Fluoroolefins as Peptide Mimetics: A Computational Study of Structure, Charge Distribution, Hydration, and Hydrogen Bonding

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The design of peptide mimetic compounds is greatly facilitated by the identification of functionalities that can act as peptide replacements. The fluoroalkene moiety has recently been employed for that purpose. The purpose of this work is to characterize prototypical fluoroalkenes (fluoroethylene and 2-fluoro-2-butene) with respect to key properties of peptides (amides) including structure, charge distribution, hydration, and hydrogen bonding. The results are compared to those obtained for model peptides (formamide, *N*-methylacetamide). Calculations have been carried out at the MP2 and B3LYP levels of theory with the 6-311++G(2d,p) and 6-311++G(2d,2p) basis sets. The results suggest that the fluoroalkene is similar in steric requirements to a peptide bond but that there is less charge separation. Calculations of the hydration free energies with the PCM bulk continuum solvent model indicate that the fluoroalkene has much smaller hydration free energies than an amide but that the difference in solvation free energy for cis and trans isomers is comparable. In studies of complexes with water molecules, the fluoroalkene is found to engage in interactions that are analogous to backbone hydrogen-bonding interactions that govern many properties of natural peptides and proteins but with smaller interaction energies. In addition, key structural differences are noted when the fluoroalkene is playing the role of hydrogen-bond acceptor which may have implications in binding, aggregation, and conformational preferences in fluoroalkene peptidomimetics. The issue of cooperativity in hydrogen-bonding interactions in complexes with multiple waters has also been investigated. The fluoroalkene is found to exhibit cooperative effects that mirror those of the peptide but are smaller in magnitude. Thus, pairwise addivitity of interactions appears to more adequately describe the fluoroalkenes than the peptides they are intended to mimic.

Introduction

The use of compounds that mimic peptides is widespread in pure and applied research of biochemical systems. Peptidomimetics have great utility in fields ranging from medicinal chemistry to nanomaterials. For example, while peptides are attractive agents for probing structure and function of drug receptors, they have very limited potential as pharmaceutical agents themselves. They have a tendency to exhibit poor bioavailability and short physiological lifetimes. The problem lies in the fact that peptidic compounds are readily destroyed by hydrolytic enzymes such as peptidases. Thus, a common strategy is to exploit the structural diversity offered by peptides to discover lead compounds and then create non-peptide versions that mimic the peptide's structure and function. Beyond drug discovery efforts, biomimetic strategies have also been applied in areas as diverse as the development of biologically inspired nanoscale devices,[1] conformationally rigid peptide analogues designed to promote β-turns,[2] and model compounds for the study of cell membrane activity.[3]

The design of an effective peptide mimetic hinges on finding a suitable replacement for the peptide bond. One strategy that has been adopted is to simply replace the peptide bond with an alkene bond.[7,8] This is a logical approach given that the peptide bond is considered to have significant partial double-bond character as evidenced by its shorter bond distance and higher barrier to rotation (as compared to a purely single C−N bond). Replacement of a peptide bond with an alkene should produce a compound that is of roughly similar size and shape as the original peptide (the term "peptide isostere" is often used to describe such compounds). But, the electrostatic potential (distribution of charge on the molecular surface) that the mimetic presents to the intended receptor may not be well represented by the nonpolar alkene. As a result, the use of fluoroolefins has been suggested because the electronegativity of the fluorine atom is expected to create an isostere that has a more accurate representation of the electrostatic potential of the original peptide (see Figure 2). For example, Bartlett has investigated the effectiveness of fluoroalkenes as inhibitors of thermolysin,[9] and Welch and co-workers employed fluoroolefin peptide mimetics in the inhibition of the dipeptidyl peptidase IV enzyme (DPP IV) and the cyclophilin enzyme.[10] Ceiplak and co-workers investigated the effectiveness of both olefins and fluoroolefins as inhibitors of the HIV-1 protease enzyme.[11] Miller and co-workers have employed olefin isosteres as mechanistic probes in the development of peptide-based enantioselective catalysts.[7] There has also been a great deal of work directed toward the synthesis[9,10,12−14] of biologically active fluoroalkenes which is further evidence of their potential as mechanistic probes and therapeutic agents.

Computational Methods

Complete geometry optimizations were carried out with the 6-311+G(2d,p) basis set at the MP2[15] and B3LYP [16,17] levels

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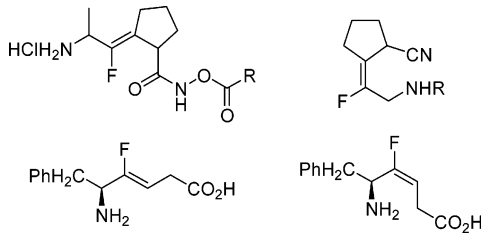

Figure 1. Examples of fluoroolefin peptide mimetics. The structure on the top-left represents compounds previously studied by Welch[4] and co-workers and the one on the top-right has been investigated by Augustyns and co-workers.[5] The bottom structures have been investigated by Niida et al.[6]

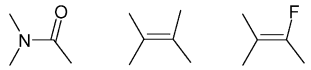

Figure 2. Peptide and olefin and fluoroolefin mimetics. Olefin and fluoroolefin peptide mimetics have been used in the study of several important biochemical and biological systems.

of theory for the cis and trans isomers of *N*-methylacetamide (NMA) and 2-fluoro-2-butene (FB) using the Gaussian03[18] program. Input structures were built with the GaussView program. All possible methyl rotamers were considered with the minimum-energy ones used to evaluate the cis−trans energy differences, hydration free energies, and partial atomic charges. Atomic charges were calculated via fits to electrostatic potentials (CHELPG),[19] with Mulliken[20] population analysis and with the generalized atomic polar tensor[21] schemes as implemented in Gaussian03 (results of the latter two provided in Supporting Information). To allow for comparison with more computationally efficient methods, calculations were also carried out at the semiempirical levels with the AM1[22] and PM3[23] Hamiltonians and at the molecular mechanics level with the MMFF[24−28] force field as implemented in the Spartan02[29] program package. Hydration free energies were calculated by subtracting the gas-phase result from that obtained with the IEF-PCI[30−32] continuum aqueous solvent model as described in the Gaussian03 documentation.[18]

Calculations on the hydrogen-bonded complexes of fluoroethylene−water (FEW) and 2-fluoro-2-butene−water (FBW) employed complete geometry optimization at the MP2/6-311++G(2d,2p) level of theory to allow for a direct comparison with Langley and Allinger's[33] previously reported results for formamide−water (FAW) complexes and *N*-methylacetamide−water (NMAW) complexes at that level. To aid in locating stationary points on the intermolecular potential energy surfaces for the hydrogen-bonded complexes of FE and FB, we often first conducted the optimization for the corresponding FA and NMA complex (thus reproducing large portions of Langley and Allinger's previous study) and then graphically edited the amide species into a fluoroalkene, with subsequent reoptimization. There were isolated instances where the minimum located in this work was slightly lower in energy than that reported by Langley and Allinger. In addition, complete geometry optimizations employing the B3LYP[17,34] hybrid functional were carried out also with the 6-311++G(2d,2p) basis set. All minima were fully characterized as such by frequency calculations. Binding energies (ΔE) were obtained by subtracting the energies of the fully optimized monomers from that of the complexes. Zero-point vibrational corrections and thermal corrections were applied to generate enthalpy differences (ΔH) at 298 K with the standard methods in Gaussian03.[18] Binding energies were corrected for basis set superposition error (BSSE) with the counterpoise (CP) method of Boys and Bernardi[35] with geometry optimization[36] (i.e., previously optimized structures of the complexes were reoptimized with the counterpoise keyword in Gaussian03). These reoptimizations resulted in minimal changes in geometry and in the magnitude of the counterpoise correction.

