

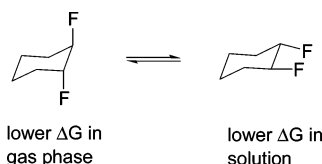
Conformational Preferences for 1,2- and 1,4-Difluorocyclohexane

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The conformational preference for 1,2-difluorocyclohexane has been studied experimentally via NMR spectroscopy and computationally using CCSD/6-311+G(2df,p). The results confirm our previous conclusions that the diaxial conformer of *trans*-1,2-difluorocyclohexane has the lower energy in the gas phase, whereas the diequatorial conformer has the lower energy in solution. SCIPCM reaction field calculations reproduce the observed solvent effects. The 1,4-difluorocyclohexanes have also been reexamined computationally.

Introduction

Fluorine is an unusual substituent in that it has the highest electronegativity of all of the elements and has a very small size.¹ As a substituent in cyclohexane, it has a much smaller conformational preference than the other halogens.² In ab initio calculations, it is necessary to include diffuse functions at fluorine in order to obtain the correct energy differences between *cis*- and *trans*-1,2-difluoroethene³ and between *gauche* and *trans*-1,2-difluoroethane.³ The high electronegativity of fluorine makes the electrons in a C–F bond strongly polarized toward the fluorine. Thus, these fluorines are quite different from a fluorine atom and more like a fluoride ion.

In a computational study of the conformational preferences of dihalocyclohexanes,⁴ we found that the effect of fluorine as a substituent was quite different than that of the other halogens. This can be seen in Table 1, that gives the results obtained at the QCISD/6-311+G(2df,p) theoretical level. An electron diffraction study of *trans*-1,4-dichlorocyclohexane found that the diaxial (aa) and diequatorial (ee) forms have essentially the same energy,⁵ and the calculations are in good agreement with this

TABLE 1. QCISD/6-311+G(2df,p)-Calculated Conformational Preference (kcal/mol)^a

compd	$\Delta\Delta G^b$
<i>trans</i> -1,4-difluoro	1.1
<i>trans</i> -1,4-dichloro	-0.1
<i>trans</i> -1,4-dibromo	-0.1
<i>trans</i> -1,2-difluoro	0.1
<i>trans</i> -1,2-dichloro	0.3
<i>trans</i> -1,2-dibromo	0.9

^a Calculated using QCISD/6-311+G(2df,p) = QCISD/6-311G* + MP2/6-311+G(2df,p) – MP2/6-311G* and the MP2/6-311G*-optimized geometries.⁴ ^b A positive value indicates that the diaxial form is the major conformer.

result. With the *trans*-1,4-dihalocyclohexanes, the small conformational preference for the dichloro and dibromo compounds probably results from a competition between the normal equatorial preference, and the Coulombic attraction between C–X dipoles in the diaxial form. Fluorine has a smaller equatorial preference than Cl or Br, and the larger C–F bond dipole will lead to a larger attraction in the diaxial form. The combination of these two factors results in a strong calculated diaxial preference for *trans*-1,4-difluorocyclohexane. Unfortunately, this compound has not as yet been prepared, and it is not possible to study the conformational preference experimentally.

The opposite trend is seen with the *trans*-1,2-dihalocyclohexanes. Here, the largest diaxial preference is found with bromine, and the difference becomes very small with fluorine. The large size of bromine will lead to a steric interaction in the diequatorial conformer, and

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TABLE 2. Calculated Conformational Preferences for 1,2- and 1,4-Difluorocyclohexane Using CCSD/6-311+G(2df,p) with MP2/6-311+G(2df,p) Structures and B3LYP/6-311+G(2df,p) Vibrational Frequencies (Energies in kcal/mol)^a

config	symmetry	ZPE	CCSD		CCSD(T)	
			H_{rel}	G_{rel}	H_{rel}	G_{rel}
aa-1,2	C_2	96.81	0.00	0.00	0.00	0.00
ae-1,2	C_1	96.80	0.54	0.08	0.51	0.05 ^a
ee-1,2	C_2	96.71	0.33	0.28	0.32	0.28
aa-1,4	C_2	96.87	0.00	0.00	0.00	0.00
ae-1,4	C_1	96.77	0.78	0.29	0.79	0.30
ee-1,4	C_2	96.78	1.21	1.12	1.25	1.17

^a The large difference between H_{rel} and G_{rel} for the ae-conformers is due to their lower symmetry and consequent different entropy change with respect to the other conformers.

this conformer will also experience a Coulombic repulsion between the C–X bond dipoles. Thus, the diaxial form, with its low dipole moment, will be favored in the gas phase. The smaller chlorine gives a smaller conformational preference. With fluorine, there is very little preference. Here, steric effects are minimal, but the repulsion between the C–F bond dipoles in the diequatorial form should be large and could lead to a relatively large preference for the aa form. However, this is not the case.

