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Computational study of stereoelectronic effects in fluorinated alkylamines[†]

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ABSTRACT: A systematic evaluation of the stereoelectronic effects in a series of fluorinated amine compounds has been carried out. A variety of computational methods have been employed, including molecular mechanics, semi-empirical, density functional and *ab initio* methods. An analysis of the natural bond orbital populations has been carried out and the effect of solvent was considered via the polarized continuum model (PCM). The results indicate a preference for conformations that result in an anti-periplanar arrangement between the nitrogen lone pair and the C—X bond (X═F or CF$_3$). There are variations in geometry and natural bond orbital population, with conformation that are consistent with a stereoelectronic effect whereby electron density from the nitrogen lone pair is delocalized into the C—X σ^* orbital. Similar results are obtained for trifluoromethyl methylamines, although the magnitude of the stereoelectronic effect is attenuated resulting in greater expected conformational diversity for these compounds. The PCM results suggest that these preferences should persist in solution. Comparison among the computational methods used reveals that there is good agreement among the *ab initio* and density functional methods (at the HF/6-31 + G(d), MP2/6-31 + G(d), MP2/6-311 + G(2d,p) and B3LYP/6-31 + G(d) levels) and these methods agree well with the available experimental data for ethylmethylamine. Published in 2005 by John Wiley & Sons, Ltd.
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KEYWORDS: stereoelectronic effects; substituent effects; conformational analysis; computational chemistry; fluoro-organic compounds

INTRODUCTION

Fluorine has been found to exert many pronounced effects on the properties of organic compounds when employed as a substituent.[1] As a result, in many areas of applied organic chemistry, including polymer chemistry[2] and biological or medicinal chemistry,[3–5] fluorinated compounds are attractive synthetic targets and the effects of fluorination on structure–activity relationships receive much scrutiny. The fluoro and trifluoromethyl groups are widely used substituents in medicinal chemistry because they are capable of imparting a large perturbation of a molecule's electron distribution and lipophilicity. In medicinal chemistry applications, fluorine is particularly attractive as a substituent because the strength of the carbon–fluorine bond imparts a great deal of metabolic stability to fluorinated bioactive compounds.[4] Also, substitution by fluorine is relatively conservative from a steric standpoint. Fluorine is larger than a hydrogen atom but is comparable in size to oxygen.[6] Fluorine also provides a very useful analytical tool in biological systems because it can be monitored easily by ^{19}F NMR,[7,8] and ^{18}F-labeled ligands are widely used in positron emission tomography (PET) imaging studies.[9,10]

The fluoro substituent also has attracted a great deal of study from the physical organic chemistry community. It has been shown to participate in stereoelectronic effects (often called hyperconjugative, negative hyperconjugative and/or generalized anomeric effects)[11–18] that can greatly bias a molecule's conformational preferences in unexpected ways. A case in point is the so-called 'gauche effect', where gauche conformers of F—C—C—F fragments tend to predominate in contrast to their hydrocarbon counterparts, which tend toward the more sterically favored *anti* arrangement.[19] The explanation that is offered most commonly as the underlying cause of the *gauche* effect is that there are favorable interactions between the filled C—H σ orbital and the vacant C—F σ^* orbital that are optimal when the C—H bond is *anti* periplanar to the C—F bond. Thus, the driving force for an *anti* arrangement of H relative to F outweighs the steric repulsion between two *gauche* F atoms. A similar

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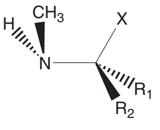
hyperconjugative effect, the generalized anomeric effect,[11,15,20–29] is seen with atoms bearing lone pairs that can be delocalized into adjacent σ^* orbitals.

In this work, a systematic evaluation has been conducted of the stereoelectronic effects in the very simple amine compounds shown in Fig. 1. These model compounds have been chosen to allow for an assessment of the role of stereoelectronic effects in N—C—F systems compared with N—C—CF_3 systems. Stereoelectronic effects in N—C—F systems have been investigated extensively in the past.[30] Very early *ab initio* studies of these effects by Radom, Hehre and Pople,[18] Reed and Schleyer[23,31] and Dunitz and co-workers[32] indicated that nitrogen lone pair delocalization into the C—F σ^* is a major contributing factor to the conformational preferences of simple N—C—F systems. In 1993, Senderowitz, Aped and Fuchs[33] examined this effect in both O—C—F and N—C—F systems and developed a parameterization scheme of Allinger's MM2[34] force field specifically to handle these effects. All of these studies were carried out at the Hartree–Fock level with basis sets ranging from 3-21G to 6-31G**. Additionally, NMR studies of *N*-benzyl-*N*-methyl-α-fluoroamine and related compounds identified large rotation–inversion barriers that support the notion that negative hyperconjugation plays a significant role in determining the conformational preferences of N—C—F systems.[35]

There have been many studies also of stereoelectronic effects in CF_3-containing compounds. However, often the focus has been on the electron-accepting ability of the C—F σ^*[23,31,36–38] (i.e. the systems under study are N—CF_2—F systems and not N—C—CF_3). There have been studies also comparing the β-carbanion stabilizing ability of a fluorine atom with that of the trifluoromethyl group.[39–41] Apeloig's *ab initio* study in 1981 concluded that the CF_3 group was able to engage in negative hyperconjugation, but to a much lesser extent than a fluorine atom.[39] Others agued that the two groups were more equally capable in their hyperconjugative abilities.[42] However, there has been far less investigation of conformational effects in neutral molecules due to these kinds of interactions (N—C—CF_3 systems, for example). The aforementioned 1988 NMR study of *N*-benzyl-*N*-methyl-α-fluoroamine compounds included studies of the trifluoromethyl analogues. These results supported Apeloig's conluclusion that hyperconjugative interactions were much more important in the fluoro case than the trifluoromethyl case.[35]



