Bredt's Rule

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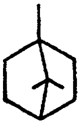
1 Introduction

In a long and fruitful working life,[1] which was centred very largely around the chemistry of camphor, Julius Bredt made several important contributions to structural chemistry and stereo-chemistry. For example, we owe to him the bridged bicyclic structure of camphor and the concept of *exo/endo* isomerism. But today he is remembered chiefly for the rule that bears his name—compounds of the camphane (1) and pinane (2) series cannot have a double bond at the bridgehead.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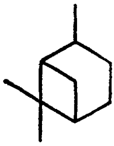
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This simple truth can be verified readily by molecular models but it can be overlooked in a two-dimensional drawing and so it has survived in organic chemistry as a useful rule of thumb, empirical but reliable.

More recently, a critical re-examination of the evidence upon which it rests has raised doubts, and indeed several bridgehead alkenes which were previously classified as forbidden have since been synthesized. These successes raise the question, is Bredt's rule still valid? They have also precipitated an appraisal of the stress factors which are operative in strained double bonds.

This review, which comes just 50 years after Bredt propounded his rule, summarizes and assesses the early evidence upon which it was based and attempts to show how our present understanding of strain enables us to set it in a wider context.

2 Historical

Bredt's formal enunciation[2] of his rule in 1924, at the age of 69, was the outcome of some 30 years' experience in which he and others had repeatedly noted anomalies associated with the bridgehead position of bridged bicyclic compounds.

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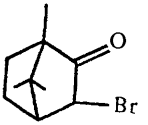
[1] P. Lipp, *Ber.*, 1937, **70**, *A*, 150.

[2] J. Bredt, H. Thouet, and J. Schmitz, *Annalen*, 1924, **437**, 1.

Thus it has been found that bromocamphor (3) resisted dehydrobromination and the diacid (4) could not be converted into its anhydride except under forcing conditions, and then only with migration of the double bond (5). In its original form, the rule referred to 'compounds of the camphane and pinane series and similarly constituted compounds'. However, Bredt soon realized that stable bridgehead double bonds were possible if only the bridge was large enough, and in a later paper[3] he modified his rule accordingly, but without committing himself to an exact boundary line. Even so, he performed a valuable service to organic chemistry in recognizing and delineating the problem, and inspiring further experimental work.

In the years immediately following Bredt's publication, three things happened: the concept was applied to a wide variety of bridged systems; much corroborative evidence accumulated; and an effort was made to discover the limit of the rule. Apart from the failure of a variety of bridgehead eliminations, some other processes involving an intermediate bridgehead double bond were shown to be forbidden; *e.g.*, several bicyclic β-ketoacids similar in type to ketopinic acid (6) were found to be thermally stable, a fact which could be explained in terms of the Westheimer mechanism[4] (7), which implicates an enol intermediate; β-diketones such as (8) were shown to be non-enolizable;[5] and even amides which incorporated a bridgehead nitrogen (9) proved to be so inaccessible, that they were classified[6] at that time as 'forbidden amides'. Finally, and most importantly, a large number of erroneous structures were re-examined and corrected An earlier review[7] provides an excellent documented survey of all of this work.



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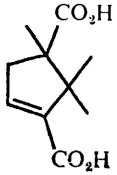

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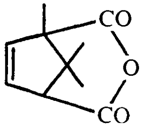

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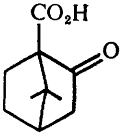

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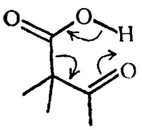

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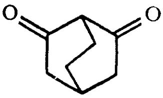

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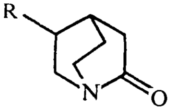

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[3] J. Bredt, *Ann. Acad. Scient. Fennicae*, 1927, **29A**, 3.

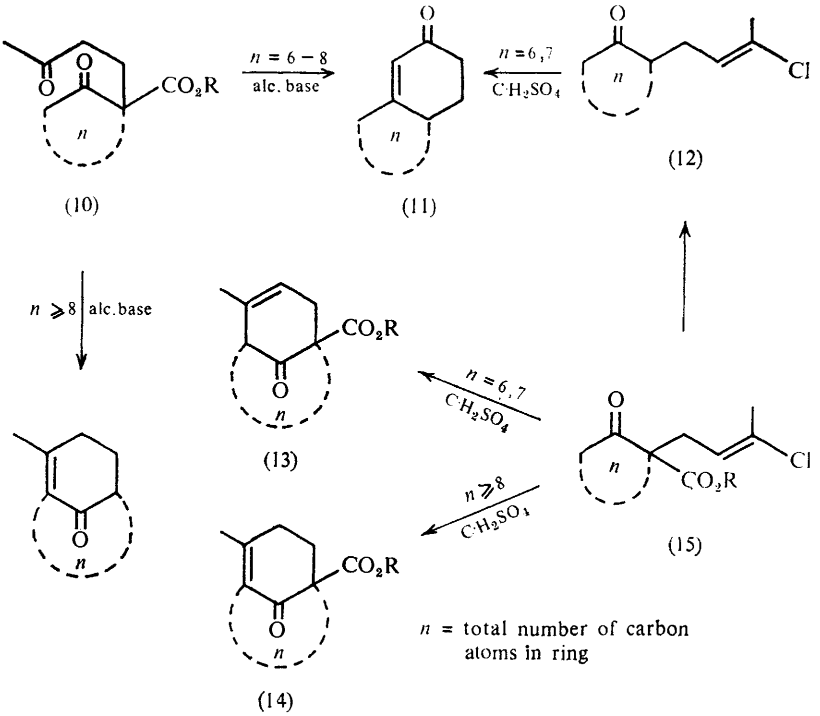
[4] F. H. Westheimer and W. A. Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 3283.

[5] P. D. Bartlett and G. F. Woods, *J. Amer. Chem. Soc.*, 1940, **62**, 2933.

[6] R. Lukes, *Coll. Czech. Chem. Comm.*, 1938, **10**, 148.

[7] F. S. Fawcett, *Chem. Rev.*, 1950, **47**, 219.

At the same time, a search for the limit of Bredt's rule was being pursued by Prelog[8] and others. From a study of the cyclization of the diketones (10) and their (*in situ*) chlorovinyl precursors (12) and (13) he concluded that bicyclo (5, 3, 1)undecane was the smallest system that could accommodate a bridgehead double bond (see Scheme 1). A later investigation of the condensation of nitromalondialdehyde with cycloalkanones seemed to confirm this conclusion; *i.e.*, the bridged nitrophenol (16) or the related dienone (17) were formed *only* when the cycloalkanone was at least 8-membered.



Scheme 1

Finally, Fawcett[7] reduced these results to a convenient numerical formula. He defined the strain number (S) in a bicyclo(x, y, z)alk-1-ene as $S = x + y + z$ (x, y and $z \neq 0$) and deduced from Prelog's results that Bredt's rule ceased to be valid when $S \geqslant 9$. He therefore concluded that 'the tentative upper limit to the ring size for which the rule forbids such double bonds, in isolable compounds, is $S = 8$'. At the same time he recognized that for transient intermediates the limit might be as low as $S = 6$. This conclusion was forced upon him by the knowledge that, for example, the ketoacid (18), which has an S number of 7

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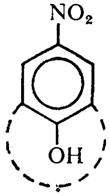
[8] V. Prelog, *J. Chem. Soc.*, 1950, 420.



