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Hydrogen Bond Donor Properties of the Difluoromethyl Group

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A theoretical and experimental study of the existence and the properties of the difluoromethyl group acting as a hydrogen bond donor has been carried out. An intramolecular CF_2H- -O=C interaction was examined using semiempirical molecular orbital calculations of both a non-hydrogen-bonded and hydrogen-bonded conformation of a CF_2H-substituted pyrazole carboxamide fungicide. Results revealed a short H- -O contact, a significant energy stabilization, and a lowering in the IR spectrum of 22 cm^{-1}. The experimental IR spectrum of this molecule gave two carbonyl stretching frequencies, one lower by 18 cm^{-1}, very similar to the calculated number. Low-temperature NMR results are also consistent with a geometry having the possibility of an intramolecular CF_2H- -O=C hydrogen bond. The hydrogen bond in this system may be related to the enhanced biological activity of the CF_2H compound over its CF_3 counterpart. In addition, ab initio molecular orbital methods were employed to examine inter- and intramolecular hydrogen-bonding models of the difluoromethyl group. The results showed that the CF_2H- -O=C interaction has a binding energy of ~1.0 kcal·mol^{-1} and a H- -O distance of ~2.4 Å.

Introduction

Hydrogen bonds are typically defined as the intermolecular interaction between a hydrogen, bonded to an electronegative atom, and another electronegative atom such as N, O, or F.[1] The magnitude of the interaction typically ranges between 2 and 15 kcal·mol^{-1} and the D−H- - -A distance is 2.0−3.0 Å (where D and A are electronegative atoms). These interactions are particularly important in the structure and function of proteins.[2] In fact, hydrogen bonding plays an important role in enzyme inhibition[3] making any nontypical hydrogen bond donor or acceptor groups very interesting with respect to the design of bioactive molecules (*vide infra*).

Although a carbon−hydrogen group is not a typical hydrogen bond donor due to the relatively low electronegativity of carbon, situations do exist where a CH group can act as a hydrogen bond donor. This phenomenon usually occurs with particularly acidic hydrogens. One well-documented case involves sp hybridized C−H bonds. Infrared and microwave analysis of the interaction of nitrogen and oxygen bases with alkynes or hydrogen cyanide have been used to demonstrate and characterize these C−H- - -A hydrogen bonds.[4] Theoretical studies have also characterized sp C−H bonds as a weak hydrogen bond donors.[5] For example, the acetylene−ammonia hydrogen bond has an interaction energy of 3.6 kcal·mol^{-1} at a H−N distance of 2.3 Å. This is the same distance determined with microwave spectroscopy.[2a] Surveys of X-ray crystal structures of C−H- - -A interactions in general, and in alkynes specifically, have revealed close contacts. These hydrogen bonds were thought to be important for crystal packing.[6]

Another class of molecules exhibiting C−H hydrogen bond donor ability are trihalomethanes. Microwave[7] and infrared[8] studies have been used to provide evidence for the interaction of chloroform and fluoroform with water or ammonia. Nonempirical molecular orbital calculations of these complexes have shown them to have short C−H- - -A distances and weak interaction energies.[9] A related example of C−H hydrogen bond donor groups belongs to the difluoromethyl group. This group is more interesting because of the possibility of incorporating it in a variety of organic molecules. Infrared[10] and ion cyclotron resonance[11] studies have shown that $(CF_2H)_2O$ and CF_3OCF_2H form hydrogen-bonded complexes with a variety of bases. The present study involves infrared, NMR, and theoretical studies of the hydrogen donor properties of the difluoromethyl group.

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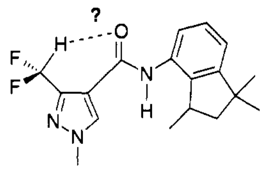
Table 1. Curative Fungicidal Activity against *Alternaria solani* on Tomato[a]

compd	rate (ppm)	% control
1	1000	90
	500	90
	100	92
	20	73
2	1000	54
	500	42
	100	62
	20	57
control		0

[a] Taken from ref 12.

