

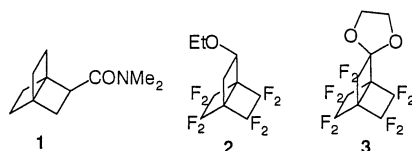
A Remarkable [2.2.2]Propellane

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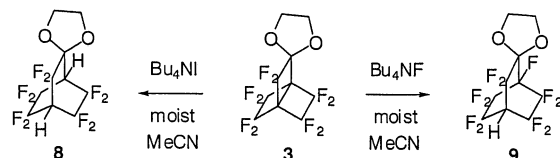
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Molecules possessing the highly strained [2.2.2]propellane ring system are very rare.² The first representative to be isolated, carboxamido derivative **1**, was synthesized in 1973;³ the highly fluorinated derivative **2** appeared in 1996.⁴ We now report the synthesis of a third [2.2.2]propellane, **3**, the structure, properties, and chemistry of which are striking.⁵



The new propellane was synthesized from dibromide **4** as shown in Scheme 1. Reductive debromination of **4** generated alkene **6**, which was efficiently trapped with *N*-benzylpyrrole to give adduct **5**. *retro*-Diels–Alder reaction of **5** made possible the isolation of the strained alkene, which underwent [2+2] cycloaddition with acetal **7** rapidly and quantitatively at room temperature. Propellane **3** is a volatile crystalline solid, mp 48–50 °C.⁷ Its X-ray crystal structure reveals that the C1–C4 bond is 1.573 Å in length (cf. cyclobutane,⁸ 1.548 Å).⁹ The propellane **1** ring opens to dimethylenecyclohexanes with a half-life of 28 min at 25 °C,³ but **3** displays extraordinary thermal stability for a [2.2.2]propellane. *It is unchanged after at least 10 h at 100 °C.* The stabilization of cyclobutane rings by fluorine substitution is presumably responsible, at least in large measure, for this contrast.¹⁰

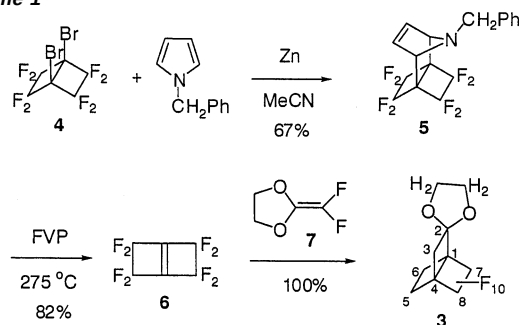
Despite its robustness, **3** is a very reactive molecule. Tetrabutylammonium iodide in moist acetonitrile cleaved the C1–C4 bond reductively, giving dihydro compound **8** immediately at room temperature. In the same medium, tetrabutylammonium fluoride yielded the HF adduct **9** and its regioisomer in the ratio 9:1. The



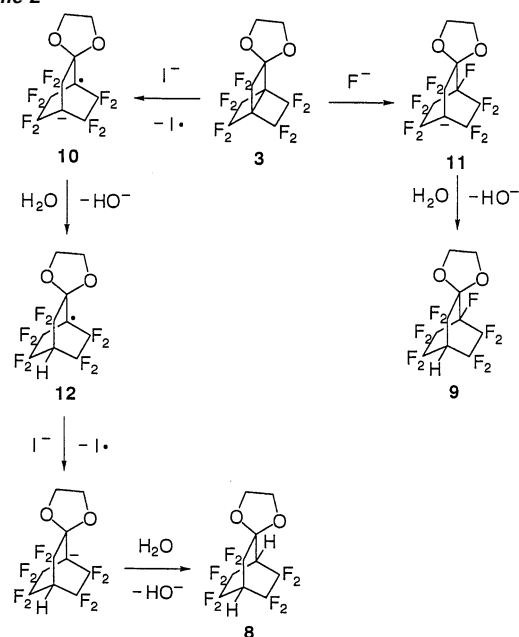
contrasting behavior reflects the great difference in reducing power of the two halide ions ($E^\circ = 0.536$ V for iodide, 2.866 V for fluoride).¹¹ These transformations probably occur as shown in Scheme 2, via radical anion **10** and bridgehead anion **11**, respectively. The favored site of fluoride ion attack (C1) is such that anionic charge develops at the bridgehead with the greater number of β -fluorines (C4); radical ion **10** is assumed to have its charge largely at that site¹² and thus to give mainly **12** upon protonation.¹³

Bromide ion ($E^\circ = 1.066$ V) displays intermediate behavior, yielding both **8** and **13**, the bromine analogue of **9**, in the ratio 4.2:1. It is noteworthy that reduction is the dominant process even with the chloride ion ($E^\circ = 1.358$ V), which gives **8** and **14** in a

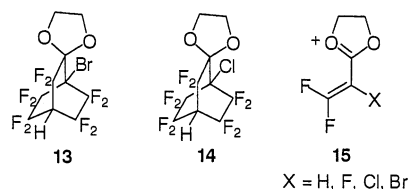
Scheme 1



Scheme 2



similar ratio, 3.7:1. The higher standard potential for chlorine/chloride is apparently compensated for by lower nucleophilicity of chloride relative to bromide ion. Assignment of regiochemistry to the HX adducts was facilitated by the fact that the base peak in the mass spectrum of compounds **8**, **9**, **13**, and **14** has the elemental composition of ion **15**.