Compound	X	R_1	R_2
F1	F	H	H
F2	F	H	CH_3
F3	F	CH_3	H
CF1	CF_3	H	H
CF2	CF_3	H	CH_3
CF3	CF_3	CH_3	H
EMA	H	H	CH_3

Figure 1. Fluorinated amines and unsubstituted amines under investigation

The aims of this work are to characterize the structural and conformational ramifications of these stereoelectronic effects in fluoromethylamines and trifluoromethylamines and to evaluate the performance of several modern computational methods in terms of describing these effects. Although, as outlined above, there are many computational studies in the literature on N—C—F systems, most of the calculations were carried out at the Hartree–Fock level with only small or moderately sized basis sets. Thus, the goals of this work include bringing the literature record on the N—C—F systems up to date and extending the studies to include direct comparisons with the corresponding N—C—CF_3 systems. Also, there is a need to evaluate the performance of several modern computational methods, including not only *ab initio* and density functional methods but also semi-empirical and force field methods, in terms of describing these effects. This benchmarking process is important because computationally efficient methods are needed to evaluate the large number of conformations (and/or configurations) that arise in systems of interest in applied areas such as medicinal chemistry and material science. But whether these more approximate methods can adequately describe the unique subtleties that are often encountered in fluorinated systems remains in question. Thus, a variety of computational methods have been employed here, including molecular mechanics, semi-empirical, density functional and *ab initio* methods. In order to ascertain the sensitivity of the stereoelectronic effects to the surrounding medium, the effect of solvent was considered via the polarized continuum model (PCM). Finally, natural bond order[24,43,44] analysis has been carried out to examine the relative importance of hyperconjugative interactions in these systems.

COMPUTATIONAL DETAILS

All calculations were carried out with the Spartan 02[45,46] and Gaussian 03[47] program packages. The molecular structures were built within Spartan and then subjected to a conformer distribution calculation using the default algorithms. This resulted in a systematic conformational search of all rotatable bonds to identify local minima, which then were optimized fully without symmetry constraints. This procedure was carried out at the merck molecular force field (MMFF),[48–52] AM1,[53] HF/6-31 + G(d), MP2/6-31 + G(d) and B3LYP/6-31 + G(d) levels, as implemented in Spartan 02.[46] For simplicity, the latter three protocols will be referred to as HF, MP2-1 and DFT, respectively. In addition, each of the conformations identified by the Spartan searching procedure at the

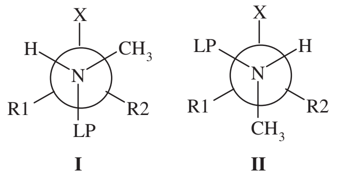


Figure 2. Staggered conformations that result from rotation about the N—C bond. The abbreviation LP is simply a schematic representation of the nitrogen lone pair and has no bearing on the actual calculations

HF level was subjected to complete geometry optimization with Gaussian 03 at the MP2/6-311 + G(2d,p) level. This set of results will be referred to as MP2-2. The range of conformations found can be described by the schematic shown in Fig. 2 and an example set of optimized structures is shown in Fig. 3. In some cases, a particular conformation was not identified as being a minimum through the Spartan conformer distribution calculation at a given level of theory. Those structures were built by hand in the conformation of interest and subjected to optimization. In all cases, the structure moved to another conformation upon optimization, thus confirming the results of the conformer distribution procedure. Frequency calculations were carried out for all structures; the minima were found to possess zero imaginary frequencies and transition states were found to possess one imaginary frequency corresponding to the appropriate mode. Table 1 contains the differences in total energies (ΔE) for the conformations (ΔE values including corrections for differences in zero-point vibrational energies are provided for the MP2-2 values). For organizational purposes, the relative energies of the conformational minima are reported in terms of conformations I, II and III for each member of the set of compounds F1, F2, F3, CF1, CF2, CF3 and EMA (ethylmethylamine). However, the stereochemical relationships among these compounds are such that nitrogen inversion of F1, for example, leads to the enantiomer of F2.

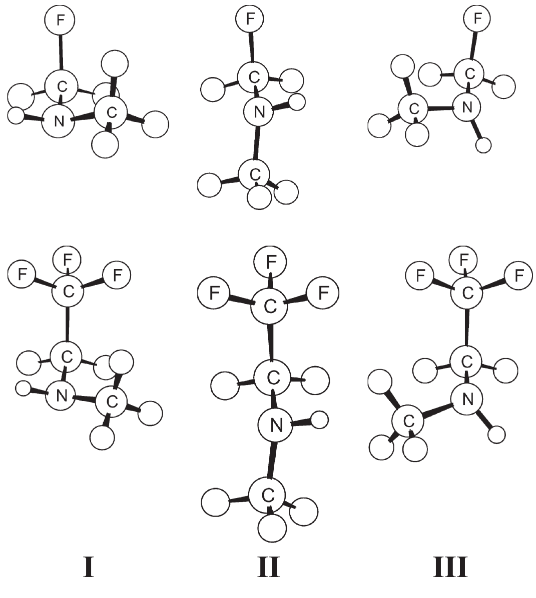


Figure 3. Optimized (MP2/6-311 + G(2d,p)) geometries of conformations I, II and III of compounds F1 (top row) and CF1 (bottom row)

Natural bond orbital (NBO) analysis was conducted using Weinhold's method[24,43,44] as implemented in Gaussian 03. This was accomplished by carrying out single-point energy calculations on the conformers found by Spartan at the HF/6-31 + G(d) level for the systems of interest (F1, CF1, EMA).

Aqueous-phase calculations were carried out with the PCM as implemented in Gaussian 03 using the default parameters for water.[54–56] These calculations were carried out via MP2/6-311 + G(2d,p) single points at the MP2/6-311 + G(2d,p) gas-phase geometries.

RESULTS

Conformational energies

Geometry optimizations were carried out on the conformations shown in Fig. 2, which are generated by rotation about the N—C bond. The gas-phase relative conformational energies (ΔE) are shown in Table 1. In all cases, the lowest energy structure was found to have the smallest dipole moment (for the MP2/6-311 + G(2d,p)-calculated dipole moments, see Supplementary material). The conformational energies shown in Table 1 are for the molecules in isolation, thus there is expected to be a preference for the conformers where the bond moments cancel.

