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Stereochemistry

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Stereochemistry of Twisted Double Bond Systems

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I Introduction

Principally, the double bond in any chiral molecule is dissymmetrically deformed even if this unsaturated center is situated far from its chiral center. However, discussions in this article are limited solely to the synthesis and stereochemistry of the compounds whose double-bond systems 1 play a decisive role in the generation of their chirality by being explicitly twisted in the molecular environment (e.g. ring) surrounding the unsaturated center.

1
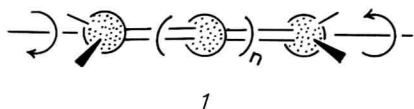
Among a variety of compounds whose molecular characteristics fall into this category, our current interests have further limited our discussion to the double-bond systems which may conveniently be classified as follows: 1. chiral (*E*)-cycloalkenes, 2. chiral anti-Bredt rule compounds, 3. trans-doubly bridged ethylenes ("betweenanenes"), 4. bridged allenes, and 5. overcrowded olefins.

II Chiral (*E*)-Cycloalkenes

The chiral nature of (*E*)-cycloalkenes, whose "jump rope" conformational inter-conversions are restricted because of non-bonding interaction across the ring, was first pointed out in 1952 when Blomquist [1] presented the enantiomeric figures of (*E*)-cyclononene in his paper describing the syntheses of cis- and trans-isomers of cyclononene.

A decade had elapsed, however, before this was first demonstrated by Cope's preparation of optically active (*Z*),(*E*)-1,5-cyclooctadiene [2] followed by his successful optical resolution of (*E*)-cyclooctene [3].

II.1 (*E*)-Cyclooctene

II.1.1 Preparation of Optically Active (*E*)-Cyclooctene

Although the racemic modification of (*E*)-cylooctene had been reported by Ziegler [4] in 1950, the optically active modification was first obtained in 1962 through resolution via chiral Pt(II) complexes containing (+)-1-phenyl-2-aminopropane [3, 5]. This pioneering work has been followed by various approaches among which some are excellent as regards their synthetic convenience and stereoselectivity.

(+)-*2*   (+)-*3*   *4*   *5*
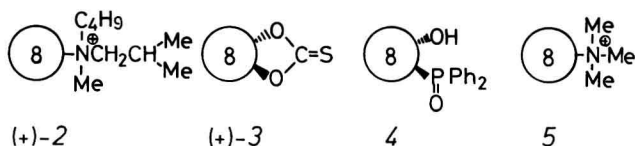
a) The Hofmann elimination of the optically active ammonium salt 2 (1.1–1.4% asymmetric induction) [6].
b) Treatment of the (+)-thioncarbonate 3 with triisooctyl phosphite (high optical purity and isomeric purity) [7].
c) "Destructive asymmetric hydroboration" of (±)-(E)-cyclooctene employing the diborane prepared from (+)-pinene (20% optical purity) [8].
d) Reductive elimination of 4 with NaH in DMF [9].
e) The Hofmann elimination of the ammonium salt 5 in 3-aryl-3,5-cholestadiene liquid crystals (poor isomeric purity and 1.3–7.2% e.e.) [10].

II.1.2 Absolute Configuration

Chirality of (E)-cycloalkene has been customarily classified as planar in nature, and specified following Cahn, Ingold and Prelog's convention [11, 12].

Shortly after the first announcement of optical resolution of (E)-cyclooctene, Moscowitz and Mislow [13] published a communication in which, on the basis of their MO calculation, they assigned the (S)-configuration to the (−)-enantiomer. Eventually, this conclusion was proved wrong [14, 15] and the opposite configuration was assigned when the absolute configuration of (−)-(E)-cyclooctene was shown to be directly correlated with that of (+)-tartaric acid [16a, b].

