 eV) between the photoelectron bands for n and π ionization is strong evidence for through-space interaction between the n and π orbitals and, incidentally therefore, for an inside lone pair in 8.[23]



17



18



19

Amine Protonation and Proton Encapsulation[3,4,36]

The pK_a values of medium-ring amines and diamines give information about the energetics of the geometric changes imposed by protonation. *Rates* become im-

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[37] R. W. Alder, A. Casson, and R. B. Sessions, *J. Am. Chem. Soc.*, 101, 3652 (1979).

[38] Prominent and highly relevant exceptions are the $R_2S\cdot\overset{+}{\cdot}SR_2$ ions investigated and reviewed by Asmus and Musker: (a) K.-D. Asmus, *Acc. Chem. Res.*, 12, 436 (1979); (b) W. K. Musker, *ibid.*, 13, 200 (1980).

[39] K. Deuchert and S. Hünig, *Angew. Chem.*, 90, 927 (1978), review many interesting π systems.

[40] For a review, see M. C. R. Symons, *Chem. Br.*, 12, 193 (1976).

[41] S. F. Nelsen, R. W. Alder, R. B. Sessions, K.-D. Asmus, K.-O. Hiller, and M. Gobl, *J. Am. Chem. Soc.*, 102, 1429 (1980).

[42] See ref 25, footnote 10.

[43] S. F. Nelsen and P. M. Gannett, *J. Am. Chem. Soc.*, 104, 4698 (1982).

Table II
Proton Affinities and pK_a Values for Some Amines and Diamines

amine	proton affinity[a]	pK_{a_1}[b]	pK_{a_2}[b]
Et_3N	979	10.8	
n-Pr_3N	988	10.7	
n-Bu_3N	994	11.0	
quinuclidine (**19**)[19]	977	10.9	
manxine (**12**)	977	9.9[c]	
hiddenamine (**9**)	908	0.6[d]	
[2.2.2]diamine (Dabco)	966	8.8	3.0
[3.3.3]diamine (**7**)	979	10.3[e]	6.5[e]
[4.4.4]diamine (**11**)	955	6.5[f]	−3.2[f]
[1.1.1]cryptand (**20**)		7.1[g]	~1[g]

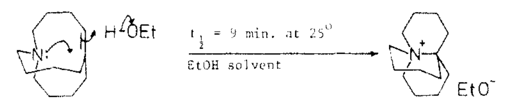
[a] Relative to NH_3, 860 kJ mol^{-1}; see ref 31. [b] Data from D. D. Perrin "Dissociation Constants of Organic Bases in Aqueous Solution", London, Butterworths, 1965, and Supplement, 1972, except where noted. [c] Reference 9. [d] Reference 24, data for 48% v/v $EtOH/H_2O$. [e] Reference 32. [f] Reference 37. [g] Reference 44.

portant with inside protonation, since getting the proton in may be difficult, despite favorable thermodynamics.

Outside Protonation

Proton affinity and pK_a data for monoamines **19**, **12**, and **9**, and for the [2.2.2]-, [3.3.3]-, and [4.4.4]diamines are collected in Table II. Hiddenamine (**9**) is an extremely weak base. It dissolves in 12 N HCl solution, but addition of an equal volume of water causes precipitation of the free amine! Comparison with *n*-Bu_3N shows a $\Delta\Delta H$ for gas-phase protonation of 86 kJ mol^{-1}.[31] Recall that the energy difference between conformations of **9** with an inside and outside lone pair was 77 kJ mol^{-1};[24] thus increase in strain on the protonation is the major factor in the weak outside basicity of **9**.

1-Azabicyclo[4.4.4]tetradec-5-ene (**8**) behaves quite differently.[23] At all acidities, it rapidly and irreversibly forms a propellane by carbon protonation–a retro-Hoffmann elimination (eq 1).

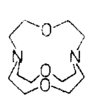


(1)

Strain effects on the protonation of the diamines are greatest with [4.4.4]diamine **11** and show up most on *second* protonation; monoprotonated **11** probably has an inside lone pair. The first pK_a of Lehn's [1.1.1]-cryptand **20** is similar to triethanolamine, but the second pK_a is affected by strain.

