(s), 1360 (br), 1280 (br), 1250 (s), 1160 (s), 1010 (s), 920 (s), 850 (br) cm^{-1}; MS, m/z 163 (ketene, EI), 329 (nitrene of hydroquinone, CI), 164 (ketene, CI).

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Registry No. 1, 20764-96-9; 2, 123834-45-7; 3, 123834-46-8; 4, 123834-47-9; 6, 123834-48-0; 7, 123834-49-1; 13, 123834-50-4; 14, 123834-51-5; lithium (trimethylsilyl)acetylide, 54655-07-1; (trimethylsilyl)acetylene, 1066-54-2.

Comparison of Reactions of Difluorocarbene with *cis*- and *trans*-Cyclooctene

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Difluorocarbene is an unusually stable and chemically selective carbene occurring as a ground-state singlet.[1] When generated in situ from triphenylphosphine, difluorodibromomethane, and inorganic fluoride salts in triglyme, it forms cyclopropanes in high yield from tri- and tetraalkyl olefins (e.g., 74–79% from 2,3-dimethyl-2-butene) and in low yield from symmetrically dialkylated olefins (*cis*-2-butene, 6%; *trans*-2-butene, 12%; cyclohexene, 21%).[2,3]

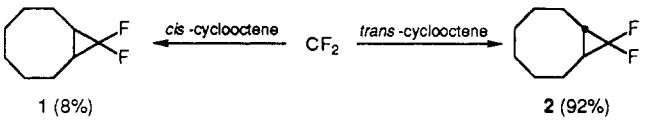
This paper summarizes the findings of an investigation of the reactions of CF_2 generated as above with *cis*- and *trans*-cyclooctene. The main purposes of the investigation are 2-fold: first, investigation of the effect of distortion of an olefinic linkage on the yield of the cyclopropanation reaction; second, generation of an "extra-strained" trans-fused bicyclo[6.1.0]nonane. This idea follows from the effects of geminal fluorines, which lengthen the vicinal bond of a cyclopropane and increase its strain by ca. 10 kcal/mol.[4-8] Thus, while the extra strain in *trans*-bicyclo[6.1.0]octane relative to the cis isomer is at most 1 kcal/mol,[9] it may be possible that inclusion of the fusion-bond-weakening fluoro substituents might enhance this difference.

The use of the Burton method[2] for generating CF_2 was suggested by two factors. First, once the 9,9-difluoro-*trans*-bicyclo[6.1.0]nonane is synthesized, exposure to temperatures above 60 °C might induce geometrical isomerization as observed for *trans*-2,3-dimethyl-1,1-difluorocyclopropane.[4] Secondly, if one were to employ the Seyferth reaction,[10] which involves phase transfer and attack of the alkene by CF_3^-, it is likely that geometrical isomerization would occur prior to ring closure as observed for CCl_2 and CBr_2 attack on *cis,trans*-1,5-cyclooctadiene.[11]

Experimental Section

trans-Cyclooctene was synthesized and purified according to a published procedure.[12] *cis*-Cyclooctene, triphenylphosphine, dibromodifluoromethane, potassium fluoride, and triglyme were obtained from Fluka Chemical Co., and 1-methylcyclohexene was purchased from Aldrich Chemical Co. *cis*-Cyclooctene and 1-methylcyclohexene were distilled prior to use. Triphenylphosphine was recrystallized from absolute ethanol, potassium fluoride was heated in a crucible over a flame and allowed to cool in a vacuum desiccator, and triglyme was dried over 5A molecular sieves. The reaction was carried out according to literature procedures,[3] the crude mixtures were distilled at room temperature at ca. 6 mm, and the distillate was trapped at −78 °C. Subsequent purification was done by gas chromatography (6 ft × $^1/_8$ in. OD ab5 100/110 mesh, apiezon b 5% w/w); column initial temperature 75 °C, increased 20 °C/min to 230 °C; injector 250 °C, detector 280 °C.