For fluorinated amines F1–F3, all methods predict conformation I to be the lowest energy structure of the conformations considered here. The lone pair is *anti* to the fluorine in this conformation and presumably the preference for this conformation is due, at least in part, to the aforementioned stereoelectronic effect where the lone-pair electron density is best delocalized into the C—F σ^* orbital. For F1, conformation II was not found to exist as a minimum on the potential energy surface at the AM1 and MP2-1 levels (it optimized to conformation I in all attempts). Conformation I was the only minimum found at the DFT level. At the HF and MP2-2 levels, all three conformations were found as minima and the calculated energy differences are similar. For instance, conformations II and III of F1 were found to lie above the ground state by 5.40 and 4.45 kcal mol^{-1}, respectively (with MP2-2, the values are 5.63 and 3.96 kcal mol^{-1}). This is in close agreement with previous computational studies of F1.[33]

It is highly desirable to be able to model fluorine-mediated stereoelectronic effects for larger systems. Thus, one of the goals of this work is to compare the results of the more approximate molecular mechanics and semi-empirical methods to the *ab initio* and DFT

Table 1. Gas-phase conformational energies ΔE (kcal mol^{-1})[a]

Method	Conformation I	Conformation II	Conformation III
Compound: F1			
MMFF[b]	0.00	1.65	2.44
AM1[c]	0.00	—	4.13
HF[d]	0.00	5.40	4.45
MP2-1[e]	0.00	—	5.05
DFT[f]	0.00	—	—
MP2-2[g]	0.00	5.91	4.38
MP2-2 + ΔZPE[h]	0.00	5.63	3.96
Compound: F2			
MMFF	0.00	2.01	0.59
AM1	0.00	2.08	3.26
HF	0.00	4.06	2.46
MP2-1	0.00	—	3.28
DFT	0.00	—	2.63
MP2-2	0.00	4.46	2.82
MP2-2 + ΔZPE	0.00	4.14	2.37
Compound: F3			
MMFF	0.00	2.62	4.28
AM1	0.00	—	3.08
HF	0.00	5.56	6.17
MP2-1	0.00	6.30	6.48
DFT	0.00	6.28	—
MP2-2	0.00	5.60	5.67
MP2-2 + ΔZPE	0.00	5.52	5.48
Compound: CF1			
MMFF	0.00	0.29	0.97
AM1	0.00	2.53	2.86
HF	0.03	0.00	0.77
MP2-1	0.58	0.00	1.02
DFT	0.00	0.48	1.13
MP2-2	0.00	0.32	0.94
MP2-2 + ΔZPE	0.00	0.26	0.88
Compound: CF2			
MMFF	0.27	1.74	0.00
AM1	0.00	0.97	1.62
HF	0.39	0.03	0.00
MP2-1	0.00	0.46	0.12
DFT	0.00	0.26	0.08
MP2-2	0.00	0.39	0.10
MP2-2 + ΔZPE	0.06	0.21	0.00
Compound: CF3			
MMFF	0.00	1.54	2.24
AM1	0.00	2.87	2.33
HF	0.00	0.92	2.76
MP2-1	0.00	0.88	2.74
DFT	0.00	1.10	2.94
MP2-2	0.00	0.45	2.48
MP2-2 + ΔZPE	0.00	0.57	2.58
Compound: EMA			
MMFF	1.61	1.86	0.00
AM1	1.77	0.00	0.83
HF	1.12	1.58	0.00
MP2-1	0.77	1.39	0.00
DFT	0.96	1.44	0.00
MP2-2	0.72	1.34	0.00
MP2-2 + ΔZPE	0.84	1.37	0.00
Expt. ΔH (Ref. 34)	0.51 ± 0.08	0.96 ± 0.10	0.00

[a] Energy differences for fully optimized structures using the indicated methods (see text). The absence of a value indicates that no minimum was found for that conformation.
[b] Merck molecular force field.
[c] AM1//AM1.
[d] HF/6-31 + G(d)//HF/6-31 + G(d).
[e] MP2/6-31 + G(d)//MP2/6-31 + G(d).
[f] B3LYP/6-31 + G(d)//B3LYP/6-31 + G(d).
[g] MP2/6-311 + G(2d,p)//MP2/6-311 + G(2d,p).
[h] Energy differences including differences in zero-point vibrational energies evaluated at MP2/6-311 + G(2d,p).

methods to allow for an evaluation of their performance. One might expect molecular mechanics to do a poor job of describing subtle stereoelectronic effects such as those considered here. For example, based on sterics alone, for F1 one might predict conformation II to be the most stable because it lacks an F—CH_3 *gauche* interaction. However, the MMFF results predict conformation I to be the ground state, in agreement with the quantum mechanical methods, and they underestimate the relative stability of conformation I compared with *ab initio* methods. The AM1 results are quite reasonable for F1. They do not predict conformation II to be a minimum, but neither do the MP2-1 results. The relative energy of conformation III is 4.13 kcal mol^{-1}, which is in reasonable agreement with the HF and MP2 results with either basis set considered here.

Compounds F2 and F3 possess a methyl on the fluorine-bearing carbon, introducing the possibility of methyl–methyl *gauche* interactions. For F2, conformation I is the most sterically crowded conformation because there is a *gauche* methyl–methyl interaction as well a *gauche* fluoro–methyl interaction, however it is still predicted to be the lowest energy structure with all methods. Presumably this enhanced crowding destabilizes conformation I resulting in a lower ΔE value for the other conformations compared with the results for F1. For F2 there is reasonable agreement among the methods, with some clear exceptions. Molecular mechanics correctly predicts conformation I to be the global minimum but significantly overestimates the stability of conformation III compared with the *ab initio* and DFT methods (0.59 compared with 2.46–3.28 kcal mol^{-1}). The HF results predict conformation III to be lower in energy than conformation II, whereas AM1 produces reverse ordering. Conformation II does not exist as a minimum on the MP2-1 or DFT potential energy surfaces. Once again, the MP2-2 results closely mirror the HF results, with conformations II and III predicted to lie at 4.14 and 2.37 kcal mol^{-1} (including ΔZPE), respectively.

For F3, once again all methods predict conformation I to be the lowest energy structure and the preference for it is far more substantial than in F2. Conformation I in F3 has the favorable *anti* arrangement between the lone pair and the C—F bond but there is better sterics than in F2 because the methyl groups are now *anti* to each other. The HF, MP2 and DFT results are all in good agreement with each other and predict the next available conformation to lie well over 5 kcal mol^{-1} above the ground state. The MMFF protocol leads to smaller ΔE values for F3, as it does for F1 and F2, which is consistent with an underestimation of the significance of the presumed stereoelectronic effect. Conformation II was not found as a minimum for AM1 but AM1 does predict conformation I to be the ground state and conformation III to be significantly higher in energy, which is qualitatively consistent with the more sophisticated methods.

