

## 251. The Reaction of Difluorocarbene with Bicyclo[2.2.2]octadiene

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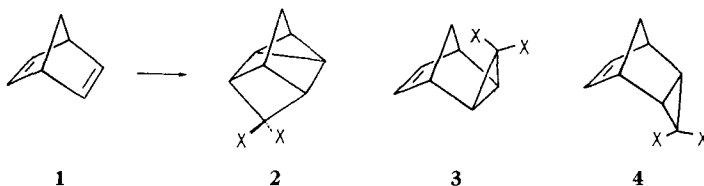
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*Summary.* The addition of difluorocarbene to bicyclo[2.2.2]octa-2,5-diene gave the *exo* and *endo* 1:1 cyclopropane adducts. In contrast to norbornadiene, no *homo*-1,4 adduct was formed. The adducts were thermally stable under the conditions of their formation and separation ( $< 170^\circ$ ). However, smooth equilibration was achieved on heating at  $250^\circ$  for 36 h. The same mixture resulted from either isomer. At  $250^\circ$   $\Delta\Delta G = 1.83$  kcal/mol; the *endo* isomer being the more stable. Heating to higher temperatures caused decomposition, rather than further reaction to the intramolecular [2+2]cyclization products. The kinetic and thermodynamic product compositions were essentially the same on extrapolating to the same temperature, viz. *endo*/*exo* = 19-22 at  $25^\circ$ . The mechanisms by which the cyclo-addition and the stereomutation of the *cis*-fused cyclopropane moiety occur are discussed.

**Introduction.** - We have recently demonstrated that dihalocarbenes react with norbornadiene (**1**) to give substantial amounts of the *homo*-1,4 adduct (**2**) in addition to the usual 1,2 adducts (**3** and **4**). This finding is unprecedented as it con-

Scheme 1



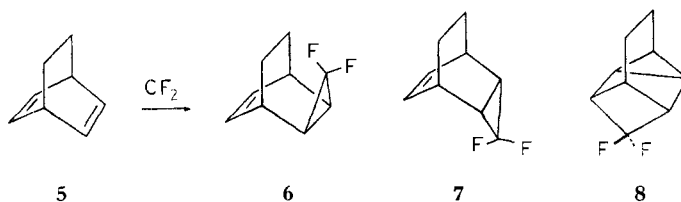
stitutes the first example of a linear cheletropic reaction of a  $\sigma^2$  carbene with a diene, albeit a *homo*-conjugated one [1]. Initially we believed that this result was confined to difluorocarbene, but it transpired that all dihalocarbenes demonstrate this behaviour [2]. Whether the 1,4 adduct is seen or not depends largely upon the interplay of steric factors in the substrate and reagent. Bulkier carbenes favour the 1,2 over the *homo*-1,4 addition mode. Conversely, obstruction on the *exo* face by a voluminous substituent at C(7) directs even bulky carbenes, e.g. dibromocarbene, to the *endo* face whereupon *homo*-1,4 addition occurs [3] [4].

The choice of norbornadiene was fortunate as the skeleton possesses the entropic particularity of permitting both linear and non-linear cheletropic reactions to compete on more or less equal terms [1]. It appears that conjugated dienes normally do not manifest 1,4 addition as the transition state for 1,2 addition is so easily attain-

able [5]. Consequently, the study of dienes structurally related to norbornadiene is desirable with the goal of defining and extending this novel reaction. In this paper the reactions of difluorocarbene with bicyclo[2.2.2]octadiene are described.

**Results and discussion.** - Difluorocarbene was generated at 25° from a threefold excess of triphenyldifluorobromomethylphosphonium bromide and potassium fluoride and allowed to interact with bicyclo[2.2.2]octa-2,5-diene (**5**) [6]. Two 1:1 adducts were obtained in a yield of 20% which were identified as the *exo* and *endo* cyclopropane adducts **6** and **7**. The reaction was repeated, but using phenyltrifluoromethylmercury and sodium iodide in a two-fold excess at 80° as the source of difluorocarbene [7]. The same two adducts, **6** and **7** were obtained in a yield of 70%. In both cases the material balance consisted of bicyclo[2.2.2]octadiene while the *exo* (**6**) and *endo* (**7**) adducts were obtained in essentially the same ratio, namely