In order to study the hydrogen bond donor properties of the difluoromethyl group, a pyrazole carboxamide fungicide (**1**) with a difluoromethyl substituent in the 3 position of the pyrazole ring, vicinyl to the amide carbonyl, was examined. The difluoromethyl group in this molecule is nicely set up to form an intramolecular hydrogen bond to the amide carbonyl group. Interestingly, this compound has been shown to exhibit increased fungicidal activity over its trifluoromethyl counterpart (designated compound **2**).[12] For example, against *Alternaria solani*, compound **1** was more effective over a range of rates than its CF_3 analog (see Table 1.). This increased activity is surprising given that the difluoromethyl and trifluoromethyl groups are very similar in both size and electrostatics, two critical properties for enzyme–inhibitor recognition.[3] Since hydrogen bonding is also very important for enzyme–inhibitor interactions,[3] the enhanced activity exhibited by the difluoromethyl compound (**1**) over that of the trifluoromethyl compound (**2**) may rest in the hydrogen bond donor ability of the difluoromethyl group.



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In this paper, the possibility of an intramolecular hydrogen bond in **1** is examined using semiempirical molecular orbital calculations and infrared spectroscopy along with supporting NMR findings. In addition, nonempirical molecular orbital calculations were performed on model systems to further explore the intra- and intermolecular hydrogen bonding properties of the difluoromethyl group.

Methods

In order to examine the intramolecular hydrogen bonding properties of the difluoromethyl group, the geometry of molecule **1** was fully optimized using semiempirical molecular orbital theory. The AM1 Hamiltonian,[13] as implemented in the MOPAC program,[14] was utilized in both geometry optimizations and frequency calculations. Two conformations of **1**, a hydrogen-bonded form (see above structure) and a non-hydrogen-bonded form (CF_2H group rotated 180° from the above conformation), were examined. Both conformations were verified as minima via normal mode analysis. In addition, the geometries and infrared carbonyl absorption frequencies of several analogs of **1** (CF_2Cl, CF_3, CH_3, Br, and I in place of CF_2H the group) were calculated. For comparison, the infrared spectra of **1** and its analogs[15a] were determined experimentally, (1% KBr).[15b] In addition, the NMR spectra of **1** and its CF_3 analog (**2**) were compared at temperatures from 25 to −60 °C.[15c]

To further investigate the CF_2H hydrogen bond donor capability, ab initio molecular orbital calculations were carried out on model systems using GAUSSIAN 92.[16] The simplest intramolecular hydrogen bonding model considered was *cis*-difluoromethylacrolein. The geometry of *cis*-difluoromethylacrolein was optimized at the MP2 level, with the frozen core approximation,[17] in order to include the effects of electron correlation, using the 6-31G* split valence basis set.[18] Both a non-hydrogen-bonded and a hydrogen-bonded conformation were examined. The same procedure was carried out on *cis*-β-methyl-, hydroxyl-, and aminoacrolein for comparison of the CF_2H group to known non-hydrogen bond and hydrogen bond donor groups. All minima were verified by normal mode calculation.

Finally, some intermolecular hydrogen bond complexes of the difluoromethyl group were examined. Complexes of difluoromethane–formaldehyde, difluoroethane–formaldehyde, and difluoroethane–acetaldehyde were located at the MP2/6-31G* level. Because of the computational expense of fully exploring the entire potential energy hypersurface of these complexes, a single point energy grid search was performed at the HF/6-31G* level of the C=O--H angle (90–180° with 15° steps) and O--H distance (2.0–3.0 Å with 0.2 Å steps) simultaneously to find the optimal values. The resulting angle and distance were used as a starting point for full optimization (MP2/6-31G* using the frozen core approximation) of the complex. It should be noted that the intent of this work was to examine the hydrogen bond donor properties of the difluoromethyl group and not to report the global minima of these complexes. Binding energies were then calculated by taking the difference between the energy of the complex and the energy of the isolated members of the complex. To account for basis set superposition error, shown to be a problem in hydrogen bond calculations,[1c] the counterpoise correction technique was utilized.[19] The same procedure was carried out for the methanol–acetaldehyde complex for comparison of the difluoromethyl group to a known hydrogen bond donor. As before, all complexes were verified as minima by normal mode calculation.