Compounds CF1–CF3 are included in this study to allow for an evaluation of the stereoelectronic effects in CF_3-containing compounds. The results in Table 1 suggest that a stereoelectronic effect still exists but its magnitude is smaller than when the electron-accepting group is a fluorine atom. In general, conformation I was still found to be the global minimum. The CF_3 group is therefore still exerting an effect that is great enough to compensate for the steric penalties associated with conformation I. The most notable result from the HF, MP2 and DFT calculations on CF1 is the fact that a strong conformational preference no longer exists, in contrast to F1. All three conformations are calculated with these levels to lie within roughly a 1 kcal mol^{-1} window of the ground state. One would expect the CF_3 group not only to exert a smaller stereoelectronic effect but also to exert a more pronounced steric effect. It is very possible that these effects nearly cancel in the case of conformation I of CF1. In general, conformations I and II are found to be very similar in energy (AM1 is the exception). As a result, not all of these computational protocols predict the same conformation to be the global minimum. Both HF and MP2-1 predict conformation II whereas the others all predict conformation I to be the lowest energy conformation. However, the consensus picture that does emerge is clearly that conformations I and II are nearly degenerate ground states and conformation III is roughly 1 kcal mol^{-1} higher in energy. The MMFF protocol reproduces this trend quite well, with conformations II and III lying 0.29 and 0.97 kcal mol^{-1}, respectively, above the ground-state structure conformation I. The AM1 protocol predicts conformation I to be lowest in energy, with conformations II and III 2.53 and 2.86 kcal mol^{-1} higher in energy, respectively. Thus, AM1 predicts the conformational preferences for CF1 to be very similar to those of F1, whereas all of the other protocols indicate that CF1 has much greater conformational diversity than its F1 counterpart, where conformation I strongly predominates.

In compounds CF2 and CF3, the possibility of CH_3–CH_3 and CH_3–CF_3 *gauche* interactions exists. For CF2, conformation I contains both CH_3–CH_3 and CH_3–CF_3 *gauche* interactions but is still predicted to be the ground state by DFT and MP2-1. At the HF level this conformation is predicted to lie only 0.39 kcal mol^{-1} above the ground state and only 0.27 kcal mol^{-1} above the ground-state conformation III with MMFF. Both MP2-1 and DFT predict a very similar set of ΔE values, with conformation I as the ground state, conformation III as a low-lying minimum (ΔE values of 0.12 and 0.08 kcal mol^{-1} for MP2-1 and DFT, respectively) and conformation II as the highest energy conformation (ΔE values of 0.92 and 0.88 kcal mol^{-1}, respectively). The MP2-2 protocol predicts conformation III to be the lowest energy structure by a slight amount (0.06 kcal mol^{-1}) with the inclusion of zero-point energy differences. There is consensus among HF, DFT, MP2-1 and MP2-2 in that they all predict the three conformations to lie within 0.50 kcal mol^{-1} of the ground state. Thus, it is noteworthy that substitution of the fluoro group by a trifluoromethyl group is not accompanied by a reduction in the population of conformers with *gauche* interactions, presumably because of the stereoelectronic effect.

For CF3 there is a very strong consensus among the most sophisticated approaches (HF, MP2-1, MP2-2 and DFT), with all ΔE predictions within roughly 0.2 kcal mol^{-1} of each other. Conformation I is predicted to have the lowest energy. It has the lone pair *anti* to the CF_3 group and has a *gauche* CH_3–CF_3 interaction. The next highest conformation is II (ΔE values of 0.57–1.10 kcal mol^{-1}), which has a CH_3–CH_3 *gauche* interaction. Conformation III is predicted to be the highest in energy (ΔE values of 2.58–2.94 kcal mol^{-1}) and it has both CH_3–CH_3 and CH_3–CF_3 *gauche* interactions. These results are nearly reproduced by the more approximate methods (MMFF and AM1), although AM1 gives a reversed ordering of conformations II and III.

Ethylmethylamine (EMA) is included in this study to serve as a standard so that the fluoro and trifluoromethyl substituent effects can be elucidated more easily. The HF, MP2-1, MP2-2 and DFT methods all predict conformation III of EMA to have the lowest energy. Presumably, this is due to the lack of a *gauche* interaction. Conformation I is found to lie 0.77–1.12 kcal mol^{-1} above the ground state (by the *ab initio* and DFT methods). Conformation II is slightly higher in energy (1.39–1.58 kcal mol^{-1}). Variable-temperature infrared studies[57] indicate that conformation III is the lowest energy structure under the conditions of the experiment (−110 to −150 °C in liquid krypton), with conformation I next in energy at 0.51 kcal mol^{-1} followed by conformation II at 0.96 kcal mol^{-1}. The HF, MP2-1, MP2-2 and DFT results are in reasonable agreement with this. In fact, all of the methods employed here, except AM1, produce the same qualitative ordering of EMA conformations.

Rotation and inversion barriers

Table 2 contains the barriers to rotation about the N—C bond for compounds F1, CF1 and EMA, as well as the nitrogen inversion barriers for these compounds (in conformation I), calculated at the MP2-2 level. Earlier studies, at the Hartree–Fock level with smaller basis sets, have reported that the stereoelectronic effect in N—C—F systems results in a lowering of the barrier to inversion at nitrogen and a raising of the barrier to rotation about the C—N bond.[26,31–33] In fact, previous studies of F1 have predicted its inversion barrier to be smaller than its C—N rotational barrier, which is opposite to the situation in ethylamine where the rotation barrier is the smaller of the two.[33] The values in Table 2 for F1 support this finding. At the MP2/6-311 + G(2d,p)//MP2/6-311 + G(2d,p) level the inversion barrier is found

Table 2. The MP2/6-311 + G(2d,p)//MP2/6-311 + G(2d,p)-calculated rotation and inversion barriers[a]

Compound	INV[b]	ROT1[b]	ROT2[b]	ROT3[b]
F1	4.68 (3.67)	11.16 (10.94)	8.54 (8.08)	5.92 (5.57)
CF1	3.94 (2.99)	6.94 (6.87)	3.17 (2.91)	1.87 (1.63)
EMA	6.09 (5.17)	3.13 (2.98)	6.60 (6.65)	3.50 (3.43)

[a] Values represent the difference in energy (in kcal mol^{-1}) between the indicated transition and the ground-state conformation for that compound. Values in parentheses are corrected for differences in zero-point vibrational energies.

