Organic & Biomolecular Chemistry

PAPER

The conformers of 3-fluoroalanine. A theoretical study†‡§

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Quantum chemical calculations (DFT, SCS-MP2) show that the relative energies of the four principal alanine conformations are only marginally altered by the introduction of a single fluorine substituent into the methyl group. The fluorine *gauche* effect and attractive interactions of fluorine to the O–H or N–H moieties (formation of hydrogen bridges) do stabilize particular conformers of 3-fluoroalanine. This is true for the neutral molecule both in the gas phase and in aqueous solution (CPCM-model), but also for the zwitterionic forms and the conformers of the related carboxylate ions and also for the respective ammonium ions in aqueous solution. In water (CPCM calculations), the zwitterion is almost equal in energy to the most stable conformer of the neutral 3-fluoroalanine. Compared to alanine the atomic charges of the amino group and the carboxyl function of 3-fluoroalanine are not significantly influenced by the fluorine at C3, which relates to the fact that both experimental pK_a values are almost equal for alanine and 3-fluoroalanine.

Introduction

The specific properties of fluorine such as extreme electronegativity and small size, high carbon-fluorine bond energy as well as strong influence on acidity/basicity and hence the reactivity of neighboring groups made fluorinated molecules extraordinary targets both for chemical synthesis and for bioorganic applications.[1] Synthesis of fluorinated amino acids[2] and biomedicinal applications of peptides derived from the latter compounds enjoyed widespread interest.[3] A few years ago, 3-fluoroalanine was incorporated in peptide scaffolds[4] and other fluorinated amino acids emerged as valuable building blocks for the design of hyperstable protein folds[5] and as factors directing highly specific protein-protein interactions.[6] One of the reasons for the modification of biological properties of amino acids fluorinated in aliphatic position close to the amino group and peptides derived from it are due to the strong electron withdrawing effect of fluorine substituents. This effect is generally responsible for changes in the pK_a values of the amino function in particular.[1c,7,8]

The presence of a fluorine substituent close to the amino group will also influence the relative energy of different conformers of amino acids. In this paper we report results of theoretical studies of the conformations of alanine and its 3-fluoro analogue, its zwitterionic as well as of its *N*-protonated and *O*-deprotonated forms.

Several years ago, the gas phase conformations of alanine have been investigated by various *ab initio* methods.[9] At the MP2/6-31+G* level of theory four families of conformers exhibiting different types of stabilization by intramolecular hydrogen bridging were identified by Gronert and O'Hair[9a] (Fig. 1).

For conformers of type **A**, the near-atom interaction energy (determined by linear regression analysis) of the O–H to the carbonyl oxygen within the carboxyl group was determined to be −5.7 kcal mol⁻¹. Therefore, this form is highly favored in most carboxylic acids. Seven of the ten lowest energy (within 6.5 kcal mol⁻¹) conformers belong to this type. By rotation about the α-C–C-bond, conformations with additional stabilizing interactions of the carbonyl oxygen to the hydrogen atoms of the amino group are possible (near-atom interaction energy −2.2 kcal mol⁻¹). The global minimum conformer **A** exhibits both of these intramolecular hydrogen bonds. The second type **B** has strong hydrogen bonds of the carboxylic OH group to the
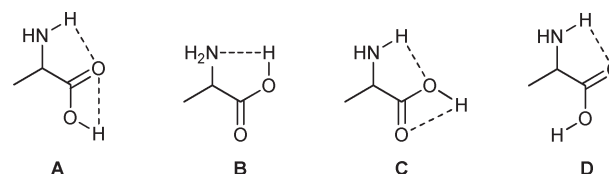
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†Dedicated to Professor Gerhard Erker on the occasion of his 65th birthday
‡Influence of a fluorine substituent on the physicochemical properties and chemical reactivity of fluorinated amino acids. Part 1
§Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob06492h

Fig. 1 Types of stabilization by intramolecular hydrogen bridging of alanine conformers.

nitrogen atom. The near-atom interaction energy was determined to −8.0 kcal mol⁻¹. Two conformers belong to this group being about 1 kcal mol⁻¹ less favorable comparing to conformer **A**. The third type **C** is characterized by near atom interaction of the N–H to the oxygen of the hydroxyl group (near-atom interaction energy, −1.3 kcal mol⁻¹). Four conformers belong to this group being 1.0–2.0 kcal mol⁻¹ less stable than the most stable structure. All the latter species also have a hydrogen bond of the O–H to the carbonyl oxygen. The only conformer among the ten lacking the latter as well as an O–H⋯N interaction (type **D**) is by far the least favourable isomer (+6.4 kcal mol⁻¹) showing only the N–H⋯O═C interaction.[9a]

Methods

Theoretical calculations

The theoretical calculations were performed using the GAUS-SIAN 03 program.[10] For the DFT calculations Becke's three-parameter exchange–correlation functional[11] was employed together with the correlation functionals of Lee–Yang–Parr (B3LYP).[12] The geometries were optimized at the B3LYP/6-311++G(d,p) level of theory. Single point energies were obtained by Grimme's SCS-MP2 method,[13] which is known for its general good performance in energy determinations, including also systems involving hydrogen bonding.[14] The energies obtained by this method are close to the CCSD(T)-values both for RHF-and B3LYP-optimized geometries (Table 1). Furthermore, for comparison additional current methods like B97-D[15] (including dispersion correction) and B2PLYP[16] with the def2-TZVP basis set[17] were used. In special cases restricted Hartree–Fock (RHF) calculations with the 6-311++G(d,p) basis set were performed for comparison.

In order to study the influence of water as solvent we used the models of the Self Consistent Reaction Field (SCRF) theory developed by Tomasi and coworkers, the Polarized Continuum Model (PCM)[18] and the Polarizable Conductor Calculation Model [CPCM, option: scf = tight, scrf = (cpcm,solv = h2o)].[19]

All structures studied were minima at all levels of theory and positive frequencies were obtained for all structures. In the following discussion we concentrate on geometries, NBO charges and solvation energies evaluated at the B3LYP/6-311++G(d,p) level and SCS-MP2 single point energies (SCS-MP2/6-311++G(d,p)//B3LYP/6-311++G(d,p)) including zero point correction for the gas phase species. The energies for species in water were also determined at the SCS-MP2 level including the solvent sphere. These are not corrected for zero point energies.

The calculated geometrical data, the NBO charges and the dipole moments discussed here are summarized in the Tables S-1 to S-30 of the ESI.§ The complete set of calculated total and relative energies, dipole moments and solvation energies is found in Tables S-31 and S-32. Dimeric structures of both alanine and 3-fluoroalanine were not included.

