

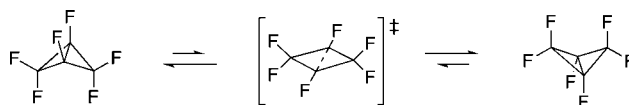
The Effect of Fluorine Substitution on Ring Inversion in Bicyclo[1.1.0]butanes

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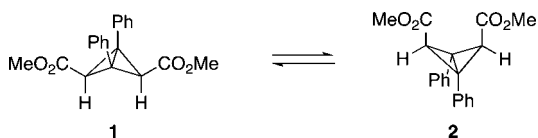
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Degenerate ring inversion in bicyclo[1.1.0]butane and eight of its fluorinated derivatives has been studied at the B3LYP/6-311G**+ level of theory. Fluorine substitution lowers the inversion barrier impressively; reasons for this phenomenon are discussed.

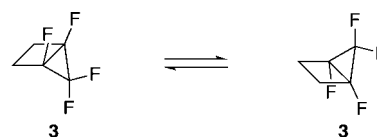
Introduction

Ring inversion in bicyclo[2.1.0]pentanes has been well studied,^{1,2} but only a single experimental observation exists of ring inversion in bicyclo[1.1.0]butanes (**1** ⇌ **2**).³ In this pair of isomers phenyl substitution at the two bridgehead positions greatly facilitates opening of the 1,3-bond with the help of benzylic resonance. A preliminary kinetic investigation found $\Delta H^\ddagger = 26 \pm 2$ kcal/mol, $\Delta S^\ddagger = 9 \pm 4$ eu for the interconversion of **1** and **2**. The barrier to inversion in the parent bicyclo[1.1.0]butane has been computed at many levels of theory with values ranging from 30 to 90 kcal/mol; multireference CI calculations have predicted a barrier of about 50 kcal/mol.⁴ This barrier is presumably quite inaccessible experimentally, as the bicyclo[1.1.0]butane ring opens without cleavage of the central bond to butadiene with $E_a = 40.58$, $\log A = 14.02$.⁵



1,4,5,5-Tetrafluorobicyclo[2.1.0]pentane (**3**) was synthesized in our laboratory and found to undergo degenerate inversion with $\Delta G^\ddagger = 6.8 \pm 0.2$ kcal/mol (-55 °C),² as compared with $E_a = 37.8$ kcal/mol, $\log A = 13.9$ for the (deuterium-labeled)

parent hydrocarbon.⁶ Thus, fluorine substitution lowered the inversion barrier very dramatically. Hybrid density functional calculations at the B3LYP/6-311G**+ level of theory predicted $\Delta G^\ddagger = 8.80$ kcal/mol for this process at the same temperature, in reasonable agreement with the experimental finding. Calculations using the same method for the unknown hexafluorobicyclo[1.1.0]butane predicted a barrier about half as high; if theory exaggerates the height a little as it does for **3**, the actual barrier is tinier yet. This striking finding has prompted us to investigate more fully the influence of fluorine substitution on bicyclo[1.1.0]butanes.



Methods of Calculation. Because the B3LYP/6-311G**+ level of theory sufficed to predict the inversion barrier for bicyclo[2.1.0]pentane **3** with fair accuracy, that method has been employed throughout the present investigation.⁷ It reproduces well the experimental C–C bond distances in bicyclo[1.1.0]butane (C1–C3, 1.493 Å vs lit.⁸ 1.497 ± 0.003 Å; C1–C2, 1.500 Å vs lit.⁸ 1.498 ± 0.004 Å). It is likely that the true barriers for the series of bicyclo[1.1.0]butanes that we have chosen for investigation are somewhat lower than those calculated, as was the case in the bicyclopentane study, where we also found that barrier height decreased as basis set size was increased. Enthalpies and free energies of activation are corrected for zero-point energy differences.