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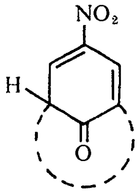

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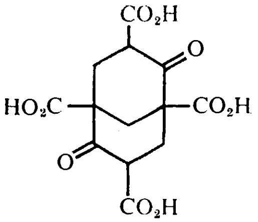

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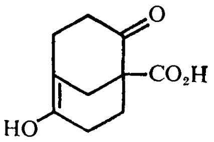
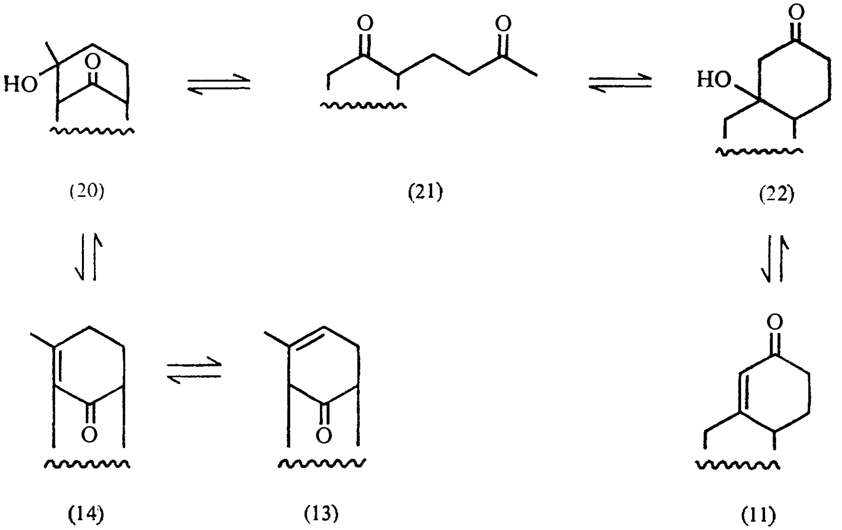


(19)

could be (totally) decarboxylated;[9] a process involving enol intermediates such as (19).

3 Reassessment

In fact, the evidence concerning the boundary line was less meaningful than it seemed. Firstly, Prelog's investigations related solely to bridged cyclohexenones, with the carbonyl group located in the smallest bridge. This is a rather limited basis on which to test a general stereochemical rule. Secondly, all of his experiments were carried out under equilibrating conditions and consequently yielded only the thermodynamically preferred product. It is now apparent[10,11] that in such cyclizations, three equilibria are involved (see Scheme 2), intercon-



Scheme 2

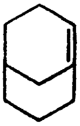
[9] H. Meerwein, *J. prakt. Chem.*, 1922, **104**, 1.

[10] G. L. Buchanan, *Topics in Carbocyclic Chem.*, 1969, **1**, 205.

[11] G. L. Buchanan and G. A. R. Young, *Chem. Comm.*, 1971, 643.

verting structural isomers (20), (21) and (22) as well as double bond isomers (13) and (14). Consequently, the isolation of one product rather than another merely reflects the difference in their free energies. It tells us nothing of the products that might arise under conditions of kinetic control.

Fawcett's contribution to the subject was considerable. In particular, he made the distinction between *isolable* alkenes and *transient* intermediates. His restatement of Prelog's results (see above) in terms of S numbers is remarkably accurate; so accurate that a recent reviewer[12] has chosen to retain it in modified form as an expression of Bredt's rule. Even so, it is an oversimplification. It has no theoretical basis and, more importantly, it fails to differentiate isomeric alkenes such as (23) and (24) which may have the same strain number ($S = 7$) but obviously differ in strain energy. The difference is exemplified by the high stability[13] of the β-ketoacid (25) on the one hand, and the ready decarboxylation of (18)[9] and (26),[14] on the other. Yet, in spite of these shortcomings, Fawcett's S-formula survived for 17 years.



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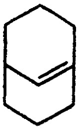

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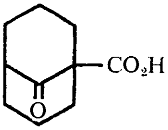

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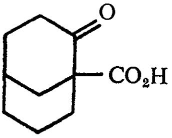

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4 Revision

A more fundamental and yet satisfyingly simple approach was proposed by Wiseman[15] in 1967. Pointing out that a bridgehead double bond in any bicyclic alkene (27) is endocyclic to two of the rings, and must lie *trans* within one of these [that defined by ac in (27)], he postulated that 'the strain of bridgehead alkenes is closely related to the strain of *trans*-cycloalkenes'.* On this basis, he went on to predict that, since *trans*-cyclo-octene is a highly reactive, but isolable compound, bridgehead alkenes which incorporate a *trans*-cyclo-octene should be isolable, albeit highly reactive. By the same token he forecast that bridgehead alkenes incorporating a *trans*-cycloheptene might be isolable and would be detectable as transient intermediates.

This revision of Bredt's rule now allows us to predict that, for a given carbon skeleton, the double bond will be more stable if it is *trans* within the larger of the

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* This concept of Bredt's rule had apparently occurred to Sir Robert Robinson, and is mentioned in a well-known text;[16] another reviewer[12] has quoted a similar precognition, published in a German text in 1933.

[12] G. Köbrich, *Angew. Chem. Internat. Edn.*, 1973, **12**, 464.

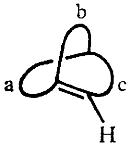
[13] A. C. Cope and M. E. Synerholm, *J. Amer. Chem. Soc.*, 1950, **72**, 5228.

[14] J. P. Ferris and N. C. Miller, *J. Amer. Chem. Soc.*, 1963, **85**, 1325.

[15] J. R. Wiseman, *J. Amer. Chem. Soc.*, 1967, **89**, 5966; J. R. Wiseman and W. A. Pletcher, *ibid.*, 1970, **92**, 956.

[16] Chemistry of Carbon Compounds, ed. Rodd., Elsevier, London, 1956, Vol. IIA, p. 275.

two rings in which it is endocyclic; *e.g.*, (28) should be more stable than (29), since the latter incorporates a *trans*-cyclohexene. It also predicts that (30), which may be regarded as a bridged *trans*-cyclononene, should be more stable than its isomer (28). However, it tells us nothing about the relative stabilities of (30) and (31).



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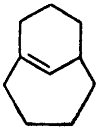

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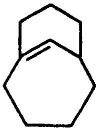

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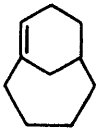

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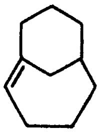

(31)

These ideas have greatly clarified our thinking on Bredt's rule. For example, the observed difference in the thermal stabilities of the two ketoacids (25) and (26) now becomes clear. However, the most compelling support for the Wiseman postulate comes from the synthesis of several 'anti-Bredt' alkenes, previously classified as forbidden. These syntheses, together with other evidence, are discussed below, the examples being grouped, for convenience, according to the size of the ring containing the *trans* double bond.

