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THERMALLY INDUCED SKELETAL INVERSION AND RING OPENING OF HEXAMETHYLBICYCLO[2.2.0]HEXANES[1]

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Abstract—Hexamethylbicyclo[2.2.0]hexanes underwent *endo,exo* isomerization (skeletal inversion) and stereoselective supra, antara cleavage at 140–250°. The kinetics were studied and the products isolated and identified. The reactions are discussed in terms of a common 1,4-π-bonded intermediate which evolves to the invertomer or opens conrotatorially to methyl-substituted hexadienes.

Our study of the hydrogenation of hexamethylbicyclo[2.2.0]hexa-2,5-diene revealed the facile thermal *endo,exo* isomerization (skeletal inversion) of all-*endo*-hexamethylbicyclo[2.2.0]hexane.[2] Goldstein and Benzon recently reported skeletal inversion of the parent compound;[3] apparently, this process is typical for bicyclo[2.2.0]hexane systems.[4] Besides skeletal inversion, bicyclo[2.2.0]hexane[3] and a large number of its derivatives[2,5] exhibit thermal cleavage reactions with sometimes remarkable stereoselectivity.

In the present paper we report the skeletal inversion and ring opening of a number of stereoisomeric hexamethylbicyclo[2.2.0]hexanes. On the basis of these results, the reaction mechanism will be discussed.

RESULTS

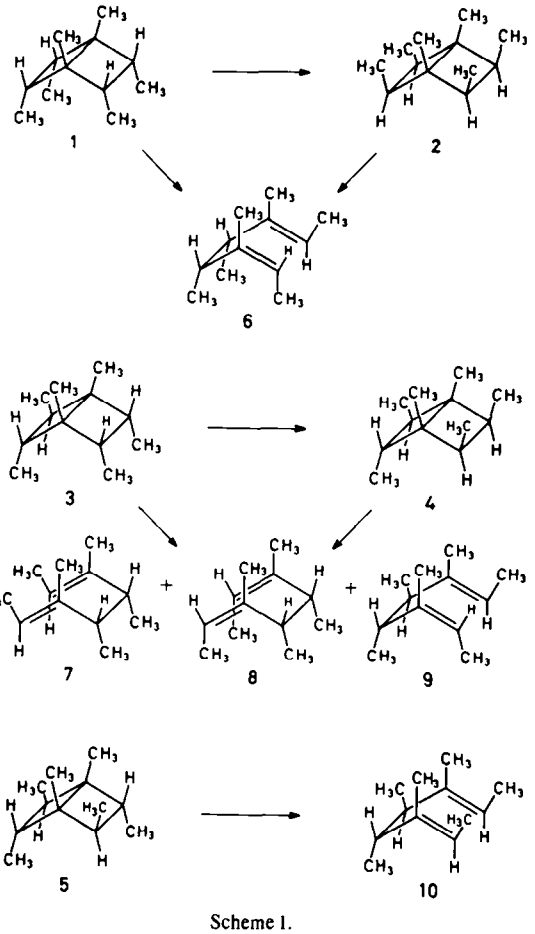
Thermal rearrangement of all-*endo*-hexamethylbicyclo[2.2.0]hexane (**1**) at 140–175° gave mainly the more stable invertomer (**2**); besides, stereoselective cleavage resulted in *erythro*-(*E,Z*)-3,4,5,6-tetramethylocta-2,6-diene (**6**).

The somewhat less strained[2] 1,2-*endo*,3-*endo*,4,5-*endo*,6-*exo*-hexamethylbicyclo[2.2.0]hexane (**3**) reacted similarly at higher temperatures (196–216°). Skeletal inversion gave the mono-*endo*-hexamethylbicyclo[2.2.0]-hexane **4**; cleavage of the C_1–C_4 and C_5–C_6 bonds resulted in *erythro*-(*E,E*)-3,4,5,6-tetramethylocta-2,6-diene (**7**) and a minor amount of the *erythro*-(*Z,Z*)-isomer (**8**), whilst *threo*-(*E,Z*)-3,4,5,6-tetramethylocta-2,6-diene (**9**) resulted from cleavage of the C_1–C_4 and C_2–C_3 bonds (*cf.* Scheme).

The inverted products **3** and **4** also exhibited ring opening, but elevated temperatures were required. Thermolysis of **2** at 220–250° gave mainly **6**, together with a small amount of an (*E,E*)-diene (presumably **7**, formed by supra-supra cleavage).