Results and discussion

Gas phase conformations

For the investigation of the fluorine substituent effect on conformations and other physicochemical properties, we concentrate

on four important alanine conformations **1–4** (Fig. 1), which belong to the four types **A**–**D** mentioned above.

These conformers were calculated to be very similar in energy compared to those ten structures calculated by Gronert and O'Hair[9a] (Fig. 2, Table 1).

Table 1 Relative energies of alanine conformers **1–4** in the gas phase calculated by different methods, without zero point correction (kcal mol⁻¹)

Calculational method / Alanine conformers	1	2	3	4
RHF/6-311++G(d,p)//RHF/6-311++G(d,p)	0.00	2.48	1.20	6.72
B3LYP/6-311++G(d,p)//B3LYP/6-311++G(d,p)	0.00	0.01	1.07	5.72
B97-D/def2-TZVP//B97-D/def2-TZVP	0.00	0.12	1.15	4.19
B2PLYP/def2-TZVP//B2PLYP/def2-TZVP	0.00	0.33	1.21	5.02
MP2/6-31+G*//RHF/6-31+G* [9a]	0.00	0.90	1.00	6.40
SCS-MP2/6-311++G(d,p)//B3LYP/6-311++G(d,p)	0.00	0.96	0.93	5.47
CCSD(T)/6-311++G(d,p//B3LYP/6-311++G(d,p)	0.00	0.58	1.00	5.64
CCSD(T)/6-311++G(d,p)//RHF/6-311++G(d,p)	0.00	0.80	1.05	5.66

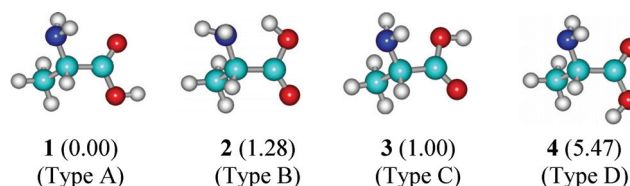**1 (0.00)** (Type A)   **2 (1.28)** (Type B)   **3 (1.00)** (Type C)   **4 (5.47)** (Type D)

Fig. 2 Four typical conformations of alanine and relative energies (kcal mol⁻¹) of (SCS-MP2/B3LYP 6-311++G(d,p) + ZPE). The (S)-enantiomer is shown.

Recently, the relative energies, geometries and molecular vibrations of ten alanine conformers were re-investigated by DFT-GGA calculations.[20] The electronic excitation of alanine conformers was also studied.[21] Three additional lowest energy conformations (relative energies of about +10 kcal mol⁻¹) were also identified.[9c,22] A couple of years ago, the most stable conformers **1** and **2** have been observed experimentally by laser-ablation molecular-beam Fourier transform microwave spectroscopy and were also found by MP2/6-311++G(d,p) calculations.[23]

The most stable conformer **1** belongs to type **A** and is identical to that found in the literature to be the energy minimum.[9a,9c,22] Conformer **2** belongs to Type **B** and is identical with the second most stable structure calculated by Gronert and O'Hair,[9a] while structure **3** is identical to the seventh most stable conformer in their study and belongs to type **C**. Structure **4** is the least favoured isomer in all studies. Dipole moments, NBO-charges and structural parameters of these conformers are given in Tables S-1 and S-2 in the ESI.§

In the following discussion of the influence of a single fluorine atom at C3 (3-fluoroalanine) on the relative energy of the resulting conformers we concentrate on the four types **1–4** of alanine conformers. Rotation around the C2–C3 bond leads to each three alternative species **1Fa-c**, **2Fa-c**, **3Fa-c** and **4Fa-c**. Additional conformers are created by rotation about the C–N bond. In Fig. 3 the atom numbering is depicted for the
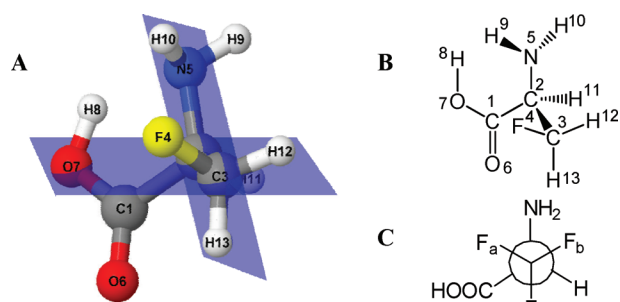
Fig. 3 Atom numbering in the 3-fluoroalanine conformer **2Fa**.

1Fa (0.00) 1Fb-1 (1.43) 1Fb-2 (1.50) 1Fc (1.31)

2Fa-1 (1.25) 2Fb (1.18)

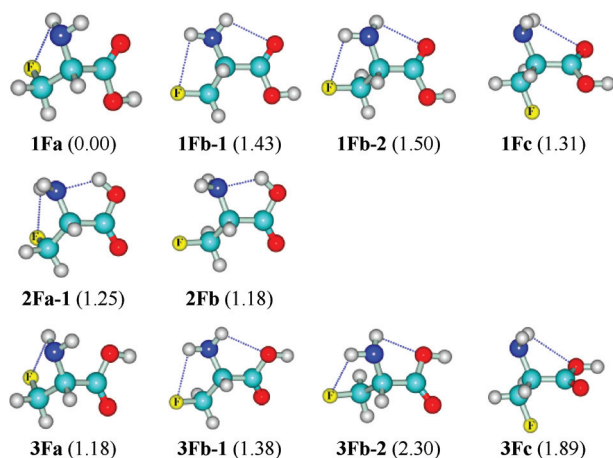3Fa (1.18) 3Fb-1 (1.38) 3Fb-2 (2.30) 3Fc (1.89)

Fig. 4 Lowest energy 3-fluoroalanine conformers **1Fa–3Fc** (basic types **1–3** of alanine) and relative energies (kcal mol^{-1}) of (SCS-MP2/B3LYP 6-311++G(d,p). The (S)-enantiomer is drawn.

3-fluoroalanine conformer **2Fa**. Ten conformations with relative energies <2.3 kcal mol^{-1} are shown in Fig. 4. Table 2 contains selected bond lengths, intramolecular atom distances and dipole moments of these conformers.

Fig. S-1 and Table S-3a in the ESI§ summarize the parameters of twenty studied conformers with relative energies <8.3 kcal mol^{-1}. Tables S-3b and S-4 contain the dipole moments, the NBO charges and structural parameters of all these molecules.