A. Eight-membered Rings.—The alkene (23) was synthesized simultaneously in two laboratories *via* irreversible elimination reactions. Wiseman[15] obtained it from the quaternary salt (32) by a Hofmann elimination, or from the 1,2-dibromide (33) by the action of sodium t-butoxide. Marshall[17] employed decarboxylative elimination of the *endo*-methane-*p*-sulphonate (34). Here, in the transition state, the molecule presumably adopts the rare boat–boat conformation and, predictably, the β-lactone (35) is a byproduct. However, since the latter decarboxylates only at a distinctly higher temperature than (34), it is unlikely to be an intermediate in the reaction. The structure of (23) has been amply confirmed by chemical degradation.[15,17]

The validity of Wiseman's *trans*-cycloalkene analogy is further underlined by his synthesis[18] of the isomeric alkenes (36) and (37) as co-products from the appropriate bridgehead quaternary ammonium hydroxide. The related enone (39) is also known;[19] either of the toluene-*p*-sulphonates (38a) and (38b) could be transformed by boiling collidine into a mixture of enones of which (39) was the minor component. This isomer was the sole product (40%) when the *exo*-chloride was employed. A focus of interest in these reactions is the mechanism, which might involve an intermediate *trans*-cycloheptenolate anion (40), an

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[17] J. A. Marshall and H. Faubl, *J. Amer. Chem. Soc.*, 1970, **92**, 948.
[18] J. R. Wiseman, H. F. Chan, and C. J. Ahola, *J. Amer. Chem. Soc.*, 1969, **91**, 2812.
[19] W. Carruthers and M. I. Qureshi, *J. Chem. Soc. (C)*, 1970, 2238.

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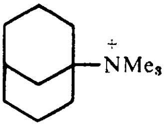

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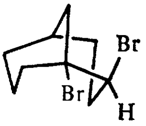

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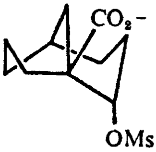

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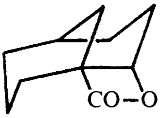

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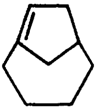

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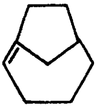

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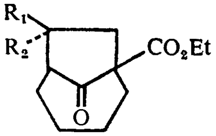
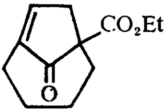


(38) (a) $R_1 = H$; $R_2 = OTs$
(b) $R_1 = OTs$; $R_2 = H$
(c) $R_1 = Cl$; $R_2 = H$

(novel) inductively-stabilized bridgehead carbanion or a synchronous *syn*-elimination.

The enamino-ketone (41a)[20] and the enones (41b) and (41c)[21] have also been



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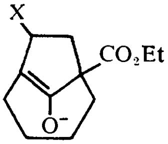

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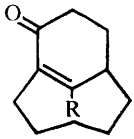
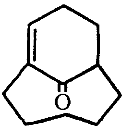


(41) (a) $R = N(C_2H_4)_2O$
(b) $R = H$
(c) $R = Ph$



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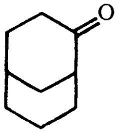

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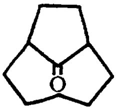

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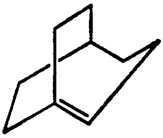
[20] J. R. Hargreaves, P. W. Hickmott, and B. J. Hopkins, *J. Amer. Chem. Soc.*, 1969, 592.
[21] G. L. Buchanan and G. Jamieson, *Tetrahedron*, 1972, **28**, 1129.

prepared and, in particular, the instability of (41b) compared with (42)[21] is satisfactorily consistent with Wiseman's hypothesis. The observed[22] bridgehead bromination or deuteriation of (43) and (44) is equally consistent with Wiseman's restatement of Bredt's rule.

B. Seven-membered Rings.—By analogy with *trans*-cycloheptene, it was not expected that bridged alkenes of this class would be readily isolated; however Wiseman was able to show that they could exist briefly. Using the same, well tried, Hofmann elimination route he formed[23] a mixture of the bicyclononenes (45) and (46). They dimerised too rapidly to allow conventional identification, but n.m.r. evidence, together with the isolation of adducts and derivatives leaves no doubt that they were formed. Less satisfying, but nonetheless valid, evidence comes from the deuteriation[24] of copacamphor (47) and the decarboxylation of (48), (49)[25] and (50).[15] However, it is noticeable that these reactions require more strenuous conditions than those described in Section 4A.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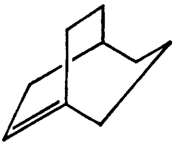
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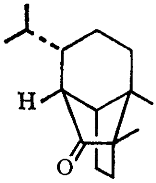

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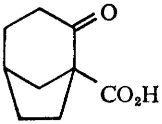

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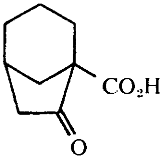
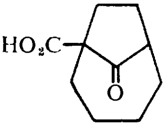


(49)



(50)

During his investigations of the mixture of alkenes (45) and (46), Wiseman noted[23] that the less stable (and, by inference, the more strained) isomer was that formed in greater amount in the Hofmann elimination. It would be of great interest to identify this isomer for, as we have indicated above, Wiseman's cycloalkene analogy makes no distinction between such isomers. Unfortunately,

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[22] J. P. Schaefer and J. C. Lark, *J. Org. Chem.*, 1965, **30**, 1337; K. Biemann, 'Mass Spectrometry', McGraw Hill, New York, 1962, p. 246.

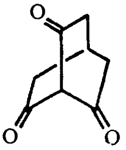
[23] J. R. Wiseman and J. A. Chong, *J. Amer. Chem. Soc.*, 1969, **91**, 7775.

[24] K. W. Turnbull, S. J. Gould, and D. Arigoni, *J.C.S. Chem. Comm.*, 1972, 597.

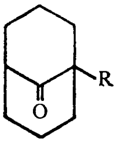
[25] J. P. Ferris and N. C. Miller, *J. Amer. Chem. Soc.*, 1966, **88**, 3522.

no evidence is available. On the other hand, evidence is available with respect to the bicyclo(3,2,1)octene system. The decarboxylation temperatures of the isomeric ketoacids (48) and (49) have been measured[25] and found to be, respectively, 260 °C and 320 °C. This suggests that it is energetically more expensive to place a double bond in the smaller ring; at least in this bridged system.

C. Six-membered Rings.—At the present time, there is no firm evidence for the existence of *trans*-cyclohexene even as a transient intermediate and so it might be imagined that bridgehead alkenes of this class would be totally inaccessible. Indeed, neither the enolization of ketones nor (more convincingly) the decarboxylation of β-ketoacids has been observed in any case where the reaction intermediate would be a *trans*-cyclohexenol or enolate. For example, the trione (51) is reported[26] to be non-enolic, the ketone (52a) did not react with bromine,[27] and the β-ketoacids (52b) and (53) were found to be thermally stable.[13,28]



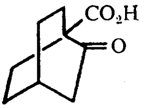
(51)



(*a*) R = Br

(*b*) R = CO_2H

(52)



(53)

Consequently the recent detection of bridgehead alkenes of this class is particularly significant. Ironically, the best documented examples are derived from bicyclo(2,2,1)hept-1-ene, one of the structures explicitly forbidden by Bredt in his original paper.