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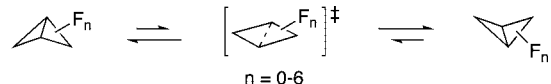
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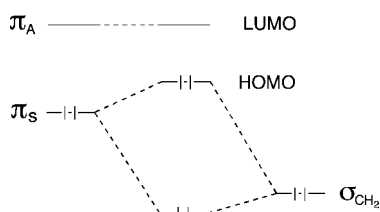
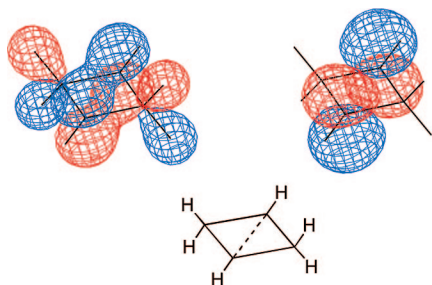
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TABLE 1. Energetic Parameters for Degenerate Ring Inversion of Bicyclobutanes^a


	ΔH^\ddagger	ΔS^\ddagger	ΔG^\ddagger	HOMO [†]	LUMO [‡]	$\Delta(\text{FO}^\ddagger)^b$
BCB	71.8	1.6	71.4	-106.9	-69.5	37.4
1-fluoroBCB	52.4	-0.8	52.3	-113.9	-61.6	52.3
2,2-difluoroBCB	45.2	-1.3	45.6	-153.7	-91.1	62.6
1,3-difluoroBCB	36.1	-5.2	37.7	-120.9	-53.4	67.5
1,2,2-trifluoroBCB	29.6	-1.0	29.8	-158.1	-83.4	74.8
2,2,4,4-tetrafluoroBCB	26.0	-1.7	26.5	-193.8	-108.9	85.0
1,2,2,3-tetrafluoroBCB	15.9	-3.3	16.9	-162.0	-76.7	85.3
1,2,2,4,4-pentafluoroBCB	13.4	-3.4	14.4	-195.4	-101.5	93.9
hexafluoroBCB	3.1	-5.2	4.6	-196.8	-95.3	101.5

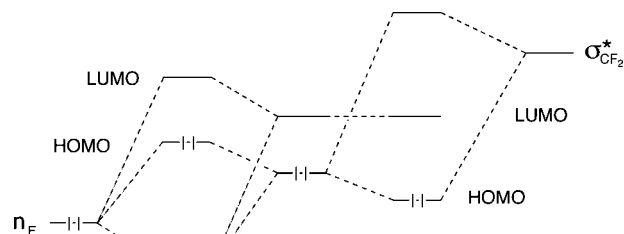
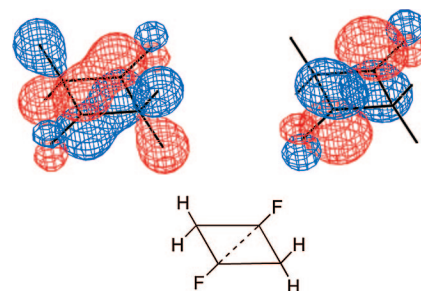
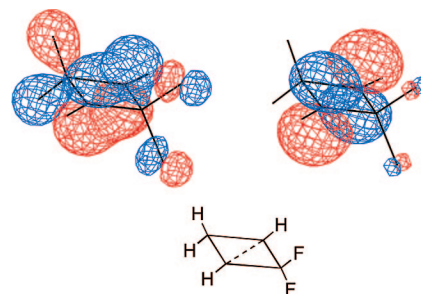
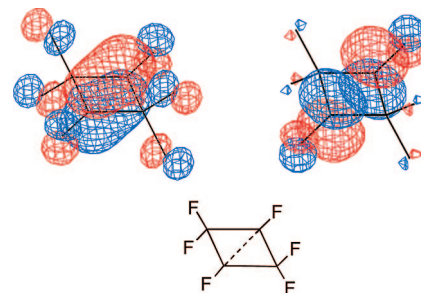
^a All energies are in kcal/mol; entropies are in cal/mol·K. ΔG^\ddagger values are for 25 °C. ^b The transition state HOMO–LUMO gap.

