Conformational preferences and basicities of monofluorinated cyclopropyl amines in comparison to cyclopropylamine and 2-fluoroethylamine†

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Received 16th June 2008, Accepted 23rd July 2008
First published as an Advance Article on the web 22nd September 2008
DOI: 10.1039/b810108f

Fluorine substituents in organic molecules do dramatically influence the electronic structure of neighbouring functional groups and the conformation of molecules. Hence the presence of fluorine in a compound changes its chemical reactivity and biological activity. On the basis of MP2 and SCS-MP2 calculations, we discuss the conformational preferences and basicity of the diastereoisomeric 2-fluorocyclopropylamines (*cis*-**2** and *trans*-**2**) in comparison to those of cyclopropylamine (**1**) and 2-fluoroethylamine (**3**). **1** and **2** are viewed as model compounds for the antidepressant drug tranylcypromine (*trans*-2-phenylcyclopropylamine, **1′a**) and its fluorinated derivatives **2′**. The potential energy profile for the rotation of the amino group in *cis*-**2** differs from that of *trans*-**2** and **1** which have very similar rotational curves. For **2** the global minimum conformer is *trans*-**2a** and the lowest energy *cis*-conformer **2c** is less stable by 2.57 kcal mol^{-1}. The calculated enthalpy differences between the conformers *gauche*-**1b** and s-*trans*-**1a** (2.0 kcal mol^{-1}) as well as between *gauche*-**3b** and *gauche*-**4a** (0.2 kcal mol^{-1}) agree well with the available experimental data of 2.0 kcal mol^{-1} and 0.1 ± 0.3 kcal mol^{-1}, respectively. The calculated gas phase proton affinities (PA) of **1** (217.6 kcal mol^{-1}), *cis*-**2c** (215.6 kcal mol^{-1}), and *trans*-**2a** (209.3 kcal mol^{-1}) follow the trends of the pK_a values measured in solution for the diastereomeric 2-phenylcyclopropylamines **1′a** and **1′b** and their fluorinated derivatives *cis*-**2′** and *trans*-**2′**. It is shown that the conformational preferences and basicity of the investigated molecules are due to stereoelectronic effects from hyperconjugative interactions which lead to different local charge distributions and different hybridization of the nitrogen lone-pair. The basicity of *gauche*-**3a** (PA = 215.3 kcal mol^{-1}) and *anti*-**3b** (PA = 210.1 kcal mol^{-1}) is controlled by the charge of the nitrogen atom, while that of *cis*-**2c** and *trans*-**2a** is overlap controlled as a result of different hybridization of the nitrogen lone-pair [sp$^{4.34}$ (*cis*-**2c**), sp$^{4.07}$ (*trans*-**2a**)].

Introduction

Due to the specific effects of fluorination on structure–activity relationships, fluorinated compounds are attractive synthetic targets in many areas of organic, biological, and medicinal chemistry. The effects of a fluorine substituent on chemical reactivity and biological activity of molecules as well as its influence on the electronic structure of neighbouring functional groups and intermolecular interactions have been intensely studied in recent years.[1] In recent papers, we published work on the inhibitory effect of monofluorinated tranylcypromine (*trans*-2-phenylcyclopropylamine) derivatives on different monoamine oxidases.[2–4] In order to find a correlation between the actual biological activity and the physical chemical properties of these compounds, we determined their pK_a values. We found that the isomers with a *trans*-arrangement of the amino group and the fluorine have a significantly lower pK_a value than those with a *cis*-arrangement, while no such effect of the configuration was observed for the non-fluorinated parent compounds **1′a** and **1′b** (Scheme 1).[2]

Tranylcypromine (**1'a**), X = H, pK_a = 8.50
***cis*-2'**, X = F, pK_a = 7.35

epi-Tranylcypromine (**1'b**), X = H, pK_a = 8.47
***trans*-2'**, X = F, pK_a = 6.98

Scheme 1

Fluorine is the most electronegative element in the periodic table and a decrease of the basicity of an organic molecule by 1–2 units is to be expected when fluorine is introduced in the β-position.[5] In accordance with that, we observed for both *cis*- and *trans*-**2′** lower pK_a values than for **1′a** and **1′b** (Scheme 1).[2] However, one would expect *cis*-**2′** to exhibit a lower basicity than *trans*-**2′** as fluorine is in the vicinity of the amino group and therefore can more easily influence the electron density distribution at nitrogen. Since experiments disprove these expectations, other