In 1965, Tatlow and his group announced[29] that the carbanion (54) derived from 1*H*-undecafluoronorbornane decomposed quite rapidly at room temperature to yield a short-lived intermediate which behaved as if it were (55). It reacted with furan to give two stereoisomeric adducts with the structure (56), or with the bromide ion (followed by loss of fluoride) to give (57) (see Section 7). In a very full investigation,[30] they were able to generate the same intermediate from the 1-bromomagnesio-compound as well as by decarboxylative elimination of F^- from (58). The parent hydrocarbon (59) was first described in 1971 by Keese and Krebs.[31] By treating 1,2-dihalogenonorbornanes with butyl-lithium in the presence of furan, these authors obtained two stereoisomeric adducts

[26] W. Theilacker and E. Wegner, *Annalen*, 1963, **664**, 125.

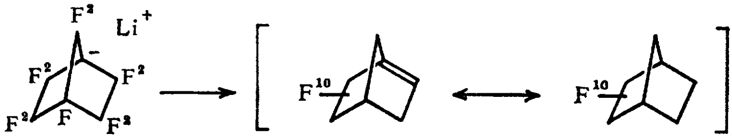
[27] A. C. Cope and E. S. Graham, *J. Amer. Chem. Soc.*, 1951, **73**, 4702.

[28] G. L. Buchanan, N. B. Kean, and R. Taylor, *J.C.S. Chem. Comm.*, 1972, 201.

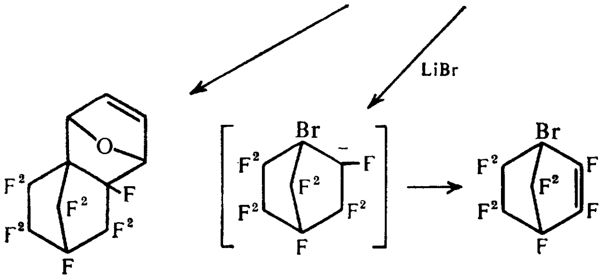
[29] S. F. Campbell, R. Stephens, and J. C. Tatlow, *Tetrahedron*, 1065, **21**, 3008.

[30] S. F. Campbell, J. M. Leach, R. Stephens, and J. C. Tatlow, *J. Fluorine Chem.*, 1971/72, 85; S. F. Campbell, J. M. Leach, R. Stephens, J. C. Tatlow, and K. N. Wood, *ibid.*, 1971/72, 103; R. Stephens, J. C. Tatlow, and K. N. Wood, *ibid.*, 1971/72, 165.

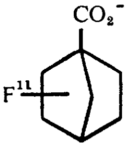
[31] R. Keese and E. P. Krebs, *Angew Chem. Internat. Edn.*, 1971, **10**, 262; *ibid.*, 1972, **11**, 518.



(54) (55)

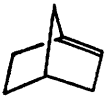


(56) (57)

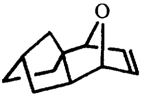


(58)

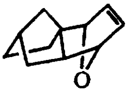
which yielded the same 1,2-*exo*-norbornane dicarboxylic acid on oxidative degradation, and which must therefore be (60a) and (60b). Irrespective of the nature or even the configuration of the halogens employed, the proportions of



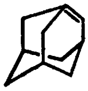
(59)



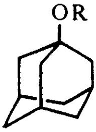
(60a)



(60b)

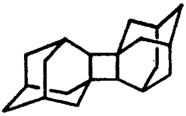


(61)

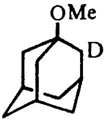


(*a*) R = $COCH_2Ph$
(*b*) R = Me
(*c*) R = OCH_2CH_2OH

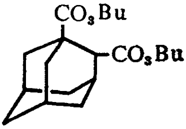
(62)



(63)



(64)



(65)

(60a) and (60b) remained constant and this is compelling evidence for a common intermediate. Whether it [or (55)] can be truly described as an alkene is another and more difficult question.

The latest, and most strained member of this class of anti-Bredt compounds to be claimed, is adamantene (61). In such a rigid molecule, the opportunity for distributing the strain over several bonds is at a minimum, and the distortion of the double bond in (61) must be very severe. It is therefore no surprise that β-ketoacid derivatives of adamantane are exceptionally stable.[32] However, the alkene (61) has been generated as a transient intermediate both from 1,2-diiodoadamantane by the action of butyl-lithium[33] and from the ester (62a) by a photochemical Norrish type II fragmentation.[34] The former route yielded only dimer (63); attempts to trap the intermediate as a furan adduct were not successful. On the other hand, the photochemically generated intermediate could be trapped by solvent. Photolysis of either 1-adamantyl phenylacetate (62a) or its 2-isomer in methanol, yielded 1-methoxyadamantane (62b); in glycol the product was (62c), and in deuteriomethanol the deuteriated ether (64) was formed. Taken together, these two approaches convincingly demonstrate the existence of an unstable intermediate which behaves as if it were the alkene (61). Such a molecule would be highly twisted and it is not surprising that it failed to undergo 4 + 2 cycloadditions. Severe twisting of the *p*-orbitals of the 'double bond' would provide, almost exactly, the symmetry requirements for a ${}_{\pi}2_{s} + {}_{\pi}2_{a}$ cycloaddition whilst disfavouring the (supra–supra) 4 + 2 reaction. Another group[35] has claimed that (61) is formed by thermolysis of the bis-perester (65), and can be trapped as its Diels–Alder adduct with dimethylfuran. However, these conditions might equally lead, via homolysis, to an adamantyl diradical, and thence to the product, *i.e.*, formation of a carbon–carbon double bond is not necessary.

D. Smaller Ring Systems.—To date, no claim has been laid to a bridgehead alkene of the *trans*-cyclopentene class and the β-ketoacids of this type are singularly stable.

E. Heterocyclic Bridged Systems.—In its original form, Bredt's rule made no mention of heterocyclic systems. However the same geometric constraints must surely apply, except in cases where elements below the first row are present at bridgeheads; and indeed the available evidence bears this out.

The smallest isolable example[36] (66) is eight-membered and is formed from the corresponding dihydro-compound by lead tetra-acetate oxidation. A similar oxidation of the amide (67) to (68) is believed[37] to involve a seven-membered

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[32] O. Böttger, *Ber.*, 1937, **70**, 314.

[33] D. Grant, M. A. McKervey, J. J. Rooney, N. G. Sammon, and G. Step, *J.C.S. Chem. Comm.*, 1972, 1186; D. Lenoir, *Tetrahedron Letters*, 1972, 4049.

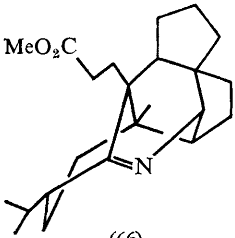
[34] J. E. Gano and L. Eizenberg, *J. Amer. Chem. Soc.*, 1973, **95**, 972.

[35] A. H. Alberts, J. Strating, and H. Wynberg, *Tetrahedron Letters*, 1973, 3047.