Results and Discussion

The AM1-optimized structures of the hydrogen-bonded form and the non-hydrogen-bonded form of **1** are displayed in Figures 1 and 2, respectively. Examination of the hydrogen-bonded conformation reveals that the hydrogen of the difluoromethyl group forms a very close contact with the carbonyl oxygen of 2.16 Å, forming a favorable six-membered ring. This distance is consistent with a typical hydrogen bond distance.[1] In addition to supporting geometrical evidence, the difference in calculated ΔH_f between the two forms, 4.92 kcal·mol^{-1},

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(16) Gaussian 92: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P; Pople, J. A. Gaussian Inc., Pittsburgh PA, 1992.

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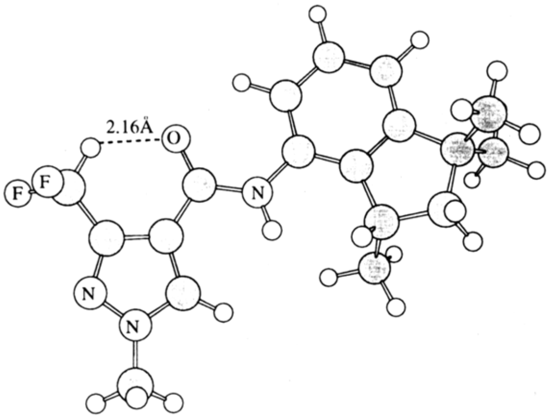


Figure 1. Hydrogen-bonded form of **1**. MOPAC/AM1 $\Delta H_f = -58.26$ kcal·mol^{-1}.

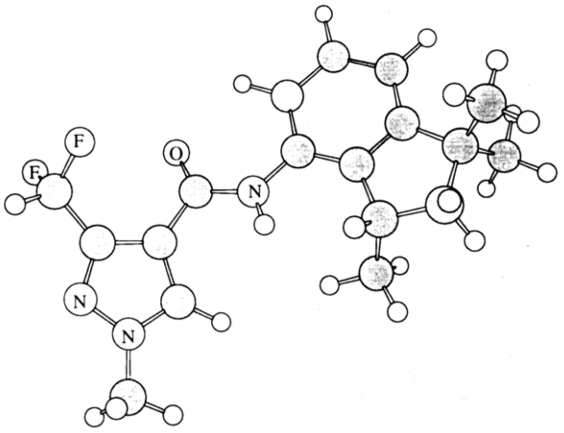
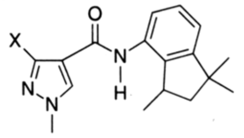


Figure 2. Non-hydrogen-bonded form of **1**. MOPAC/AM1 $\Delta H_f = -53.34$ kcal·mol^{-1}.

Table 2. Comparison of Experimental and Calculated C=O Stretching Frequencies of Various Analogs of 1



molecule (X)	exptl $\nu_{C=O}$ (cm^{-1})	MOPAC/AM1 $\nu_{C=O}$ (cm^{-1})
CF_2H	1651, 1633	2011, 1989[a]
CF_2Cl	1635	2010
CF_3	1637	2010
CH_3	1640	1996
Br	1661	2011
I	1664	2007

[a] Two different conformations (H-bonded and non-H-bonded) were calculated for molecule **1**.

Table 3. Selected Proton Resonances (ppm) from Low-Temperature NMR Spectra of 1 and 2

	1		2	
T (°C)	NH	pyrazole CH	NH	pyrazole CH
25	7.93	8.01	7.60	8.04
0	7.98	8.04	7.63	8.07
−20	8.02	8.05	7.65	8.08
−40	8.08	8.05	7.67	8.10
−60	8.14	8.04	7.69	8.11

shows that the hydrogen-bonded form is significantly more stable than the non-hydrogen-bonded form. This stabilization is well within the range of a typical hydrogen bond, although the entire energy difference between the two conformations probably cannot be attributed solely to the hydrogen bond. There may be an unfavorable nonbonded interaction between the fluorine atoms and the carbonyl oxygen, for example, which may explain the slight rotation of the carbonyl oxygen out of the plane of the pyrazole ring in the non-hydrogen-bonded conformation (see Figure 2).