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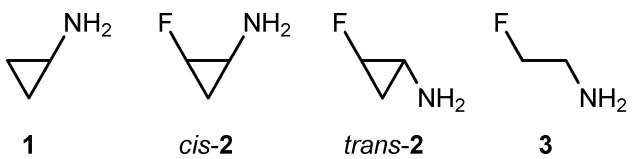
† Electronic supplementary information (ESI) available: Optimized parameters of the conformers of **1**, **2**, and **3** (Table S1), MP2/TZVPP vibrational frequencies of the global and local minima of **1**, *trans*- and *cis*-**2** (Table S2), and NBO analysis of the important hyperconjugative interactions of the protonated species 1H$^+$, *cis*-2H$^+$, and *trans*-2H$^+$ (Table S3) together with Scheme S1 showing the labeling of atoms. See DOI: 10.1039/b810108f

effects seem to play a more important role for the basicity of the amino group. An effect that is often mentioned in conjunction with acyclic fluorinated alkyl compounds is the *gauche effect*.[6] A classical example of the fluorine-*gauche effect* is 1,2-difluoroethane (**4**), where the supposedly disfavoured (by steric and electrostatic reasons) *gauche* conformer has a lower energy than the *anti* one.[7–9] The origin of the *gauche* effect has been discussed in terms of bond bending.[6b] Substituents with larger electronegativity increase the C–C bond bending which in turn destabilizes the *anti*-conformer in favour of the *gauche* conformer. Another simple explanation for the predominance of a conformation is commonly related with favourable hyperconjugative interactions.[8e,f,10] In view of the recent investigations on donor and acceptor properties of the C–H and C–F bonds,[10] one can postulate that in the *gauche*-1,2-difluoroethane there are stabilizing σ(C–H) → σ*(C–F) interactions between an *anti* to fluorine lying σ-C–H bond that is a better σ-donor than the C–F bond in the case of the *anti*-conformer. Due to the gain in energy from such σ(C–H) → σ*(C–F) hyperconjugation, the *gauche* arrangement should be the most stable structure.[8e,f]

In the cyclopropane compounds *cis*-**2′** and *trans*-**2′**, the configuration of fluorine and the amino group is fixed leading to either a *staggered* (*cis*) or an *anti* (*trans*) arrangement. Consequently the *gauche* effect cannot stabilize or destabilize one or the other isomer. Nevertheless, hyperconjugation may influence the properties of these compounds since it is inherently connected with electron density reorganizations at the particular molecular sites.[10] The shifts of electron density may change the basicity and stabilize the particular conformations. In order to rationalize the experimental findings concerning the basicity of fluorinated tranylcypromine derivatives, we present here the calculated gas phase proton affinity of the parent compounds: cyclopropylamine (**1**) and its fluorinated counterparts *cis*-**2** and *trans*-**2** (Scheme 2).



Scheme 2

The electronic structures and conformational preferences as well as the nature of interactions in the global minimum structures of **1**, *cis*-**2** and *trans*-**2** are the main focus of this paper. Since hyperconjugation depends on the overlap of orbitals and their intrinsic properties such as polarizability and energy,[10] in the case of cyclopropane compounds this may be inhibited or enhanced by the rigid structure of the small carbocycle. Thus, with the aim of comparison we included 2-fluoroethylamine (**3**) in our investigations.

Computational details

The calculations were carried out with the TURBOMOLE[11] and the Gaussian 03[12] suite of programs. All structures were geometry optimized at the second order Møller–Plesset perturbation theory (MP2) level.[13] Energetic properties of all investigated molecules were also examined at the SCS-MP2 level[14] and for the energetically close conformers of 2-fluoroethylamine (**3**) at the QCISD(T) level.[15] The SCS-MP2 approach improves the accuracy of the correlation energies calculated in the framework of the MP2 method and outperforms MP2 for reaction energies and activation barriers.[14] The QCISD(T) method provides energy predictions quite similar to those obtained with the CCSD(T) approach,[16] and therefore the QCISD(T) energies computed in this work should be reliable. The QCISD(T) calculations were carried out with the RICC program[17] which was designed as a TURBOMOLE extension. The MP2, SCS-MP2, and QCISD(T) calculations were carried with the resolution of the identity technique (RI)[18] by using the TURBOMOLE software. According to prior experience, errors resulting from the RI approximation are negligible for both, the relative energies and the optimized structural parameters. In both approaches, the 1 s electrons of carbon, nitrogen and fluorine were frozen in the correlation treatment. All atoms were described with valence triple-ζ basis sets augmented with polarization functions: (11s6p2d1f)/[5s3p2d1f] for C, N, and F, and (5s2p1d)/[3s2p1d] for H. These basis sets and the corresponding auxiliary basis sets for the RI approximation were taken from the TURBOMOLE basis set library where they are denoted as TZVPP.[19] In addition to conformational searches, stereoelectronic effects were also investigated with the NBO program[20] implemented in the GAUSSIAN 03 package. The hyperconjugative energies, $\Delta E_{\sigma\sigma^*}^{(2)}$, were calculated with the second-order perturbation theory approach according to eqn (1).[21]

$$\Delta E_{\sigma\sigma^*}^{(2)} = n_\sigma F^2_{\sigma\sigma^*}/(\varepsilon_{\sigma^*} - \varepsilon_\sigma) \quad (1)$$

$F_{\sigma\sigma^*}$ is the Fock matrix element in the NBO basis between the donor (σ) and acceptor (σ*) NBOs, ε_σ and ε_{σ^*} are the energies of σ and σ* NBOs, and n_σ is the population of the donor NBO(σ). The NBO analyses were carried out for the Hartree–Fock electron densities and with a threshold of 0.5 kcal mol^{-1} for the $\Delta E_{\sigma\sigma^*}^{(2)}$ values.