Scheme I



1 (8%) 2 (92%)

7,7-Difluoro-1-methylbicyclo[4.1.0]heptane: mass spectrum, m/e 104 (base peak) ($C_5H_6F_2$), 146 (M) (27), 131 (82), 118 (33), 117 (50), 103 (44), 91 (41), 90 (61), 81 (41), 77 (50), 68 (46), 67 (72), 55 (58); ^{19}F NMR ($CDCl_3$, relative to $CFCl_3$; $CF_3C_6H_5$ was used as an external standard and 63.7 ppm added to place the chemical shifts on the $CFCl_3$ scale) 145.3 (d, 1 F, $^2J_{FF}$ = 151 Hz), 135.9 ppm (dd, 1 F, $^2J_{FF}$ = 152 Hz, $^2J_{HF}$ = 15 Hz); ^1H NMR ($CDCl_3$, TMS): 1.1 ppm (s, 3 H), other peaks 1.05–1.8 ppm (9 H). The Yield based upon the GC chromatogram was 22%.

***cis*-9,9-Difluorobicyclo[6.1.0]nonane (1)**: mass spectrum, m/e 41 (base peak), 160 (M) (5), 90 ($C_4H_4F_2$) (94), 81 (54), 77 (79), 67 (51), 55 (77), 54 (42), 51 (38), 39 (88); ^{19}F NMR [$CDCl_3$, relative to $CFCl_3$ (see above); $CF_3C_6H_5$ was used as external standard] 154.2 (d, 1 F, $^2J_{FF}$ = 151 Hz), 126.1 ppm (dt, 1 F, $^2J_{FF}$ = 151 Hz, $^2J_{HF}$ = 15 Hz). The yield based upon the GC chromatogram was 8%. The ^{19}F NMR spectrum is in agreement with published data on this compound[13] with the larger $^2J_{HF}$ tentatively assigned to the exo fluorine by analogy to the monofluoro analogues.[14] Other spectral data are also published.[10]

***trans*-9,9-Difluorobicyclo[6.1.0]nonane (2)**: mass spectrum, m/e 90 (base peak) ($C_4H_4F_2$), 160 (M) (2.6), 81 (44), 77 (61), 67 (40), 55 (48), 41 (56), 39 (48); ^{19}F NMR [$CDCl_3$, relative to $CFCl_3$ (see above)] 139.0 ppm (broadened singlet with some splitting); ^1H NMR ($CDCl_3$, TMS) 1.0–1.25 (complex group of peaks, 8 H), 1.47 (m, 2 H), 1.9–2.0 ppm (m, 4 H). The yield based upon the GC chromatogram was 92%.

Discussion

The yield of the CF_2 reaction with *trans*-cyclooctene is much higher than for *cis*-cyclooctene (Scheme I). It is probably easiest to understand this in terms of the ionization energies of the olefins[15] and frontier orbital analysis known to be applicable to carbene–olefin reactions.[16] Thus, the adiabatic ionization energies for 2,3-dimethyl-2-butene (8.30 eV), 2-methyl-2-butene (8.67 eV), and 1-methylcyclohexene (8.67 eV) are relatively low. In contrast,

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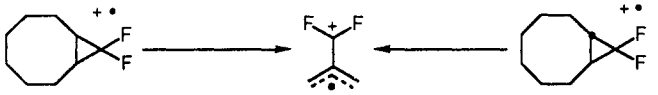
Scheme II



3 (m/e 90)

the values for *cis*-cyclooctene (8.82 eV), cyclohexene (8.95 eV), *cis*-2-butene (9.11 eV), and *trans*-2-butene (9.10 eV) are all relatively high. [2-Methylpropene (9.23 eV) appears to be an anomaly since it reacts with CF_2 in high yield;[2] however, here we suspect a markedly unsymmetric transition state due both to steric and to electronic effects.] The high reactivity of *trans*-cyclooctene is readily understood through comparison of its adiabatic ionization energy (8.53 eV[17,18]) with that of the cis isomer, which is ca. 0.3 eV higher. Thus, twisting of the π-bond pushes up the highest occupied molecular orbital (HOMO) and has the same effect as electron donation by alkyl groups, which also makes the HOMO higher in energy. This principle also appears relevant to the observation of CF_2 attack on some bicyclo[1.1.0]alkanes.[19]