Our choice of methods for use in the study of the fluoroalkene−water complexes was motivated by a desire to provide data that could be directly compared with that which exists in the literature for amide−water complexes (Langley and Allingers' MP2/6-311++G(2d,2p) study[33]) and to strike an appropriate balance between accuracy and computational efficiency. The latter is important here because, while the systems under study are not particularly large, the weak nature of the interactions presents certain technical difficulties. For example, in some cases, it was difficult to locate minima along the potential energy surface resulting in the need for the consideration of many input configurations. And, because of the shallow nature of the minima, many steps were often required for convergence. Also, there is enough data in the literature to evaluate the performance of this method for closely related systems. For example, Vargas et al. conducted a very thorough study of the homodimer complexes of formamide and *N*-methylacetamide.[37] A series of five formamide dimer complexes were optimized at the MP2/aug-cc-pVDZ and MP2/aug-cc-pVTZ levels. Binding energies were evaluated at the MP2/aug-cc-pVXZ levels for X = D, T, and Q with extrapolation to the complete basis set (CBS) limit. Results at the B3LYP/6-311++G(2d,2p) level for the same formamide dimer complexes were recently reported by Lu et al.[38] Also, Langley and Allinger considered four of these formamide dimers in their MP2/6-311++G(2d,2p) study. Comparison of the results reported in these three studies on the same system allows for trends to be identified. Both MP2/6-311++G(2d,2p) and B3LYP/6-311++G-(2d,2p) give reasonable results with the highest levels of theory (the extrapolated MP2/CBS results of Vargas et al.). The counterpoise-corrected binding energies obtained with B3LYP and MP2 (with the 6-311++G(2d,2p) basis set) are consistently smaller in magnitude than the MP2/CBS (extrapolated) results of Vargas et al. by an average of 0.97 kcal/mol for MP2 and 1.43 kcal/mol for B3LYP, which corresponds to average percent deviations of 8.87% and 17.26%, respectively. If no correction for BSSE is applied to the MP2 and B3LYP results with 6-311++G(2d,2p), then there is actually better agreement with the MP2/CBS values. Uncorrected B3LYP/6-311++G(2d,2p) values consistently underestimate the magnitude of the MP2/CBS interaction energies by an average of 1.09 kcal/mol (13.92%). This tendency of B3LYP to underestimate hydrogen-bond strengths, relative to MP2 (and coupled-cluster methods), has been noted in the literature[39] (although the water dimer is a notable exception).[40] However, much better agreement is seen if uncorrected MP2/6-311++G(2d,2p) ΔE values are compared to the MP2/CBS results. The uncorrected MP2/6-311++G(2d,-2p) binding energies are consistently slightly larger in magnitude (more favorable interactions) than the MP2/CBS values by an average of only 0.34 kcal/mol (3.28%). We have reported binding energies both with and without corrections for BSSE in this work. On the basis of the formamide results, we expect the uncorrected MP2/6-311++G(2d,2p) results to be an accurate indicator of the complexation energies (relative to MP2/CBS) and the uncorrected B3LYP/6-311++G(2d,2p) to consistently underestimate the hydrogen-bond energies by 10−15%.

During the final stages of writing this paper, a very interesting study was published by Dannenberg[41] of the enthalpy of hydration of NMA by one, two, and three waters. This work employed the B3LYP/D95++(d,p) level of theory, and the results are very comparable to the B3LYP NMA hydration

TABLE 1: Selected Calculated[a] Distances[b] for *N*-Methylacetamide (NMA) and 2-Fluoro-2-butene (FB)

	N−C (in NMA) C═C (in FB)		C═O (in NMA) C−F (in FB)		$CH_3\cdots CH_3$	
	MP2	B3LYP	MP2	B3LYP	MP2	B3LYP
trans NMA	1.361	1.365	1.227	1.220	3.802	3.819
trans FB	1.332	1.325	1.365	1.369	3.930	3.934
cis NMA	1.366	1.367	1.227	1.221	2.886	2.932
cis FB	1.332	1.325	1.368	1.371	3.191	3.206

[a] 6-311++G(2d,p) basis set employed. [b] In angstrom units.

TABLE 2: MP2/6-311++G(2d,p) CHELPG Charges for Selected Atoms in NMA and FB

	C═**O** (NMA) C−**F** (FB)	**C**═O **C**−F	C−**N** C═**C**	N−**H** C−**H**
trans NMA	−0.731	1.015	−0.746	0.182
trans FB	−0.519	0.554	−0.145	0.028
cis NMA	−0.796	1.076	−0.742	0.176
cis FB	−0.562	0.589	−0.152	0.042

results that will be reported in this work (vide infra). The Dannenberg study has an advantage over the Allinger and Langley work for our purposes in that it addresses the issue of cooperativity. Thus, the current work will present a set of results regarding the cooperativity of hydrogen bonding to fluoroalkenes that parallels the Dannenberg study of NMA.

Results

Comparison of Fluoroolefin and Amide Moieties. As an initial evaluation of the suitability of the fluoroolefin moiety to mimic a peptide we present here a comparison of the geometries, charge distribution, hydration free energies, and cis−trans energy differences for the very simple model compounds *N*-methylacetamide (NMA) and 2-fluoro-2-butene (FB). The results are presented in Tables 1−4.

Geometries. Table 1 presents a comparison of the geometries of NMA and FB as calculated at the MP2 and B3LYP levels of theory with the 6-311++g(2d,p) basis set. Comparisons between the calculated and experimental geometries for NMA and FB will not be presented here because numerous such comparisons can be found in the literature for NMA[42−45] and we have not been able to locate appropriate experimental structural data for FB. The focus here is to compare the geometrical parameters of the fluoroolefin moiety with those of a peptide fragment to evaluate the steric characteristics of the two. The results indicate that, while the C═C bond of FB is shorter than the corresponding C−N bond of NMA, and the C−F bond is longer than the C═O bond, the overall dimensions of the flouroolefin moiety are reasonably similar to the peptide. The methyl-to-methyl distance is slightly longer in FB than in NMA, in both the cis and trans isomers (by ca. 0.3 Å in the cis and 0.1 Å in the trans). This could possibly affect conformational properties of a long-chain system if a fluoroolefin for peptide substitution was carried out. It also interesting to note that there is a bigger difference in the methyl-to-methyl distance between the trans and cis isomers for NMA than for FB. The same trends are observed with both MP2 and B3LYP, and the results presented here are consistent with previous quantum mechanical studies of NMA[43−47] and FB.[48]

Charges. Table 2 presents a comparison of the charges derived from fits to electrostatic potential using the CHELPG[19] formalism as implemented in Gaussian03 for the key atoms of interest in the amide NMA and the model fluoroolefin peptide mimetic FB. Charges derived from standard Mulliken population analysis[20] and generalized atomic polar tensor population analysis[21] have also been determined and may be found in the Supporting Information.