The proton affinity (PA) is calculated as a negative value of the enthalpy change of the protonation reaction: $B + H^+ \rightarrow BH^+$.[22] Using standard thermochemistry formulas for an ideal gas,[23] the change of enthalpies at 298.15 K and 1 atmosphere was calculated from the differences between the total electronic energies (E_{elec}), zero-point-vibrational-energy (ZPVE), and thermal energies (E_{th}) of the product (*i.e.*, the conjugate acid BH^+) and the reactants (*i.e.*, $B + H^+$, the neutral base and the proton) and corrected for the molar work term [$\Delta(PV)$] (eqn (2)).

$$PA = -\Delta H_{298};\ \Delta H_{298} = \Delta E_{elec} + \Delta ZPVE + \Delta E_{th} + \Delta(PV) \quad (2)$$

Zero-point energies were obtained from MP2 harmonic vibrational frequencies (unscaled) which were obtained with the SNF program.[24] The thermal energy contributions (ΔE_{th}) correspond to the sum of the changes in translational, rotational, and vibrational energies when going from 0 to 298.15 K. For an ideal gas the $\Delta(PV)$ term is equal to ΔnRT.[23] For graphical displays we used the MOLDEN program.[25]

Conformational preferences of *cis*- and *trans*-2-fluorocyclopropylamines (*cis*-2 and *trans*-2) *vs.* cyclopropylamine (1)

The conformational preferences of cyclopropylamine (**1**) were investigated decades ago with semiempirical (CNDO/2)[26] and *ab initio* (HF)[27] methods using very small basis sets and fixed

geometries. Therefore, we recalculated the potential energy profile for the amine rotation in **1** at the MP2/TZVPP level. Conformational analyses for the 2-fluorocyclopropylamines *trans*-**2** and *cis*-**2** were not discussed so far. The potential energy profile of **1** obtained from constrained geometry optimization, that is, for fixed rotation angle of the amino group relative to the cyclopropyl ring and with all other parameters relaxed is shown in Fig. 1. The analogous graphs obtained for *trans*-**2** and *cis*-**2** are displayed in Fig. 2. The minima of **1**, *trans*-**2** and *cis*-**2** were optimized with all parameters relaxed. Relative energies of the stationary points **1a**–**1e** are compared with available experimental data[28,29] in Table 1. Selected optimized parameters of the lowest energy conformers, **1a**, *trans*-**2a**, and *cis*-**2c**, are depicted in Fig. 3. The comparison of bond lengths and bond angles of all conformers is provided in the ESI (Table S1).† According to the suggestion of one reviewer, we added to the ESI the calculated harmonic vibrations for the minima of **1**, *trans*-**2**, and *cis*-**2**. All investigated minima exhibit few low vibrational frequencies. In general, compared to the local minima, the low frequencies are slightly larger for the global minima (Table S2).†

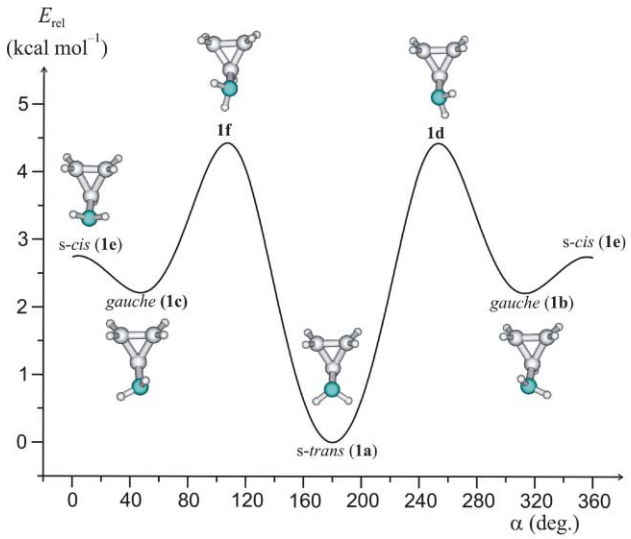


Fig. 1 MP2 potential energy profile for the rotation of the amino group relative to the cyclopropyl ring in **1** derived from constrained geometry optimizations with an interval of 20° for the rotational angle α. All parameters were relaxed in optimizations of the global and local minima. The rotational angle $\alpha = 0°$ corresponds to the s-*cis* conformer **1e**.