1,2-*Exo*,3-*endo*,4,5-*exo*,6-*endo*-hexamethylbicyclo-[2.2.0]-hexane (**5**) gave mainly *threo*-(*E,E*)-3,4,5,6-tetramethylocta-2,6-diene (**10**). Further data are compiled in Table 1, which Table also contains some kinetic data. Interconversion of the products of the cleavage reaction was relatively slow.

The bicyclic product **4** and the dienic products **6–10** were isolated by means of chromatography over silver nitrate-impregnated silica. The configurations of the dienic products were established by ozonolysis and ^1H and ^{13}C NMR spectroscopy.



Scheme 1.

DISCUSSION

Application of the concept of conservation of the nodal properties of molecular orbitals[6] to the concerted thermal fragmentation of the cyclobutane ring reveals that reaction via the suprafacial pathway of least motion would proceed through an antiaromatic[7] transition state. On the other hand, supra,antara cleavage via an aromatic transition state would require a considerable distorsion of the four-membered ring. Successive disruption of the two σ-bonds, with the intermediate formation of a tet-

Table 1. Thermolysis of hexamethylbicyclo[2.2.0]hexanes[a]

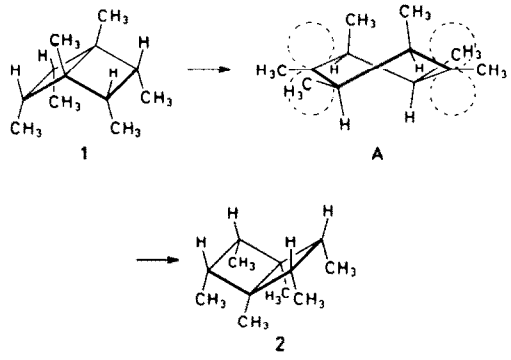
Compound	t (°C)	k_{conv} ($s^{-1} \times 10^5$)	time (min)	Products in %										
				1	2	3	4	5	6	7	8	9	10	unid.
1	140.6	18.2	600	53	35				12					
2	213.9	18.0	660		48				48	4				
3	198.0	66.4	200			51	15			17	1	15		
			400			24	24			19	3	23		
4	210.0	22.8	415				59			20	7	17		
			700				39			33	9	19		
5	230.7	32.9	390					49					41	10

[a] In sealed glass, 10% solution in heptane or decane.

ramethylene diradical or zwitterion, constitutes the alternative. Actually, the thermal fragmentation of cyclobutanes is not readily achieved whilst the activation parameters strongly indicate a flexible transition state.[8,9]

As to our present results, we shall first discuss the skeletal inversion process, which formally constitutes a [1,1] antara, antara sigmatropic rearrangement, and which may also be regarded as the interconversion of two cyclohexane-1,4-diradicals in a compressed boat conformation. Two reaction pathways have been envisaged.

(1) *Via a* 1,4-π-*bonded intermediate.* Twisting of the 6-membered ring will interconvert **1** and **2** via the 1,4-π-bonded transition state **A**, which is further stabilized by interaction of the occupied π-level and the σ^*-levels of the edge bonds. It is pertinent to note in this connection that the bicyclo[2.2.0]-hexane skeleton is definitely skewed,[10] whilst the twisting motion corresponds with the across-the-ring vibrations which have been observed for bicyclo[2.2.0]hexa-,2,5-dienes.[11]



(2) *Via a cyclohexane*-1,4-*diradical.* Stretching of the bridge bond in **1** will result in a rather weakly 1,4-σ-bonded species (**B**), which might also be regarded as a cyclohexane-1,4-diradical in a boat conformation with through-space coupling of the radical centers.[12] Conversion to the corresponding species connected with **2** (**C**) may be accomplished through twisting via **A** (essentially process **1**), or via the corresponding 1,4-diradical in a chair conformation (**D**).

However, the ring opening of **D** would compete with conversion into **C**. In view of the activation energy which would be required for the latter process, estimated to be 40 kJ mole^{-1}, we feel that the route **B**→**D**→**C** can be excluded.

As to the ring opening process, the discussion has largely centered on the question whether the reaction proceeds through a cyclohexane-1,4-diradical or with synchronous breaking and making of bonds.[3,5,12] Although the steric course of the ring opening seems to agree with the concerted option,[3,5e] the geometry of the transition state was considered incompatible with the bicyclic system.[5e]

The activation parameters (see Table 2) yield no decisive evidence whether a concerted or a stepwise mechanism is involved in the ring opening process. The effect of substituents on the reaction rate, however, may serve as a mechanistic probe: substituents which stabilize partial bonding through delocalization[13]—like carbonyl, cyano, and phenyl groups—will enhance the reaction rate if a vicinal bond is partially broken in the transition state.[14] Experimentally, carbonyl and cyano groups at the 1- and 4-positions lowered the energy of activation of the ring opening by approx. 32 kJ mole^{-1}.[5g,l,n] Replacement of the 5- and 6-methyl groups in **1** and **3** by methoxycarbonyl groups rather has the opposite effect,[15] showing that the edge bonds are not broken or appreciably lengthened in the transition rate.