Inside Protonation

Simmons and Park[3] were the first to demonstrate substantial barriers to the inside protonation of their macrobicyclic diamines, e.g., [8.8.8]diamine; however, two protons could be inserted and removed. For [1.1.1]cryptand **20** the barriers are substantially higher

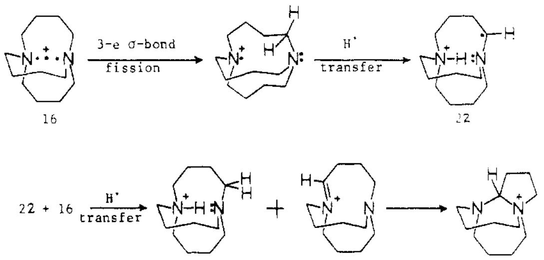


20

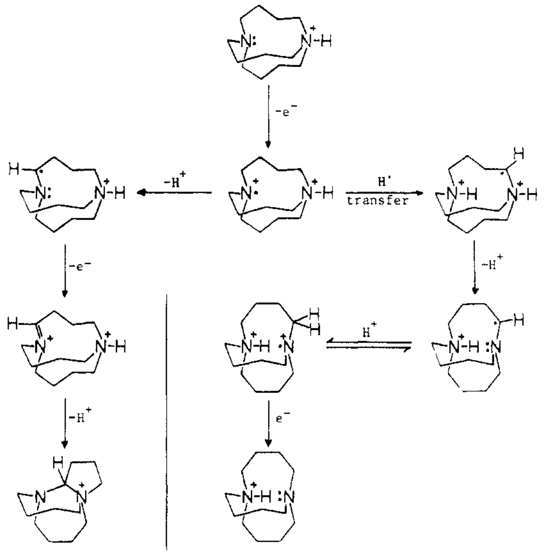
21

and no way has been found to deprotonate the inside monocation.[13,44] We have found a number of diamines that can be inside protonated and, in some cases, deprotonated by a normal proton-transfer mechanism; in a rough order of decreasing rate of protonation, these are (currently) the [5.4.2]-, [5.5.2]-, [5.5.3]-, [6.4.3]-, [6.5.3]-, and [5.5.4]diamines.[20,45] Our studies on these diamines are at an early stage, but the determining factor is presumably the energy cost of achieving a conformation in which one (or both?) lone pair emerges through a large ring (see **21**).

Scheme VI



Scheme VII
Mechanism for the Oxidant-Promoted Formation of *in*-[4.4.4]H$^+$ [a]



[a] Formation of the tricyclic α-amino ammonium ion product is only competitive at lower acidities (<60% H_2SO_4).

We also discovered[37] a quite unexpected, nonproton transfer mechanism by which inside-protonated [4.4.4]-, [5.4.3]-, [6.3.3]-, [5.4.4]-, and [5.5.4]diamines can be formed. In these reactions the inside proton comes not from the solvent but from one of the CH_2 groups of the amine. A further surprise is that these reactions are promoted by one-electron oxidants! A clue to the mechanism came from the thermal decomposition of **16**·BF_4. The two products, formed in 1:1 ratio, are reasonably accounted for by Scheme VI. The key intermediate is probably a radical cation *without* a three-electron σ bond and with an outside pyramidalized nitrogen permitting a Hofmann–Loeffler–Freytag type hydrogen atom transfer. A similar, perhaps protonated, species is probably involved in "inside protonation" in acid solution. A further remarkable feature of the preparation of in [4.4.4]H$^+$ in D_2O/D_2SO_4 solution is that under appropriate conditions, *extensive*

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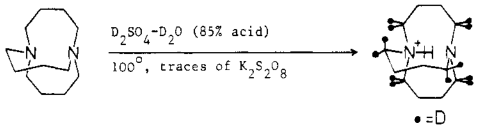
(44) P. B. Smith, J. L. Dye, J. Cheney, J.-M. Lehn, *J. Am. Chem. Soc.*, **103**, 6044 (1981).

(45) R. W. Alder, R. E. Moss, and R. B. Sessions, *J. Chem. Soc., Chem. Commun.*, in press.