Another indication of the existence of a hydrogen bond involves the infrared stretching frequency of the bonds to the atoms involved in the hydrogen bond. Both the C−H bond of the donor group and the C=O acceptor group will be weakened due to donation of electron density from these bonds to the formation of the hydrogen bond.[1c] This effect manifests itself as a shift to lower frequency in the IR spectrum. Frequency calculations were carried out on **1** and several of its analogs in order to examine the effect of the putative hydrogen bond on the carbonyl stretching frequency. This stretch was chosen because it is easily identified in the experimental spectrum. Table 2 lists both the calculated and experimentally determined carbonyl stretching frequencies of **1** and several of its analogs.[20] The calculated results show that the carbonyl stretching frequency of the hydrogen bonded form is lower by 22 cm^{-1}. This is the expected behavior for a hydrogen bond.[1] The experimental spectrum of **1** (see Table 2) also exhibits two carbonyl stretching frequencies, one at 1651 cm^{-1} and the other at 1633 cm^{-1}, a difference of 18 cm^{-1}. All of the other analogs, which contain groups incapable of forming a hydrogen bond, yielded spectra with only one sharp carbonyl stretching peak. This result along with the observation that the measured and calculated difference in the two carbonyl stretching frequencies (18 and 22 cm^{-1}) are similar may indicate the existence of both a hydrogen-bonded and a non-hydrogen-bonded form of **1**, as shown in Figures 1 and 2. It should be noted that the existence of the two experimental peaks may be the result of phenomena other than hydrogen bonding, for example, Fermi resonance.

Additional evidence for the CF_2H--O=C hydrogen bond may come from the proton NMR spectra of **1** and **2**.[15c] At 25 °C, the only significant difference between the CF_2H (**1**) and CF_3 (**2**) analogs is the position of the amide NH resonance. In **1**, the proton is observed as a fairly broad signal at 7.93 ppm; the corresponding broad resonance for the CF_3 analog appears at 7.60 ppm. There may be several reasons other than an intramolecular CF_2H--O=C bond to account for this downfield shift, but initially one might have expected that the CF_3 analog would appear at lower field due to the greater electronegativity of the CF_3 group compared to the CF_2H. Furthermore, as the temperature of the samples is lowered, the NH resonance in **1** shifts to lower field, while the NH resonance in **2** shows little change (Table 3). The shift is easily followed when compared to the nearby shift of the pyrazole CH resonance, which remains essentially constant for both analogs. At 0 °C, the NH resonance in **1** has shifted to 7.98 ppm, and at −60 °C the resonance appears at 8.14 ppm, a shift of about 0.2 ppm over the temperature range studied. The minor shift of the NH resonance in **2** (from 7.60 to 7.68 ppm) resulting from lowering the tempera-

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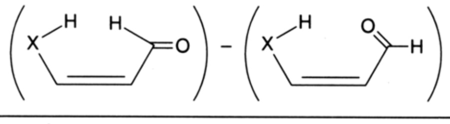
(20) The AM1 vibrational frequencies calculated here differ from their experimental values by ~18%. It has been shown that AM1 vibrational frequencies typically have ~20% rms error as compared to experiment. See: Coolidge, M. B.; Marlin, J. E.; Stewart, J. J. P. *J. Comput. Chem.* **1991**, *12*, 948−952.

Table 4. AM1 and MP2/6-31G*//MP2/6-31G* Comparison of the Energy Differences and Carbonyl Stretching Frequencies of the Non-Hydrogen-Bonded and Hydrogen-Bonded Forms for Various Model Systems



(X)	AM1 $\Delta(\Delta H_f)^a$	MP2/6-31G* ΔE^b	AM1 $\Delta\nu(C{=}O)^c$	MP2 $\Delta\nu(C{=}O)^c$	AM1 r_{HO} (Å)^d	MP2 r_{HO} (Å)^d
CF_2	0.18	0.71 (0.67)	5.0	-5.2	2.187	2.264
CH_2	−0.05	−0.35 (−0.30)	6.2	-5.3	2.275	2.268
NH	4.08	7.79 (7.62)	24.6	12.7	2.201	1.942
O	4.19	10.67 (9.94)	27.3	26.3	2.073	1.737

[a] Energies in kcal·mol^{-1}. [b] Energies in kcal·mol^{-1}. Values with zero point energies includes in parentheses. [c] Frequency differences in cm^{-1}. [d] H−O distance in H-bonded form.