The diaxial conformer is similar to *trans*-1,2-difluoroethane, whereas the diequatorial conformer is similar to *gauche* 1,2-difluoroethane. Despite the *gauche* interactions in the latter, it has the lower energy in the gas phase.⁶ We have proposed that the type of C–C bond bending caused by fluorine substitution destabilizes the *trans*-form.^{3,7} The same explanation may be used for the 1,2-difluorocyclohexanes.

Results and Discussion

To confirm the calculated effect of fluorine substitution on cyclohexane, we have carried out higher level calculations for the 1,2-difluoro compounds. We have also carried out experimental studies aimed at determining the conformational preference. The added conformational study seemed important since the relative energies of the aa and ee conformers are sensitive to the theoretical level that was used. It is now possible to carry out geometry optimizations and subsequent calculations using higher theoretical levels than were possible in our previous study. CCSD is recognized as one of the best single determinant methods for correcting for the effects of electron correlation,⁸ and it was used to obtain the final calculated energies.

Geometry optimizations were carried out at the MP2/6-311+G(2df,p) level for all three conformers of 1,2-difluorocyclohexane. The corresponding 1,4-difluorocyclohexanes also were examined to allow a comparison with the 1,2-difluorides. Vibrational frequencies needed for the zero-point energy corrections were estimated using B3LYP/6-311+G*, and CCSD(T)/6-311+G(2df,p) calculations were carried out using the MP2 geometries. The geometries and calculated total energies are available in the Supporting Information, and the relative energies are given in Table 2. Here, ZPE is the zero-point

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TABLE 3. Solvent Effect on the Equatorial/Axial Ratio for *trans*-1,2-Difluorocyclohexane

solvent	ϵ	$K = \text{eq/ax}$	ΔG^a (kcal/mol)
methylcyclohexane	2.0	4.4	0.57
di- <i>n</i> -butyl ether	3.1	7.6	0.78
tetrahydrofuran	7.6	29.8	1.30
acetone	20.7	51.3	1.51

^a Estimated uncertainty in ΔG is ± 0.05 kcal/mol. The temperature is 193 K.

energy, H_{rel} is the relative enthalpy difference between pairs of conformers at 298 K including the zero-point energy difference, and G_{rel} is the corresponding free energy term. These data confirm our previous conclusion that with the 1,2-difluorides there is a small preference for the aa conformer. With the 1,4-difluorides, the aa preference is increased to 1.2 kcal/mol. It might also be noted that the aa-1,4-difluoride has a lower energy than the aa-1,2-difluoride (2.4 kcal/mol)⁹ probably because of the electrostatic repulsion between the 1,2-carbons that bear a considerable positive charge. The relative energies calculated using CCSD are only slightly different than those we reported previously using QCISD.⁴ The good agreement gives us confidence that the relative energies are correct.

Solvents will have an important effect on the ratio of the diaxial and diequatorial forms since the latter has a large dipole moment and will be stabilized by polar solvents. The conformational preference has been examined in solution by Zefirov et al.¹⁰ via a ¹⁹F NMR study at -78 °C. They found a preference for the diequatorial form in carbon disulfide (1.03 kcal/mol) and in acetone (1.62 kcal/mol), and assuming CS₂ to be a nonpolar solvent, they extrapolated from these data a gas-phase preference for the diequatorial form of 0.59 kcal/mol. This conclusion is the opposite of that found in our computational study.