(−)-6   (+)-7   (+)-8   (+)-9
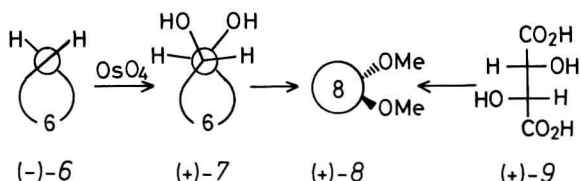
Osmium tetroxide oxidation of (−)-(E)-cyclooctene (6) afforded the (+)-diol 7 whose absolute configuration was related to that of (+)-tartaric acid (9) via the (+)-dimethoxy derivative 8. The (R)-configuration assigned by this correlation has been confirmed by a number of direct or indirect approaches.
a) X-ray analysis of (E)-dichloro[(−)-(E)-cyclooctene][(+)-α-methylbenzylamine] [17].
b) X-ray analysis of the (+)-dibromocarbene adduct 10 prepared from (−)-(E)-cyclooctene [18].
c) Correlation of (−)-(E)-cyclooctene with (+)-(E)-1,2-cyclooctanediol 7 via the (+)-thioncarbonate 3 [7].
d) Through the [$2_\pi + 4_\pi$]addition product 11 obtained from (+)-(E)-cyclooctene and butadiene [9, 19].

(+)-10   (+)-6   11

3
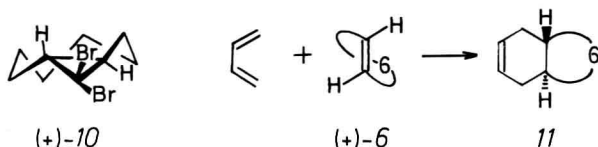
II.1.3 Optical Stability of (E)-Cycloalkenes

Studies of the rate of racemization [20] of optically active (E)-cyclooctene enabled Cope and coworkers to calculate the following $t_{1/2}$: 122 h (132.7 °C), 15 h (156.4 °C), and 1 h (183.9 °C). These values can be compared with the $t_{1/2}$ value of 6 sec (30 °C) exhibited by optically active (E)-cyclononene [21], which was prepared by optical resolution via a chiral Pt(II) complex.

n	$t_{1/2}$
2	10^5 year
3	10 s
4	10^4 s
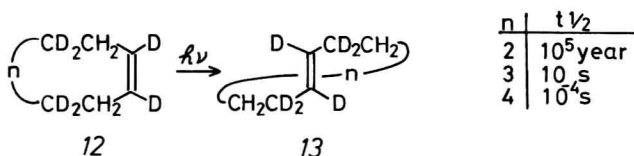
Although an unsuccessful optical resolution [21] of (E)-cyclodecene suggested its optical instability, Robert's dynamic NMR studies [22] of the racemization process in deuterated (E)-cycloalkenes 13 succeeded in providing a $t_{1/2}$ value of 10^{-4} sec (room temperature). This optical instability, found in the parent compound, could explain Westen's fruitless attempt to prepare the chiral (E)-cyclodecenone 16 from the (+)-methanesulfonate 15 [23].

(+)-14 (+)-15 16
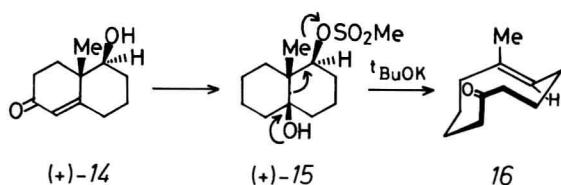
The cross-conformation 17 of (−)-(R)-(E)-cyclooctene was first disclosed by an X-ray analysis [17] of (E)-dichloro [(−)-(E)-cyclooctene][(+)-α-methylbenzylamine]-

(R)–cross 18   (S)–chair 19

17

(R)–chair 21   (S)–cross 20
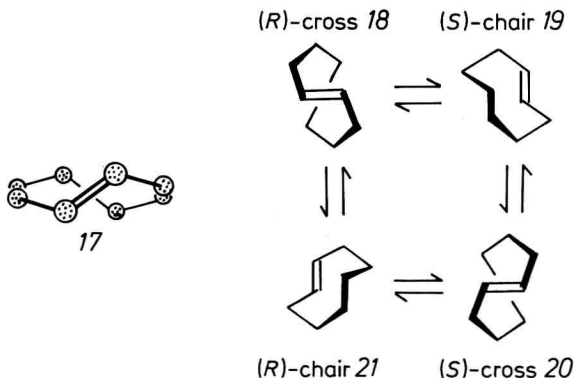
Pt(II), and this cross structure has been supported by another X-ray analysis [24] of (E)-2-cyclooctenyl-3′,5′-dinitrobenzoate as well as an electron diffraction study [25] of (E)-cyclooctene itself. Force-field calculations [26a ·] have revealed that the racemization of (E)-cyclooctene should follow the pathway: (R)-cross 18→ (S)-chair 19 → (S)-cross 20, and that the former pathway is rate determining.