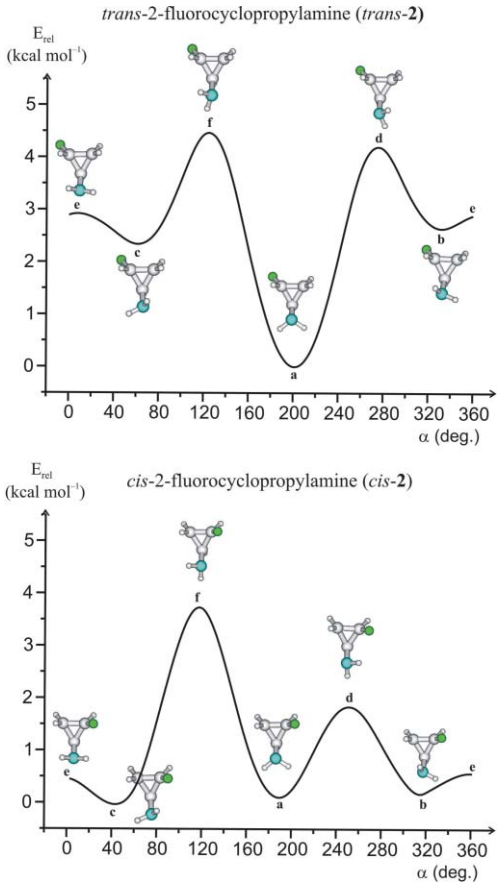


Fig. 2 MP2 potential energy profile for the rotation of the amino group relative to the cyclopropyl ring in *trans*-**2** (top) and *cis*-**2** (bottom) derived from constrained geometry optimization with an interval of 20° for the rotational angle α. All parameters were relaxed in optimizations of the global and local minima.

The conformational potential function of cyclopropylamine (**1**) was estimated experimentally from the measured infrared and Raman spectra.[28,29] The lowest energy structure was found to correspond to the symmetric s-*trans* conformer **1a** and the ΔH of the *gauche* conformer **1b**/**1c** was estimated as 2 kcal mol^{-1} [28] or 1.69 kcal mol^{-1}, respectively.[29] In the following, s-*trans* means that the protons at nitrogen point away from the *cis*-protons at carbon relative to nitrogen and s-*cis* means that the protons at nitrogen point towards the *cis*-protons at carbon.

Table 1 Relative energies (kcal mol^{-1}) of the minima (**a**–**c**) and maxima (**d**–**f**) on the potential energy curves for the rotation of the amino group in **1**, *trans*-**2**, and *cis*-**2**

Compound	Method	**a**	**d**	**b**	**e**	**c**	**f**
1	Exp.[a]	0.00	3.44	2.00	3.40	2.00	3.44
	Exp.[b]	0.00	3.62	1.69	2.88	1.69	3.62
	MP2/TZVPP	0.00	4.42	2.21	2.73	2.21	4.42
	SCS-MP2/TZVPP	0.00	4.29	2.17	2.72	2.17	4.29
trans-**2**	MP2/TZVPP	0.00	4.16	2.65	2.89	2.34	4.43
	SCS-MP2/TZVPP	0.00	4.07	2.65	2.93	2.33	4.45
cis-**2**	MP2/TZVPP [c]	0.09	1.71	0.12	0.50	0.00	3.74
		(2.60)	(4.22)	(2.63)	(3.01)	(2.51)	(6.25)
	SCS-MP2/TZVPP[c]	0.02	1.65	0.01	0.47	0.00	3.58
		(2.59)	(4.22)	(2.58)	(3.04)	(2.57)	(6.15)

[a] Ref. 28. [b] Ref. 29. [c] Values in parentheses refer to relative energies with respect to the global minimum *trans*-**2a**.

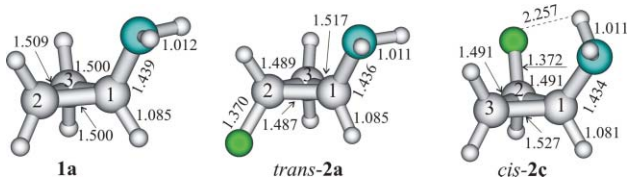


Fig. 3 Optimized bond distances (Å) of **1a**, *trans*-**2a**, and *cis*-**2c**.

The calculated ΔE between the *gauche*-**1b/1c** and s-*trans*-**1a** conformers [2.21 kcal mol^{-1} (MP2), 2.17 kcal mol^{-1} (SCS-MP2)] is closer to the experimental ΔH values than the previous theoretical estimates which range from 2.53 kcal mol^{-1} to 4.40 kcal mol^{-1}.[26,27] Adding zero-point vibrational energies and thermal corrections gives ΔH_{298} of 2.02 kcal mol^{-1} (SCS-MP2) which is in excellent agreement with the experimental value of 2.00 kcal mol^{-1} from ref. 28.

In accord with experimental estimates from ref. 29, the calculated barrier for the *gauche* → *gauche* rotation is lower than that for the *gauche* → s-*trans* one. Note, that according to ref. 28, both rotational barriers should be the same (Table 1).

The introduction of the fluorine substituent in the *trans* position to the amine does not have a strong influence on the rotational energy profile of the amino group (Fig. 2, top). The stationary points of *trans*-**2** are similar to those of **1** and differ only slightly in the amino group rotational angles. The dissymmetry introduced by the *trans*-fluorine substituent results in slightly different energies of the local minima *trans*-**2b** *vs.* *trans*-**2c** and of the maxima *trans*-**2d** *vs.* *trans*-**2f** but their relative energies are close to the values of the energetically degenerated structures **1b/1c** and **1d/1f**, respectively (Table 1).