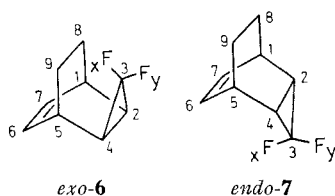
Scheme 2



1:19 and 1:12 respectively<sup>1)</sup>. A careful search of the reaction mixtures revealed no *homo*-1,4 adduct **8**. Nevertheless, there was a third product formed in trace amounts of less than 0.5% which could neither be isolated nor identified. In order to establish which was which, the major and minor adducts were separated, analysed thermally and studied by NMR. spectroscopy.

**NMR. spectral analysis.** - The typical *A,B*-patterns and the fine structure of the  $^{19}\text{F}$ -NMR. spectra immediately permit the identification of both **6** and **7** as difluorocyclopropane derivatives. The distinction between the two structures and the stereochemical assignments are based essentially on the characteristic long-range shieldings exerted by the cyclopropane ring on the vinyl protons. Thus, the vinyl protons of the *endo* adduct (**7**) appear at significantly higher field than those of the minor *exo* adduct **6** ( $\Delta\delta = 0.47$ ). Similar correlations are not only found for the vinyl protons of **3** and **4** ( $\Delta\delta = 0.40$ ) [1], but also for structurally related derivatives of the bicyclo[3.2.2.0<sup>2,4</sup>]nonene skeleton [8-10]. Furthermore, it is only the *syn*-oriented fluorine atom ( $\text{F}_x$ ) of **7** which shows through-space coupling with the vinyl protons ( $^5J_{\text{HF}} = 1.5$  Hz). Additional characteristic NMR. parameters (confirmed by heteronuclear decoupling) are listed in Tables 1 and 2.

<sup>1)</sup> The prefixes used here for the bicyclo[2.2.2]octadiene adducts are patterned on the mode of norbornadiene. The *endo* side is designed by the presence of the olefinic bridge.

Table 1.  $^1\text{H-NMR}$ , <sup>a)</sup> and  $^{19}\text{F-NMR}$ , <sup>b)</sup> chemical shifts in  $\text{DCCl}_3$ 


Compound	H—C(1) (H—C(5))	H—C(2) (H—C(4))	H—C(6) (H—C(7))	H—C(8) (H—C(9))	F <sub>x</sub>	F <sub>y</sub>
<b>6</b> (minor)	3.00	1.63	6.53	1.95 1.05	151.0	103.0
<b>7</b> (major)	3.03	1.70	6.06	1.6 1.3	144.7	115.4

<sup>a)</sup> At 100.1 MHz expressed in  $\delta$  [ppm] relative to internal TMS.

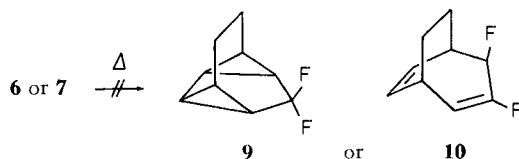
<sup>b)</sup> At 94.1 MHz expressed in  $\delta$  [ppm] upfield from internal  $\text{FCCl}_3$ .

Table 2. Characteristic coupling constants (in Hz)

Compound	$^2J_{\text{F}, \text{F}}$	$^3J_{\text{H}, \text{F}_x}$	$^5J_{\text{H}-\text{C}(6,7), \text{F}_x}$
<b>6</b> (minor)	165.0	15.5	$\sim 0$
<b>7</b> (major)	160.0	16.0	1.5

**Thermal equilibration of 3,3-difluorotricyclo[3.2.2.0<sup>2,4</sup>]non-6-enes **6** and **7**.** – The adducts **6** and **7** proved to be remarkably thermally stable. They remained unchanged at 170° even after heating for 24 h. However, at 250° after 36 h equilibration started to occur; heating either **6** or **7** separately gave practically the same mixture of isomers. Heating the minor, the less stable, isomer **6** gave a ratio of 85.3:14.7, whereas a ratio of 85.6:14.4 was obtained from the major, the more stable, isomer **7**. No other products were detected and further heating at higher temperature resulted only in decomposition, rather than the formation of the possible tetracyclic intramolecular addition product **9** or the allylic rearrangement product **10**.