The variation of the total energy (a.u.) during rotation of the CH$_2$F group is shown in Fig. 5 for the conformers of type **2**.
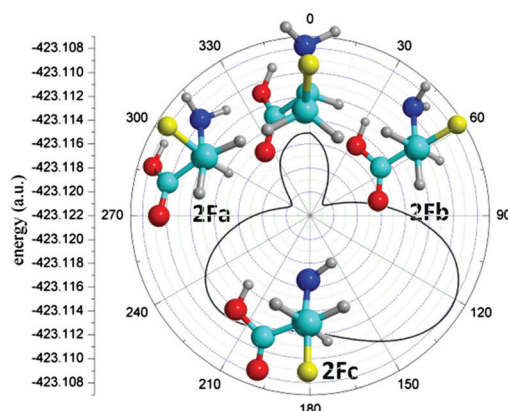

Fig. 5 Rotation barriers of CH$_2$F group around the C2–C3 bond [B3LYP 6-311++g(d,p)].

The rotation around the C2–C3 bond and/or the C–N bond can either lead to stabilization as a consequence of additional attractive N–H···F–C interactions or to destabilization due to repulsion of the lone pairs of nitrogen and fluorine. Moreover, the *gauche*-effect of the fluorine atom has an influence on the local conformation concerning the substituents at C2 and C3, as the interaction of σ*$_{CF}$ with σ$_{CH}$ is stronger than that of σ*$_{CF}$ with σ$_{CC}$ or σ$_{CN}$.[24]

From Tables 1 and 2 and Fig. 4 one can conclude that the presence of a fluorine substituent leads to an increased number of conformers with very similar relative energies, but resulted also in some changes of the relative energy of conformers of type **A** and type **B** with respect to the C1–C2 arrangement of alanine. The conformer **1Fa** (0.00) represents the most stable structure. The conformers **1Fb-1** (1.43 kcal mol^{-1}), **1Fb-2** (1.50), **1Fc** (1.31), **2Fa-1** (1.25), **2Fb** (1.18), **3Fa** (1.18), **3Fb-1** (1.38) and **3Fc** (1.89) form a group of conformers of quite similar relative energy. They are basically derived from alanine conformations **1**, **2**, and **3** and are significantly more stable than the fluorinated analogues of alanine conformer **4** (see Fig. S-1 and Table S-3§).

Table 2 Selected bond lengths, intramolecular atom distances (Å) and dipole moments (D) of the ten most stable 3-fluoroalanine conformers **1Fa–3Fc** [B3LYP 6-311++G(d,p)]

Conformer parameter	1Fa	1Fb-1	1Fb-2	1Fc	2Fa-1	2Fb	2Fc	3Fa	3Fb-1	3Fb-2	3Fc
Dipole [D]	2.424	2.015	2.000	1.932	5.602	3.752	6.047	1.874	2.354	2.225	2.882
C–F	1.405	1.405	1.402	1.399	1.406	1.403	1.394	1.406	1.406	1.401	1.399
O–H	0.969	0.970	0.970	0.970	0.982	0.982	0.978	0.969	0.969	0.969	0.969
N–H9	1.014	1.013	1.014	1.013	1.012	1.013	1.013	1.013	1.015	1.014	1.013
N–H10	1.015	1.014	1.015	1.016	1.016	1.016	1.016	1.014	1.014	1.015	1.014
N···H–O	—	—	—	—	1.921	1.930	1.994	—	—	—	—
C=O···H–O	2.306	2.300	2.307	2.308	—	—	2.308	2.294	2.302	2.304	2.306
N–H9···O–H	—	—	—	—	—	—	—	—	2.629	—	—
N–H10···O–H	—	—	—	—	—	—	—	2.763	2.429	2.417	2.657
N–H9···O=C	2.701	—	—	3.342	—	—	—	—	—	—	3.409
N–H10···O=C	2.876	2.381	2.423	2.570	—	—	—	—	—	—	—
C–F···H9–N	3.775	2.619	2.485	—	3.493	2.888	—	3.760	2.489	2.550	—
C–F···H10–N	2.539	—	—	—	2.345	2.983	—	2.510	—	—	—
C–F···H–O	—	—	—	3.870	—	—	—	—	—	—	—
C–F···H11	—	—	—	2.665	—	—	2.439	—	—	—	2.677

The conformers of type **A**, **1Fa**, **1Fb-1**, **1Fb-2** and **1Fc**, are characterized by interactions of the carbonyl oxygen to one or both N–H groups (distance: 2.381 Å to 2.701 Å) and strong interaction of the O–H to the carbonyl oxygen (2.300 Å to 2.308 Å). Moreover, conformers **1Fa**, **1Fb-1** and **1Fb-2** show relatively close C–F⋯H–N contacts (2.485 Å to 2.619 Å). The sum of the van der Waals radii is 2.67 Å.[25] These conformers have different *gauche* arrangements of fluorine with regard to the amino group. In conformer **1Fa** the C–F and the C2–H bonds are *anti* to each other giving rise to an optimal fluorine *gauche* effect. Both contributions do stabilize conformation **1Fa**. In contrast, in the least stable conformer of type **A** (**1Fb-3**) there is a C–F⋯H–N distance >3.5 Å, but a closer contact between the carbonyl oxygen and N–H10 (2.514 Å). Moreover, the C–F and the C2–C1 bonds are in the *anti*-conformation resulting in a weaker fluorine *gauche* effect.

In conformer **1Fc** (1.31 kcal mol^{-1}) the repulsion between the fluorine atom in **c** position (see Fig. 3C) and the hydroxyl oxygen atom causes a rotation around the C1–C2 bond. In this structure H11, C2, C1 and O7 are almost in a plane (12.7°). A relatively long N–H10⋯O=C distance (2.570 Å) is observed. This second most stable conformer of type **A** does not have any short C–F⋯H–X contacts.

In the second group of conformers (type **B**) only two low energy structures were found. Conformers **2Fa-1** (1.25 kcal mol^{-1}) and **2Fb** (1.18 kcal mol^{-1}) are characterized by strong hydrogen bridges of the O–H to the nitrogen of the amino group (1.921 Å for **2Fa-1** and 1.930 Å for **2Fb**). In addition to these characteristic interactions for type **B** structures, there is a close contact of fluorine to H10 in **2Fa-1** (C–F⋯H10–N distance is 2.345 Å). The conformer **2Fb** is the second most stable structure of 3-fluoroalanine, stabilized mostly by the strong O–H⋯N hydrogen bridge and probably by a fluorine *gauche* effect.