ture is no greater than the shifts observed due to fluctuations in the instrument. Thus, NMR results do not support a CF--H−N hydrogen bond, as such an interaction would be stronger in the CF_3 than the CF_2H analog due to the greater electronegativity of the CF_3 group and the statistically greater number of possible interactions, three vs two. The downfield shift of the NH proton in **1** could be accounted for by the reinforcement of a geometry in which the NH is held so as to encounter the deshielding environment of the pyrazole ring, the phenyl ring, the carbonyl, or a combination of two or more of these; such a shift is consistent with intramolecular H-bonding (see Figure 1). As the temperature is lowered, one might expect the putative CF_2H--O=C bond to cause further population of those conformations which result in the downfield shift of the NH resonance observed at room temperature. It should be noted that the CF_2H proton resonance changes less than 0.03 ppm over the temperature range studied;[15c] thus, there does not appear to be a direct inductive effect accounting for the shift in the NH resonance in **1** as such an interaction would be reciprocated.

Although the above results may point to the existence of the a CF_2H--O=C hydrogen bond, some of the properties of this putative interaction, such as strength and H--O distance, remain unclear. For example, it is doubtful that the entire ~5 kcal·mol^{-1} energy difference between the two forms of **1** can be attributed to the putative hydrogen bond. The problem may be attributed to a steric interaction (*vide supra*) or to the AM1 method, whose use has been questioned in the examination of hydrogen bonds.[21]

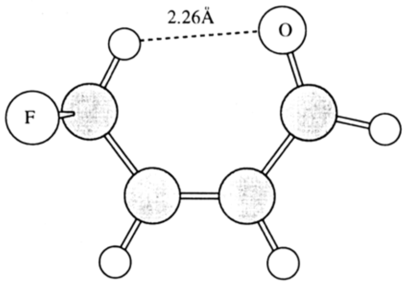


Figure 3. MP2/6-31G*//MP2/6-31G* geometry of hydrogen-bonded form of (difluoromethyl)acrolein.

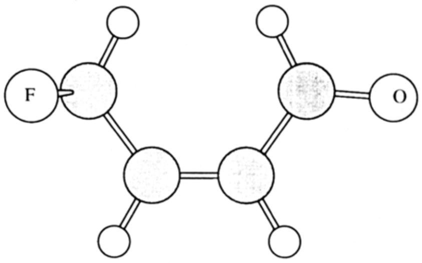


Figure 4. MP2/6-31G*//MP2/6-31G* geometry of non-hydrogen-bonded form of (difluoromethyl)acrolein.

To examine the hydrogen bond donor properties of the difluoromethyl group further, ab initio molecular orbital calculations of some model systems were carried out. As a model system, *cis*-(difluoromethyl)acrolein's geometry was optimized at the AM1 and MP2/6-31G* level in both a hydrogen-bonded and non-hydrogen-bonded form (displayed in Figures 3 and 4, respectively). Instead of changing the torsion angle of the difluoromethyl group, as was done in the pyrazole carboxamide case, the two forms here differ by a rotation about the carbonyl group. This eliminates the unfavorable interaction of the difluoromethyl group's fluorine atoms with the carbonyl oxygen, an interaction that is unavoidable in molecule **1**. The energy difference between the two forms (non-hydrogen-bonded−hydrogen bonded) of *cis*-(difluoromethyl)acrolein is listed in Table 4. The AM1 values compare very well to the MP2/6-31G* with respect to the general trends. The results show that the hydrogen-bonded form is stabilized by 0.71 kcal·mol^{-1} (0.18 kcal·mol^{-1} at the AM1 level). This indicates that the difluoromethyl group is a weak hydrogen bond donor compared to groups that do not hydrogen bond, CH_3, and strong hydrogen bond donor groups, NH_2 and OH. The CH_3 group is slightly destabilizing (−0.35 kcal·mol^{-1}) while the NH_2 and OH groups are strong donors. The H--O distance in the difluoromethyl hydrogen bond is within the range of a hydrogen bond distance; however, the distance is very close to the H--O distance in the methyl compound. This is a limitation of studying intramolecular interactions where the distances are restricted. The difference in carbonyl stretching vibrations, on the other hand, show that the non-H-bonded form is slightly lower than the H-bonded form. This may be attributed to the small difference in frequencies with respect to the error in calculating vibrational frequencies in these acrolein systems.[22]