TABLE 3: Calculated Cis−Trans Energy Differences[a] for Peptide NMA and Peptide Mimetic FB

method	ΔE_{NMA}	ΔE_{FB}
MMFF	1.93	0.95
AM1	0.16	0.90
PM3	−0.45	−0.22
B3LYP/6-31+G(d)	2.30 (2.29)	1.30 (1.28)
B3LYP/6-311++G(2d,p)	2.42 (2.48)	1.30 (1.26)
HF/6-31+G(d)	2.61 (2.28)	1.62 (1.58)
MP2/6-311++G(2d,p)	2.33 (2.34)	1.36 (1.26)
experimental ΔH[b]	2.3	

[a] In kcal/mol, defined as $E_{trans} - E_{cis}$. For AM1 and PM3, differences in the heats of formation are reported. For ab initio and DFT methods, the values in parentheses are the enthalpy differences at 298 K. [b] From experimental gas-phase IR study.[49]

We are particularly interested in comparing the charge on the atoms of NMA that participate in hydrogen bonding (i.e., the carbonyl oxygen and amide hydrogen) with the corresponding atoms in FB (the fluorine and vinylic hydrogen) as these play a key role in determining the conformational properties of peptides. All three sets of charges depict the oxygen of NMA as bearing a larger negative charge than the fluorine of FB and the amide hydrogen of NMA as more positive than the vinylic hydrogen of FB. This is true for both the cis and trans isomers and suggests that FB should be much less effective in hydrogen-bonding interactions than NMA. In fact, it begs the question as to whether FB should engage in hydrogen bonding at all. This question is addressed in detail in subsequent sections. The fluorine of FB possesses a CHELPG charge of −0.519 as compared to the value of −0.731 on the NMA oxygen. However, the vinylic hydrogen's charge is only positive by a slight amount (0.028 for the trans isomer and 0.042 for the cis).

Cis/Trans Energy Differences and Hydration Free Energy. Table 3 contains the cis−trans energy differences in the gas phase for the model peptide (ΔE_{NMA}) and fluoroolefin mimic (ΔE_{FB}) at a variety of computational levels. For NMA, the ab initio and density functional methods produce ΔE_{NMA} values that range from 2.30 to 2.61 kcal/mol and ΔH values that range from 2.29 to 2.48 kcal/mol. These results are in very good agreement with numerous quantum mechanical results that have been previously reported in the literature for NMA. For example, Jorgensen and Gao[43] reported a value of 2.15 kcal/mol at HF/6-31G(d) in 1988. More recently, Kang reported values ranging from 2.19 to 2.83 kcal/mol with basis sets ranging from 6-31G(d) to 6-311++G(d,p) at the Hartree−Fock, MP2, and B3LYP levels of theory.[44] These are also representative of the DFT values reported by Martinez et al.[45] and Avalos et al.[46] (2.52 kcal/mol at B3LYP/6-311++G(d,p), for example).

The ΔH values obtained with B3LYP and MP2 with the 6-311++G(2d,p) basis set (2.36 and 2.34 kcal/mol, respectively) are in very good agreement with the experimental ΔH estimate of 2.3 kcal/mol.[49] For FB, the trans isomer is found to be lower in energy than the cis by 1.30 kcal/mol with B3LYP and by 1.36 kcal/mol at MP2/6-311++G(2d,p). Our searches of the literature have not revealed an experimental value for ΔE_{FB}. The results reported here are in accord with the computational study of FB reported by Kanakaraju and Kolandaivel.[48] We are very interested in the performance of more approximate molecular modeling methods in describing the fluoroolefin moiety as these methods are much more amenable to the study of larger systems and the evaluation of large numbers of conformations. This is certainly desirable with the flurolefin class of compounds given their potential as peptide replacements. The

TABLE 4: Calculated[a] Hydration Free Energies (ΔG_{Hyd}) and Relative Hydration Free Energies[b] ($\Delta\Delta G_{Hyd}$) for the Model Peptide NMA and Peptide Mimetic FB

	peptide				mimetic			
	cis NMA		trans NMA		cis FB		trans FB	
	MP2	B3LYP	MP2	B3LYP	MP2	B3LYP	MP2	B3LYP
ΔG_{Hyd}	−9.29	−9.62	−9.10	−9.06	−2.38	−2.41	−2.05	−2.09
$\Delta\Delta G_{Hyd}$	−0.19	−0.56			−0.33	−0.32		

[a] Calculated as the total energy in the aqueous phase minus the total energy of the gas phase. Single-point calculations were carried out at the gas-phase geometry. The IEF-PCI continuum solvent model for water, with the 6-311++G(2d,p) basis set, and the indicated level of theory (MP2 or B3LYP), was employed, in kcal/mol. [b] Calculated as the ΔG_{Hyd} value for the cis isomer minus the ΔG_{Hyd} value for trans isomer, in kcal/mol.

MMFF[24−28] force field reproduces the general trends that are seen with the higher level ab initio and density functional methods with ΔE_{NMA} and ΔE_{FB} values of 1.93 and 0.95 kcal/mol, respectively. This is better agreement than that which has been reported for NMA with the MMX (as implemented in PCModel) force field where a value of 0.66 kcal/mol has been obtained.[45] Unfortunately, the semiempirical methods investigated here did not provide such encouraging results. AM1 produces a reasonable value for ΔE_{FB} but significantly underestimates the ΔE_{NMA} value (a problem that has been previously noted),[45] thus resulting in the incorrect qualitative ordering for ΔE_{NMA} and ΔE_{FB}. PM3 incorrectly predicts the cis isomer to be more stable than trans for both NMA and FB.

The hydration free energies of both isomers of NMA and FB are presented in Table 4. It is well documented that the cis−trans equilibrium for NMA exhibits a negligible aqueous solvent effect indicating that the cis and trans isomers are equally well solvated. Avbelj et al.[50] have reported an experimental value of −10.07 kcal/mol for the aqueous solvation free energy of NMA (and −17.07 kcal/mol for the enthalpy of solvation). Wolfenden's earlier experimental work established that the hydration free energy for NMA is approximately −10 kcal/mol and that the values for the cis and trans isomers differ by less than 0.1 kcal/mol.[51−53] This result has important implications in protein structure and function. If the position of the cis−trans equilibrium for a peptide bond was highly dependent on the solvent medium, then it should follow that the population of cis and trans peptide bonds found in proteins might be very different at the surface of a globular protein and in its interior. Obviously, this is not the case as trans peptide bonds predominate in both environments; a fact that is easily explained given the lack of a solvent effect on the cis−trans equilibrium for NMA. For a fluoroolefin, the presence of a true π bond makes rapid interconversion and a resulting equilibrium mixture of cis and trans isomers under physiological conditions not a matter of concern. Thus, in the case of FB, we are not interested in the relative hydration of the two isomers because of an expected solvent effect on the equilibrium distribution of cis and trans, but because fluoroolefin peptide mimetics of both isomers have been investigated as therapeutic agents and this parameter provides a useful benchmark.[54] For example, in the case of DPP IV inhibitors, the natural substrate of the target enzyme contains a proline and thus cis peptide bonds play a major role. Also, from a purely physical organic chemistry standpoint, it is interesting to establish how many of the hallmark properties the fluoroolefin moiety shares with the peptide bond it is intended to mimic.