II.2 Substituted (E)-Cycloalkenes

In the attempted optical resolution by complexing with chiral Pt(II) complexes, both the benzo derivatives 22 [27] and 23 [28a, b] afforded the corresponding diastereomeric pairs of Pt(II) complexes. But their decomposition to the optically active modifications were found unsuccessful. This optical instability of 22 is especially surprising when this is compared with that of (E)-cyclononene [21] which, though labile, could be resolved under a similar condition (vide supra).
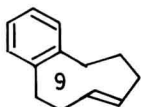
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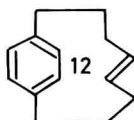
23

Expecting that the introduction of 1,2-dimethyl substituents to (E)-cycloalkenes should increase non-bonding interaction across the ring, Marshall and coworkers [29] prepared (—)-(E)-1,2-dimethylcyclodecene (27a) and showed that this compound is optically quite stable. In their synthetic approach to 27a, they started from the β-keto ester 24 which was converted into (+)-25 through a sequence of reactions involving condensation with 3-buten-2-one, LiAlH₄ reduction, and resolution via the camphor-

24

(+)-25

LiAlH₄

(-)-26

(-)-(S)-27a

(S)-27 (-)-a n= 8
(+)-b n= 9
c n=10

(-)-28

(+)-(R)-29

5
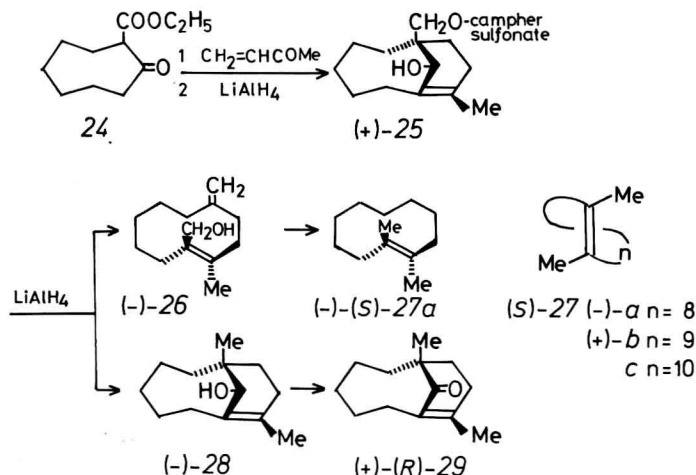
sulfonate. Cleavage of (+)-25 with LiAlH₄ yielded the (—)-cyclodecene derivative 26, accompanied by (—)-28. The routine synthetic sequence converted (—)-26 into the (—)-(E)-cyclodecene 27a whose (S)-configuration was established by correlating it with that of the by-product (—)-28. This by-product 28 was oxidized to the (+)-α,β-unsaturated ketone 29, which exhibited a (+)-Cotton effect, indicating that the (R)-configuration was present at the quaternary asymmetric carbon atom.

(+)-(S)-(E)-1,2-Dimethylcycloundecene (27b) was also prepared by a similar method and was found to be optically stable, but preparation of the cyclododecene derivative 27c in an optically active modification was unsuccessful.

II.3 (Z),(E)- and (E),(E)-1,5-Cyclooctadienes

As mentioned earlier, preparation of (Z),(E)-1,5-cyclooctadiene (31) in an optically active modification [2] first demonstrated the chiral nature of (E)-cycloalkenes. In this classical experiment, Cope and coworkers obtained (+)-31 by the Hofmann elimination of the (+)-ammonium salt 30. They were also successful in obtaining (+)-31 by optical resolution of racemic 31 through complexing with a chiral Pt(II) complex [5, 30].

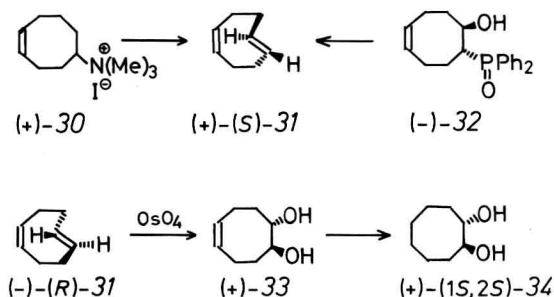(+)-30   (+)-(S)-31   (—)-32

(—)-(R)-31   (+)-33   (+)-(1S,2S)-34

The (+)-enantiomer 31 which has the highest optical rotation ($[\alpha]_D + 171°$) so far recorded, was reported to be formed by reductive elimination [9, 31] of (—)-32 using NaH-DMF. Osmium tetroxide oxidation discriminated the two unsaturated centers in (—)-31, yielding the unsaturated (+)-cis-diol 33 whose conversion into (+)-(1S,2S)-34 established the (R)-configuration of (—)-31 [32].