[b] INV, transition state for inversion at nitrogen of conformation I; ROT1, rotational transition state for conformation III → conformation I; ROT2, rotational transition state for conformation I → conformation II; ROT3, rotational transition state for conformation II → conformation III.

to be 4.68 kcal mol^{-1} and the rotational barriers range from 5.92 to 11.16 kcal mol^{-1}. These results are in general agreement with the previously reported HF/6-31G(d) results.[33] The current work allows for an analysis of the effect of the trifluoromethyl group on the stereoelectronic effect. For compound CF1, the inversion and rotation barriers are much closer to each other in magnitude than is seen for F1, suggesting that the magnitude of the stereoelectronic effect is smaller than in F1. The highest energy rotational transition state (ROT1) contains eclipsing interactions between the methyl and trifluoromethyl groups. The rotational barriers are lower for the CF_3-containing compound than for the fluoro analogue. The same trend has been observed in variable-temperature NMR studies in non-polar solvents on compounds of the $PhCH_2$-$N(CH_3)$-CH_2-X type (X = F or CF_3), where the barriers measured at low temperatures were 10.1 kcal mol^{-1} for the fluoro compound and 7.3 kcal mol^{-1} for the CF_3 compound.[35]

Geometries

The calculated C—N, C—H, and C—F bond lengths for compounds F1, CF1 and EMA are presented in Table 3. Some trends emerge regarding the various computational methods. For example, The MMFF C—N bond lengths show much less sensitivity to conformation than do the quantum mechanical methods. For F1 at the MP2/6-311 + G(2d,p) level, the C—N bond lengths are 1.404 and 1.430 Å and the C—F bond lengths are 1.426 and 1.391 Å, respectively in conformations I and II, respectively. These geometrical changes are consistent with what one would expect to accompany the stereoelectronic effect where lone-pair delocalization into the C—F σ^* orbital occurs (see Fig. 4). Conformation I is the structure expected to be the best at facilitating this effect because the lone pair is *anti* to the fluorine, therefore it is not surprising that it has the shortest C—N bond and the longest C—F bond. Conformation II is not found to be a minimum at the AM1 and MP2-1 levels, but both of these methods do produce a shorter C—N and a longer C—F bond in conformation I than in conformation III.

Table 3. Selected calculated bond lengths (Å) for conformations I, II and III of compounds F1, CF1 and MEA

Method	Bond distance	Conformation I	Conformation II	Conformation III
Compound: F1				
MMFF[a]	C—N	1.451	1.448	1.452
	C—F	1.356	1.357	1.356
AM1[b]	C—N	1.450		1.457
	C—F	1.394		1.387
HF[c]	C—N	1.404	1.425	1.414
	C—F	1.393	1.367	1.376
MP2-1[d]	C—N	1.405		1.408
	C—F	1.445		1.427
DFT[e]	C—N	1.403		
	C—F	1.444		
MP2-2[f]	C—N	1.404	1.430	1.415
	C—F	1.426	1.391	1.405
Compound: CF1				
MMFF	C—N	1.485	1.483	1.484
	C—C	1.541	1.541	1.544
AM1	C—N	1.425	1.440	1.432
	C—C	1.580	1.569	1.576
HF	C—N	1.434	1.439	1.440
	C—C	1.518	1.510	1.514
MP2-1	C—N	1.445	1.451	1.450
	C—C	1.519	1.508	1.513
DFT	C—N	1.445	1.451	1.450
	C—C	1.532	1.520	1.526
MP2-2	C—N	1.443	1.448	1.448
	C—C	1.516	1.505	1.510
Compound: EMA				
MMFF	C—N	1.462	1.462	1.464
	C—H	1.096	1.096	1.096
AM1	C—N	1.450	1.450	1.446
	C—H	1.128	1.128	1.132
HF	C—N	1.454	1.452	1.450
	C—H	1.094	1.086	1.086
MP2-1	C—N	1.465	1.463	1.461
	C—H	1.107	1.096	1.097
DFT	C—N	1.466	1.464	1.462
	C—H	1.109	1.098	1.099
MP2-2	C—N	1.463	1.462	1.460
	C—H	1.103	1.094	1.095

[a] Merck molecular force field.

[b] AM1//AM1.

[c] HF/6-31 + G(d)//HF/6-31 + G(d).

[d] MP2/6-31 + G(d)//MP2/6-31 + G(d).

[e] B3LYP/6-31 + G(d)//B3LYP/6-31 + G(d).

[f] MP2/6-311 + G(2d,p)//MP2/6-311 + G(2d,p).

It is instructive to compare these bond lengths in F1 with the corresponding bond lengths in the parent EMA compound that does not contain fluorine. At the HF, MP2-1, MP2-2 and DFT levels the C—N bond in F1 is significantly shorter than the C—N bond in EMA. For example, for conformation I at MP2/6-311 + G(2d,p) the C—N bond is 1.404 Å for F1 and 1.463 Å for EMA. This is in contrast to what is expected based on sterics (i.e. the F in F1 is replaced by an H in EMA).

Similar results are seen for the trifluoromethyl compound CF1. All of the quantum-based methods (AM1, HF, MP2-1, MP2-2, DFT) predict conformation I to have the shortest C—N bond. Even the C—CF_3 bond in CF1 shows a trend that is analogous to that seen for the C—F bond in F1. The C—CF_3 bond is longest in conformation I (e.g. at the MP2/6-311 + G(2d,p) level it is 1.516 Å versus 1.505 Å and 1.510 Å for conformations II and III,

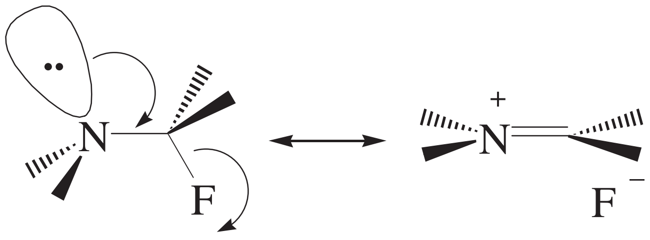


Figure 4. Hyperconjugative delocalization of lone-pair electron density

respectively). And, as for F1, the MMFF force field does not exhibit this subtle conformational effect on bond lengths. Also, comparison with the EMA bond lengths reveals the same trends for CF1 as were seen for F1. The C—N bond is shorter in CF1 than for EMA. This is true for all three conformations but the effect is most pronounced for conformation I.