Given the lack of experimental data for the FB hydration free energies, we will evaluate the PCM water solvent model by examining the results for NMA. PCM gives good agreement with the experimental values cited above for NMA with either the MP2 or B3LYP levels of theory. It does predict the cis isomer to be slightly better solvated than the trans; but, at least with MP2, the difference of 0.19 kcal/mol is only just beyond the 0.1 kcal/mol limit suggested by Wolfenden.[51] With B3LYP, the cis isomer is calculated to be better solvated by a larger margin of 0.56 kcal/mol. For FB, the absolute values of the hydration free energies are much smaller than those of NMA. This is to be expected. NMA has a rather large hydration free energy compared with other common small neutral molecules, and one would certainly expect FB to be the more lipophilic of the two. For FB, with the PCM water model, the cis isomer is calculated to be better solvated as was the case for NMA. But, again, the difference is very small (∼0.3 kcal/mol). Also, the MP2 and B3LYP results are in very good agreement with each other. Thus, while FB does not enjoy interactions with surrounding water that are nearly as favorable as those of an actual peptide bond, it is interesting to see that the *relative* hydration free energies of the two isomers of FB do mirror those of the peptide.

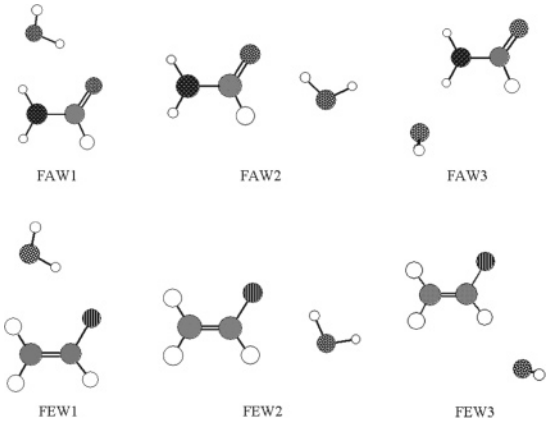

Figure 3. MP2/6-311++G(2d,2p)-calculated geometries of formamide−water (FAW) and fluoroelthylene−water (FEW) complexes. The FAW complexes were originally reported by Langley and Allinger.[33]

Hydrogen-Bonded Complexes. Formamide−Water (FAW) and Fluoroethylene−Water (FEW). In addition to bulk solvation phenomena, we are interested in evaluating the extent to which specific local intermolecular interactions of a peptide are mimicked by a fluoroalkene. For this reason, we have investigated a variety of hydrated complexes. The MP2/6-311++G(2d,2p) optimized structures of the monohydrated complexes of fluoroethylene are compared to the corresponding formamide−water complexes in Figure 3. The key geometrical parameters are reported in Tables 5 and 6. Nearly identical structures were obtained with B3LYP/6-311++G(2d,2p) (not shown). The binding energies for these complexes are presented in Table 7.

In the FAW/FEW systems, the fluoroalkene mimic engages in interactions that are structurally very similar to those of the amide. In all cases, the nonbonded distances are larger for the FEW structures than the corresponding FAW complexes, which is consistent with the weaker interactions in the former. Also, the MP2/6-311++G(2d,2p) nonbonded distances tend to be shorter than the B3LYP values. Structure FEW1 is a cyclic hydrogen-bonded complex that is analogous to FAW1. The water in this structure tilts out of the plane of the fluoroalkene in a manner similar to that seen for the FAW1 structure. The other structures exhibit nearly C_s symmetry (although the optimizations were carried out without symmetry constraints). Our initial optimization of structures FAW2 and FEW2 with

TABLE 5: Calculated Hydrogen-Bonding Geometries[a] in Formamide−Water Complexes

		C═O···H−O interaction				N−H···O interaction			
structure[b]	method[c]	O···H	C═O···H	O···H−O	O···O	H···O	N−H···O	H···O−H	N···O
FAW1	MP2[d]	1.902	106.7	151.1	2.792	2.050	137.4	80.4	2.876
	B3LYP	1.908	107.7	150.8	2.800	2.080	137.3	80.0	2.909
FAW2	MP2	1.907	99.9	156.1	2.820				
	B3LYP	1.901	105.5	160.0	2.834				
FAW3	MP2					2.006	178.0	73.6	3.012
	B3LYP					2.037	178.3	124.1	3.046

[a] Distances are in angstroms, and angles are in degrees. [b] Refer to Figure 3. [c] With the 6-311++G(2d,2p) basis set. [d] Originally reported by Langley and Allinger.[33]

TABLE 6: Calculated Hydrogen-Bonding Geometries[a] in Fluoroethylene−Water Complexes

		C−F···H−O interaction				C−H···O interaction			
structure[b]	method[c]	F···H	C−F···H	F···H−O	F···O	H···O	C−H···O	H···O−H	C···O
FEW1	MP2	2.073	113.9	151.1	2.962	2.487	134.4	74.8	3.331
	B3LYP	2.117	115.7	152.5	3.005	2.587	134.0	74.0	3.427
FEW2	MP2	2.133	102.0	133.4	2.879				
	B3LYP	2.187	103.5	133.4	2.933				
FEW3	MP2					2.319	179.2	119.3	3.398
	B3LYP					2.366	179.1	118.9	3.447

[a] Distances are in angstroms, and angles are in degrees. [b] Refer to Figure 3. [c] With the 6-311++G(2d,2p) basis set.