The (E),(E)-isomer 35 [33] of 1,5-cyclooctadiene was reported to be formed (1.5% yield) when a solid residue, obtained from an UV irradiation product of bis[chloro-((Z),(Z)-1,5-cyclooctadiene)Copper(I)], was decomposed with NaCN solution. It has been claimed that the same compound 35 was also formed (2.4% yield) by the double Hofmann elimination of (Z)- or (E)-1,5-bis-(dimethylamino)cyclooctane dimetho-

35   36   37
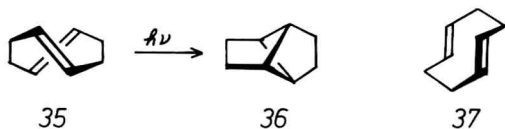
iodide. The highly strained structure inherent in 35 seems to be reflected in its labile nature toward O_2 and acid. UV irradiation of 35 was reported to give the tricyclic 36. A force-field calculation [26b] suggested that the cross-conformation 35 of D_2 symmetry appears to be 5.35 kcal/mol more stable than the chair form 37.

II.4 Other Related Systems

An X-ray analysis [34a] of $(E),(E),(E)$-1,5,9-cyclododecatriene (38) suggested that this molecule is most comfortable in a twisted chiral conformation of D_3 symmetry, and a dynamic NMR study and a force-field calculation [34b] estimated $\Delta G^* = 8.6$ kcal/mol for the racemization process between two enantiomeric D_3 conformers. A pseudo-chair conformation of similar D_3 symmetry was also suggested [35] for 1,5,9-cyclodo-decatriyne (39), following an *ab initio* STO-3G calculation and photoelectron spectroscopy.

   Although the (E)-cycloalkene structures have been found in a large variety of natural products especially in macrolides [36a–c], only a brief comment on the conformational aspects of some sesquiterpenes [37] will conclude this section.
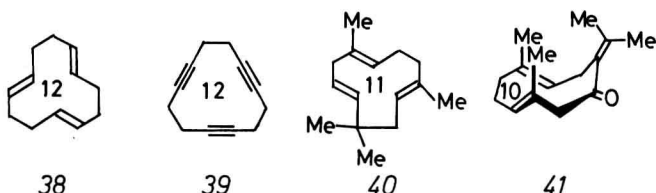

While a dynamic NMR study [38] was carried out to reveal rather complicated patterns of conformational interconversion in some eleven-membered sesquiterpenes including humulene (40) and zermbone, an interesting controversy concerning conformational stability in the germacrone family of sesquiterpenes is worth mentioning here.

   Tori and coworkers' dynamic NMR studies [39] of germacrene concluded that this system is free in conformational inversion, suggesting that the optically active modification should not be isolated because of the low energy barrier between enantiomeric conformers. Hill and coworkers [40], however, succeeded in preparing (—)-germacrone (41), which has an optical rotation as high as $[\alpha]_D^{33}$ —42.5° (EtOH). Osawa's force-field calculation [41] of this system gave $\Delta H^* = 23$ kcal/mol as the lowest energy barrier between the enantiomeric conformers, and this seems to mean that optical resolution of germacrone should be feasible at room temperature.

III Chiral anti-Bredt Rule Compounds

Considering the impressive accumulation of review articles [42a–f] on the Bredt rule and number of papers reporting exotic anti-Bredt rule compounds, it is rather sur-

prising to realize that the chiral nature of anti-Bredt rule compounds had not been explicitly pointed out until Nakazaki's papers [43a, b)] on the synthesis and absolute configuration of the first optically active anti-Bredt rule compound appeared.
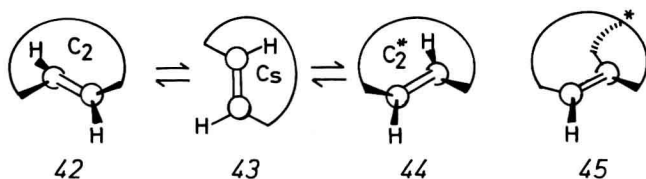
The close relationship [44a, b)] between bridgehead olefins and (E)-cycloalkenes had been discussed solely with regard to their strained characteristics, but, a careful examination revealed that this relationship should be extended to their chiral natures.