**FIGURE 1.** Schematic derivation of the frontier orbitals of the BCB transition structure.**FIGURE 2.** HOMO (left) and LUMO (right) of the BCB transition structure.

For all of the transition states calculated, a single negative vibrational frequency was found representing motion toward the ground state, and intrinsic reaction coordinate calculations were carried out on selected systems to ensure that the transition states were correct. Calculated without symmetry constraints, the transition structures for all nine systems had, to a good approximation, maximum symmetry, but the computer found them all to belong to the C_1 point group. Thus, they were recalculated constrained to their apparent symmetry, and for six of the systems the new energies were nearly identical with the originals. The data reported below are from these symmetrized structures. In the case of bicyclobutane itself, symmetrizing led to a D_{2h} transition state lying 0.24 kcal/mol below the original, but it distorted in D_2 fashion instead of C_{2v} as required to reach the ground state. As noted in Table 1, in one of the remaining cases the symmetrized structure failed to converge; in the other the symmetrical transition state that was found lay 0.17 kcal/mol above the original, so the data reported are taken from the latter.

Results and Discussion

Energetic Considerations. Eight fluorinated bicyclo[1.1.0]-butanes (BCBs), all unknown compounds, were chosen for

**FIGURE 3.** Schematic derivation of the transition structure frontier orbitals of 1-fluoroBCB (left) and 2,2-difluoroBCB (right) from those of BCB. The two central orbitals are the frontier orbitals of the parent BCB.**FIGURE 4.** HOMO (left) and LUMO (right) of the 1,3-difluoroBCB transition structure.**FIGURE 5.** HOMO (left) and LUMO (right) of the transition structure for 2,2-difluoroBCB. Note that in the HOMO the CF_2 carbon orbital overlaps in phase with the C1–C3 π orbital.**FIGURE 6.** HOMO (left) and LUMO (right) of the transition structure for hexafluoroBCB.

study, together with the parent hydrocarbon. Their symmetry is such that ring inversion would be a degenerate process in every case. Calculated values of the thermodynamic parameters for the inversion are presented in Table 1. While the small-to-modest entropies of activation vary erratically through the series, the enthalpies and free energies of activation diminish remarkably with increasing fluorine substitution. Comparison of 1,3- with 2,2-difluoroBCB reveals that fluorine at bridgehead positions has a greater effect on the inversion barrier than fluorine on a bridge, and this difference is apparent again in the pair of

TABLE 2. Transition State Geometric Parameters^a

	symmetry	C1–C3	$\Delta(\text{C1–C3})$	C1,3-F	$\Delta(\text{C1,3-F})$	C2,4-F	$\Delta(\text{C2,4-F})$
BCB	C_1^b	1.911	0.418				
1-fluoroBCB	C_1^c	1.819	0.353	1.336	-0.022		
2,2-difluoroBCB	C_{2v}	1.951	0.399			1.413	0.043
1,3-difluoroBCB	D_{2h}	1.760	0.305	1.334	-0.015		
1,2,2-trifluoroBCB	C_1^d	1.885	0.353	1.310	-0.033	1.408	0.047
2,2,4,4-tetrafluoroBCB	D_{2h}	1.982	0.359			1.387	0.031
1,2,2,3-tetrafluoroBCB	C_{2v}	1.836	0.304	1.312	-0.024	1.405	0.045
1,2,2,4,4-pentafluoroBCB	C_{2v}	1.930	0.301	1.296	-0.029	1.383	0.028
hexafluoroBCB	D_{2h}	1.890	0.198	1.299	-0.017	1.380	0.021

^a All bond distances and increments (transition state – ground state) are in Å units. ^b Very nearly D_{2h} . ^c Very nearly C_{2v} . ^d Very nearly C_s .

tetrafluorinated compounds. From the calculated free energy of activation, the hexafluoro derivative is predicted to flap its wings at the rate of $2.6 \times 10^9 \text{ s}^{-1}$ at 25 °C!