In order to obtain a better approximation of the optimal O--H distance, some intermolecular model systems were investigated. MP2/6-31G* geometry optimizations were carried out on a series of CF_2H--O=C complexes. In order to find a local minima, a partial scan of the potential

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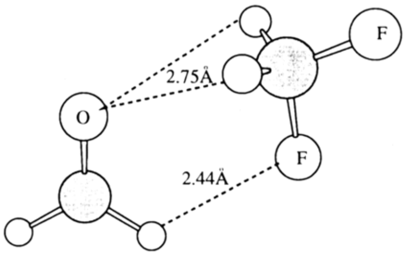

Figure 5. MP2/6-31G*//MP2/6-31G* intermolecular complex of difluoromethane and formaldehyde.

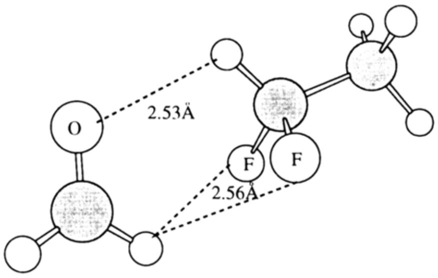

Figure 6. MP2/6-31G*//MP2/6-31G* intermolecular complex of 1,1-difluoroethane and formaldehyde.

Table 5. Results of HF/6-31G* Angle and Distance Scan of Intermolecular Complexes (The Lowest Energy Angle and Distance Values Are Shown)

complex	distance (Å)	angle (deg)
$CF_2H_2-C(O)H_2$	2.6	119.0
$CH_3CF_2H-C(O)H_2$	2.8	104.0
$CH_3CF_2H-C(O)HCH_3$	2.6	134.0
$CH_3OH-C(O)HCH_3$	2.0	119.0

energy surface was conducted by varying the H--O distance and H--O=C angle simultaneously at the HF/6-31G* level to find a starting geometry for complete minimization. The results of these scans are shown in Table 5. In general, the optimal distance was ~2.6 Å and the optimal angle was ~120°. Once optimal distances were found, full MP2/6-31G* geometry optimizations were performed. The first complex examined was difluoromethane–formaldehyde, the simplest system where a hydrogen bond between a CF_2H group and a carbonyl group is possible. The geometry of the optimized complex is displayed in Figure 5. The H--O distance is quite long for a hydrogen bond, 2.75 Å, and is equivalent for both hydrogens of the difluoromethyl group, indicating a bifurcated hydrogen bond. In addition, there is a fairly short contact between one of the formaldehyde hydrogens and a fluorine of difluoromethane. This interaction may mask the properties of the difluoromethyl group acting as a donor.

In an attempt to remove the possibility of a bifurcated hydrogen bond, the difluoroethane–formaldehyde complex was examined (Figure 6). The H--O distance is significantly reduced (to 2.53 Å) in this complex; however, an interaction between the fluorine atoms of the difluoromethyl group and the hydrogen of formaldehyde may persist as suggested by the close contact. The F--H distance is 2.56 Å between the formaldehyde hydrogen and both of the fluorine atoms, indicating an interaction between the formaldehyde hydrogen and both fluorine atoms.

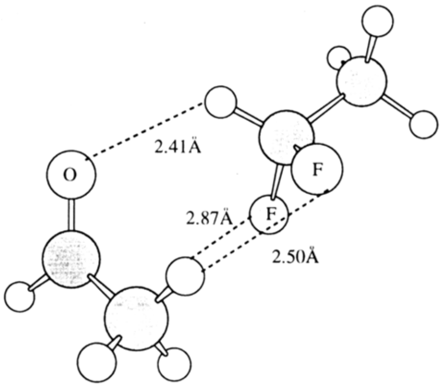

Figure 7. MP2/6-31G*//MP2/6-31G* intermolecular complex of 1,1-difluoroethane and acetaldehyde.