TABLE 7: Calculated Binding Energies[a−c] (ΔE) for Formamide−Water (FAW) and Fluoroethylene−Water (FEW) Complexes

	FAW1	FAW2	FAW3
MP2[d]	−9.94	−7.00	−5.57
MP2(CP)	−8.52	−5.99	−4.77
B3LYP	−8.82	−6.14	−4.82
B3LYP(CP)	−8.45	−5.89	−4.56
	FEW1	FEW2	FEW3
MP2	−3.67	−3.64	−2.56
MP2(CP)	−2.94	−2.94	−2.03
B3LYP	−2.60	−2.58	−1.93
B3LYP(CP)	−2.38	−2.36	−1.70

[a] In kcal/mol. [b] With the 6-311++G(2d,2p) basis set. [c] See Figure 3. [d] MP2 results for the FAW complexes originally reported by Langley and Allinger.[33]

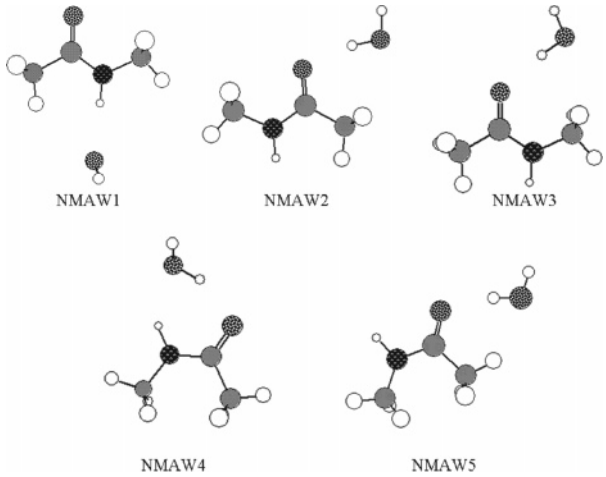

Figure 4. MP2/6-311++G(2d,2p)-calculated geometries of *N*-methylacetamide−water (NMAW) complexes (originally reported by Langley and Allinger[33]).

B3LYP led to stationary points that exhibited one imaginary frequency involving out-of-plane rocking of the water. The water was tilted slightly out of plane and the complex reoptimized to produce mimina with slightly tilted water that were lower in energy by a negligible amount (on the order of 0.01 kcal/mol). FEW2 exhibits a hydrogen-bonding pattern that is analogous to FAW2. The greatest difference between the amide and mimic structures is seen for FEW3. Upon optimization, the water migrated away from the H attached the unsubstituted alkene carbon to the hydrogen on the fluorine-bearing carbon.

Presumably, this is simply a manifestation of the inductive effect of fluorine on C−H acidity (partial charge). It is possible, therefore, that replacement of a peptide with a fluoroalkene may have an impact on conformational and/or binding properties if the N−H group of the peptide plays a key role in the interaction of interest.

Inspection of Table 7 reveals that the binding energies for the fluoroalkene mimic are much weaker than those obtained for the formamide−water system. Also, as is seen with the formamide dimers,[38,55] at a given basis set, the B3LYP binding energies are consistently smaller than the MP2 values.

It is interesting to note that the preference for a cyclic structure is largely diminished in the FEW system. With MP2, the binding energy for FAW1 is −9.94 kcal/mol, but it is only −3.67 kcal/mol for FEW1. The similarity of the FEW1 and FEW2 binding energies (−3.67 and −3.64 kcal/mol, respectively) suggests the relative unimportance of the hydrogen on the unsubstituted carbon atom on fluoroethylene in the binding of water in this structure. For the formamide−water system, the binding energy of the cyclic FAW1 structure is 2.94 kcal/mol greater than that of FAW2 (which contains the O−H···O interaction but lacks the N−H···O interaction). The distance relationships in Tables 5 and 6 are consistent with this trend as well. The water in FEW1 is closer to the fluorine atom (and more distant from the C−H group) than is the case in FAW1 where the water is more centrally located above the amide bond.

***N*-Methylacetamide−Water (NMAW) and 2-Fluoro-2-butene−Water (FBW).** Figure 4 contains the set of the *N*-methylacetamide-water complexes that have been investigated previously at the MP2/6-311++G(2d,2p) level by others[33] and with B3LYP/6-311++G(2d,2p) in this work. Figure 5 shows the MP2/6-311++G(2d,2p) optimized structures of the fluorobutene−water (FBW) system that have been identified in this work. For brevity, only the MP2 structures are depicted in the figures, but in all cases, very similar structures are obtained at the B3LYP/6-311++G(2d,2p) level. Specific structural features

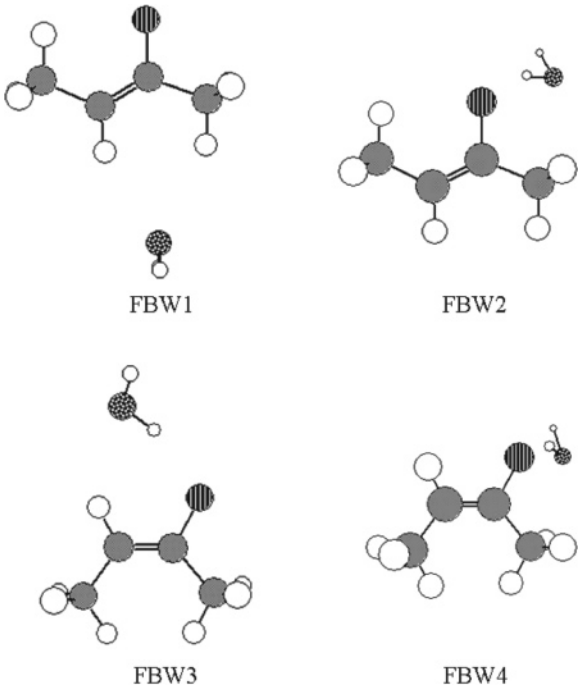

Figure 5. MP2/6-311++G(2d,2p)-calculated geometries of 2-fluoro-2-butene−water (FBW) complexes.

are provided in Tables 8 and 9, and the binding energies are shown in Tables 10 and 11.

Our MP2/6-311++G(2d,2p) studies of the five NMAW complexes largely reproduce the work that has been previously reported by Langley and Allinger.[33] There are some minor differences. The binding energies we obtained for structures NMAW1 and NMAW2 are slightly larger than those reported previously by 0.47 and 0.01 kcal/mol, respectively. The B3LYP/6-311++G(2d,2p) binding energies are consistently smaller (by a factor of roughly 0.8) than the MP2 results with this basis set. This is consistent with what has been seen in this work for the formamide−water system and what has been reported in the literature for the formamide−dimer system.[38,55] For all of the NMAW complexes, the water oxygen lies in a nearly coplanar position relative to NMA.

The hydrogen-bond distances for O···H−C and F···H−O interactions of the FBW complexes are longer than those seen for the more conventional O···H−O and O···H−N interactions with the NMAW system. Only four minima were identified for the FBW system. For the NMAW system, there are two discrete minima with water hydrogen bonded to the carbonyl oxygen (NMAW2 and NMAW3). However, for the fluoroalkene, optimizations starting with either of these types of input geometries led to the FBW2 structure. In this structure, the water is skewed out of the plane of the FB but is closer to the methyl carbon than the sp^2 carbon (i.e., FBW2 is more like NMAW2 than NMAW3). The $CH_3-C-F\cdots O$(water) dihedral angle is 52.9°. A similar result is seen for the cis fluoroalkene complex FBW4 where the water is also oriented to the side of the alkene rather than in the plane. Here, the $CH_3-C-F\cdots O$(water) dihedral angle is 54.7°. Structures FBW1 and FBW3 exhibit geometries that are a good reflection of their counterparts in the NMAW system (NMAW1 and NMAW4). Although, there is a slight difference in the orientation of the water in the NMAW1 and FBW1 structures with the former being more consistent with an O···H−N hydrogen bond and the latter more consistent with a dipole−dipole arrangement. But, there are very clear differences seen for the complexes involving fluorine as a hydrogen-bond acceptor (FBW2 and FBW4) relative to their amide counterparts (NMAW2, NMAW3, NMAW5). This suggests that peptide replacement by a fluoroalkene could result in differences in conformational preferences, binding affinities, aggregation tendencies, and other events where this interaction plays a key role.