Similar to the case of **1**, the relative energies of the structures **a–f** of *trans*-**2** and *cis*-**2** calculated at the MP2 level are very close to those from the SCS-MP2 level. For the sake of clarity we continue our discussion with the later values.

The rotational energy profile of *cis*-**2** differs significantly from those calculated for **1** and *trans*-**2** (Fig. 2, bottom). The three minima *cis*-**2a**, *cis*-**2b**, and *cis*-**2c** have almost the same energy. The lowest energy minimum corresponds to *cis*-**2c**. Due to the repulsive interactions between the lone pairs of fluorine and nitrogen the conformer *cis*-**2a** is less stable than *trans*-**2a** by 2.59 kcal mol^{-1}. Large differences are also discernible for the rotational barrier *cis*-**2d** (1.65 kcal mol^{-1}) *vs.* **1d** (4.29 kcal mol^{-1}) and *trans*-**2d** (4.07 kcal mol^{-1}). The energetic stabilization of *cis*-**2b**, *cis*-**2c**, and *cis*-**2d** is due to the N–H $\cdots$ F–C interaction, which to some extent makes up for F $\cdots$ N repulsion. The optimized F $\cdots$ H contacts of *cis*-**2c** (2.257 Å) and *cis*-**2d** (2.285 Å) are short and that of *cis*-**2b** (2.610 Å) is also below the sum of the fluorine and hydrogen van der Waals radii (2.67 Å).[30] The rotational energy profile of the amino group in *trans*-2-fluorocyclopropylamine (*trans*-**2**) suggests that the thermally most populated form will be the conformer *trans*-**2a**. For *cis*-2-fluorocyclopropylamine (*cis*-**2**), the situation is less clear. Due to the low energy barriers, at elevated temperature the conversion of *cis*-**2c** through *cis*-**2e** to *cis*-**2b** and further through *cis*-**2d** to *cis*-**2a** is possible and all conformers may coexist.

The optimized structure of **1a** agrees well with the experimental and previously calculated data.[31] In **1a** the amino group is pyramidalized and the lone-pair of the nitrogen points into the cyclopropyl ring. The C–C bonds adjacent to the amino substituent are shorter than the opposite C–C bond (Fig. 3). Such structural properties were commonly discussed on the basis of the Walsh/Bent model.[32] According to this model, an electronegative substituent increases the s-character in the adjacent C–C bonds and consequently these bonds are shorter.

With respect to **1**, fluorine substitution does not change the C–N bond distance, but influences the C–C bond lengths of the cyclopropyl ring. In accord with the Walsh/Bent model,[32] the vicinal to fluorine C–C bonds of *trans*-**2** and *cis*-**2** are significantly shorter and the opposite C–C bond is longer than in the conformers of cyclopropylamine (**1**) (Fig. 3, Table S1†).

Conformational preferences of 2-fluoroethylamine (3)

The optimized structures of the conformers of **3** and their relative energies are shown in Fig. 4. All these conformers correspond to true minima. Similar to the case of **1**, *trans*-**2**, and *cis*-**2**, three minima corresponding to the rotamers of the amino group were obtained for *gauche*-**3** and *anti*-**3**. During geometry optimization, the structure *syn*-**3a** converged to the *gauche*-**3b**.

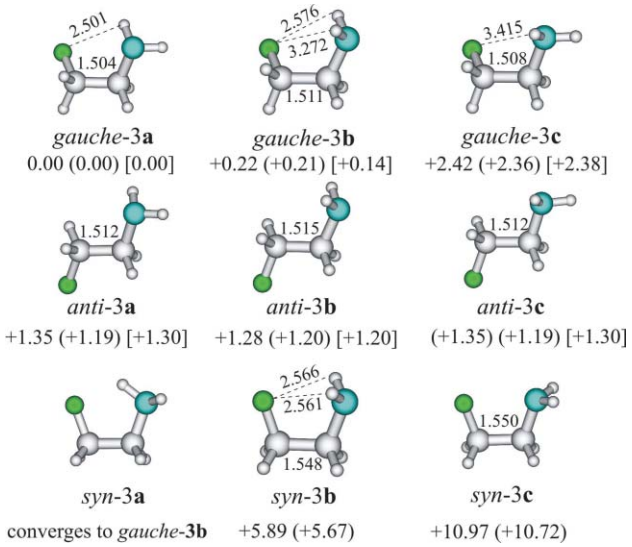


Fig. 4 MP2/TZVPP optimized structures and relative energies (ΔE kcal mol^{-1}) of the conformers of 2-fluoroethylamine (**3**). The SCS-MP2 and QCISD(T) relative energies are given in parentheses and brackets, respectively. Distances are given in Å.