The conformers of type **C** derived from alanine conformer **3**, with an *s-trans* conformation within the carboxyl group, are characterized by short contacts of one or both NH groups to the hydroxyl oxygen (2.417 Å to 2.898 Å). **3Fa** (1.18 kcal mol^{-1}, energetically equal to conformer **2Fb**) is characterized by a bisected (2.629 Å and 2.763 Å) interaction and gains additional stabilization from a close C–F⋯H–N (2.510 Å) hydrogen bridge and from the fluorine *gauche* effect. Striking for conformers **3Fb-1** (1.38 kcal mol^{-1}) and **3Fb-2** (2.30 kcal mol^{-1}) are short C–F⋯H–N contacts (2.489 Å or 2.550 Å, respectively) and short C–O(H)⋯H–N contacts (2.429 Å or 2.417 Å, respectively). In the conformer **3Fc** (1.89 kcal mol^{-1}) the repulsion between the fluorine atom and the carbonyl oxygen may cause rotation of the carboxyl group. This structure is very similar to **1Fc** (type **A**). The atoms H11, C2, C1 and O6 form almost a plane (dihedral angle −8.73°).

The conformers derived from **4** (type **D**) are the highest energy ones within the studied series (see Fig. S-1§).

The fluorine atom in all **c** conformers interacts with the α-hydrogen H11. This is characterized by short C–F⋯H11 distances of 2.439 Å in **2Fc** and 2.586 Å in **4Fc** (Fig. S-1§). For the conformers **1Fc** and **3Fc**, where the carboxyl group is almost perpendicular to the plane of C3–C2–N, the distance C–F⋯H11 is a little longer: 2.665 Å and 2.677 Å, equal to the sum of the van-der-Waals radii. In addition, there is a singular very short

C–F⋯H–O distance (1.896 Å) in **4Fc** (Fig. S-1 and Table S-3a§) not seen in any other conformation.

Analyzing the evolution of the NBO charges (B3LYP) of all 3-fluoroalanine conformations in comparison to those of the alanine conformers in Tables S-1 and S-3b,§ significant decrease of the negative charge of C3 from *ca.* −0.58 for the alanine conformers to 0.10 for the fluoro derivatives is observed. A distinct change was also found for C2 having NBO charges of −0.15 to −0.17, which is more than the alanine value (−0.12 to −0.13). The charge at C1 is only little influenced by the fluoro substitution and shows slight dependence on the conformation. The interactions between the fluorine atom in F**c** and F**b** conformers and H11 determine the increase of the charge of H11 of approximately 0.02 in comparison to the value for the alanine structure. For the **Fa** and **Fb** conformers the hydrogen bridge between fluorine and H10 (2.3–2.5 Å) causes a small increase of +0.01 to +0.02 at the hydrogen atoms H9 or H10, respectively. The NBO charges of the fluorine atoms amount from −0.386 to −0.414. Most importantly, except for the least stable **4F** conformations, there is almost no influence of the fluorine substituent on the NBO charges of H8 (OH-group) or H9 and H10 (NH$_2$ group). This is in agreement with the observation of almost no difference in the pK_a-values both for the amino and the carboxyl function of alanine (9.87 and 2.35) and 3-fluoroalanine (9.8 and 2.4).[7b]

Aqueous phase conformations

The influence of water molecules on the structure and the relative energy of alanine and 3-fluoroalanine conformers was investigated using the self consistent reaction field (SCRF) method. The static isodensity surface polarized continuum model (IPCM)[26] single point, Polarizable Continuum Model (PCM, Tomasi model)[18] and Polarizable Conductor Calculation Model (CPCM)[19] – optimized structures – have been used for the calculation of relative energies of conformers in aqueous solution. The energy differences of conformers in the gas phase and in the solvent models [B3LYP 6-311++G(d,p)] are depicted in Fig. 6 and 7. The solvation by water causes a stabilization of 15–30 kcal mol^{-1} for all alanine and 3-fluoroalanine conformations for both solvent models.
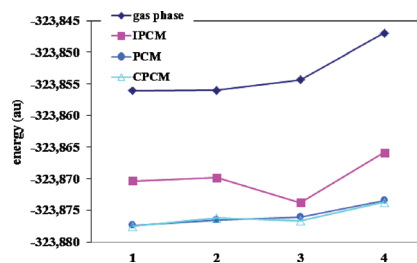

Fig. 6 Energy differences of alanine conformers **1–4** in the gas phase and in aqueous solution [B3LYP 6-311++G(d,p)].

The NBO charges, dipole moments, relative energies, the optimized bond lengths, bond angles, and dihedral angles in water for the alanine conformers **1$_{aq}$–4$_{aq}$** and 3-fluoroalanine conformers **1Fa$_{aq}$–4Fc$_{aq}$** are summarized in Tables S-5 to S-8.§

For both compounds, alanine and 3-fluoroalanine, the solvent sphere reduces the relative energies of the conformers and halves
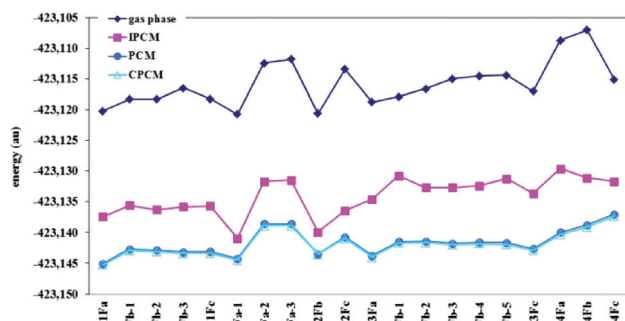
Fig. 7 Relative energies of 3-fluoroalanine conformers **1Fa–4Fc** in the gas phase and in Tomasi's models [B3LYP 6-311++G(d,p)].

approximately the range between the lowest and the highest energy conformers investigated. For alanine conformers, the same relative order of the energies is observed in the gas and in the water phases, for the fluoroalanines only minor changes in the energetic sequence are found.

Comparison of the geometrical parameters with those for the gas phase in Tables 2 and S-4§ shows that the F–C3 bond is about 0.01 to 0.02 Å longer in water. Moreover, the N–H bonds are about 0.01 Å longer and the distance between N and H–O in conformers **2Fa–2Fc** are 0.04 to 0.05 Å shorter in aqueous medium. The largest differences are observed for the orientation of the amino group as seen from the respective dihedral angles.