The chiral C_2-conformer 42 of a (E)-cycloalkene can transform into the enantio-meric C_2^*-conformer 44 through a planar C_s-conformer 43, and this "rope jump" racemization can be prevented by anchoring one end of the unsaturated center onto the ring by means of an extra-bridge. This bridging creates a bicyclic anti-Bredt rule compound 45, revealing that all anti-Bredt rule compounds (45) with one double bond are necessarily asymmetric (C_1 symmetry) and have one asymmetric carbon atom.

The synthetic approach towards optically active bicyclo[3.3.1]1(2)-nonene (49) [45a−c)] started from the (−)-(1R,3S)-hydroxycarboxylic acid 47 [46)], whose absolute configuration and optical purity were determined by converting this into (+)-(R)-3-methylcyclohexanone (46). Conversion of (−)-47 to the Wittig compound 48 followed the routine synthetic sequence, involving protection of the carbonyl group and extension of the side chain. The final intramolecular ring closure of 48 [45c)] was accomplished by heating 48 with NaH in tetraglyme to yield the (−)-(S)-anti-Bredt rule compound 49.
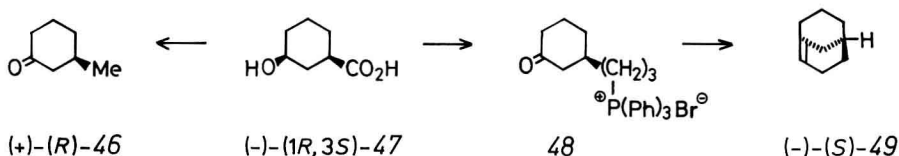

Comparison of (−)-(R)-(E)-cyclooctene (50) and the (−)-(S)-anti-Bredt rule compound 51 would suggest their close structural relationship, and this is reflected in their respective absolute rotation values [5,16b)]: $[\alpha]_{Dabs}$ −458° (neat) and −725° (CHCl$_3$) as well as in their respective (−)-Cotton curves: $[\theta]$ −1.4 × 10^5 at 196 nm (cyclohexane) and −13.6 × 10^5 at 213 nm (isooctane).
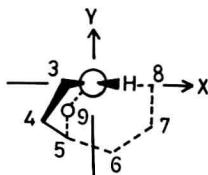
These chiroptical properties are compatible with the prediction made by Scott's octant rule [47)] which says that both compounds, which have polymethylene bridges in the (−)-regions (see 52), should exhibit (−)-Cotton effects.

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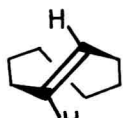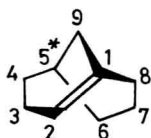
(−)-(R)-50   (−)-(S)-51   52

The (E)-cyclooctene moiety can also be seen in bicyclo [4.2.1]1(8)-nonene (53) and bicyclo[4.2.1]1(2)-nonene (54), "the smallest isolable members" among anti-Bredt rule compounds [48].
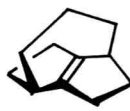
The interesting tricyclic compound 55 [49], which has (E)-cycloheptene moiety, was found to be very labile and could only be trapped by condensing with diphenyl-isobenzofuran.
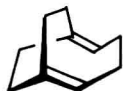
53   54   55

Since a "single" anti-Bredt rule compound is neccessarily asymmetric, combination of two of them should afford "double" anti-Bredt rule compounds ("bridgehead dienes") either of C_s (or C_i) symmetry or of C_2 symmetry depending upon the ways in which the enantiomers are combined to make up the molecules.

56   57

While the achiral "double" anti-Bredt rule compound 56 [50] of C_s symmetry was isolated in an impure state and was found to be very labile toward O_2 and heat, the chiral 57 of C_2 symmetry was assumed to exist very briefly in the pyrolysis of 3,6-dimethylidene-1,7-octadiene [51].

IV (E)-Doubly Bridged Ethylenes ("Betweenanenes")

A hypothetical compound "bis-((E)-polymethylene)ethylene" 58 of D_2 (V) symmetry had been formulated by Cahn, Ingold, and Prelog [11] for the sake of illustrating its planar chirality, but what aroused our independent interests in the synthesis and stereochemistry of this type of compound was a close structural relationship between

9