Two intermediates have been considered for the ring opening reaction: the π-bonded species **A**, which is closely related to the transition state of the conrotatory cleavage of cyclobutene;[16] and the cyclohexane-1,4-diradical **D** which would be expected to open stereo-

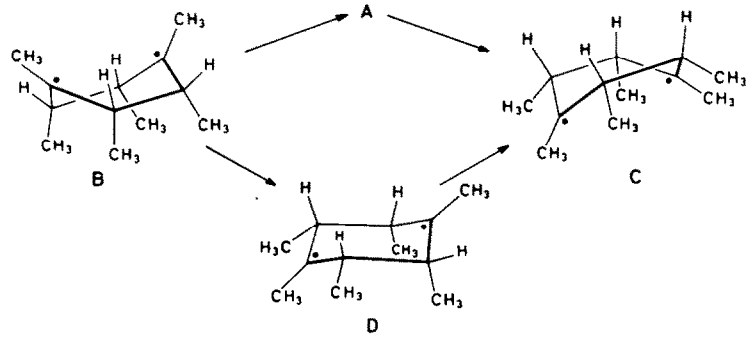
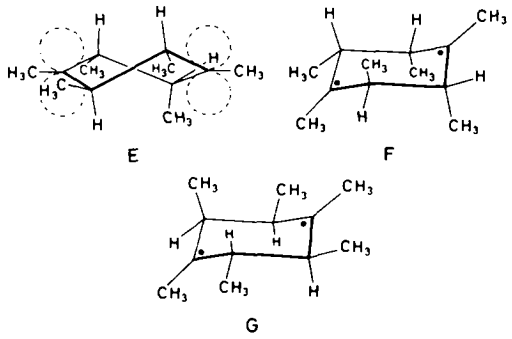


Table 2. Activation parameters

Compound	temp. range (°C)	$\Delta H^{\ddagger}$ (kJ mole^{-1})	$\Delta S^{\ddagger}$ (J mole^{-1} K^{-1})
$1_{inv.}$	140-175	139.2 ± 0.8	-4 ± 2
$1_{cleav.}$		139.4 ± 1.4	-13 ± 3
$2_{se\ cleav.}$	220-250	175.8 ± 0.9	+18 ± 2
$2_{ss\ cleav.}$		184	+13
$3_{inv.\ +\ cleav.}$	192-217	137 ± 6	-6 ± 3
$4_{cleav.}$	210-245	166.5 ± 1.2	+11 ± 3
$5_{cleav.}$	230-250	165.3 ± 1.3	-8 ± 3

specifically due to the through-bond coupling of the radical centers.[12,17] Further insight into the cleavage mechanism can be obtained from the geometry of the products. Consider the cleavage of the C_1–C_4 and C_5–C_6 bonds in **3** and **4**, which yielded predominantly the (*E,E*)-diene **7**. Cleavage via the 1,4-π-bonded species **E** would involve an outward rotation of the 5- and 6-methine carbon atoms, which is evidently the expected process. The corresponding cyclohexane-1,4-diradical could exist in two conformations (**F** and **G**), of which the conformer **F** is definitely more likely than the alternative conformer **G**, in which three interactions of eclipsing methyl groups are present. Since cleavage of the C_5–C_6 bond in **F** would give rise to the (*Z,Z*)-diene (**8**), contrary to the observed results, we conclude that the bicyclo[2.2.0]hexane cleavage proceeds mainly via the 1,4-π-bonded intermediate (**A**, **E**).[18]



E F

G

EXPERIMENTAL

Reagent grade solvents were used for all hydrogenation reactions and kinetic experiments. Reaction products were analyzed by means of a Perkin-Elmer F11 gas chromatograph equipped with a 50 m capillary PPG column (*ex* Chrompack). NMR spectra were recorded on Varian T-60 and XL-100 instruments. All chemical shifts are in ppm downfield from internal TMS.