The influence of water is also visible in deviations of the NBO charges. The values for this parameter are included in Tables S-5 and S-7.§ Comparison with NBO charges of the alanine conformers **1–4** in the gas phase (B3LYP, Table S-1§) spotlights their increase in absolute values. For the carbon atoms it increases by 0.01 to 0.1 for **1–4** upon solvation, while it becomes more negative at oxygen and nitrogen. The situation is ambivalent for the conformers of 3-fluoroalanine. While for C1 the charge increases in all conformers, it decreases at C2 (for **1Fa**, **2F**, **3Fa**) or increases (for **1Fc**, **3Fc**). At C3 the charge decreases for **1Fb-2**, **2Fa-1** and **3Fb-2** and increases for the **1Fc** conformer. On an average the charges at the fluorine atom become more negative by about 0.05, at the nitrogen atom and the carbonyl oxygen by about 0.1, and by 0.06 for the oxygen of the hydroxyl group. For the hydrogen atoms of the OH and the NH₂ groups the (positive) charges increase by about 0.08 for H8 and 0.05 for H9 and H10 with regard to alanine.

The variation of Mulliken charges of 3-fluoroalanine conformers **1Fa–4Fc** in the gas phase and aqueous solution [CPCM, B3LYP 6-311++G(d,p)] are illustrated in Fig. S-2.§

Zwitterionic forms

The calculated relative energies of neutral alanine and 3-fluoroalanine conformers discussed in former sections deliver the best approximation to understand the inherent properties of these peptide building blocks. However, in the solid state or in pure water amino acids exist in the zwitterionic form.[27] The knowledge of the conformational flexibility of amino acids in aqueous environment is important to understand the molecular structure and interactions of proteins in biological systems. Consequently, zwitterionic structures of the mentioned amino acids were

investigated next. The zwitterion of alanine in the gas phase was found to be about 25 kcal mol⁻¹ less stable comparing to the neutral molecule, which is in good agreement with earlier calculations (6-31++G*) by Micu *et al.*[28] The difference is smaller in case of 3-fluoroalanine possibly due to intramolecular hydrogen bonding.

Two conformations of zwitterionic alanine were determined in the literature (Fig. 8).
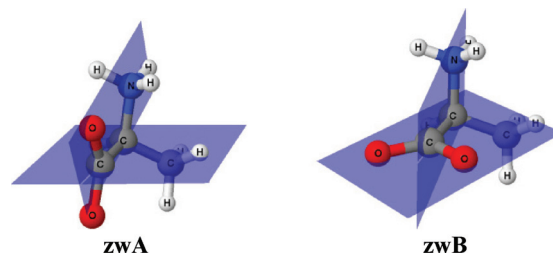

Fig. 8 Zwitterionic conformers of (*S*)-alanine.

In accordance with experimental findings[27b,29] **zwA** is characterized by bifurcated intramolecular H-bonds between the N–H groups and one oxygen atom. The second conformer **zwB** is characterized by a 90° turn around the C1–C2 bond leading to a perpendicular arrangement of the NH₃⁺ group relative to the C1–O1–O2 plane.

The relative energies of these conformers are strongly dependent on the number of water molecules present.[30] In the absence of water the **zwA** conformation is more stable by 9–15 kcal mol⁻¹, while addition of 1–4 water molecules changes the relative energies in favor of **zwB**.[22a,31]

For the investigation of zwitterionic forms of alanine we used the **zwA** and **zwB** structures illustrated in Fig. 8. These structures were optimized in the gas phase and in aqueous solution (CPCM). In the gas phase both zwitterionic forms of alanine are not stable but evolve to the same neutral conformer **2**. This proceeds without energy barrier, similar to the glycine case.[32] In the absence of water or of external stabilization the ground state of all amino acids is the neutral form.[33] The structural changes during the optimization of the zwitterionic conformers of alanine in the gas phase and aqueous solution are displayed in Fig. S-3.§

In aqueous solution, two zwitterionic structures of type **A** with almost identical energy are the only stable ones (CPCM). Their calculated relative energies compared to the best neutral form in water are slightly positive (*ca.* 1–2 kcal mol⁻¹), indicating that the CPCM-model alone is not sufficient to reproduce the experimentally found strong preference of the zwitterionic form in water. No proton transfer does occur. The mutual arrangement of oxygen and nitrogen is not eclipsed, but rotation of the carboxylate group with relation to the ammonium moiety is possible either to the "**r**ight" leading to **zwAr**$_{aq}$ (0.0 kcal mol⁻¹) or to the "**l**eft" leading to **zwAl**$_{aq}$ (0.1 kcal mol⁻¹), Fig. S-4.§ According to the calculations, the **zwB** conformer is not stable in aqueous solution. During optimization, the COO⁻ group rotates either to the left or to the right delivering **zwAr**$_{aq}$ or **zwAl**$_{aq}$, respectively, as final structures. These structural parameters including NBO charges are given in Tables S-9 and S-10.§

Both stable zwitterionic structures of alanine in aqueous solution are characterized by a large molecular dipole of 14.32 D

for **zwAr$_{aq}$** and 14.06 D for **zwAl$_{aq}$**. These values are in a good agreement with experimental data and other theoretical investigations, which range from 10.8 to 15.4 D.[34]

Using the same technique we calculated the relative energies of 3-fluoroalanine zwitterionic structures. Again, in the gas phase zwitterions are not stable and the neutral molecules are obtained after proton transfer from NH$_3^+$ group to carboxyl group, similar to the alanine case. Consequently, the neutral forms **2Fa**, **2Fb** or **2Fc** are obtained with the fluorine position as depicted in Fig. 4. In aqueous solution, however, the 3-fluoroalanine zwitterionic structures are calculated to be stable, although the CPCM-method calculates a relative energy of 2–3 kcal mol^{-1} for these structures relative to the best neutral form **1Fa** in water. The structural parameters and the NBO charges for all conformers are presented in Tables S-11 to S-14.§ Like in the alanine case, the conformers related to **zwB** with perpendicular arrangement of the carboxyl group turn to the conformers of coplanar type **zwA**, which are stabilized by strong interactions of the ammonium ion and the carboxyl group. In conformer **zwAFa$_{aq}$**, this geometry is additionally stabilized by a hydrogen bridge (2.45 Å) of fluorine and H10 of the NH$_3^+$ group (Table S-11§). The dipole moment of 14.20 D is in agreement with this geometry. We can conclude that in aqueous solution, the N⋯H–O hydrogen bond (1.88 Å) and 2.51 Å of F⋯H10 determine a slightly better energy of the neutral conformer **1Fa** compared with the N–H⋯O=C hydrogen bond (1.98 Å) and 2.45 Å of F⋯H10 in zwitterionic form **a** in Fig. 9.
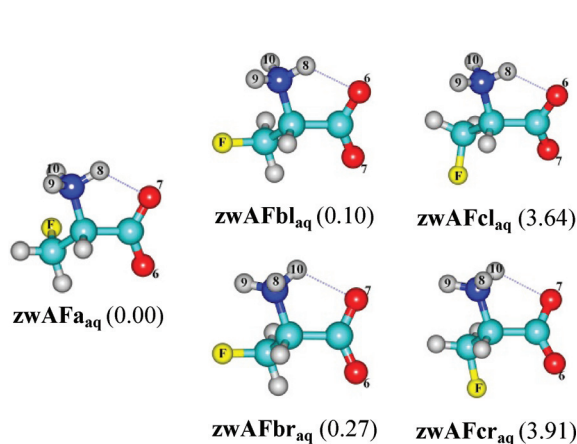