[36] M. Toda, Y. Hirata, and S. Yamamura, *Chem. Comm.*, 1970, 1597.

[37] M. Toda, H. Niwa, K. Ienaga, and Y. Hirata, *Tetrahedron Letters*, 1972, 335.

intermediate, as shown, but no corresponding six-membered case is known. Nor is the bridgehead amide (69) appreciably stabilized by resonance, which would of course demand some double bond character at the bridgehead. Its basicity and its ν_{CO} (1762 cm^{-1}) both suggest[38] that the heteroatom exerts no more than an inductive effect. However, solvolysis studies[39] on (70) and (71) indicate that they react appreciably faster than their all-carbon analogues and this must involve some stabilization of the developing carbonium ion by *p*-orbital overlap from the adjacent nitrogen.



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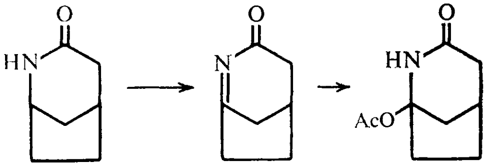
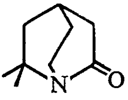


(67)

(68)



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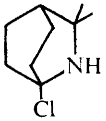
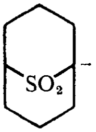
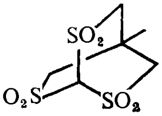


(70)

(71)



(72)



(73)

Second-row heteroatoms such as *S* are not subject to the same restrictions. There is strong evidence[40] for the intermediacy of the carbanion (72), stabilized inductively or, more probably, by d_π–p_π orbital overlap and the trisulphone (73) has been shown[41] to be highly acidic (pK_a 3.3 in water).

It is obvious from the above discussion, that all of the evidence is consistent with Wiseman's restatement of Bredt's rule in terms of *trans*-cycloalkenes, and the present reviewer can see no virtue in perpetuating the use of the *S*-number formula. The comparison with *trans*-cycloalkenes is qualitative, and its shortcomings have already been mentioned; however, it is simple and accurate enough for most purposes.

5 'Exceptions'

Excluding the sulphones mentioned above, a small number of apparent excep-

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[38] H. Pracejus, M. Kehlen, H. Kehlen, and H. Matschiner, *Tetrahedron*, 1965, **21**, 2257.

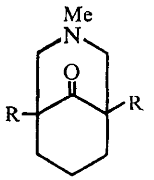
[39] R. D. Fisher, T. D. Bogard, and P. Kovacic, *J. Amer. Chem. Soc.*, 1972, **94**, 7599; P. G. Gassman, R. L. Cryberg, and K. Shuds, *ibid.*, 1972, **94**, 7600.

[40] L. A. Paquette and R. W. Houser, *J. Amer. Chem. Soc.*, 1969, **91**, 3870.

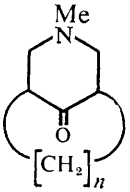
[41] W. E. Doering and L. K. Levy, *J. Amer. Chem. Soc.*, 1955, **77**, 509.

tions to Bredt's rule have appeared in the literature. However none has survived close scrutiny.

The smooth decarboxylation of (74a) to (74b), and the equally ready deuteriation of the latter in D_2O–DCl appear to involve *trans*-cyclohexenol intermediates. More remarkably, the rate of deuterium incorporation in the series (75) (n = 2, 3 and 4) is observed to fall with increase in ring size. These reactions were shown[42] to proceed *via* a retro-Mannich intermediate (76) in which there is no barrier to decarboxylation to proton exchange.



(74) (*a*) R = CO_2H
(*b*) R = H
(*c*) R = D



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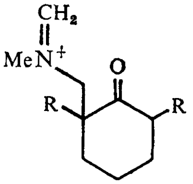

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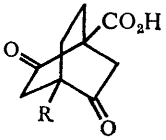
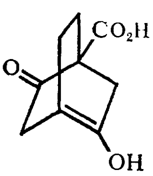
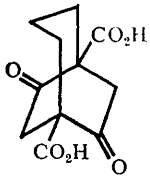


(77) (*a*) R = CO_2H
(*b*) R = H

Another example of an anomalous decarboxylation (77a to 77b) was originally reported[43] in 1939 and has since been corroborated.[28] Only one of the carboxyl functions is lost and the conventional mechanism (7) requires an intermediate *trans*-cyclohexenol. A re-investigation, using optically active starting material has shown that the decarboxylation occurs with complete racemization.[28] Accordingly, the enol (78) cannot be an intermediate and an alternative mechanism which involves consecutive ring opening, decarboxylation, and ring closure has been proposed. Significantly, the homologue (79) is totally decarboxylated whereas the analogous simple β-ketoacid (53) is completely stable.



(78)



(79)

The thermal stability of acids such as ketopinic acid (6) was known to Bredt and is often cited as an example, illustrating his rule. However, under fierce reaction conditions, CO_2 is in fact lost.[44] The product (82) clearly results from

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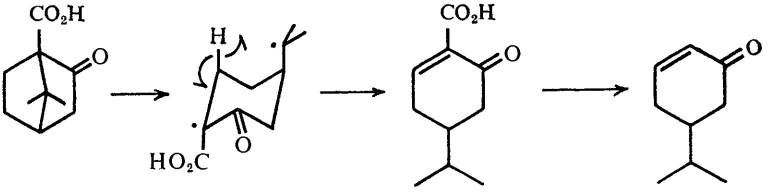
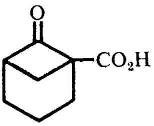
[42] H. O. House and H. C. Müller, *J. Org. Chem.*, 1962, **27**, 4436.
[43] P. C. Guha, *Ber.*, 1939, **72A**, 1359.
[44] E. Wedekind, *Z. Angew. Chem.*, 1925, **38**, 315.

bridge rupture and unless decarboxylation can be shown to precede rearrangement, this reaction does not infringe Bredt's rule. A radical mechanism [(80) → (81) → (82)] can account for the observed products, and a similar mechanism can be drawn for the observed[45] conversion (83) → (84), although an alternative explanation has been advanced in this instance.[25]



(6) (80) (81) (82)



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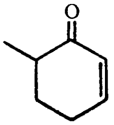
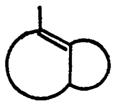


(84)

6 Fused Ring Systems

For 50 years it has been accepted as axiomatic that Bredt's rule referred to bridged, but *not* to fused bicyclic systems. However if the strain is in fact related to the presence of a *trans*-cycloalkene, as Wiseman has suggested, fused bicyclic alkenes such as (85) should be subject to the same strain when the *trans*-alkene component is ⩽ eight-membered. Does Bredt's rule then apply equally to fused bicyclic rings? This question has been pursued by Köbrich, who has argued the case cogently in a recent review.[12]

A stable *trans*-cyclononene example (86) has been prepared from 9-bromobicyclo(6,1,0)nonane, by elimination of HBr. More interestingly, Köbrich has succeeded in synthesizing the eight-membered and seven-membered analogues



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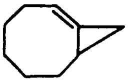

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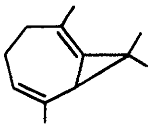

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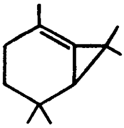

(88)

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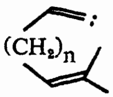
[45] J. Beckmann and I. S. Ling, *Chem. Ber.*, 1961, 94, 1899.