To obtain further information, we have repeated the NMR study in solution giving the results summarized in Table 3. Whereas Zefirov et al. used a mixture of the *cis*- and *trans*-1,2-difluorocyclohexanes prepared by the method of Olah et al.,¹¹ we separated the two isomers by gas chromatography and examined a pure sample of the *trans* form. The preference for the diequatorial form in methylcyclohexane is significantly smaller than reported for carbon disulfide as the solvent. This is a common occurrence, where solvents with zero dipole moments (and consequently small dielectric constants) but significant quadrupole moments, such as benzene, carbon tetrachloride, and carbon disulfide, behave as relatively polar solvents.¹² It is necessary to use cyclohexane or a similar saturated hydrocarbon as the nonpolar solvent if the extrapolation to the gas phase is to be successful.

In other solvent effect studies making use of the reaction field model¹³ we have found that a plot of free

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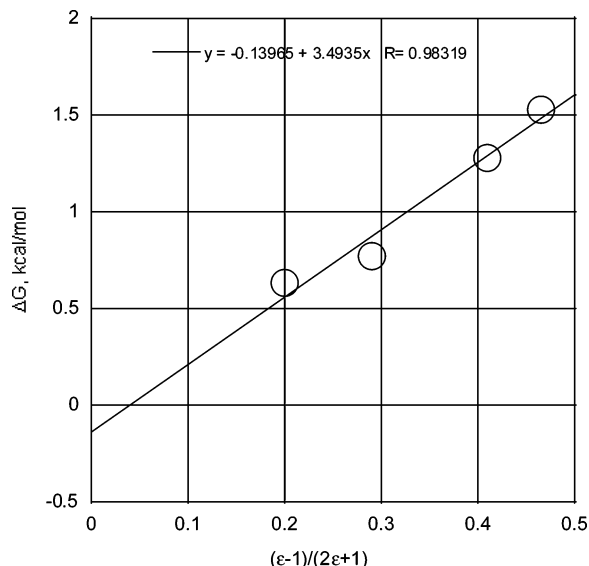


FIGURE 1. Correlation between the free energy difference between conformers and the Onsager dielectric constant function.

energy differences against the Onsager¹⁴ dielectric constant function $(\epsilon - 1)/(2\epsilon + 1)$ gives a smooth curve from high dielectric constant solvents (function value ~ 0.5) to the gas phase (function value = 0.0) when solvents such as those in Table 3 are used. A plot for the present case is shown in Figure 1. The circles are drawn with a radius of ~ 0.05 kcal/mol, corresponding to the uncertainty in the experimental data. An extrapolation to the gas phase, where the function has a zero value, suggested that the diaxial isomer would be slightly favored (-0.14 kcal/mol) in agreement with our calculated result that indicated the aa form to have a slightly lower free energy in the gas phase (-0.28 kcal/mol). A “best” estimate based on these results is that the energy difference is -0.2 ± 0.1 kcal/mol favoring the aa conformer. As the polarity of the solvent increases, the preference for the diequatorial form increases and with a quite polar solvent such as acetone, it is favored by 1.5 kcal/mol.

The above is based on a linear extrapolation to the gas phase. However, this may not be correct since curvature is sometimes found in these plots. Therefore, we have also tried to gain information on the conformational preference in the gas phase via NMR. At temperatures where the difluoride will have a reasonable vapor pressure, the interconversion of the two forms will be rapid, and only the average chemical shift will be observed. However, the shift will be temperature dependent since the proportion of the form having the higher free energy will increase as the temperature is increased. Thus, the observed chemical shift will move toward that of the minor form as the temperature is increased.

The NMR spectrum was obtained for the gas-phase difluoride using trifluorotoluene as an external standard at 25 °C for a series of temperatures from 60 to 125 °C. The results are shown in Table 4. In solution, the chemical shifts at a low temperature relative to fluo-

TABLE 4. Gas-Phase NMR Chemical Shifts for *trans*-1,2-Difluorocyclohexane

T (°C)	shift (ppm)
60	-198.37
90	-198.09
125	-197.76

TABLE 5. SCIPCM-Calculated Solvent Effects^a

conformer	ϵ	E_{rel}^b	μ (D)	$r(C-F)$
ee	1.0	0.00	3.880	1.406
	2.0	-1.64	4.252	1.411
	3.1	-2.45	4.434	1.414
	7.6	-3.55	4.684	1.417
	20.7	-4.13	4.815	1.419
aa	1.0	0.0	1.005	1.415
	2.0	-1.04	1.085	1.418
	3.1	-1.53	1.124	1.420
	7.6	-2.18	1.170	1.422
	20.7	-2.52	1.191	1.423

^a Calculated using B3LYP/6-311+G* and $\rho = 0.0004$ e/au³.