Fig. 9 The 3-fluoroalanine zwitterionic conformers and relative energies (kcal mol^{-1}) in aqueous solution, CPCM (SCS-MP2/6-311++ G(d,p) level). The atom numbering is as in Fig. 3.

Two stable conformations of the 3-fluoroalanine zwitterion in aqueous solution with fluorine in position **b** are derived from **zwA**. These are almost equal in energy, **zwAFbl$_{aq}$** (0.10 kcal mol^{-1}) and **zwAFbr$_{aq}$**, (0.27 kcal mol^{-1}), and are formed by rotation of the carboxyl group to the "left" or to the "right" with regard to the ammonium group. The interactions between fluorine and oxygen, respectively, with the corresponding hydrogen atoms of the ammonium group determine the different orientations and the different values of structural parameters of these conformers. Important changes of the 8,5,2,1 and 5,2,1,7 dihedral angles are observed. Both structures are weakly stabilized by the interaction of fluorine with H9 of the NH$_3^+$ group (2.87 Å

for **zwAFbl$_{aq}$** and 2.48 Å for **zwAFbr$_{aq}$**) and hydrogen bridges between O6 and H8 (2.03 Å in **zwAFbl$_{aq}$**) and between O7 and H10 (2.07 Å in **zwAFbr$_{aq}$**), respectively (Table S-12§).

Two other conformers **zwAFcl$_{aq}$** and **zwAFcr$_{aq}$** are considerably higher in energy by about 3.64–3.91 kcal mol^{-1}.

The NBO charges for the 3-fluoroalanine zwitterionic forms are presented in Table S-14.§

For understanding of particular biochemical transformations the knowledge about monoionic forms, *i.e.* cations and anions, of alanine and 3-fluoroalanine are of considerable interest, too. The calculated (B3LYP) structure and energetic parameters of conformers in the gas phase and in aqueous solution will be discussed in the following sections.

N-Protonated alanine and 3-fluoroalanine conformers

Formally, alanine can be protonated at three different positions: (i) at the amino group (NH$_3^+$), (ii) at the carbonyl oxygen (geminal diol structure, C(OH)$_2^+$) or (iii) at the hydroxyl oxygen (CO$^+$ + H$_2$O).[35] The most favorable protonation site is the amino nitrogen.[36] For our discussion we concentrate on the alanine ammonium ions **p1** and **p3** (**p** means protonated) based on the most stable conformers of neutral alanine shown in Fig. 2. Fig. 10 presents the corresponding local minima conformations of alanine cation calculated on the B3LYP 6-311++G** level in the gas phase.
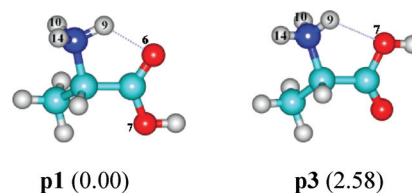

Fig. 10 Two low energy conformers of protonated alanine with relative energies (kcal mol^{-1}).

There is no stable cation structure based on the neutral alanine conformer **2** because of the lack of attractive interactions between the NH$_3^+$ function and the hydrogen of the hydroxyl group. During the geometry optimization of the NH$_2$-protonated conformer **2** rotation of the carboxyl group takes place giving the least stable conformer **p4** (8.94 kcal mol^{-1}) (Fig. S-5§). The most stable cation conformers **p1** and **p3** (2.58 kcal mol^{-1}) correspond to the respective alanine conformers **1** and **3**. Some structural parameters for the cation conformations of alanine in the gas phase are presented in Table S-15.§ The relative energy of the structures **p1** and **p3** is determined by two or three, respectively, intramolecular hydrogen bridges. One of these in **p1** is between N–H9⋯O6 (1.91 Å) and the other is between O6⋯H8–O7 (2.38 Å). In **p3** three close X–H⋯O contacts do exist: N–H9⋯O7 (2.22 Å) N–H10⋯O7 (2.75 Å) are longer than in **p1**, while the O7–H8⋯O6 contact (2.38 Å) has the same value as in **p1**.

Moreover, the influence of water on the relative energy of the cation structures of alanine has been investigated using Tomasi's CPCM self-consistent reaction field approximation. The relative energies and solvation energies of the two energy lowest protonated alanine conformers in water are listed in Table 3.

Table 3 Relative and solvation energies of protonated alanine conformers in water (SCS-MP2/CPCM)

Conformation	Relative energy (kcal mol^{-1})	Solvation energy (kcal mol^{-1})
p1$_{aq}$	0.00	−80.35
p3$_{aq}$	1.47	−84.43

Thus, the alanine cation conformer **p1** is also the most stable in water. However, in comparison to the gas phase (Fig. 10) the energy differences of the second best conformers becomes smaller (Table 3). Detailed structural data of alanine cation conformers are included in Table S-17.§

The most important differences in NBO charges of different alanine cation conformations in the gas phase (Table S-16§) and in water (Table S-18§) have been observed for the carboxyl group. The charge at O6 decreases by about 0.01 for **p1$_{aq}$** and **p3$_{aq}$**. Decreases are also observed at O7 by about 0.02 for **p1$_{aq}$** and **p3$_{aq}$**. Also the charge of H8 (OH group) increases by 0.01 in average for all structures investigated. Smaller deviations were obtained for H11 and H14.