Scheme 3



By way of comparison, the thermal behaviour of the difluorocarbene adduct (**11**) obtained from bicyclo[2.2.2]oct-2-ene was also examined. A sample was tested at various temperatures in the probe of the NMR. spectrometer and the  $^{19}\text{F}$  spectrum was monitored. No change in the signal was seen on heating up to 194°. It had been hoped

to observe a time averaged spectrum as the cyclopropane ring flipped back and forth. The result does not rule out stereomutation, but simply means that if it does occur then it is slow on the NMR. time scale.

**Discussion.** – Despite the similarity between bicyclo[2.2.2]octadiene and norbornadiene, the absence of *homo*-1,4 adduct is remarkable. The order of the bonding and anti-bonding orbitals is reckoned to be the same for both homodienes, but with the difference that the interaction through space of the pair of double bonds is expected to be much less for **5** [11]. An exchange reaction can be envisaged between the HOMO and LUMO's for diene and carbene, but this clearly is not enough. It can be tentatively assumed that the skeletal deformations needed to reach the transition state leading to **8** are simply insuperable. In fact a scrutiny of the literature reveals no examples of the related [2 + 2 + 2] cyclo-additions for **5** which nevertheless are commonplace for norbornadiene [12]. The only case of a possible *homo*-1,4 reaction occurring is the hydrogenation of **5** to give the cyclopropane derivative, however it should be remembered that the skeletal deformation here will be smaller owing to the less demanding steric requirements for the 1,4 addition of hydrogen [13].

The equilibration experiment reveals that the two adducts are thermally stable for long periods of time at temperatures much greater than those used for the generation of carbene. Therefore it can be confidently assumed that the product mixtures obtained are purely kinetic in origin. Thus the ratio of adducts can be taken as a reflection of the difference in transition state energies for the *endo* and *exo* approaches of difluorocarbene to the double bond. For the two different methods of carbene generation performed at 25° and 80° the values of  $\Delta G^\ddagger$  at 25° are identical, namely 1.75 kcal/mol, which incidentally implies that free difluorocarbene is the responsible species.

At first sight this result appears to run counter to that experienced with norbornadiene [1]. For the 1,2 addition mode, *exo* attack was strongly favoured over *endo* attack; unfortunately, a precise value of the difference in transition state energies could not be obtained in this instance as the *endo* adduct was labile under the reaction conditions, epimerizing easily to the *exo* adduct. However, inspection of models reveals a fundamental difference between the *exo* environment of the double bond in norbornadiene and bicyclo[2.2.2]octadiene. The transition state for cyclopropanation requires that the carbene approaches an off-center point above the double bond with ligands projecting forward describing a lateral trajectory [14]. Norbornene and norbornadiene which have just a methylene group centrally disposed on the *exo* side offer a convenient port of entry. *Endo* approach is impeded in norbornene by the ethane bridge, whereas the *endo* side of norbornadiene is more approachable since any possible obstruction arising from the *endo* hydrogen atoms on C(5) and C(6) will be missing. Bicyclo[2.2.2]octadiene, on the other hand fends off attacking carbene with its ethane bridge on the *exo* face thereby favouring formation of the adduct on the *endo* face.

Another observation is that the kinetic and thermodynamic *endo/exo* product ratios are very similar, namely 19 and 22 at 25°. Accordingly it may be concluded that the transition state is approximated sterically by the situation obtaining in product.

**Epilogue.** – The interconversion of the *exo* and *endo* isomers is a nice illustration of the reversible stereomutation of a *cis*-fused cyclopropane ring. All other examples of this phenomenon have been irreversible since one of the epimers has selectively reacted or rearranged further [15]. The presence of *gem*-difluoromethylene grouping is felicitous; not only is the equilibrium rendered spectroscopically visible, but the rupture of the cyclopropane  $\sigma$ -bond common to the two rings is facilitated by the fluorine substituent effect [16]. The absence of intramolecular [2 + 2] cyclo-addition could be due in the first place to the fact that the reacting cyclopropane electron pair stays in a symmetric orbital throughout [17] and secondly that the skeleton is unable even under more vigorous conditions to adapt to the tetracyclic product **9**. It can also be inferred that skeletal constraints are largely responsible for the stiffness of the cyclopropane ring flip in the tricyclononane series (*e.g.* **6**  $\rightarrow$  **7**) compared with the ease of this movement in the lower homologues (*e.g.* **4**  $\rightarrow$  **3**).