Partial atomic charges

One might expect the partial atomic charges for these systems to vary with conformation in a predictable manner that is consistent with charge flow, as depicted in Fig. 4. The natural atomic charges[43,44]for selected atoms of F1, CF1 and EMA are presented in Table 4. For F1 the charge on the fluorine is most negative in conformation I, which presumably allows the greatest charge flow from N to F because of the *anti* arrangement of the lone pair with respect to the fluorine. An analogous examination of the CF_3-containing compound CF1 is also provided. Here the CF_3 group has been treated as a single unit by summing the individual atomic charges for the carbon and three fluorines into the single value provided in the table. Once again, the CF_3 group bears a slightly more negative charge in conformation I than in II or III. As a comparison, the variation of the charge on the hydrogen atom in EMA (which occupies the same position as F in F1 and CF_3 in CF1) is shown as a function of conformation. The charges are positive for all three conformations but the value is least positive for conformation I. Thus, the NBO method does seem to pick up the transfer of charge to the electron-withdrawing group (F or CF_3) via the stereoelectronic effect and this charge flow is correlated with the geometrical changes expected based on the hyperconjugative effects depicted in Fig. 4. The picture is not as clear when the charge on nitrogen is examined. One might expect the nitrogen charge to be more positive in conformation I due to the stereoelectronic effect, but this is found only for F1 and to a very small extent.

Table 4. Natural partial atomic charges(in electron units) at the HF/6-31 + G(d) level

Compound	Atom(s)	Conformation I	Conformation II	Conformation III
F1	F	−0.475	−0.444	−0.455
CF1	CF_3	−1.547	−1.534	−1.540
EMA	H	0.181	0.215	0.210

Natural bond order analysis

Natural bond orbital (NBO) analysis[24,43,44] was carried out on compounds F1, CF1 and EMA at the HF/6-31 + G(d) level to investigate the degree of nitrogen lone-pair (n_N) delocalization in these systems and determine its dependence on conformation. All three conformations are predicted to be minima for these three compounds with HF and MP2-2, and the conformational energy differences are very similar. The HF results were chosen for NBO analysis because there are additional options (NBO deletions) available in Gaussian 03 at the HF level. The results of the NBO analysis are summarized in Table 5. Of particular interest is the delocalization of the nitrogen lone-pair electrons into the C—F σ^* orbital, as well as the analogous $n_N \rightarrow \sigma_{C—C}{}^*$ interaction in the trifluoromethyl compound CF1. In NBO analysis, a search for a natural Lewis structure is conducted and the percentage of total electron density that populates the NBOs associated with that Lewis structure is reported. The remaining percentage of the total electron density is reported as the non-Lewis contribution and that parameter is reported in Table 5 for conformations I, II and III of compounds F1, CF1 and EMA. This parameter indicates the degree to which non-Lewis NBOs (antibonding and/or Rydberg) are populated and is reported also as a percentage of the total electron density. To provide a benchmark to allow interpretation of these results, NBO analysis was carried out on formamide, a compound regarded as having a significant amount of nitrogen lone-pair delocalization.

For F1 the non-Lewis population is found to be highly dependent on conformation, with the greatest value obtained for conformation I. Inspection of the results indicates that the most significant cause of non-Lewis delocalization is the aforementioned stereoelectronic effect (i.e. $n_N \rightarrow \sigma_{CF}{}^*$). The nitrogen lone-pair occupancy is lowest for F1 in conformation I at 1.903 electrons. The corresponding value for the formamide standard is 1.804. The NBO analysis also provides second-order perturbative estimates of specific donor–acceptor interactions in the NBO basis. These are expressed in kcal mol^{-1} and represent the stabilizing effect due to the interaction between filled Lewis-type NBOs and unoccupied non-Lewis (i.e. antibonding or Rydberg) NBOs. The most significant interactions are listed as $E^{(2)}$ values for each conformation of each compound in Table 5. Inspection of these results indicates that, for F1, delocalization of the nitrogen lone pair into the CF antibonding orbital is the dominant interaction, with an $E^{(2)}$ value of 29.2 kcal mol^{-1}. The next highest ranking interactions

Table 5. Summary of natural bond orbital analysis[a]

	Conformation		
	I	II	III
Compound: F1			
Non-Lewis population (e)	0.222	0.066	0.071
Percentage of total electron density	0.652%	0.194%	0.209%
$\mathrm{n_N}$ occupancy (e)	1.903	1.931	1.913
Most significant stabilization energies (in kcal mol^{-1}) of non-Lewis delocalizations	(1) 29.2 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CF}}^*$	(1) 11.6 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$	(1) 17.2 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CF}}^*$
	(2) 10.9 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CN}}^*$	(2) 11.5 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$	(2) 11.4 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$
	(3) 10.7 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$	(3) 10.5 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CN}}^*$	(3) 10.3 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$
		(4) 7.2 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CF}}^*$	(4) 10.2 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CN}}^*$
ΔE (kcal mol^{-1})	0.00	5.40	4.45
$\Delta E^{\mathrm{nostar}}$ (kcal mol^{-1})	4.26	0.00	3.21
$\Delta E^{\mathrm{noCF*}}$ (kcal mol^{-1})	10.68	0.00	6.14
Compound CF1			
Non-Lewis population (e)	0.470	0.461	0.446
Percentage of total electron density	0.811%	0.794%	0.769%
$\mathrm{n_N}$ occupancy	1.932	1.940	1.934
Most significant stabilization energies (in kcal mol^{-1}) of non-Lewis delocalizations	(1) 15.9 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$	(1) 16.0 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$	16.4 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$
	(2) 15.4 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$	(2) 15.7 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$	16.0 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$
	(3) 15.3 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$	(3) 14.1 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$	14.7 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$
	(4) 14.5 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CC}}^*$	(4) 12.4 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$	13.3 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$
	(5) 13.2 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$	(5) 12.1 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$	13.1 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$
	(6) 13.0 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$	(6) 12.1 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$	12.2 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$
	(7) 12.7 $\mathrm{n_F} \rightarrow \sigma_{\mathrm{CF}}^*$	(7) 11.2 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$	11.2 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$
	(8) 11.5 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$		11.0 $\mathrm{n_N} \rightarrow \mathrm{C}^*$
		(30) 3.27 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CC}}^*$	9.31 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CC}}$
ΔE (kcal mol^{-1})	0.03	0.00	0.77
$\Delta E^{\mathrm{nostar}}$ (kcal mol^{-1})	6.21	0.00	0.98
$\Delta E^{\mathrm{noCF*}}$ (kcal mol^{-1})	8.40	0.00	5.20
Compound: EMA			
Non-Lewis population (e)	0.167	0.168	0.168
Percentage of total electron density	0.491%	0.494%	0.494%
$\mathrm{n_N}$ occupancy	1.940	1.941	1.941
Most significant stabilization energies (in kcal mol^{-1}) of non-Lewis delocalizations	11.31 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$	12.2 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$	11.4 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$
	10.7 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$	11.9 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CC}}^*$	11.1 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$
ΔE (kcal mol^{-1})	1.12	1.58	0.00
$\Delta E^{\mathrm{nostar}}$ (kcal mol^{-1})	0.33	3.77	0.00
Compound: formamide			
Non-Lewis population (e)	0.362		
Percentage of total electron density	1.507%		
Most significant stabilization energies (in kcal mol^{-1}) of non-Lewis delocalizations	90.92 $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CO}}^*$		
$\mathrm{n_N}$ occupancy	1.804		