(87) and (88) from the appropriate vinyl carbene (89). Both were isolable, although the latter slowly decomposed. Even the bicyclo(3,1,0)hexene (90) was formed transiently, but could not be isolated. Its existence was inferred from the isolation of a [2 + 2] dimer. When the same reaction was applied to the synthesis of the next lower homologue, only intermolecular condensation was observed.



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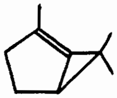

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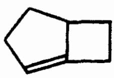

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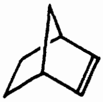

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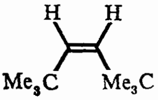

(93)

These results seem to suggest a stepwise increase in strain with decreasing ring size, reminiscent of that shown by conventional anti-Bredt alkenes. However it should be pointed out that the cyclobutane derivative (91), which also incorporates a *trans*-cycloheptene ring, is a readily isolated compound and appears to be much more stable[46] than its analogues (45), (46), and (88). These variations within the *trans*-cycloheptene class underline the fact that the degree of strain is not precisely the same in each of these cases, *i.e.*, the comparison with *trans*-cycloalkenes is at best approximate.

The common factor in all of these cases is a molecular geometry that distorts the double bond, and it is unrewarding to debate whether Köbrich's compounds should or should not be classified as anti-Bredt. It is more meaningful to group fused and bridged bicycloalk-1-enes together with *trans*-cycloalkenes as members of the general class of distorted alkenes of which, for example, *cis*-1, 2-di-t-butylethylene is yet another example.

Two types of distortion are recognized:

(*a*) in-plane deformations as illustrated in Figure 1a. An example is norborn-2-ene (92) in which the C=C—C bond angle is calculated to be 102.7°.[47]

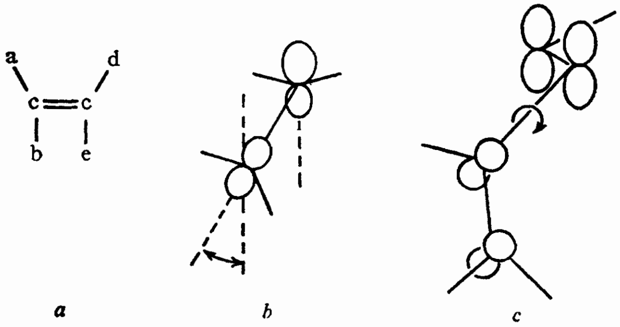

Figure 1

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[46] A. D. Ketley, *Tetrahedron Letters*, 1964, 1687.

[47] M. J. S. Dewar and W. W. Schoeller, *Tetrahedron*, 1971, **27**, 4401.

(*b*) out-of-plane deformations as illustrated in Figure 1b. An example is *cis*-1,2-di-t-butylethylene (93) in which the dihedral angle (Bu—C=C—Bu) is estimated[48] to be 5°.

In any given molecule, *both* deformations may come into play and the evidence concerning bridgehead alkenes is discussed in Section 7.

7 Properties of Bridgehead Alkenes

Relatively few alkenes of this type have been submitted to close study. The most interesting examples, *i.e.*, the highly strained members, adamantene and norborn-1-ene, have only been trapped as adducts. However, in the course of a very thorough investigation[29,30] of perfluoronorborn-1-ene (55), the Birmingham group have uncovered a large number of interesting transformations (see Scheme 3). Mechanistically, these are simply nucleophilic addition reactions, but the variety of products is remarkable. Thus apart from trapping (55) as a furan adduct, they found that it reacted with LiI (a by-product from the preparation of LiMe from MeI) to give (94), which eliminated fluoride ion to yield (95). The corresponding bromoperfluoronorborn-2-ene was produced if MeBr was employed as the source of LiMe. When the salt (54) was allowed to decompose in the presence of LiMe the dimethylated products (99) and (100) were formed by a series of addition–elimination reactions; and when the bridgehead alkene (55) was generated from (58) by decarboxylative elimination, a new series of products (96)—(98) and (101)—(103) were produced as shown below.

In contrast to adamantene and norborn-1-ene, the less strained bicyclo-(3,3,1)non-1-ene (23) is thermally stable, but reactions which lead to saturation of the double bond take place with despatch.[15,17] The addition of bromine affords the dibromide (33) by *syn*-addition and presumably involves the carbonium ion (104) rather than the bromonium ion (105), for rearside attack is impossible. *trans*-Cyclo-octene is reputed to behave similarly. Acid-catalysed hydration of (23) yields only (106a) and here too, the addition may by *syn*, although the point has not been tested. Hydroboration also leads to a significant amount of (106a), after the usual oxidative work up. Epoxidation and Diels–Alder addition proceed normally and nucleophilic addition of RLi gives rise to (106b).

The isomeric *trans*-cyclo-octene derivatives (36) and (37) resemble (23) in stability whereas (45) and (46), being *trans*-cycloheptene-like, are stable only at low temperature and have not been chemically investigated.

The only experimentally derived physical description of a bridgehead alkene comes from an *X*-ray crystallographic examination[49,50] of (107). This is a relatively unstrained example, but it is amenable to study in the free state rather than as a ligand. The strain appears to manifest itself both in warping (see Figure 1b) of the double bond (8.6°) and in bond angle deformation, particularly around the bridgehead position (see Figure 1a). A crude calculation has suggested

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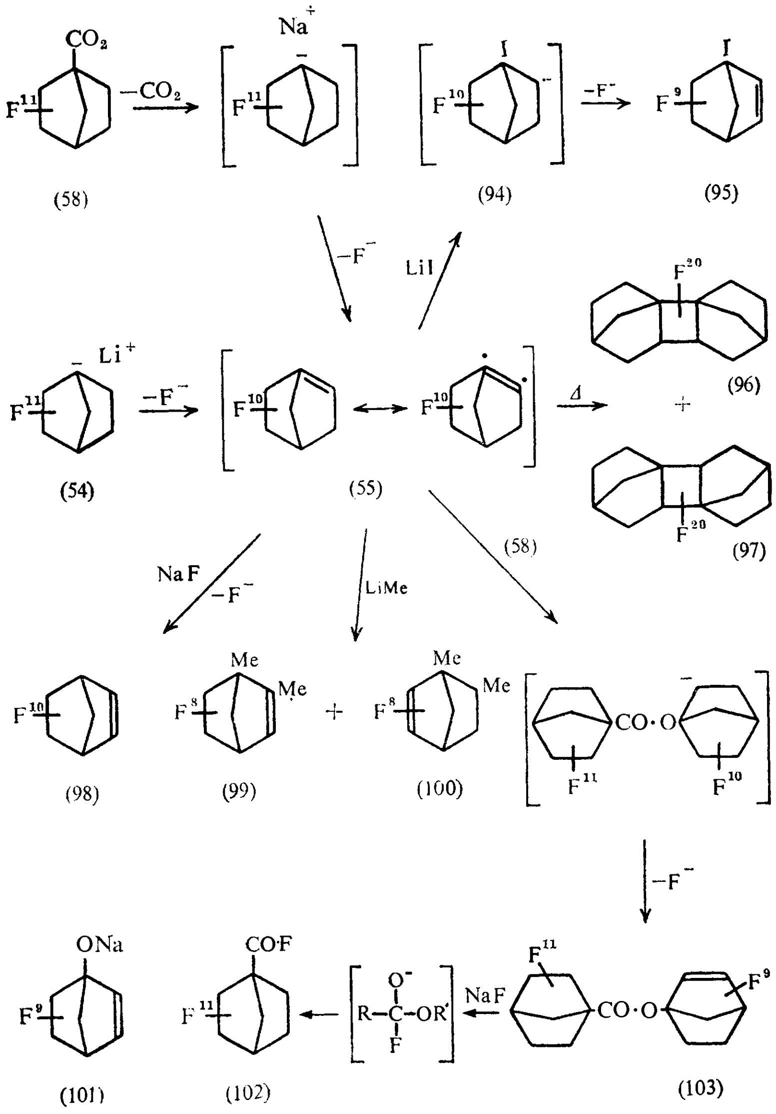
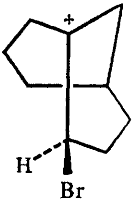
[48] O. Ermer and S. Lifson, *J. Amer. Chem. Soc.*, 1973, **95**, 4121.
[49] A. F. Cameron and G. Jamieson, *J. Chem. Soc.* (*B*), 1971, 1581.
[50] G. L. Buchanan and G. Jamieson, *Tetrahedron*, 1972, **28**, 1123.