It is worth repeating that the *gem*-difluorocyclopropane moiety constitutes a special case compared to cyclopropane itself. Another factor which ought to be considered to explain the weakening effect on the opposite cyclopropane  $\sigma$ -bond is the interaction of lone pairs on fluorine<sup>2)</sup>. As there are two pairs available on the two fluorine atoms, the doubly occupied antisymmetric negative contribution will interact progressively with the breaking  $\sigma$ -bond. Disrotation turns the latter into a  $\pi$ -type bond, the anti-symmetric LUMO of which is increasingly fed with electronic charge thereby contributing to the ease of rupture of the bond (Fig. 1).

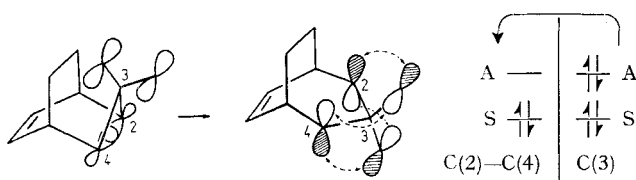


Fig. 1. Interaction of the occupied antisymmetric lone pair orbital of the *gem*-difluoro grouping on C(3) with the LUMO of the  $\pi$ -bond developing from the  $\sigma$ -bond between C(2) and C(4) (symbolism of Klopman used [18])

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### Experimental Part

*Generalities.* For details of the chromatographic and spectroscopic methods as well as the procedures used for generating difluorocarbene see [1].

*Bicyclo[2.2.2]oct-2-ene* was prepared by standard methods [19] [20].

*Bicyclo[2.2.2]octa-2,5-diene (5).* As the existing methods for the preparation of this diene were unsatisfactory [22], a new, simple route has been devised. Bicyclo[2.2.2]oct-2-en-5-one [22] was converted to its N-tosylhydrazone in 94% yield using N-tosylhydrazine in ethanol [23].

<sup>2)</sup> We thank *A. Streitwieser, Jr.*, for drawing our attention to this possibility.

To a stirred solution of the N-tosylhydrazone (26.1 g, 90 mmol) in dry ether (350 ml) under nitrogen methylolithium in ether (115 ml of a 2M solution) was added dropwise over 1 h [24]. The temperature was kept at  $20 \pm 5^\circ$  using a water bath. After 40 h the orange solution was quenched with water (50 ml). A further quantity of water (150 ml) was added and the layers separated. The ethereal layer was washed with water ( $4 \times 100$  ml) and the combined aqueous layers were further extracted with ether ( $2 \times 75$  ml). The final ether solution was dried over  $\text{Na}_2\text{SO}_4$  and then distilled through a 25 cm *Vigreux* column until some 50 ml remained. This was diluted with pentane (100 ml) and re-concentrated by distillation. Repetition of this procedure afforded a solution which was chromatographed over neutral alumina (250 g), eluting with pentane (800 ml). The eluate was distilled at 12 Torr (bath temperature  $40^\circ$ ) over a cold finger ( $-15^\circ$ ). The pentane was removed while the olefin condensed. The oil so obtained contained about 60% of **5** as judged by GLC. (8% FFAP on chromosorb W,  $115^\circ$ ) and NMR. Bicyclo[2.2.2]octene, benzene and toluene were present to the extent of 15, 15 and 10%. The total distillate weighed 5.34 g, of which 2.86 g (27 mmol) consisted of **5** representing an overall yield of 30%. Final purification of **5** was effected by GLC. (20% FFAP on HP chromosorb W, helium flow rate 100–120 ml/min,  $3 \text{ m} \times 8 \text{ mm}$ ,  $T_R \approx 30$  min).