As expected, the interaction energies for the FBW complexes are weaker than those for the NMAW complexes. With MP2/6-311++G(2d,2p), the uncorrected and counterpoise-corrected binding energies for the water dimer are −5.36 and −4.44 kcal/mol, respectively. This provides a useful benchmark for evaluating the relative strengths of hydrogen bonds. Thus, the interactions between water and the fluoroalkene are weaker than those between two waters. However, the binding energies are sizable enough to suggest that the fluoroalkene, when employed as a peptide replacement, could engage in specific intermolecular interactions that are similar to those of an amide (given the caveat of the geometrical perturbations that are described above). For the fluoroalkene, the greatest binding energies are obtained for complexes where fluorine is acting as a hydrogen-bond acceptor, FBW4, FBW2, and FBW3 with MP2 values of −4.30, −4.11, and −4.10 kcal/mol, respectively.

Figure 6 contains the B3LYP/6-311++G(2d,2p) optimized structures of the complexes of two waters with *N*-methylacetamide (NMAW6, NMAW7) and fluorobutene (FBW5, FBW6). Very similar structures were obtained with MP2/6-311++G(2d,2p) except in the case of FBW5, where a minimum with at the MP2 level was not found (the water beneath the alkene (as depicted in Figure 6) migrated to a hydrogen bond to the other water upon optimization). Two binding motifs have been explored. NMAW6 includes hydrogen-bond donation from water to the carbonyl oxygen and donation from the amide NH to water. FBW5 is the fluoroalkene analogue to this arrangement. In NMAW7, both waters are donating hydrogen bonds to the carbonyl oxygen and FBW6 is the analogous fluoroalkene structure.

Once again, there are clear structural differences between the peptide and the fluoroalkene mimic when fluorine is the hydrogen-bond acceptor. The NMAW6 complex does not have strict C_s symmetry but both water oxygens are nearly in the same plane as the heavy atoms of the NMA molecule. However, in FBW5, the water interacting with the fluorine is clearly out of plane in a manner similar to that discussed above for structures FBW2 and FBW4. This effect carries over in a very interesting manner for complex FBW6 where both water molecules are interacting with the fluorine. In the amide version of this complex (NMAW7), a complex of approximately C_s symmetry is obtained. But, in FBW6, the waters are oriented out of plane and nearly 180° with respect to each other. The $CH_3-C-F\cdots O$(water) dihedral angles involving the two waters are −53.6° and 120.8°. Also, the water oxygens are nearly collinear with the fluorine atom with an O···F···O angle of 155.1°. These structural differences in the optimal configuration for interactions with nearby groups could certainly impact binding affinities to an enzyme active site or receptor binding site for a fluoroalkene peptide mimetic if hydrogen bonding to the peptide backbone is important.

The calculations on complexes with multiple waters allows for an investigation of the issues pertaining to cooperativity in binding to the peptide and the fluoroalkene mimic. Thus, we are in a position to evaluate the extent to which the binding energies of the complexes with multiple waters are predicted by simply summing binding energies of the component interactions. Cooperativity, or nonadditivity of pairwise interactions,

TABLE 8: Calculated Hydrogen-Bonding Geometries[a] in *N*-Methylacetamide−Water (NMAW) Complexes

		C═O···H−O interaction				N−H···O interaction			
structure[b]	method[c]	O···H	C═O···H	O···H−O	O···O	H···O	N−H···O	H···O−H	N···O
NMAW1	MP2[d]					2.023	179.8	124.9	3.029
	B3LYP					2.084	176.8	126.2	3.090
NMAW2	MP2	1.856	111.2	166.5	2.810				
	B3LYP	1.861	116.1	168.8	2.824	2.824	2.824	2.824	2.824
NMAW3	MP2	1.870	133.9	174.3	2.837				
	B3LYP	1.879	135.5	174.8	2.849	2.849	2.849	2.849	2.849
NMAW4	MP2	1.850	104.0	154.0	2.759	2.034	143.1	76.0	2.908
	B3LYP	1.849	110.7	154.5	2.765	2.082	143.2	74.8	2.957
NMAW5	MP2	1.855	115.2	166.5	2.808				
	B3LYP	1.858	118.0	167.6	2.818	2.818	2.818	2.818	2.818

[a] Distances are in angstroms, and angles are in degrees. [b] Refer to Figure 4. [c] With the 6-311++G(2d,2p) basis set. [d] Structures with C_s symmetry were originally reported by Langley and Allinger.[33] See text for description of the slight differences seen in this work for these structures that are very nearly C_s.

TABLE 9: Calculated Hydrogen-Bonding Geometries[a] in 2-Fluoro-2-butene−Water (FBW) Complexes

		C−F···H−O interaction				C−H···O interaction			
structure[b]	method[c]	F···H	C−F···H	F···H−O	F···O	H···O[d]	C−H···O	H···O−H	C···O
FBW1	MP2					2.536/2.592	155.1	122.0	3.545
	B3LYP					2.717/2.679	155.3	122.0	3.690
FBW2	MP2	2.014	108.7	156.7	2.921				
	B3LYP	2.044	117.3	161.8	2.975	2.975	2.975	2.975	2.975
FBW3	MP2	2.016	116.9	160.2	2.939	2.531	139.8	66.6	3.429
	B3LYP	2.044	120.8	163.9	2.982	2.736	138.8	61.8	3.622
FBW4	MP2	2.010	108.1	156.2	2.915				
	B3LYP	2.034	116.4	160.8	2.962				

[a] Distances are in angstroms, and angles are in degrees. [b] Refer to Figure 5. [c] With the 6-311++G(2d,2p) basis set. [d] Distance to vinylic hydrogen/distance to methyl hydrogen.

TABLE 10: Calculated Binding Energies[a] (ΔE) for *N*-Methylacetamide−Water (NMAW) Complexes[b]

	NMAW1	NMAW2	NMAW3	NMAW4	NMAW5
MP2	−5.67	−8.27	−8.25	−10.62	−8.15
MP2(CP)	−4.75	−7.07	−7.03	−8.99	−6.99
B3LYP	−4.28	−7.07	−6.92	−9.31	−7.14
B3LYP(CP)	−3.98	−6.76	−6.59	−8.91	−6.85

[a] In kcal/mol. With the 6-311++G(2d,2p) basis set. [b] Refer to Figure 4.

TABLE 11: Calculated Binding Energies[a] (ΔE) for 2-Fluoro-2-butene−Water (FBW) Complexes[b]

	FBW1	FBW2	FBW3	FBW4
MP2	−2.42	−4.11	−4.10	−4.30
MP2(CP)	−1.82	−3.17	−3.20	−3.36
B3LYP	−1.37	−2.80	−2.99	−3.05
B3LYP(CP)	−1.16	−2.57	−2.70	−2.75

[a] In kcal/mol. With the 6-311++G(2d,2p) basis set. [b] Refer to Figure 5.