Preparation of compounds

Compound **1** was prepared from hexamethyl[2.2.0]hexa-2,5-diene (supplied by J. T. Baker Chemicals) by hydrogenation over Ru (10% on C, *ex* H. Drijfhout, Amsterdam) at 25° and 150 atm.[2]

Compounds **3** *and* **5**. A 1 l shaking vessel was equipped with a dropping funnel. A solution of $H_2PtCl_6 \cdot 6H_2O$ (2.07 g, 4 mmoles) and anh. LiBr (6.25 g, 72 mmoles) in 2-propanol (450 ml) was placed in the vessel. The dropping funnel was charged with $SnCl_2 \cdot 2H_2O$ (5·41 g, 24 mmoles) and 2-propanol (50 ml). The entire apparatus was flushed thrice with N_2 and the $SnCl_2$ soln was added. After 1 hr H_2 was admitted and hexamethylbicyclo[2.2.0]hexa-2,5-diene (20.2 g, 0.125 mole) introduced. After consumption of 1 eq. of H_2 (2 days) the solution was poured into 2 N HCl (3 l) and extracted with pentane (500 + 5 × 100 ml). The combined extracts were washed with $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated *in vacuo*.

The resulting mixture of hexamethylbicyclo[2.2.0]hexenes[2] (19,1 g, 95%) was hydrogenated over 5% Pt on C (3 g) in heptane (450 ml) at 70° and 1 atm. After 3 days 1 g of fresh catalyst was added. When the H_2 consumption had ceased, the catalyst was removed by filtration, the solvent was evaporated, the residue, which consisted of a mixture of **1**, **3** and **5** was subjected to preparative GLC (SE 30 column, 100°). 1,2-*Endo*-3-*endo*,4,5-*endo*,6-*exo*-hexamethylbicyclo[2.2.0]hexane (**3**) and 1,2-*endo*,3-*exo*-4,5-*endo*,6-*exo*-hexamethylbicyclo[2.2.0]hexane (**5**) were collected.

Tris(3-*trifluoroacetyl*-d-*camphorato*)*europium*(III). Eu_2O_3 (0.704 g, 2 mmoles) was dissolved in 12 N HCl (20 ml). After evaporation, the residue was dried over P_2O_5 *in vacuo*. The resulting $EuCl_3$ was dissolved in EtOH (20 ml) and added to a solution of bis(3-trifluoroacetyl-*d*-camphorato)barium(II) (*ex* Strem Chemicals) in EtOH (60 ml). After 4 hr, the mixture was poured into water (200 ml) and extracted with hexane. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue (2.5 g, 70%) solidified upon standing.

Threo- *and* erythro-3,4-*dimethylhexa*-2,5-*dione*. 3,4-Dimethylhexa-2,5-dione (prepared by dimerization of 2-butanone in the presence of PbO_2[19]) was subjected to preparative GLC (OV-17 column, 80°). The diastereomers were collected as separate fractions. ^{1}H NMR, *threo* (C_6D_6): δ = 0.71 (m, 6H); 1.86 (s, 6H); 2.60 (m, 2H) *erythro* (C_6D_6): δ = 0.85 (m, 6H); 1.75 (s, 6H); 2.52 (m, 2H).

The ^{1}H NMR spectra of the diastereomers in the presence of tris(3-trifluoroacetyl-*d*-camphorato)europium(III)[20] revealed the configuration:[21] the isomer of lowest GLC retention time showed a complex signal of the 3- and 4-protons, which collapsed into two singlets upon irradiation of the 3- and 4-methyl groups. Thus, this isomer possesses the *threo* configuration. A similar experiment with the *erythro* isomer was inconclusive, since resolution of the enantiotopic 3- and 4-protons was not accomplished.

Kinetics

Thermal isomerization runs for kinetic purposes were conducted as follows: 15 samples, each containing 10 μl of a 10% v/v solution of bicyclohexane in heptane or decane, were sealed in glass capillary tubes and immersed in a thermostatted oil bath. With appropriate intervals, samples were removed and analyzed. First order rate constants were calculated by least squares approximation.

For each bicyclic compound, 9–10 kinetic runs were carried out over a suitable temperature range. The thermodynamic activation parameters (see Table 2) were calculated from $\ln k - \ln T = \ln(k/h) + \Delta S^{\ddagger}/R - \Delta H^{\ddagger}/RT$.

Isolation of products

The isomerization products of **1**, **2**, **3** and **5** were subjected to chromatography over a 120 × 20 mm $AgNO_3$-impregnated SiO_2[22] column. The *threo*-dienes **9** and **10** proved to be much more firmly complexed to the stationary phase than the *erythro*-dienes **6–8**, providing a basis for facile separation as well as tentative identification.