The rotamers of **3** were investigated in the vapour phase in a microwave study.[33] Only the *gauche*-**3a** and *gauche*-**3b** rotamers were observed and the existence of a large fraction of other conformers was ruled out. The enthalpy difference was estimated as 0.1 ± 0.3 kcal mol^{-1}, with *gauche*-**3a** as the most stable conformer.[33] Our result [0.17 kcal mol^{-1}(MP2), 0.16 kcal mol^{-1} (SCS-MP2), 0.09 kcal mol^{-1} (QCISD(T))] agrees well with this experimental value. The conformers *gauche*-**3a**,**b** and *anti*-**3a**,**b** were investigated decades ago by theoretical methods. It is interesting to note that the energetic order found in earlier *ab initio* studies:[34] *gauche*-**3a** < *gauche*-**3b** < *anti*-**3b** < *anti*-**3a** is the same as from the present

work, but due to small basis sets used previously, differences are discernible for relative energy values.[34] Note that at the SCS-MP2 level, *anti*-**3a** and *anti*-**3b** are energetically almost equivalent (Fig. 4). Also a recent DFT study found *gauche*-**3a** and *gauche*-**3b** as the most stable structures.[35]

The larger stability of *gauche*-**3a** and *gauche*-**3b** with respect to the other conformers was attributed to intramolecular C–F···H–N hydrogen bonding which should be possible in these structures.[33–35] Indeed, the optimized F···H contacts in *gauche*-**3a** (2.501 Å) and *gauche*-**3b** (2.576 Å) are short, while that of *gauche*-**3c** (3.415 Å) excludes any stabilization from a C–F···H–N hydrogen bridge. Short F···H contacts are also calculated for *syn*-**3b** (2.566/2.561 Å) (Fig. 4) suggesting that this structure is also stabilized by intramolecular hydrogen bonding. However, *syn*-**3b** is less stable than all *gauche*- and *anti*-conformers (Fig. 4) and consequently an intramolecular hydrogen bridging cannot be the decisive factor that controls the conformational preferences of **3**. To finish this section we notice that the only experimental values reported for the molecular structure of **3** are those for the dihedral angle NCCF and the angle NCC.[33] The optimized values for the dihedral angle NCCF of 64.8° (*gauche*-**3a**) and 60.8° (*gauche*-**3b**) compare well with the experimental estimates of 64 ± 2° and 63 ± 2°, respectively.[33] According to the experimental studies, the angle NCC of *gauche*-**3a** of 110 ± 1° opens in *gauche*-**3b** to 114.5 ± 1°.[33] This behaviour is also very well reproduced by our calculations. The optimized NCC angle is 109.4° for *gauche*-**3a** and 115.3° for *gauche*-**3b**.

Proton affinities and molecular structures of the protonated species

The optimized structures of the protonated conformers of **1**, **2**, and **3** are shown in Fig. 5. The calculated proton affinities are collected in Table 2. There is only one minimum for cyclopropylammonium (**1H**$^+$), as well as one minimum for each of the protonated

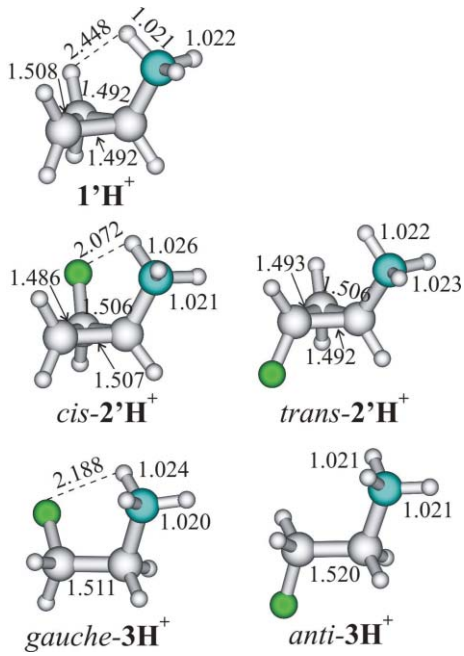


Fig. 5 Optimized distances (Å) of the protonated conformers of **1**, **2**, and **3**.

Table 2 Calculated energetics (kcal mol^{-1}) of the protonation reactions of the representative conformers of cyclopropylamine (**1**), *cis*- and *trans*-2-fluorocyclopropylamines (*cis*-**2** and *trans*-**2**), and 2-fluoroethylamine (**3**)

	$-\Delta E$		PA = $-\Delta H_{298}$
Protonation reaction	MP2	SCS-MP2	SCS-MP2
1a + H$^+$ → **1H**$^+$	222.4	224.5	217.6
cis-**2c** + H$^+$ → *cis*-**2H**$^+$	221.4	223.4	215.6
trans-**2a** + H$^+$ → *trans*-**2H**$^+$	215.0	217.0	209.3
gauche-**3a** + H$^+$ → *gauche*-**3H**$^+$	221.4	223.2	215.3
anti-**3b** + H$^+$ → *anti*-**3H**$^+$	216.1	218.1	210.1

cis-**2a–c**, *trans*-**2a–c**, *gauche*-**3a–c**, and *anti*-**3a–c** structures. The later minima are labelled below as *cis*-**2H**$^+$, *trans*-**2H**$^+$, *gauche*-**3H**$^+$, and *anti*-**3H**$^+$ (Fig. 5).