**3,3-Difluorotricyclo[3.2.2.0<sup>2,4</sup>]nonane (11)**. Phenyltrifluoromethylmercury (1.6 g, 4.6 mmol), bicyclo[2.2.2]oct-2-ene (1.33 g, 12.3 mmol), sodium iodide (2.75 g, 18.3 mmol) and benzene (10 ml) were heated under reflux for 72 h. The mixture was diluted with *n*-pentane (15 ml) and filtered through a short column of silica gel. The product **11** was isolated by GLC. (20% FFAP on chromosorb W on a column  $3 \text{ m} \times 8 \text{ mm}$  with helium flowing at 100–120 ml/min;  $125^\circ$ ). The component having  $T_R = 30$  min was collected giving 72 mg of **11** (0.46 mmol, 10% yield). –  $^1\text{H-NMR}$ . (60 MHz, hexachlorobutadiene): 1.5–2.4 (*m*, 12H) (reference is external TMS). –  $^{19}\text{F-NMR}$ . (94.1 MHz, triglyme): 16.1 ( $F_x$ ,  $^2J_{\text{FF}} = 165$  Hz), 49.0 ppm ( $^3J_{\text{F}_y\text{H}_{\text{cis}}} = 15$  Hz) (downfield from internal  $\text{C}_6\text{F}_6$ ). – MS. 158 (17), 143 (13), 138 (14), 130 (56), 129 (29), 116 (40), 115 (35), 104 (65), 90 (41), 81 (53), 79 (100%).

$\text{C}_9\text{H}_{12}\text{F}_2$  (158.19) Calc. C 68.34 H 7.65% Found C 68.40 H 7.84%

*Exo- and endo-3,3-Difluorotricyclo[3.2.2.0<sup>2,4</sup>]non-6-enes (6 and 7)*. (a) The reaction mixture [6] consisted of triphenylphosphine (2.62 g, 10 mmol), triglyme (10 ml), dibromodifluoromethane (2.8 g, 13.3 mmol) and bicyclo[2.2.2]octadiene (370 mg, 3.5 mmol) with potassium fluoride (3.5 g, 60 mmol) left at  $25^\circ$  for 90 h. The mixture was treated with water (50 ml) and extracted with pentane ( $3 \times 25$  ml). The extract was washed with water ( $4 \times 25$  ml) and dried. Inorganic residues were removed by passage through a short silica gel column. Pentane was removed by distillation and the product was isolated by GLC. (15% FFAP, column  $3 \text{ m} \times 8 \text{ mm}$ , nitrogen flow rate 100–120 ml/min,  $100^\circ$ ). The *endo* and *exo* adducts were separated giving a ratio of 19:1 in an overall yield of 20%.

(b) The reaction mixture [7] consisted of trifluoromethylphenylmercury (2.86 g, 8.25 mmol), sodium iodide (3 g, 20 mmol), benzene (25–30 ml), bicyclo[2.2.2]octadiene (400 mg, 3.78 mmol) and a few drops of dimethoxyethane. After 40 h of heating under reflux, the mixture was diluted to 50 ml with pentane and then filtered through a short silica gel column, using pentane as eluant. Excess solvents were evaporated and the oil so obtained was dissolved anew in pentane and filtered through silica gel. The residue was subjected to GLC. as above. The *endo* and *exo* adducts were obtained in a 92:8 ratio in a 50% yield (MS.: 156 ( $M^+$ ), 141, 128, 109, 92, 91, 79, 78, 77). The structures of the *exo* and *endo* isomers were identified from their NMR. spectra (Tables 1 and 2).

*Thermal isomerization*. Samples of the *exo* (**6**) and *endo* (**7**) adducts in  $\text{CDCl}_3$  containing 2% TMS were sealed in separate NMR. tubes. After recording the NMR. spectrum of each, the two tubes were sealed in a single thick-walled tube containing chloroform (to compensate for the increase in pressure in the sample tubes). The thick-walled tube was then heated under determined conditions in a *Carius* oven. After cooling, the tube was opened and the NMR. spectra of the samples recorded. The isomer composition was determined by analytical GLC. (15% FFAP,  $120^\circ$ , digital integration). The critical temperature for equilibration was  $250^\circ$  and after 126 h at this temperature both samples furnished the same mixture of **6** and **7**. Starting from **7** and **6** the equilibrium constants were  $K = 5.814$  and  $5.935$  respectively, **7** being the more stable isomer.

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