[a] See text for definition of terms.

are $\mathrm{n_F}$ to σ_{CN}^*, and $\mathrm{n_N}$ to the σ^* of the *anti* CH bond on the $\mathrm{CH_3}$ group. For conformation II, the dominant interaction is delocalization of the nitrogen lone pair into the σ_{CH}^* orbital of the hydrogen *anti* to the lone pair. The $E^{(2)}$ value for the $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CF}}^*$ interaction drops to 7.2 kcal mol^{-1}, ranking it behind the nitrogen lone pair to CH antibonding delocalizations as well as the fluorine lone pair to C—N antibonding delocalization. In conformation III, $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CF}}^*$ interaction is also the dominant delocalization, although its magnitude is less than it is in conformation I. In the optimized structure of conformation III there is a near *syn* arrangement between the C—F bond and the expected spatial arrangement of the lone pair (see Fig. 3).

The significance of the stereoelectronic effect in conformation I of F1 can be placed in context by comparison with the highly delocalized formamide standard. The $\mathrm{n_N}$ to π_{CO}^* $E^{(2)}$ value in formamide is 90.92 kcal mol^{-1}. As a benchmark at the low interaction end of the spectrum one could consider the $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$ interactions for F1 or he $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CH}}^*$ and $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CC}}^*$ interactions in EMA. These all fall within a range of 10.7–12.2 kcal mol^{-1}. Thus, although the $\mathrm{n_N} \rightarrow \sigma_{\mathrm{CF}}^*$ in F1 is not as significant as a true resonance type of delocalization, as in an amide, it is pronounced enough to influence greatly the conformational preferences of the molecule.

The conformational ramifications of this stereoelectronic effect can be elucidated further by examining the ΔE, ΔE^{nostar} and $\Delta E^{\text{noCF*}}$ values. The ΔE value is simply the difference in the HF/6-31 + G(d) energies for each conformation, whereas ΔE^{nostar} and $\Delta E^{\text{noCF*}}$ incorporate NBO deletions in the calculations. The ΔE^{nostar} set of conformational energies is the difference in energies obtained when all non-Lewis-type interactions are removed from the calculation. Thus, this value represents the conformational energy differences for the perfectly localized (each Lewis NBO doubly occupied) system. In other words, the stabilizing effect due to delocalization is deleted from the calculation. The $\Delta E^{\text{noCF*}}$ values are arrived at in a similar manner except that only the specific $n_N \rightarrow \sigma_{CF}$* interaction has been deleted. Deletion of these orbital interactions has a profound effect on the HF/6-31 + G(d) conformational energy differences. For F1, the stability of conformer I can be attributed largely to delocalization effects. In the absence of these effects, it lies far above the ground state (4.26 kcal mol^{-1} when neglecting all delocalizing interactions and 10.68 kcal mol^{-1} when neglecting $n_N \rightarrow \sigma_{CF}$* delocalization). These NBO results are consistent with the notion that the stereoelectronic effect is greatest when the lone pair is *anti* to the acceptor orbital. They also suggest that *syn* delocalization plays a role in determining the conformational energies and that the magnitude of these stereoelectronic effects is significant enough to overcome steric effects in even simple prototypical compounds such as these.

The NBO analysis was carried out also on compound CF1 to determine the significance of N lone-pair delocalization into the σ* of the C—CF$_3$ bond in a fashion analogous to that of F1. It is interesting to note that the total extent of non-Lewis delocalization is actually more significant in CF1 than in F1. However, this is due primarily to a large number of less important interactions involving delocalization of the fluorine lone pairs ($n_F \rightarrow \sigma_{CF}$*). And, in fact, the particular stereoelectronic effect that is the subject of this work ($n_N \rightarrow \sigma_{CX}$*, X = F, CF$_3$) is actually less important in CF1 than it was in F1. It does, however, exhibit a similar conformational dependency. The $n_N \rightarrow \sigma_{CC}$* interaction ranks eighth in significance among the non-Lewis delocalizations found in conformation I of CF1. Its ranking drops to 30th in conformation II and 9th in conformation III. The $E^{(2)}$ value for this interaction is 11.54 kcal mol^{-1} in conformation I, making it similar in strength to the $n_N \rightarrow \sigma_{CH}$* interactions in F1. It is interesting that the interaction is so much more significant in conformation III than in conformation II. A possible explanation lies in the optimized geometries, which indicate that there is more of a *syn* alignment between the lone pair and the C—CF$_3$ bond in conformation III but in conformation II these are more *gauche* to each other.

Aqueous solvation effects

The effect of an aqueous medium on the conformational energies of these compounds has been investigated with the polarized continuum model (PCM)[54–56] as implemented in Gaussian 03. The degree to which aqueous solvation is relevant to fluorinated amine compounds will depend on the specific application. The goal here is simply to elucidate how sensitive the conformational energy differences for these model compounds are to the surrounding medium by comparing results obtained at the two extremes: the absence of any solvent (gas phase results) and the presence of a highly interacting solvent (aqueous PCM results). The PCM calculations were performed on the gas-phase MP2/6-311 + G(2d,p) geometries. Thus, relaxation of the structure in water is ignored but this is not expected to vary greatly among the conformations. The results are summarized in Table 6. For each compound, the hydration free energy, ΔG_{Hyd}, is given for each conformation as well as the relative hydration free energies among the set of three conformations ($\Delta\Delta G_{\text{Hyd}}$ values). For compounds F1, F2 and F3, conformation I is the least well hydrated ($\Delta\Delta G_{\text{Hyd}}$ value set to 0). In the gas phase, conformation I was found consistently to be the ground state for these compounds when using the quantum mechanical methods. It appears that this trend should persist in an aqueous environment because the magnitude of the hydration effect that acts against conformation I is not great enough to counter the stereoelectronic effect that gives it its intrinsic stability. This is evidenced by the ΔE_{aq} values in Table 6, which rank the relative energies of the conformations, including the effect of solvent. Presumably, in less polar solvent media conformation I would be the ground state just as it is in the gas phase. It is interesting to note that the fluoroamine compounds (F1, F2 and F3), are predicted using the PCM to be better solvated than EMA (i.e. they have larger hydration free energies).