^b Calculated energies relative to those for the gas phase (kcal/mol).

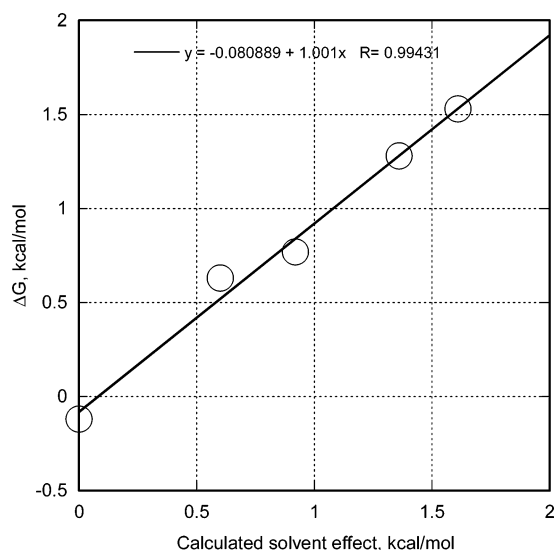


FIGURE 2. Correlation between the observed free energy difference between conformers and the solvent effect calculated using the SCIPCM reaction field model.

robenzene are -196.5 ppm for the diaxial form and -182.9 ppm for the diequatorial form. The observed gas-phase chemical shift is close to the solution value for the diaxial form, and the increase in chemical shift toward that of the diequatorial form with increasing temperature indicates that the latter is the minor isomer in the gas phase. The range of temperatures that could be used was not large enough to allow a more quantitative estimate of the conformer ratio.

It is clear that whereas the diequatorial form is preferred in all solvents, including cyclohexane, the diaxial form is preferred in the gas phase. It is possible to further test this conclusion by carrying out reaction field calculations for the effect of solvents. We made use of the SCIPCM model¹⁵ at the B3LYP/6-311+G** level to calculate the effect of solvents. In this model, the only

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parameters are the starting geometry, the electron density (ρ) for the isodensity surface that defines the cavity occupied by the solute, and the observed dielectric constant of the solvent. The value of ρ that gives a cavity that agrees with the observed molar volumes of a series of compounds is 0.0004 e/au^3 .¹⁶

Geometry optimizations were carried out for each solvent, and the calculated dipole moments and C–F bond lengths are given in Table 5. The other geometrical parameters were relatively unchanged. As expected the energy changes for the ee-conformer were significantly larger than those for aa. The experimental ΔG values in Table 3 are compared with the relative energies given by the SCIPCM calculations in Figure 2. The fit is quite good and the slope is unity.

Summary

Both high-level calculations and two types of experiments agree that aa-1,2-difluorocyclohexane with a small dipole moment has the lower free energy in the gas phase. However, in all solvents, the ee conformer with a relatively large dipole moment has the lower free energy, and the preference increases with increasing polarity of the solvent. The corresponding dichlorides and dibromides have somewhat larger aa-conformational preferences in the gas phase.

Calculations

The ab initio calculations were carried out using Gaussian-03.¹⁷ The solvent effects were calculated using the SCIPCM method that is contained in the above program.

Experimental Section

A mixture of the 1,2-difluorocyclohexanes was prepared using the method of Olah, et al.¹⁰ The trans form was separated from the mixture via gas chromatography using a 20% carbowax column.

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The NMR spectra were recorded using 300 and 400 MHz spectrometers. Solution-phase spectra were referenced relative to C_6F_6 at -164.9 ppm ($5 \mu\text{L}$ per sample). An insert containing deuterated acetone was used for locking and shimming. Gas-phase spectra were recorded using sealed tubes containing a few drops of *trans*-1,2-difluorocyclohexane. Gas-phase spectra were referenced externally to $\text{C}_6\text{H}_5\text{CF}_3$ (-63.72 ppm , 0.05% in C_6D_6) at $25 \text{ }^\circ\text{C}$. The external reference was checked before and after an overnight data acquisition, and the value had changed by only 0.02 ppm . Both reference compounds were set relative to CFCl_3 at 0.00 ppm .¹⁸

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Supporting Information Available: Tables of MP2/6-311+G(2df,p)-optimized geometries and calculated total energies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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