The protonation of the amino group changes the distances of the adjacent C1–C2/C3 bonds. Compared with **1**, the C2–C3 bond length of **1H**$^+$ is practically the same but that of the C1–C2/C3 bonds decreases from 1.500 Å in **1** to 1.492 Å in **1H**$^+$ (Fig. 3,5). Fluorination of C2 elongates the C1–C2 bond distance and shortens the C1–C3 distance.

The protonated structures *cis*-**2H**$^+$ and *gauche*-**3H**$^+$ are by 3.9 kcal mol^{-1} (MP2), 3.8 kcal mol^{-1} (SCS-MP2), and 6.6 kcal mol^{-1} (MP2), 6.3 kcal mol^{-1} (SCS-MP2) more stable than *trans*-**2H**$^+$ and *anti*-**3H**$^+$, respectively. The later value compares well to that obtained in DFT studies (5.8 kcal mol^{-1}).[35a] Note that despite small differences between MP2 and SCS-MP2 levels for relative energies, the SCS-MP2 protonation energies are 1.8–2.1 kcal mol^{-1} larger than the corresponding MP2 values (Table 2).

The protonated species *cis*-**2H**$^+$ and *gauche*-**3H**$^+$ are characterized by strong intramolecular C–F···H–N hydrogen bridging. The optimized F···H(N) distance of *cis*-**2H**$^+$ (2.072 Å) and *gauche*-**3H**$^+$ (2.188 Å) is significantly shorter than that in the neutral species *cis*-**2a** (2.257 Å) and *gauche*-**3a** (2.501 Å). Furthermore, as in the case of conventional (so called "red shifted") hydrogen bridged systems,[36] the H–N bond involved in the C–F···H–N interaction is longer than the other two H–N bonds (Fig. 5).

The calculated proton affinities (PA) of cyclopropylamine (**1**) and the *cis*- and *trans*-2-fluorocyclopropylamines (*cis*-**2** and *trans*-**2**) follow the trends observed for the measured pK_a values of the tranylcypromine and its monofluorinated derivatives. The SCS-MP2 PA value of **1a** is larger than that of both fluorinated congeners and the PA value of *trans*-**2a** is lower than that of *cis*-**2c** (Table 2). Taking into account that the PAs of *gauche*-**3a** and *anti*-**3b** are almost the same as those of *cis*-**2c** and *trans*-**2a** (Table 3), this suggests that similar effects should be responsible for the basicity of these species. Different basicities of fluorinated cyclopropylamines are one factor influencing the activity and selectivity of monoamine oxidase inhibitors.[4a]

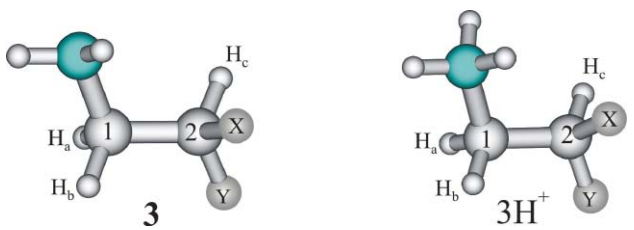
Hyperconjugative interactions, conformational preferences and basicity of the investigated conformers

In the frame of the NBO analysis, the second-order perturbative estimates of specific donor–acceptor interactions ($\Delta E^{(2)}$) give the opportunity to clarify stereoelectronic effects in molecules. Due to the electron density delocalization from filled Lewis-type NBOs to the unoccupied non-Lewis, that is, antibonding or Rydberg NBOs, the interaction energies $\Delta E^{(2)}$ can be regarded

Table 3 Strengths of the hyperconjugative interactions in the *gauche*- and *anti*-conformers of **3** and **3H**$^+$. $\Delta E^{(2)}{}_{\sigma\sigma}$ is given in kcal mol^{-1}, and $\varepsilon_{\sigma^*} - \varepsilon_{\sigma}$, and $F_{\sigma\sigma^*}$ in E_h