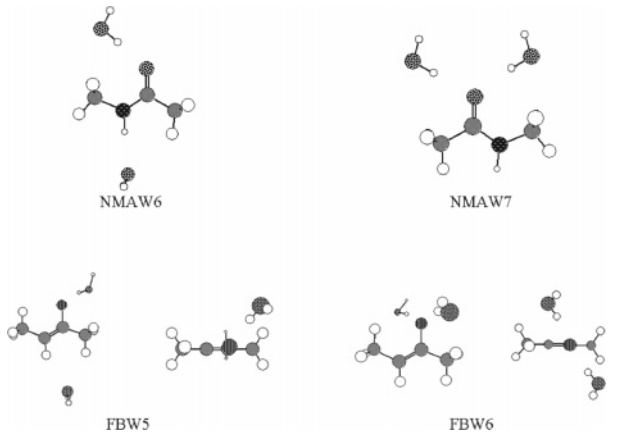

Figure 6. B3LYP/6-311++G(2d,2p)-calculated geometries of dihydrate complexes of *N*-methylacetamide (NMAW6, NMAW7) and 2-fluoro-2-butene−water (FBW5 and FBW6). Two views are shown for FBW5 and FBW6. Atom sizes are scaled to provide depth perspective.

has been the focus of several studies of hydrogen bonding in peptides[41,56−60] and other systems.[61,62] Here, we extend those studies to the fluoroalkene peptide mimetic. Table 12 contains the binding energies for the formation of the complexes NMAW6 and FBW5 as well as the corresponding additive prediction that results from summing the binding energies for the formation of the component interactions (NMAW1 + NMAW2 and FBW1 + FBW2). For the amide, the MP2/6-311++G(2d,2p) binding energy for the formation of the dihydrate complex NMAW6 from one NMA and two waters is −14.48 kcal/mol (−12.26 kcal/mol after counterpoise corrections). The sum of the binding energies of the component hydrogen bonds at this level is −5.67 + −8.27 = −13.94 kcal/mol. Thus, the NMAW6 complex is more stable, by 0.54 kcal/mol, than the additive prediction. This is expressed in Table 12 as a cooperative effect of −0.54 (−0.44 kcal/mol including counterpoise corrections). The same analysis was reported for the same system by Guo and Karplus at the HF/6-31G level of theory in 1992.[58] They reported a cooperative effect of −0.7 kcal/mol. The B3LYP/6-311++G(2d,2p) binding energies are consistently smaller than those obtained with MP2/6-311++G-(2d,2p). However, the differences in binding energies agree well with the two methods. The B3LYP/6-311++G(2d,2p) cooperative effect is −0.57 kcal/mol for NMAW6. For FBW5, an appropriate minimum was not found with MP2, but the B3LYP result allows the cooperative effect to be assessed. The value is −0.19 kcal/mol at the B3LYP/6-311++G(2d,2p) level. Thus, like the peptide, the FBW5 complex of the peptidomimic is more stable than one would predict based on additivity. However, the nonadditive (cooperative) effect is smaller than for the amide.

TABLE 12: Calculated Binding Energies (ΔE) and Cooperativity Effects for *N*-Methylacetamide Dihydrate NMAW6 and 2-Fluoro-2-butene Dihydrate FBW5[b]

				corrected for water−water	
	NMAW1 + NMAW2	NMAW6	cooperativity	water−water interaction[c]	cooperativity
MP2	−13.94	−14.48	−0.54	−0.02	−0.54
MP2(CP)	−11.82	−12.26	−0.44	−0.02	−0.46
B3LYP	−11.35	−11.77	−0.57	0.00	−0.57
B3LYP(CP)	−10.74	−11.10	−0.36	0.00	−0.36
	FBW1 + FBW2	FBW5	cooperativity	water−water interaction	cooperativity
MP2	−6.53				
MP2(CP)	−4.99				
B3LYP	−4.23	−4.42	−0.19	−0.09	−0.28
B3LYP(CP)	−3.73	−3.90	−0.17	−0.08	−0.27

[a] In kcal/mol. With the 6-311++G(2d,2p) basis set. [b] Refer to Figure 6. [c] Interaction energy of the water molecules with the NMA or FB removed in a single-point calculation.

TABLE 13: Calculated Binding Energies[a] (ΔE) and Cooperativity Effects for *N*-Methylacetamide Dihydrate NMAW7 and 2-Fluoro-2-butene Dihydrate FBW6[b]

				corrected for water−water	
	NMAW2 + NMAW3	NMAW7	cooperativity	water−water interaction[c]	cooperativity
MP2	−16.52	−15.76	+0.76	0.94	−0.18
MP2(CP)	−14.10	−13.33	+0.77	0.92	−0.15
B3LYP	−13.99	−13.13	+0.86	0.92	−0.06
B3LYP(CP)	−13.35	−12.45	+0.90	0.96	−0.06
	FBW2 + FBW2	FBW6	cooperativity	water−water interaction	cooperativity
MP2	−8.20	−7.78	+0.42	0.29	+0.13
MP2(CP)	−6.40	−5.76	+0.64	0.30	+0.34
B3LYP	−5.98	−5.11	+0.87	0.43	+0.44
B3LYP(CP)	−5.40	−4.47	+0.93	0.34	+0.59

[a] In kcal/mol. With the 6-311++G(2d,2p) basis set. [b] Refer to Figure 6. [c] Interaction energy of the water molecules with the NMA or FB removed in a single-point calculation.

A similar analysis can be conducted on the bonding motif where two waters share the same acceptor atom (the O in NMAW7 or the F in FBW6) using the data presented in Table 13. The stability of the NMAW7 complex (binding energy of −15.76 kcal/mol at MP2) is less than the additive prediction (−16.52 kcal/mol at MP2) resulting in a cooperative effect of +0.76 kcal/mol. This is in the opposite direction to that seen above for NMAW6 and is consistent with the Guo and Karplus HF/6-31G result of +1.2 kcal/mol.[58] For the corresponding mimic complex, FBW6, the same trend is observed with a cooperative effect of +0.42 kcal/mol. Thus, once again, the cooperative effect for the mimic is in the same qualitative direction as the amide but with lesser magnitude.