For the trifluoromethyl compounds (CF1, CF2 and CF3), the hydration free energies are generally smaller in magnitude than those for F1, F2 and F3. Also, because the intrinsic conformational preferences are far less pronounced than for the fluoroamines, the solvation energies can affect which conformation is the global minimum. For example, for CF1 at the MP2-2 level conformations I and II are near-degenerate ground states, but upon consideration of hydration effects conformation II becomes the global minimum by a very small margin (0.16–0.35 kcal mol^{-1}). Because the energy differences among conformations are so small in many cases for the CF$_3$-containing compounds, the conformation predicted to be the global minimum is not an instructive metric to use for these systems. However, what is significant is that the inclusion of hydration effects does not alter the general observation that these compounds (CF1, CF2, CF3) are expected to be more conformationally labile

Table 6. The PCM-calculated relative hydration free energies (kcal mol^{-1}) at MP2/6-311 + G(2d,p) geometries and relative conformation energies in aqueous solution

Method	Conformation I	Conformation II	Conformation III
Compound: F1			
$\Delta(E+\mathrm{ZPE})_{\mathrm{gas}}$[a]	0.00	5.63	3.96
ΔG_{Hyd}[b]	−5.74	−6.60	−6.81
$\Delta\Delta G_{\mathrm{Hyd}}$[c]	0.00	−0.86	−1.07
ΔE_{aq}[d]	0.00	4.77	2.89
Compound: F2			
$\Delta(E+\mathrm{ZPE})_{\mathrm{gas}}$	0.00	4.14	2.37
ΔG_{Hyd}	−5.78	−6.86	−6.32
$\Delta\Delta G_{\mathrm{Hyd}}$	0.00	−1.08	−0.53
ΔE_{aq}	0.00	3.06	1.83
Compound: F3			
$\Delta(E+\mathrm{ZPE})_{\mathrm{gas}}$	0.00	5.52	5.48
ΔG_{Hyd}	−5.56	−6.11	−7.04
$\Delta\Delta G_{\mathrm{Hyd}}$	0.00	−0.54	−1.48
ΔE_{aq}	0.00	4.97	4.00
Compound: CF1			
$\Delta(E+\mathrm{ZPE})_{\mathrm{gas}}$	0.00	0.26	0.88
ΔG_{Hyd}	−4.96	−5.56	−6.03
$\Delta\Delta G_{\mathrm{Hyd}}$	0.00	−0.61	−1.07
ΔE_{aq}	0.35	0.00	0.16
Compound: CF2			
$\Delta(E+\mathrm{ZPE})_{\mathrm{gas}}$	0.06	0.21	0.00
ΔG_{Hyd}	−4.87	−5.73	−5.51
$\Delta\Delta G_{\mathrm{Hyd}}$	0.00	−0.86	−0.64
ΔE_{aq}	0.71	0.00	0.01
Compound: CF3			
$\Delta(E+\mathrm{ZPE})_{\mathrm{gas}}$	0.00	0.57	2.58
ΔG_{Hyd}	−4.71	−5.08	−6.11
$\Delta\Delta G_{\mathrm{Hyd}}$	0.00	−0.37	−1.41
ΔE_{aq}	0.00	0.19	1.18
Compound: EMA			
$\Delta(E+\mathrm{ZPE})_{\mathrm{gas}}$	0.84	1.37	0.00
ΔG_{Hyd}	−3.64	−3.83	−3.55
$\Delta\Delta G_{\mathrm{Hyd}}$	−0.09	−0.28	0.00
ΔE_{aq}	0.75	1.09	0.00

[a] MP2/6-311 + G(2d,p)//MP2/6-311 + G(2d,p) gas-phase zero-point energy-corrected conformational energy differences.

[b] Hydration free energy: difference in free energy between the MP2/6-311 + G(2d,p) structure in the aqueous phase and in isolation. Greater negative values indicated better solvation.

[c] Relative hydration free energy: hydration free energies normalized so that the least-well-solvated conformer is assigned a zero value.

[d] Relative energy in solution: relative differences in the quantity $\Delta(E+\mathrm{ZPE})_{\mathrm{gas}}+\Delta G_{\mathrm{Hyd}}$ normalized so that the lowest value is assigned zero.

than their F1, F2 and F3 counterparts. For the fluoroamines there is a clear preference for conformation I in the gas phase and in solution, but for the trifluoromethylamines generally there are multiple low-lying conformations both in the gas phase and in solution.

CONCLUSIONS

A variety of computational techniques have been used to investigate the conformational preferences in a set of model amines bearing fluoro and trifluoromethyl substituents. The results have allowed for a characterization of the $n_N \rightarrow \sigma_{CX}{}^*$ ($X = F$, CF_3) stereoelectronic effect in terms of conformational energies, charge distribution, geometrical effects and orbital donor–acceptor interactions. The dependence of the conformational energies on the surrounding medium was also probed by carrying out a comparative set of calculations in the gas phase and in aqueous solution.

Conformation I is most often identified as the global minimum for the fluoro compounds and the trifluoromethyl compounds. This conformation contains an antiperiplanar relationship between the nitrogen lone pair and the C—X bond (where $X = F$ or CF_3) and predominates even in those cases where it results in methyl groups *gauche* to each other. In general, the preference for this conformation is stronger for the fluoro compounds (F1, F2, F3) than for the CF_3-containing compounds (CF1, CF2, CF3). There is a high degree of consistency among the HF, MP2 and B3LYP levels of theory (with the 6-31 + G(d) and 6-311 + G(2d,p) basis sets). Also, the MMFF force field often captures the salient features of these conformational effects.

The bond lengths vary with conformation in a way that is qualitatively consistent with delocalization of the nitrogen lone pair via the stereoelectronic effect depicted in Fig. 4. Analysis of the NBO interactions also suggests that this stereoelectronic effect plays a major role in stabilizing conformation I. The hydration free energies are larger for the fluoro compounds than for the trifluoromethyl compounds, but they do not vary enough among the three conformations to result in a conformational distribution that is significantly different from that in the gas phase.

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Supplementary material

Tables containing Cartesian coordinates, total energies, zero-point vibrational energies and dipole moments at the MP2/6-311 + G(2d,p) level of theory for conformations I, II and III and transition states INV, ROT1, ROT2 and ROT3 of compounds F1, F2, F2, CF1, CF2, CF3 and EMA are available in Wiley Interscience.

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