Compounds **2** *and* **6**. A sample of **1** (0.25 g) was heated (neat, in sealed glass) for 125 min at 175°. The reaction products were separated by means of chromatography over $AgNO_3/SiO_2$. Elution with hexane-C_6H_6 (10:1) afforded first 1,2-*exo*,3-*exo*,4,5-*exo*,6-*exo*-hexamethylbicyclo[2.2.0]hexane (**2**), then *erythro*-(*E,Z*)-3,4,5,6-tetramethylocta-2,6-diene (**6**) [^{1}H NMR ($CDCl_3$): δ = 0.78 (d, 3H); 0.82 (d, 3H); 1.60 (m, 12H); 2.04 (dq, 1H); 2.62 (dq, 1H); 5.4 (m, 2H)].

Compounds **4** *and* **7–9**. A sample of **3** (0.25 g) was heated (neat, in sealed glass) for 10 h at 200°. Chromatography over $AgNO_3/SiO_2$ afforded upon elution with hexane-C_6H_6 (10:1) 1,2-*exo*,3-*exo*,4,5-*endo*,6-*exo*-hexamethylbicyclo[2.2.0]hexane (**4**) [^{1}H NMR (CCl_4): δ = 0.7–1.0 (m, 18H); 1.45 (m, 2H); 2.00 (quint, 1H); 2.80 (quint, 1H)], *erythro*-(*Z,Z*)-3,4,5,6-tetramethylocta-2,6-diene (**8**) [^{1}H NMR ($CDCl_3$): δ = 0.81 (m, 6H); 1.62 (m, 12H); 2.64 (m, 2H; 5.28 (m, 2H)] and *erythro*-(*E,E*)-3,4,5,6-tetramethylocta-2,6-diene (**7**) [^{1}H NMR ($CDCl_3$): δ = 0.84 (m, 6H); 1.50 (m, 12H); 2.00 (m, 2H); 5.26 (m, 2H)] successively in separate fractions. Further elution with C_6H_6 afforded *threo*-(*E,Z*)-3,4,5,6-tetramethylocta-

Table 3. ^{13}C NMR data[a]

Compound	methyl carbon atoms	methine carbon atoms	olefinic carbon atoms
6	11.5; 13.2; 13.3; 17.7; 18.1; 18.4	36.6; 47.0	119.3; 119.7; 139.0
7	11.5; 13.3; 18.7	47.0	119.0; 139.9
8	13.0; 16.8; 18.3	36.2	120.1; 139.0
9	12.0; 13.0; 13.2; 17.1; 18.2; 18.6	37.2; 45.4	117.8; 139.7; 140.3
10	12.2; 13.2; 16.6	45.2	117.6; 140.0

[a] $CDCl_3$ solution, chemical shifts in ppm downfield from internal TMS.

2,6-diene (**9**) [^1H NMR ($CDCl_3$): $\delta = 0.96$ (d, 3H); 1.00 (d, 3H); 1.51 (m, 12H); 2.11 (dq, 1H); 2.60 (dq, 1H); 5.10 (m, 2H)].

Compound **10**. A sample of **5** (0.25 g) was heated (neat, in sealed glass) for 240 min at 248°. The product mixture was subjected to chromatography over $AgNO_3/SiO_2$. Elution with hexane-C_6H_6 (1:1) afforded *threo*-(*E,E*)-3,4,5,6-tetramethylocta-2,6-diene (**10**) [^1H NMR ($CDCl_3$): $\delta = 0.93$ (m, 6H); 1.50 (m, 12H); 2.12 (m, 2H); 5.13 (m, 2H)].

Configurational assignments

The configurations of the alkenic moieties were assigned on the basis of the ^{13}C NMR spectra (see Table 3). An allylic carbon *trans* to a carbon atom will resonate 7–10 ppm downfield relative to an allylic carbon atom *trans* to hydrogen.[23] This effect is clearly observed for the methine carbon atoms in **8**, and **7** and **10**, which appear at $\delta = 37$ and 46, respectively, the (*E,Z*)-dienes **6** and **9** providing a basis for comparison.

The *threo-erythro* configurations were determined by means of ozonolytic degradation.[24] Ozonolysis of **6** and **7** resulted in complex mixtures which contained *erythro*-3,4-dimethyl-hexa-2,5-dione, according to GC and GC/MS, the *threo*-diastereomer being absent. Similarly, *threo*-3,4-dimethylhexa-2,5-dione was present in the ozonolysis product of **9**. With the configuration of **7** established, **10** had to be assigned the *threo*-configuration. The configuration of **8** was assigned on the basis of the rather low affinity for Ag(I).

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