The influence of fluorine on the relative energy of 3-fluoroalanine ammonium ion conformations in the gas phase is presented in Table S-19.§ The most stable conformers of the 3-fluoroalanine cation are **p1Fa** (0.00 kcal mol^{-1}) and **p1Fb** (0.37 kcal mol^{-1}) corresponding to the most stable conformer of the cationic alanine structure **p1** (Fig. 10) followed by **p3Fa** (2.59 kcal mol^{-1}) and **p3Fb** (2.94 kcal mol^{-1}) (Fig. 11). All other conformations exhibit relative energies >7 kcal mol^{-1} (Fig. S-6 and Table S-19§).

p1Fa (0.00)   **p1Fb** (0.37)

p3Fa (2.59)   **p3Fb** (2.94)
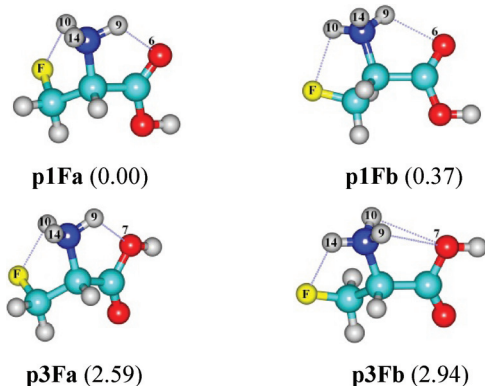
Fig. 11 Low energy conformers of protonated 3-fluoroalanine with relative energies in the gas phase (kcal mol^{-1}).

In **p1Fa** and **p3Fa** the presence of the fluorine atom causes the rotation of the amino group and lead to tight hydrogen bridges, F⋯H10–N (2.16 Å). Another hydrogen bridge, F⋯H14–N, characterizes the 3-fluoroalanine cation conformers with fluorine atom in **b** position: 2.16 Å in **p1Fb** and 2.21 Å **p3Fb**. Other strong hydrogen bridges (distance 1.98 Å) are present in **p1Fa** between O6 (or O7) of the carboxyl group and H9 (H10 respectively) of the NH$_3$$^+$ group. These hydrogen bridges determine the increase of the bond lengths N–H9 of 1.038 Å in **p1Fa** compared to about 1.024 Å for the other N–H

bond lengths in the NH$_3$$^+$ group for this conformer. The same effect has been observed for **p1Fb** (N–H10 = 1.034 Å) (N–H10⋯O6 = 2.10 Å) (Fig. 11).

The protonated structure **p1Fb** is similar to **1Fb-1** and **1Fb-2**, while the fluoroalanine cation conformer **p3Fb** corresponds to the structures **3Fb-1** and **3Fb-2**.

The NBO charges of the protonated 3-fluoroalanine conformers in the gas phase (Table S-20§) do change similarly to those of the protonated alanine conformers (Table S-16§).

The calculated total energies of the neutral and protonated forms allow the estimation of the gas phase proton affinities of the neutral forms. Thus, alanine is predicted to have a proton affinity of −224.0 kcal mol^{-1}, that of 3-fluoroalanine is lower by about 4 kcal mol^{-1} (−220.1 kcal mol^{-1}), indicating the small, but significant substituent effect of the fluorine atom in 3-position (for discussion of C–F⋯H–X interaction energies see ref. [37]).

In aqueous solution the energy differences between the protonated 3-fluoroalanine conformers (CPCM method) become smaller in relation to the gas phase values, but the order of conformers remains unchanged (see Table S-21§). The presence of water determines the rotation of the NH$_3$$^+$ group to form hydrogen bridges between two hydrogen atoms (H9 and H10) and O6 (or O7 for the 3-fluoroalanine cation conformer corresponding to **p1aq**); in the gas phase only one of these hydrogen bridges is formed: N–H9⋯O6(7) or N–H10⋯O6(7). The average distance between N–H9⋯O6(7) is 2.55 Å in **p1F** type conformers and 2.47 Å in **p3F**. The H-bridge N–H10⋯O6(7) has the following average value: 2.65 Å in **p1F$_{aq}$** and **p3F$_{aq}$**. The N–H bond lengths in the NH$_3$$^+$ group have about the same value for all hydrogen atoms in this group (1.034–1.035 Å). The O–H bond length increases a little (0.03 Å) for all 3-fluoroalanine cation conformers in water. The rotation of the NH$_3$$^+$ group leads to changes of the relative position of this group with regard to the plain of the carboxyl group.

The solvation energy of 3-fluoroalanine cation conformations is depicted in Table 4.

Table 4 Solvation energy (kcal mol^{-1}) of 3-fluoroalanine cation conformers (MP2-CPCM)

Conformer	p1Fa$_{aq}$	p1Fb$_{aq}$	p3Fa$_{aq}$	p3Fb$_{aq}$
Solvation energy	−86.48	−84.58	−89.85	−88.24

The proton affinity of alanine in water is calculated to −285.6 kcal mol^{-1}, that of 3-fluoroalanine is lower by only 2.9 kcal mol^{-1} (−282.7 kcal mol^{-1}), indicating the significantly reduced substituent effect of the fluorine atom in 3-position compared to the gas phase due to competing interactions with water (*ca.* 1 pK_a unit).

The NBO charge distribution of 3-fluoroalanine cation conformers in aqueous solution is included in Table S-22.§

Anionic structures

For the *O*-deprotonated alanine, the two alanine anion conformers **a1r** and **a1l** derived from alanine conformers **1** and **4** with

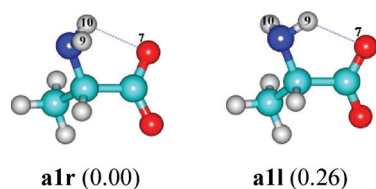a very small energy difference were found in the gas phase as shown in Fig. 12.

Fig. 12 The alanine anion conformers and its relative energy in the gas phase (kcal mol^{-1}).

The main difference between these conformers is the hydrogen bridge N–H⋯O=C. In **a1r** bridging is found between N–H10⋯O7 (2.206 Å) (atom notation as in Fig. 3, hydrogen bond is on the right of the plane of the carboxyl group), and between N–H9⋯O7 (2.140 Å) (hydrogen bond is on the left) in the **a1l** conformer. The distance of H12 to O6 is about 2.56 Å in **a1l** and 2.83 Å in **a1r**. The corresponding O6⋯H11 distances were calculated to be 2.55 and 2.70 Å, respectively. The value of the angle H10, O7, H9 amounts to 29.36° in **a1l** and 30.48° in **a1r**. The other structural parameters for alanine anion conformers in the gas phase have been included in Table S-23.§

The NBO charges for the two alanine anion conformers are reported in the Table S-24.§ Comparing these data, only small differences at C3, H4 of 0.01 are observed for the two alanine anion conformers.