The effects of fluorine substitution on BCB inversion are understandable in terms of concepts developed by Borden for fluorinated cyclopentenediyls.^{9,10} In the transition structures for all of the BCBs studied, the carbon skeleton and the atoms bonded to C1 and C3 all lie in a plane (exactly or to an excellent approximation), and the HOMOs and LUMOs are derived from the p orbitals at C1 and C3 perpendicular to the plane. Because in every case those orbitals lie close enough for considerable interaction, the resulting symmetric (π_S) and antisymmetric (π_A) combinations are well separated in energy even before perturbations are considered. In the transition structure for BCB itself, the gap is narrowed by mixing of the CH_2 bonding orbital of proper symmetry with π_S but not with π_A , as shown schematically in Figure 1. The resulting HOMO and LUMO are depicted graphically in Figure 2.

Figure 3 shows schematically the effects of introducing a fluorine at C1 or a pair of fluorines at C2. Regarding the former case, a lone pair on F1 mixes with both BCB transition state FOs, and the HOMO–LUMO gap widens even though the unperturbed HOMO lies closer in energy to the lone pair orbital. This happens because the unperturbed HOMO (which spans the whole molecule) has smaller coefficients at C1 and C3 than the unperturbed LUMO. The key finding is that there is net stabilization resulting from the lowering of the lone pair orbital, and of course this stabilization is enhanced when fluorine is also present at C3. Figure 4 depicts the FOs of the 1,3-difluoroBCB transition structure.

When a CF_2 is present, the unperturbed HOMO mixes with the antisymmetric combination of CF_2 σ^* orbitals, but the LUMO has the wrong symmetry to mix and remains unchanged except for a small 1,3-antibonding interaction with fluorine lone pairs oriented parallel to the ring plane. Again the key interaction is stabilizing, as the HOMO is lowered in energy. The FOs for the 2,2-difluoroBCB transition structure are shown graphically in Figure 5.

Returning to Table 1, one finds that the transition state HOMO level is lowered every time the number of fluorines is increased, a consequence of fluorine's high electronegativity. As expected from Figure 3 (where that effect is not accounted for), the lowering is small when fluorine is introduced at the 1- or 3-position but large at the 2- or 4-position. The latter effect also reflects the fact that substitution by fluorine eliminates the HOMO-raising influence of the CH_2 group at those positions.

Transition state LUMO levels do not drop monotonically with the increase in fluorine numbers. Substitution at the 2- or 4-position does cause considerable lowering by the electronegativity effect, but that is overcome when fluorines are present at the 1- or 3-position because of their strong LUMO-raising effect. The transition state HOMO–LUMO gap invariably increases with the number of fluorines since both kinds of substitution widen it. Figure 6 shows the FOs of hexafluoroBCB. As the model predicts, the HOMO results from bonding interaction of π_S with CF_2 σ^* orbitals and antibonding interaction with lone pairs on F1 and F3. The LUMO is derived by antibonding mixing of π_A with the same lone pairs, together with a minor antibonding 1,3-interaction with lone pairs on the other four fluorines that lie parallel with the ring plane.

The effects of fluorine substitution at the bridge and bridgehead positions might be expected to be synergistic because bridgehead fluorines enhance electron density in π_A , while bridge fluorines deplete it in π_S .¹¹ That may be so, but both the energetic and geometric data (Table 2) suggest that synergism is at best a small effect, presumably because electron withdrawal through the bridgehead C–F σ bonds compensates for the π donor effect. In 1-fluoroBCB, for example, the HOMO is lowered almost as much as the LUMO is raised relative to the parent molecule.