The above analysis of cooperativity uses the method of Guo and Karplus[58]where the binding energy of the doubly hydrated NMA complex is compared to the sum of the component water−NMA hydrogen bonds. The result of that analysis is that the interactions found in NMAW6 are cooperative but are anticooperative in NMAW7. However, Dannenberg[41] recently addressed the cooperativity issue in the NMA−water system by also including the water−water pairwise interaction in the analysis. He found that, when one considers the water−water interactions, both binding motifs are seen to be cooperative. The difference is due to the fact that in the NMAW6 binding motif there is minimal interaction between the waters, but there is a considerable repulsive interaction, on the order of 1 kcal/mol, between the waters in NMAW7. We have included the water−water interactions for NMA and reach the same conclusion (see Tables 12 and 13). For the fluoroalkene hydrates, the same trend is observed where the water−water interactions are more repulsive in the binding motif of FBW6 (both waters on F) than in FBW5 (waters on opposite sides of the FB). However,

TABLE 14: Calculated[a] Thermochemical Parameters[b] for Fluoroalkene Hydrates[c]

structure	level	ΔE	ΔE^{zpe}	ΔE^{298}	ΔH^{298}
FEW1	MP2	−3.67	−2.26	−1.68	−2.27
FEW2	MP2	−3.64	−2.51	−2.30	−2.89
FEW3	MP2	−2.56	−1.65	−0.64	−1.23
FBW1	MP2	−2.42	−1.61	−0.54	−1.13
FBW2	MP2	−4.11	−2.74	−2.10	−2.69
FBW3	MP2	−4.10	−2.72	−2.07	−2.66
FBW4	MP2	−4.30	−2.91	−2.28	−2.87
FBW5	MP2				
FBW6	MP2	−7.78	−5.24	−3.82	−5.01
FEW1	B3LYP	−2.60	−1.30	−0.63	−1.22
FEW2	B3LYP	−2.58	−1.42	−0.65	−1.25
FEW3	B3LYP	−1.93	−1.10	−0.03	−0.62
FBW1	B3LYP	−1.37	−0.59	0.52	−0.07
FBW2	B3LYP	−2.86	−1.60	−0.86	−1.45
FBW3	B3LYP	−2.99	−1.74	−1.00	−1.59
FBW4	B3LYP	−3.05	−1.76	−1.04	−1.63
FBW5	B3LYP	−4.42	−2.38	−0.38	−1.71
FBW6	B3LYP	−5.11	−2.73	−1.16	−2.34

[a] Employing the 6-311++G(2d,2p) basis at the indicated level of theory. [b] ΔE is the difference in total energies. ΔE^{zpe} includes correction for differences in zero-point vibrational energy. ΔE^{298} includes thermal corrections at 298 K and ΔH^{298} is the enthalpy differences at 298 K. [c] See Figures 3−6 for structures.

the difference is far less pronounced in the fluoroalkene case than in the amide case (only 0.30 to 0.34 kcal/mol for the water−water interaction in FBW6). This is expected when one considers that the lesser hydrogen-bond strength in the case of the fluoroalkene leads to larger distances between waters. Thus, for the fluoroalkenes, consideration of the water−water interactions does not change the qualitative conclusions regarding cooperativity. FBW5 is found to exhibit cooperativity, and FBW6 is found to exhibit anticooperativity. The cooperativity values, including water−water interactions, are −0.27 and +0.59 kcal/mol (with B3LYP(CP)) for FBW5 and FBW6, respectively. Regardless of which analysis of cooperativity is employed, the result is that pairwise-additivity of interactions provides a better prediction of complex stability for the fluoroalkene hydrates than it does for the amide hydrates.

Thermochemical corrections to the binding energies for the mono and dihydrates of the fluoroalkenes are reported in Table 14. The ΔH values at 298 K for the complexes are 1 to 1.5 kcal/mol smaller in magnitude than the corresponding ΔE values for the monohydrated fluoroalkenes. The same trend is observed for the dihydrates, but the differences between the ΔE and ΔH^{298} values are larger. Similar trends have been reported for the ΔE and ΔH values for mono, di, and trihydrated complexes of NMA.[41]

Conclusions

The fluoroalkene moiety has been characterized in terms of several hallmark properties of peptides to assess its relevance as a peptide replacement for the generation of peptidomimetic compounds. Structurally, the fluoroakene unit is found to be very similar in terms of steric demand to a peptide bond. The charge distribution, as evaluated by comparison of CHELPG, Mulliken, and GAPT atomic charges for formamide to those of fluoroethylene, indicates that the fluoro substituent imparts the proper polarity to mimic that of an amide but the magnitude of the charge separation is less. With MP2/6-311++G(2d,p), the cis and trans isomers of FB are predicted to have solvation free energies of −2.38 and −2.05 kcal/mol, respectively, as compared to −9.29 and −9.10 kcal/mol for cis and trans NMA (comparable results are obtained with B3LYP). Thus, in both cases, the cis isomer is predicted to be only slightly better solvated.

In addition to bulk solvent phenomena, we have investigated specific interaction with water molecules via a supramolecule approach. The monohydrated complexes of fluoroethylene and 2-fluoro-2-butene show interactions that are generally similar to those seen with their amide counterparts formamide and *N*-methylacetamide, respectively. The binding energies for the fluoroalkenes are far weaker ranging from −2.42 to −4.30 kcal/mol as compared to −5.67 to −10.62 kcal/mol for the amides (at MP2/6-311++G(2d,2p). However, it is expected that these interactions are strong enough to influence the conformational preferences, binding abilities to receptor or enzyme active sites, and aggregation tendencies of biomimetic compounds that make use of the fluoroalkene as a peptide replacement. In addition, significant differences are noted in the structures of complexes where fluorine is acting as a hydrogen-bond acceptor as compared to the corresponding complexes with amides where the carbonyl oxygen is the hydrogen-bond acceptor. Specifically, the binding waters tend to locate themselves off the mean plane of the alkene moiety in contrast to the amide complexes where the waters are in the plane. The cooperativity effects in the binding of multiple waters have also been investigated. The fluoroalkene is found to exhibit cooperative effects that are smaller in magnitude than those seen in the model peptide.

Finally, the question remains as to the overall effectiveness of fluoroalkenes as peptide mimics. There are a multitude of effects that determine if a group is an effective peptidomimetic including sterics, intermolecular interactions (charge distribution), hydrolytic stability, toxicity, bioavailability, and so forth. For some of these, an effective peptide mimetic should reproduce the properties of a peptide group as closely as possible. For others, hydrolytic stability for instance, one desires that the peptide mimetic have substantially different properties than a native peptide. Thus, how closely a group resembles a peptide in terms of hydrogen-bonding properties may or may not be a good predictor of that group's ability to serve as a peptidomimetic in the physiological sense. Specifically, this work has revealed is that, while there is no question that fluoroalkenes have proven useful as peptide mimetics,[4,9,10,13,54,63] it is evident that there are substantial differences in the hydrogen-bonding properties of fluoroalkenes and peptides. Namely, the interactions are much weaker in the case of fluoroalkenes, the C−H bond of the fluoroalkene does not participate in the hydrogen bond as its NH counterpart in a peptide does, and the fluorine accepts hydrogen bonds with a much different geometry than the carbonyl of a peptide does. However, despite these differences, fluoroalkenes are still able to serve as peptidomimetics. Perhaps this indicates that, in the cases where they prove highly effective, hydrogen-bonding interactions to the peptide group that has been replaced by the fluoroalkene are not crucial or that the receptor or active site involved is able to accommodate a variety of hydrogen-bonding geometries.

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Supporting Information Available: B3LYP/6-311++G(2d,2p) and MP2/6-311++G(2d,2p) total energies and optimized Cartesian coordinates for hydrated complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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