In water (CPCM model, Table S-25§), a single conformer, **a1l$_{aq}$**, was found exhibiting an N–H10⋯O7 (2.56 Å) distance. Water causes the elongation of the H12⋯O6 distance by 0.11 Å, a diminution of the OCO bond angle by 3.5° and an increase of the dipole moment from 4.57 to 6.86 Debye. The solvation energy of the alanine anion is −75.96 kcal mol^{-1}. The NBO charges in water are included in the Table S-26.§ The absolute value for all charges increases: C1, O6 and O7 by about 0.02–0.06, and H9 by 0.04 in comparison to the gas phase (Table S-24§). The charges at C2, C3 and N are not influenced by the solvent sphere.

For the 3-fluoroalanine anion in the gas phase three low energy conformers **a1Fa**, **a1Fbr**, and **a1Fbl** were found. Their structures and relative energies are depicted in Fig. 13. The energies of the conformers with fluorine in **c** position are >3.8 kcal mol^{-1} (Fig. S-8 and Table S-27§).
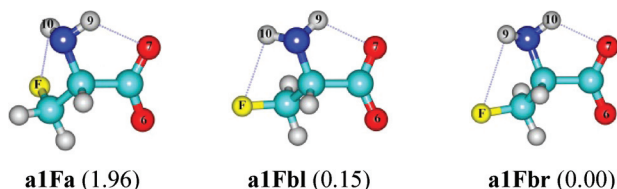

Fig. 13 Low energy conformers of 3-fluoroalanine anion and relative energies (kcal mol^{-1}) in the gas phase.

Starting the optimization with the 3-fluoroalanine anion structure corresponding to the **a1r** conformer with fluorine atom in **a** position leads to the relatively energy rich structure, **a1Fa**. Here,

the attraction of the fluorine atom and H10 causes a rotation of the amino group resulting in two hydrogen bridges: one between N–H10⋯F (2.36 Å) and another between N–H9⋯O7 (2.18 Å). In the most stable anion conformer **a1Fbr**, the fluorine atom in **b** position causes a rotation of the amino group until hydrogens H9 and H10 form two relatively close contacts to remote atoms: N–H9⋯F (3.04 Å) and N–H10⋯O7 (2.06 Å). Here, the 9,5,3,4 dihedral angle amounts to 22.43° and the 10,5,1,7 dihedral angle to −4.71. The second most stable anion conformer of 3-fluoro-alanine was calculated to be **a1Fbl**. The conformers with fluorine in the **c** position are less stable (see SI).

For all anionic conformers of alanine and 3-fluoroalanine the bond lengths N–H9 and N–H10 (with the hydrogen atom engaged in a hydrogen bridge with O7) have almost the same value, 1.021 Å, It should be noticed that the hydrogen bonds N–H⋯O are shorter by 0.5–0.6 Å in comparison to the respective parameters for neutral 3-fluoroalanine (Table S-4§).

The values of the NBO charges for the 3-fluoroalanine anion conformers in the gas phase are summarized in Table S-28§ showing that compared to the neutral structures (Table S-7§) in general the negative charge increases at the oxygen atoms by about 0.2 to 0.3 and increases at maximum by 0.02 at the fluorine atom. The charges of the hydrogen atoms attached to the amino group are slightly smaller compared to neutral 3-fluoro-alanine in the gas phase.

The proton affinity of alanine in the gas phase is calculated to −351.1 kcal mol^{-1}, that of 3-fluoroalanine again is lower by 6.2 kcal mol^{-1} (−344.9 kcal mol^{-1}), indicating the significant substituent effect of the fluorine atom in 3-position on the basicity of the anions.

The presence of water (CPCM model) leads to relative energies of the 3-fluoroalanine anion conformations all within 1 kcal mol^{-1} energy difference, either derived from the "right" (**a1r$_{aq}$**) or from the "left" (**a1l$_{aq}$**) alanine anion conformer. The essential optimized structural parameters are listed in Table S-29.§ As expected, there are virtually no energy differences between the left (**a1Fl$_{aq}$**) and the right (**a1Fr$_{aq}$**) conformers, in correspondence to the fact that there is only one stable alanine anion conformer in water (see above).

In the conformers **a** the quite short C–F⋯H10 contact and the optimal *gauche* effect due to the antiperiplanar arrangement of the C–H11 and the C–F bond might be responsible for the stability of this conformer, though all N–H⋯O distances are relatively long: N–H9⋯O7, N–H10⋯O7 (2.81 Å, 2.64 Å respectively). The other two families of conformers (type **b** and **c**) do neither have close C–F⋯H–N nor close N–H⋯O=C contacts in aqueous solution.

The water-phase proton affinity of the alanine anion is predicted to be −296.5 kcal mol^{-1}, that of 3-fluoroalanine is lower by 3.7 kcal mol^{-1} (−292.8 kcal mol^{-1}), indicating again the reduced substituent effect of the fluorine atom in 3-position in water compared to the gas phase value.

For the NBO charges of 3-fluoroalanine anion conformers in water see Table S-30.§ The positive NBO atomic charges of C1 and negative charges of C2, C3, N increase slightly (0.01 − 0.02), whereas at both oxygen atoms the negative charge increases at maximum by 0.1 as compared to the gas phase values. The charge of the fluorine atom has about the same value in water and the gas phase.

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Org. Biomol. Chem., 2012, **10**, 2084–2093 | 2091

Conclusions

Quantum chemical calculations were used to determine the relative energies of alanine and 3-fluoroalanine conformations in the gas phase and in water. Generally, the fluorine introduction into the methyl group increases the number of low energy conformations significantly. Particular conformations are stabilized by the fluorine *gauche* effect and hydrogen bridges formed due to attractive interactions of fluorine to O–H or N–H moieties. The lowest energy conformers of 3-fluoroalanine are quite similar in energy to those of alanine. Also the energetic order of the 3-fluoroalanine conformers of types **1F**–**4F** is the same as for the alanine conformers **1**–**4**. This is true for the neutral 3-fluoroalanine both in the gas phase and in aqueous solution, but also for the zwitterionic forms and the conformations of the ammonium ion and the carboxylate ion in aqueous solution. The atomic charges in water of 3-fluoroalanine are not significantly different from those of alanine. This is in good agreement with the almost equal experimental pK_a values of both the amino and the carboxylic groups in alanine and 3-fluoroalanine. In contrast, the experimental pK_a of the amino group in 2-amino-4-fluorobutyric acid is about 0.5 units lower compared to 2-aminobutyric acid.[8] We now study the conformers of these compounds by theoretical methods and will report the results in due course.

Acknowledgements

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