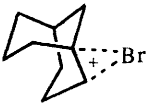


Scheme 3

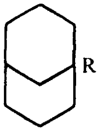
that the observed distortions contribute equally to the strain energy of the molecule. The $\alpha\beta$-enone system was also found to be twisted (by 38°) out of the ideal coplanar alignment (see Figure 1c). As a result, conjugation is inhibited and,



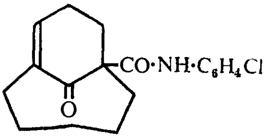
(104)



(105)



(106) (*a*) R=OH
(*b*) R=Ph or Me

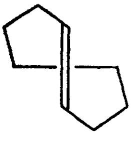


(107)

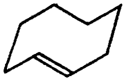
for example, the analogous simple enone (42) fails to add malonic ester under Michael conditions.[21]

The two types of distortions illustrated in Figures 1b and 1c affect the u.v. absorption of the molecule, but in different ways.[51] Warping of the π-bond induces a bathochromic shift and a rise in ϵ_{max}, whilst poor overlap between two adjacent π-bonds (*cf.* Figure 1c) leads to a drop in ϵ_{max} but no change in λ_{max} until the angle becomes severe, when the displacement is hypsochromic. These effects are illustrated in Table 1, together with the i.r. and n.m.r. data. In this connection, the 'unexpectedly high' u.v. absorption shown[19] by (39) is probably due to π-twisting. In simple alkenes π-twisting probably produces a similar displacement of λ_{max} (Table 2); however information is scarce and a meaningful interpretation depends upon choosing an appropriate (unstrained) model compound. An effect is also seen in the i.r. and n.m.r. spectra (see Table 2).

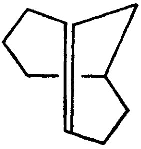
It would be of considerable interest to compare the molecular geometries of, for example, bicyclo(3,3,1)non-1-ene (23) and *trans*-cyclo-octene (108), the molecule to which it has been likened. Unfortunately there is no report of experimental work on the former and the latter has been investigated, by the *X*-ray method, only in the form of its Cu^{I} and Pt^{II} complexes.[52] If we make the assumption that these complexes accurately reflect the geometry of the parent alkene, *trans*-cyclo-octene exists in the twist conformation (108) rather than the chair (109). The comparison with its bicyclic analogue [(110) ≡ (23)] is very striking. It also appears that the double bond is twisted (*cf.* Figure 1b) so that the olefinic carbons and the two adjacent (allylic) carbons are not coplanar; the dihedral angle is 134°.



(108)



(109)



(110)

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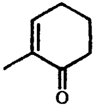
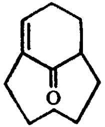
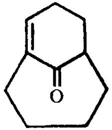
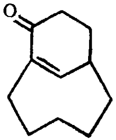
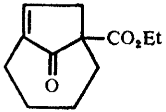
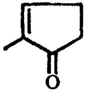
[51] H. H. Jaffe and M. Orchin, Theory and Applications of U.V. Spectroscopy', J. Wiley and Sons, London, 1962, Chapter 15; N. S. Zefirov and V. I. Sokolov, *Russ, Chem. Rev.*, 1967, **36**, 87.

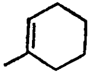
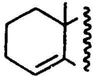
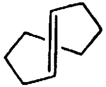
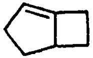
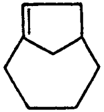
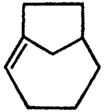
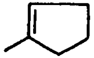
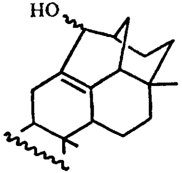
[52] P. Ganis, U. Lepore, and G. Paiaro, *Chem. Comm.*, 1969, 1054; P. C. Manor, D. P. Shoemaker, and A. J. Parkes, *J. Amer. Chem. Soc.*, 1970, **92**, 5260.

Table 1 *Spectroscopic data (enones)*

						
$\nu_{CO}^{CCl_4}$ (cm^{-1})	1675[a]	1680, 1702[b]	1710[c]	1675[b]	1715, 1740[d]	1711[e]
λ_{max}^{EtOH} (nm)	235[a]	238[b]	238[c]	254[b]	241[d]	226[e]
[ϵ]	[9400]	[5630]	[3000]	[7500]	[3908]	[8550]
=C*H* (τ)	3.32[a]	3.84[b]	4.1[c]	3.15[b]	3.24[e]	2.77[e]

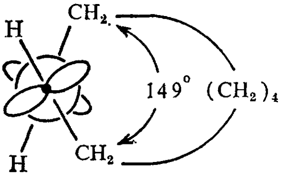
[a] W. G. Dauben, G. W. Shaffer, and N. D. Vietmeyer, *J. Org. Chem.*, 1968, **33**, 4060; [b] G. L. Buchanan and G. Jamieson, *Tetrahedron*, 1972, **28**, 1129; [c] B. G. Cordiner, M. R. Vegar, and R. J. Wells, *Tetrahedron Letters*, 1970, 2285; [d] W. Carruthers and M. I. Qureshi, *J. Chem. Soc. (C)*, 1970, 2238; [e] H. N. A. Al-Jallo and E. S. Waight, *J. Chem. Soc. (B)*, 1966, 73.