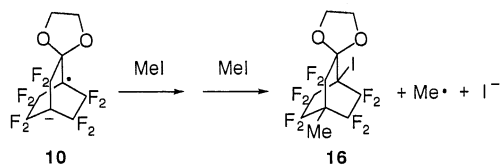


X = H, F, Cl, Br

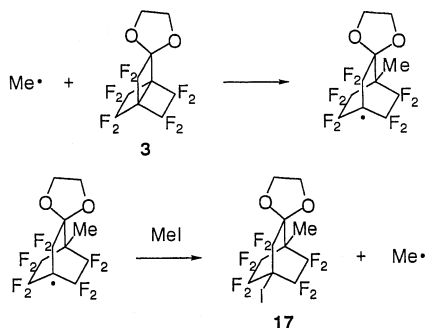
Addition of methyl iodide across the C1–C4 bond occurs in the presence of iodide ion. With a large excess of MeI and a 50:1 molar

Scheme 3

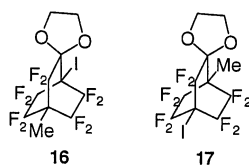
Ionic chain pathway:



Radical chain pathway:



ratio of **3** to iodide ion, adduct **16** and its regioisomer **17** are formed in the ratio 2.5:1.¹⁴ With equimolar amounts of **3** and iodide ion,

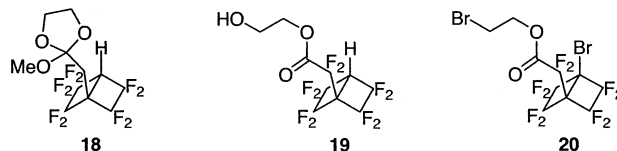


the product ratio becomes 15:1. The initially formed radical anion **10** reacts twice with methyl iodide, methylating in one step (S_N2) and abstracting an iodide atom in the other to give predominantly the expected regioisomer **16** (Scheme 3). Both iodide ion and methyl radical are generated in those steps, with the result that an ionic chain process giving predominantly **16** and a radical chain sequence yielding **17** ensue. The result with equimolar iodide shows that the ionic chain process is highly regioselective; the outcome with a trace of iodide indicates that **3** is attacked by iodide ion about 2.5 times faster than by methyl radical.

Inclusion of a small amount of acetic acid in the reaction of **3** with methyl iodide and catalytic iodide ion provided strong evidence for the above interpretation. Now only regioisomer **17** was formed, along with a lesser amount of HI adduct. Acetic acid eliminated the ionic chain pathway by protonating **10**, thereby forestalling the regeneration of iodide ion. It follows that the radical chain pathway is cleanly regioselective; because methyl is a donor radical, it attacks as nucleophiles do, at C1.

All of the reactions of propellane **3** described above occur rapidly at room temperature. In methanol, **3** undergoes slow solvolysis, forming a 1:1 adduct. In further contrast with the above transformations, the C1–C4 bond remains intact, as the product is ortho ester **18**. The C1–C2 bond apparently suffers heterolysis in this good ionizing solvent with the help of π -donation by the oxygens, stabilization of developing negative charge by four β -fluorines, and release of ring strain. That bond is the longest (1.590 Å) of the 10 cyclobutane bonds in **3**, perhaps by virtue of negative hyperconjugation.¹⁵ Analogously, the slow solvolysis of propellane **3** in aqueous acetonitrile yields hydroxyester **19**, presumably via an ortho acid.

Strong electrophiles also cleave the C1–C2 bond, not the highly electron-deficient central bond. Bromine, for example, reacts slowly with **3** in the dark to give a 1:1 adduct, dibromoester **20**. For comparison, bromine cleaves the central bond of **1** instantaneously at -70°C .³



Clearly, the consequences of heavy fluorine substitution on the nature and chemical behavior of a [2.2.2]propellane are profound. Electron withdrawal by the fluorines stoutly protects the fragile bond between bridgehead carbons from thermal cleavage and electrophilic attack, but renders it highly vulnerable to reducing agents and nucleophiles.

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Supporting Information Available: Experimental procedures and characterization data, including, for **3**, X-ray crystallographic data plus ORTEP (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (5) This molecule was chosen as a model for perfluoro[2.2.2]propellane, which has not yet submitted to synthesis. Oxygen plays a dual role as substituent, greatly facilitating propellane formation by virtue of its π donor ability, then mimicking fluorine in the product with its electron-withdrawing power as the second most electronegative element.
- (6) This new ketene acetal was prepared by treatment of 2-trifluoromethyl-1,3-dioxolane with butyllithium.
- (7) ^{19}F NMR (CDCl_3) δ -104.1(s, 2F); -106.5, -107.3 (AB q, J = 228 Hz, 4F); -106.7, -107.6 (AB q, J = 223 Hz, 4F); ^1H NMR (CDCl_3) δ 4.25 (m, 2H), 4.21 (m, 2H); ^{13}C NMR (CDCl_3 , ^{19}F decoupled) δ 119.6 (s), 115.5 (s), 115.0 (s), 111.0 (s), 66.9 (t, J = 154 Hz), 53.2 (s), 51.5 (s); HRMS (CI) calcd. for $\text{C}_{10}\text{H}_5\text{O}_2\text{F}_{10}$ ($M + \text{H}^+$) 347.0130; found 347.0127.
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- (14) The possibility that one of the hydrogens in **8** was introduced by hydrogen atom abstraction instead of protonation was ruled out by the finding that in the presence of D_2O both bridgeheads become deuterated.
- (15) The methyl group was located by NMR as follows. NOEs resulting from selective irradiation of the ^{19}F resonances permitted assignment of the ^{13}C signals for C1 and C4. In the ^{19}F broadband decoupled ^{13}C spectrum, it was the signal for C4 that was split into a quartet by the methyl protons.
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