α deuteration is observed, though the inside hydrogen remains a proton (eq 2). A mechanism to account for this is shown in Scheme VII. As shown the inside proton comes entirely from an α position in the [4.4.4]diamine. With the [5.4.3]diamine,[45] the inside proton comes only from an α-CH_2 group in the *five*-carbon bridge. The results for [6.3.3]diamine are rather more complex.[34]



(2)

What about the thermodynamics of inside protonation? Almost nothing is known yet due to the slow proton-transfer rates. Smith et al.[44] *estimate* that the pK_{a1} for inside protonation of [1.1.1]cryptand is $\geq$17.8, making it the strongest known neutral base. In the inside-protonated [1.1.1]cryptand there is no strong N^+-H:N hydrogen bond, although the proton probably interacts with the oxygens. In the inside-protonated medium-ring diamines we have made, there is a strong hydrogen bond (see below), and this should increase the inside pK_a of these diamines even further. We have so far not found any conditions that will deprotonate in [4.4.4]H^+ and produce the diamine.

Finally there are several amines, e.g., the [4.4.3]diamine and hiddenamine (**9**), for which inside protonation looks perfectly feasible but where we have been unable to make the inside H^+ species. Functional group manipulation on the bridges of these molecules could provide the key to the insertion of a proton. The recent synthesis of [1.1.1]cryptand by means of a proton template route[46] is also an interesting pointer.

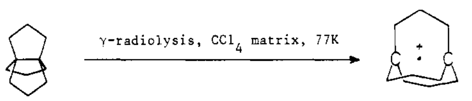
Hydrogen Bonding in Inside Protonated Diamine Ions

In the inside protonated ions we have made, there is clearly a strong N^+-H:N hydrogen bond as shown by the extremely deshielded ^1H NMR absorption ranging from δ 12.4 in *in*-[5.5.2]H^+ to δ 17.8 in *in*-[5.4.3]H^+ and by the very low N^+-H:N vibration frequency, down to 1400 cm^{-1} in *in*-[4.4.4]H^+. A chemical indication of the strength of these hydrogen bonds is the reluctance of these ions to diprotonate (inside,outside). The extreme case is *in*-[4.4.4]H^+, which dissolves unchanged in HSO_3F and requires magic acid (HSO_3F/SbF_5) to diprotonate.

These hydrogen-bonded species could be unique in that their hydrogen bonds may be under *compression* from the rest of the structure and it would be very interesting to know if their hydrogens move on single- or double-minimum potential energy surfaces. We have applied the $\Delta\delta(^1H,^2H)$ test[47] to some of these ions.[34,45] $\Delta\delta$ is an order of magnitude smaller for *in*-[4.4.4]H^+ (+0.06) than that of the other ions examined (those from the [6.3.3]-, [5.4.3]-, [5.5.3]-, and [6.4.3]diamines) where $\Delta\delta$ is in the range +0.53–0.87. Thus the hydrogen bond in *in*-[4.4.4]H^+ *may* be of the single minimum type; what does seem significant is that this is the only case where the bond *must* surely be *linear*.

Concluding Remarks

We hope our studies have uncovered some of the major themes in the chemistry of medium-ring bicyclic compounds—intrabridged chemistry, in/out isomerism, and encapsulation. Yet much remains to be done. The effects of variation in ring sizes on these phenomena deserve more attention and to this end we are engaged in making as many of the bridgehead diamines as we can. But other elements (boron, phosphorus) and functionalities (carbon radicals and ions, bridgehead alkenes) have been hardly investigated yet. A final example hints at the possibilities (eq 3). The radical ion has a one-electron bond but is only known so far in a matrix.[48]



(3)

Beyond this, one can see a family resemblance between the type of chemistry we have been pursuing and that of the cyclophanes where the two "bridgehead atoms" that come face to face are benzene rings. It is also interesting to note that both weak (antiferromagnetic coupling) and very strong (triple and quadruple bonding) interactions bwtween two transition metals have often been pursued in an intrabridgehead topology.

I wish to thank my co-workers in Bristol and collaborators elsewhere mentioned in the references for their valuable contributions. Particular thanks go to Richard Sessions; without his contributions, we would not have gotten very far. I also wish to thank the U.K. S.E.R.C. for financial support.

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(46) R. Annunziata, F. Montanari, S. Quici, and M. T. Vitali, *J. Chem. Soc., Chem. Commun.*, 777 (1981).

(47) L. J. Altman, D. Laungani, G. Gunnarsson, H. Wennerström, and S. Forsén, *J. Am. Chem. Soc.*, **100**, 8264 (1978).

(48) R. W. Alder, R. B. Sessions, and M. C. R. Symons, *J. Chem. Res., Synop.*, 82 (1981).