Table 2 *Spectroscopic data (alkenes)*

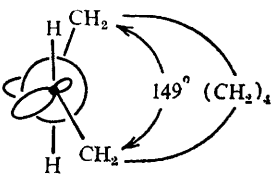
									
λ_{max} (nm)	188[a]	194[a]	206[d]	208[e]					229[k]
[ϵ]	[7100]		[7500]						[5180]
=C—*H* (τ)	4.7[b]		4.38[d]	4.66[f]	4.87[h]	4.6[i]	4.7[i]	4.75[j]	
$\nu_{C=C}$ (cm^{-1})	1676[c]		1620[d]	1658[g]	1645[h]	1607[i]	1655[i]	1660[c]	

[a] A. I. Scott, 'Interpretation of U.V. Spectra of Natural Products', Pergamon, London, 1964, pp. 20–24; [b] G. V. D. Tiers, 'Tables of τ values,' 3M Company, St. Paul, Minnesota, U.S.A., 1958, p. 10; [c] F. H. A. Rummens, *Rec. Trav. chim.*, 1965, 84, 1003; [d] J. R. Wiseman and W. A. Pletcher, *J. Amer. Chem. Soc.*, 1970, 92, 956; [e] R. D. Bach, *J. Chem. Phys.*, 1970, **52**, 6423; [f] V. I. Sokolov, L. L. Troitskaya, P. V. Petrovskii, and O. A. Reutov, *Doklady Akad. Nauk. S.S.R.*, 1970, **193**, 834; [g] N. L. Allinger, *J. Amer. Chem. Soc.*, 1958, **80**, 1953; [h] R. A. Moss and J. R. Whittle, *Chem. Comm.*, 1969, 341; [i] I. R. Wiseman, H. F. Chan, and C. Ahola, *J. Amer. Chem. Soc.*, 1969, 91, 2812; [j] G. Juppe, S. Santino, and C. Beaudet, *Z. Naturforsch.*, 1969, **24b**, 524; [k] W. E. Thiessen, H. A. Levy, W. G. Dauben, G. H. Beasley, and D. A. Cox, *J. Amer. Chem. Soc.*, 1971, 93, 4312.

Energy minimization calculations have been carried out on *trans*-cyclo-octene,[53] using a recently developed force-field method which computes energies and structures of alkenes. These calculations favour the twist conformation over the chair by 2.43 kcal mol^{-1}. They also indicate a dihedral angle of 149° about the double bond, which is somewhat larger than the value obtained from the *X*-ray work. If this distortion were accommodated solely by rotation about the π-bond [see (111)], the angle between the *p*-orbital lobes would be 31° and overlap would be poor; moreover the molecule would have a very low dipole moment. In fact *trans*-cyclo-octene has an abnormally high dipole moment (0.82 D). If, on the other hand, the ring strain is relieved by out-of-plane bending [see (112)], with rehybridization of the olefinic carbons (from sp_2 towards sp_3) the dihedral angle between the π-atomic orbital lobes is reduced, and overlap is increased. At the same time, increasing the *s* character of these lobes tilts them away from each other, so reducing the overlap. The calculated minimum energy 'compromise' corresponds to a dihedral angle of 16.3°, and from this model a dipole moment of 1.2 D has been calculated. Agreement with the experimental value is reasonable enough to suggest that the calculated structure is valid.



(111)

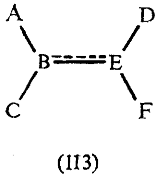


(112)

Applying the same calculation process to bicyclo(3,3,1)non-1-ene these authors[53] obtained a very similar picture. The bridgehead double bond is a little more twisted having a C_8—C_1—C_2—C_3 dihedral angle of 138° and is rehybridized to a slightly greater extent than the double bond in *trans*-cyclo-octene.

8 Conclusion

If there is any B–E double bond character in a system (113) within a molecule then the energy of the molecule will be raised by any factors such as steric com-



(113)

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[53] N. L. Allinger and J. T. Sprague, *J. Amer. Chem. Soc.*, 1972, **94**, 5734.

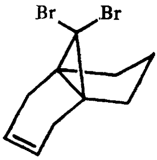
pression or ring formation which (*i*) alter the bond angles around B or E from their normal values, or (*ii*) alter the ABED or CBEF dihedral angles from their normal values. The amount by which the energy is raised for a given distortion will depend on the values of B and E.

Bridgehead (*i.e.*, anti-Bredt) alkenes provide an example of this situation, in which the strain calls into play both types of deformation; moreover, the out-of-plane twist [*i.e.*, (*ii*)] is believed[54] to be accompanied inseparably by rehybridization. This picture of bridgehead double bonds, accommodating the strain imposed upon them, makes nonsense of the early idea that there would be a threshold beyond which they could not be formed. Instead there will be a spectrum of strain, increasing as the size of the ring, which incorporates the *trans*-cycloalkene moiety, is decreased. Eventually it will be a matter of semantics whether we describe the most strained cases as 'double bonds' or as diradicals. Reactions designed to produce more highly strained members will face a mounting activation energy barrier, and success will depend on choosing appropriate reaction conditions and suitable means of detection.

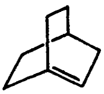
The author is indebted to Professor J. D. Loudon and Dr. J. Carnduff for much helpful discussion.

Note added in proof. Several interesting developments have recently been reported which can be mentioned only briefly here.

Silver-assisted solvolysis of (114), and its 3,4-dihydro-derivative, afforded both monocyclic and bridged-bicyclic products. These arose *via* intermediate bicyclo-[4,3,1]dec-1(10)-ene derivatives in which the double bond is presumably *trans* within the seven-membered ring.[55] The more strained alkene (115) has been claimed as an intermediate, formed from (116) by insertion into the C(1)–C(7) bond[56] and from 1-ethoxy-2-lithiobicyclo[2,2,2]octane by β-elimination.[57] In both cases, the alkene underwent a further transformation. Wiseman[58] has described the syntheses (117) and (118); both are stable at room temperature

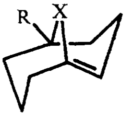


(114)



(115)

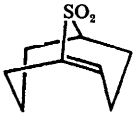
(116)



(117) X = O; R = H

(118) X = O; R = H

(119) X = SO_2; R = Me



(120)

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[54] L. Radan, J. A. Pople, and W. L. Mock, *Tetrahedron Letters*, 1972, 479.

[55] P. Warner, J. Fayos, and J. Clardy, *Tetrahedron Letters*, 1973, 4473.

[56] A. D. Wolf and Maitland Jones jun., *J. Amer. Chem. Soc.*, 1973, **95**, 8209.

[57] H. H. Grootveld, C. Blomberg, and F. Bickelhaupt, *J.C.S. Chem. Comm.*, 1973, 542.

[58] C. B. Quinn and J. R. Wiseman, *J. Amer. Chem. Soc.*, 1973, **95**, 1342 and 6120.

and are accordingly ascribed the Z-configuration shown. More remarkably, he has obtained[59] related sulphones in both the *Z* (119) and *E* (120) configurations, and was able to confirm the stereochemistry of each from Diels–Alder adducts. The stereoisomeric alkenes added t-butoxide stereospecifically; (119) afforded the 2-*exo*-t-butyl ether whereas (120) gave the 2-*endo*-isomer.

[59] C. B. Quinn, J. R. Wiseman, and J. C. Calabrese, *J. Amer. Chem. Soc.*, 1973, **95**, 6121.