Reaction with 1,2,2-trimethylbicyclo[1.1.0]butane yields a product (from concerted attack calculated to initiate at the central bond) in about 3% yield.[19] The corresponding yield from bicyclo[2.1.0]pentane is only ca. 0.5% while bicyclo[3.1.0]hexane does not react.[19] The ionization energies[15] of bicyclo[1.1.0]butane (8.70 eV), bicyclo[2.1.0]-pentane (8.7 eV), and bicyclo[3.1.0]hexane (9.16 eV) follow an expected trend. 1,2,2-Trimethylbicyclo[1.1.0]butane should have a consierably lower value by analogy with solution $E_{1/2}$ values for bicyclobutane (1.69 V), 2,2-dimethylbicyclo[1.1.0]butane (1.56 V), and 1,3-dimethylbicyclo[1.1.0]butane (1.10 V).[20]

It is worthwhile noting that while the strain energies of *cis*- and *trans*-bicyclo[6.1.0]nonanes are within 1 kcal/mol of each other, it seems possible that the fluoro substituents enhance this effect since stretching of the distal bond in *gem*-difluorocyclopropanes is associated with an increase in strain.[7,8] One small item of evidence may be seen in the comparison of the relative abundances of the *m/e* 90 ion likely to be **3** (Scheme II). In the cis isomer, the base peak is *m/e* 41 with *m/e* 90 at 94% and the parent ion at 5% (5.3% of *m/e* 90). For the trans isomer, *m/e* 90 is the base peak and the parent ion is only 2.6% of the *m/e* 90 peak. Our initial attempt to isomerize **2** to **1** at 60 °C (see ref 4) was not successful.

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Registry No. **1**, 108055-81-8; **2**, 123883-64-7; difluorocarbene, 2154-59-8; *cis*-cyclooctane, 931-87-3; *trans*-cyclooctene, 931-89-5; 7,7-difluoro-1-methylbicyclo[4.1.0]heptane, 123883-63-6.

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Nuclear Magnetic Resonance Studies of Thiol/Disulfide Chemistry. 2. Kinetics of Symmetrical Thiol/Disulfide Interchange Reactions[1]

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Introduction

The thiol group is among the most reactive groups found in biological molecules, and to a large extent the ease with which it is oxidized governs the metabolism and function of thiol-containing compounds.[2] Oxidation can occur by several mechanisms,[3,4] including thiol/disulfide interchange as described by eq 1 and 2. The net result of these two

$$RSH + R'SSR' \rightleftarrows RSSR' + R'SH \quad (1)$$

$$RSH + RSSR' \rightleftarrows RSSR + R'SH \quad (2)$$

reactions is oxidation of RSH and reduction of R'SSR', with the overall reaction proceeding through the mixed disulfide intermediate RSSR'. Thiol/disulfide interchange reactions are involved in the metabolism of endogenous thiols as well as thiol-containing drug molecules,[5-10] in the mechanism of action of penicillamine in the treatment of cystinuria,[11] and they provide a means for the reversible formation and cleavage of strong, covalent sulfur–sulfur bonds in biological molecules.[4]

Because of their importance in biological chemistry, the kinetics and mechanism of thiol/disulfide interchange reactions have been the subject of numerous studies.[12-15] Previous studies have generally been restricted to systems that form products that have some unique characteristic which can be monitored, e.g., the reaction of thiols with oxidized glutathione was monitored by an enzymatic assay for glutathione,[12b] and the reaction of a variety of thiols

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