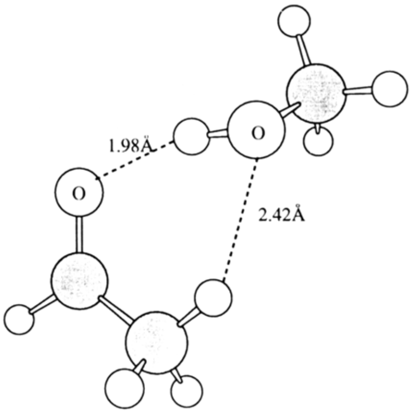

Figure 8. MP2/6-31G*//MP2/6-31G* intermolecular complex of methanol and acetaldehyde.

Table 6. MP2/6-31G*//MP2/6-31G* Binding Energies (ΔE) of Intermolecular Complexes (Values with Counterpoise Correction (CC) Are Also Listed)

complex	ΔE^a (kcal·mol^{-1})	ΔE with CC (kcal·mol^{-1})	$\Delta\nu^b$ (cm^{-1})
$CF_2H_2-C(O)H_2$	4.84 (3.84)	1.96	12.2
$CH_3CF_2H-C(O)H_2$	4.94 (4.03)	1.42	10.9
$CH_3CF_2H-C(O)HCH_3$	3.25 (2.48)	1.52	2.4
$CH_3OH-C(O)HCH_3$	8.52 (6.86)	4.58	14.9

[a] Values with zero point energies included in parentheses. [b] Carbonyl stretching frequency differences of complexes and isolated species.

To look at a complex where the CF_2H--O=C interaction is the sole hydrogen bonding event, the difluoroethane–acetaldehyde complex was examined and is shown in Figure 7. In this case, care was taken to locate a minima on the side of the methyl group of acetaldehyde, in order to eliminate any F--HC=O interaction. This complex has a H--O distance of 2.41 Å, the shortest CF_2H--O=C contact in the series. Additionally, the F--H distance to the closest methyl hydrogen is 2.5 Å, a distance longer than the CF_2H--O=C hydrogen bond. This complex appears to be a good model for the H--O distance in a hydrogen bond between a difluoromethyl and a carbonyl group. The H--O length, which is much longer than the distance in the intramolecular case, also seems reasonable for a weak hydrogen bond donor. Comparing the 2.41 Å H--O distance in the CF_2H case with the 1.98 Å distance in the methanol–acetaldehyde complex (containing the strong H-bond donor, hydroxyl, see Figure 8) emphasizes this observation.

Table 6 lists the interaction energies of the intermolecular models discussed herein. As expected,[1c] basis set superposition error has a large effect on the energies of these hydrogen-bonded complexes. For the difluoroethane–acetaldehyde case, the energy is lowered by almost 2 kcal·mol^{-1} and the methanol–acetaldehyde by almost 4 kcal·mol^{-1} by the inclusion of the counterpoise correction of Boys and Bernardi. In general, the energies of all the CF_2H complexes lie between ~1.5 and 2.0 kcal·mol^{-1}. In addition to an energy lowering upon complexation, the carbonyl stretching frequencies are lowered, consistent with the formation of a hydrogen bond.

The energies of both formaldehyde complexes are most likely clouded with interactions other than the hydrogen bond between the CF_2H group and carbonyl oxygen and, therefore, are not very informative with respect to the magnitude of the CF_2H--O=C interaction. The 1.52 kcal·mol^{-1} stabilization of the difluoroethane–acetaldehyde, on the other hand, may be a good indication of the strength of the difluoromethyl group as a hydrogen bond donor.

Conclusion

The results of this study suggest that the difluoromethyl group is able to act as a weak hydrogen bond donor. The H--O distance appears to exist at ~2.4 Å with a interaction energy of ~1 kcal·mol^{-1}. In fact, the hydrogen bond donor ability of the CF_2H group may be related to the novel activity of compound **1**, given the experimental and theoretical observations supporting the existence of a hydrogen bond in this system. More generally, the hydrogen bond donor ability exhibited by the CF_2H group makes it an interesting group with respect to the design of bioactive molecules where a hydrogen bond donor group that is more lipophilic than typical donors, such as OH and NH, is needed.

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Supplementary Material Available: Calculated structural coordinates, frequencies, and energies of all structures in Tables 2, 4, and 6 (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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