Geometric Considerations. Differences in geometry between BCB and hexafluoroBCB help to account for the extremely low barrier to ring inversion of the latter. Whereas the flap angle for BCB is calculated to be 121.9° (lit.⁸ 122°), that of the fluorocarbon is 140.5°. The computed HC1C3 angle in BCB is 129.2°, but that in the fluorinated counterpart is 143.9° (as compared with 180° in the transition state). In BCB the computed C1–C3 bond distance is 1.493 Å, but 1.692 Å in hexafluoroBCB, with the result that the C1–C3 bond opens 0.418 Å en route to the BCB transition structure, but a mere 0.198 Å in the fluorocarbon case (Table 2). Thus, the perfluoro compound lies much closer than the parent to the D_{2h} transition structure for inversion.¹²

(11) Calculations by Borden for 1,2,2,3-tetrafluorocyclopentenediyl pointed to a 3.7 kcal/mol synergistic effect.¹⁰

(12) En route to the transition state, reviewers noted, the bridgehead hydrogens of bicyclobutane move inward before they move outward, but the bridgehead fluorines of the perfluoro compound simply move outward. Inward motion of the bridgehead phenyls was observed as the flap angle increased in the x-ray structures of the series **1**, its endo-exo isomer, and **2**, and a theoretical study of ring inversion in the parent bicyclobutane concluded that inward motion occurs until the flap angle reaches $150 \pm 2^\circ$, then reverses. Gassman, P. G.; Greenlee, M. L.; Dixon, D. A.; Richtsmeier, S.; Gougoutas, J. Z. *J. Am. Chem. Soc.* **1983**, *105*, 5865. Given the considerably larger flap angle of the perfluoro relative to that of the parent compound, the lack of inward motion in the former is not surprising. As a referee pointed out, that motion in the parent molecule is consistent with Inagaki's analysis of the effects of geminal delocalization on the configurations of the bridgehead carbons in bicyclobutanes, which included several fluorinated examples. Inagaki, S.; Kakefu, T.; Yamamoto, T.; Wasada, H. *J. Phys. Chem.* **1996**, *100*, 9615.

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Table 2 shows that throughout the series of compounds the C1–F and C3–F bonds are shorter in the transition than in the ground structure, consistent with the bonding interaction between fluorine lone pairs and π_A . Correspondingly, the C2–F and C4–F bonds are invariably longer in the transition structures as a result of electron density from π_S appearing in antibonding C–F orbitals.

The transition state C1–C3 distances are consistently shorter with fluorines at C1 (and C3) than at C2 (and C4). This difference is not explained by the orbital interactions that have been described, as both electron withdrawal from the HOMO by the bridge fluorines and electron donation into the LUMO by the bridgehead fluorines would be expected to lengthen the C1–C3 bond. Hybridization effects may help to account for the difference. In accord with Bent's Rule,¹³ electronegative fluorine atoms acquire extra p character from the carbons they are bonded to, leaving extra s character for the peripheral ring bonds. The result is a wider interorbital angle for the ring bonds, which at C2 (and C4) tends to lengthen the C1–C3 bond, but at C1 (and C3) tends to shorten it.

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Conclusions

Whether at bridge or bridgehead positions in bicyclobutane, substitution of hydrogen by fluorine results in dramatic lowering of the barrier to ring inversion. The hexafluoro derivative is predicted to invert more than two billion times per second at 25 °C. The effect of fluorine is a consequence of HOMO stabilization by bridge fluorines and stabilization of lone pairs on bridgehead fluorines by the LUMO in the transition state. As a result, ring inversion barriers may be experimentally accessible by dynamic NMR methods in solution for all of the compounds studied that have four or more fluorine substituents. We hope to subject our calculations to experimental test.

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Supporting Information Available: Total energies and Cartesian coordinates at the B3LYP/6-311G**+ level of theory for all of the systems studied. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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