		X = F; Y = H					
Donor	Acceptor	*gauche*-**3a**			*gauche*-**3H**$^+$		
NBO(σ)	NBO(σ*)	$\Delta E^{(2)}{}_{\sigma\sigma}$	$\varepsilon_{\sigma^*} - \varepsilon_{\sigma}$	$F_{\sigma\sigma^*}$	$\Delta E^{(2)}{}_{\sigma\sigma}$	$\varepsilon_{\sigma^*} - \varepsilon_{\sigma}$	$F_{\sigma\sigma^*}$
σ(C1-H$_a$)	σ*(C2-X)	5.59	1.18	0.072	3.55	1.24	0.059
σ(C1-N)	σ*(C2-Y)	1.41	1.50	0.041	0.99	1.58	0.035
σ(C2-Y)	σ*(C1-N)	4.13	1.29	0.065	5.26	1.14	0.069
σ(C2-X)	σ*(C1-H$_a$)	0.94	1.76	0.036	1.02	1.75	0.038
	Total	12.07			10.83		
L.p. N	σ*(C1-H$_b$)	11.06	1.06	0.097			
		X = H; Y = F					
		anti-**3b**			*anti*-**3H**$^+$		
		$\Delta E^{(2)}{}_{\sigma\sigma}$	$\varepsilon_{\sigma^*} - \varepsilon_{\sigma}$	$F_{\sigma\sigma^*}$	$\Delta E^{(2)}{}_{\sigma\sigma}$	$\varepsilon_{\sigma^*} - \varepsilon_{\sigma}$	$F_{\sigma\sigma^*}$
σ(C1-H$_a$)	σ*(C2-X)	3.06	1.24	0.055	2.22	1.30	0.048
σ(C1-N)	σ*(C2-Y)	2.09	1.44	0.049	1.34	1.54	0.041
σ(C2-Y)	σ*(C1-N)	1.26	1.79	0.042	1.82	1.64	0.049
σ(C2-X)	σ*(C1-H$_a$)	2.90	1.28	0.055	2.80	1.26	0.053
	Total	9.31			8.18		
L.p. N	σ*(C1-C2)	9.84	1.07	0.092			

as a measure of stabilizing two-electron delocalization. For the sake of clarity we first describe the *gauche*-preferences of **3**, and **3H**$^+$. The corresponding NBO data with atom labeling according to Scheme 3 are presented in Table 3.

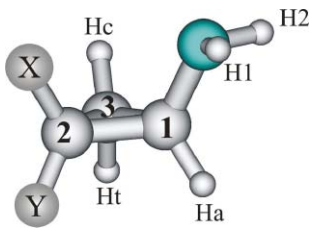


Scheme 3

From previous investigations, it is known that the acceptor ability of the σ*(C–X) orbitals from σ(C–H) donors smoothly increases in parallel to the increase in electronegativity[10b] and an inverse ordering can be expected for the donor ability of the analogous bonding counterparts. Thus, for *gauche*-**3** and *gauche*-**3H**$^+$, the strongest hyperconjugative interactions concern the σ(C–H) → σ*(C–F/N) delocalizations. Since upon going from the *gauche*-conformers to the *anti*-ones, the H and F atoms attached to C2 change their position, the strong σ*(C–F) acceptor and strong σ(C–H) donor are replaced by poorer ones. Consequently, the stabilizing effect of the hyperconjugative interactions, σ(C1-H$_a$) → σ*(C2-X) and σ(C2-Y) → σ*(C1-N), decreases significantly in the *anti*-structures (Table 3). For the same reasons, the two other interactions: σ(C1-N) → σ*(C2-Y) and σ(C2-X) → σ*(C1-H$_a$) are slightly stronger in the *anti* structures, but the gain in energy [+2.64 kcal mol^{-1} (*anti*-**3b**), +2.13 kcal mol^{-1} (*anti*-**3H**$^+$)] cannot compensate the loss of energy [−5.40 kcal mol^{-1} (*anti*-**3b**), −4.77 kcal mol^{-1} (*anti*-**3H**$^+$)] from the two former σ(C1-H$_a$) → σ*(C2-X) and σ(C2-Y) → σ*(C1-N) interactions (Table 3). Note that electron density delocalization from the nitrogen lone-pair contributes also to the stabilization of *gauche*-**3a** [L.p. N → σ*(C1-H$_b$] and *anti*-**3b** [L.p. N → σ*(C1–C2)], but once again this stabilizing effect is slightly larger in *gauche*-**3a** (Table 3). The comparable strength as well as the same nature of hyperconjugative interactions in the *gauche* structure of 2-fluoroethylamine (**3a**) and the 2-fluoroethylammonium ion (**3H**$^+$) shows that the gauche preference is of comparable magnitude in both of these species (Table 3). Thus, the larger stabilization of *gauche*-**3H**$^+$ over *anti*-**3H**$^+$ [ΔE = 6.6 kcal mol^{-1} (MP2), 6.3 kcal mol^{-1} (SCS-MP2)] as compared to that of *gauche*-**3a** *vs.* *anti*-**3b** [ΔE = 1.28 kcal mol^{-1} (MP2), 1.20 kcal mol^{-1} (SCS-MP2)] should be attributed to strong C–F ··· H–N hydrogen bridging in the protonated *gauche*-form.

The question about the origin of the stability of the cyclopropylamine s-*trans* conformer **1a** has been addressed years ago by various theoretical workers.[37] In addition to the mentioned arguments on the basis of the Walsh/Bent model,[32] interactions between the nitrogen lone-pair orbital and the C–C σ and σ* MOs of the cyclopropyl ring have also been considered.[37] The widely presented interpretation referred to the electron density delocalization from the nitrogen lone-pair (L.p.) orbital to the unoccupied 4e′ MO of cyclopropane in which the interactions of the C1 atom with the C2 and C3 atoms have antibonding character.[37c]

The strengths of the important hyperconjugative interactions in the conformers of **1** are compared to those of *cis*-**2** and *trans*-**2** in Table 4. The results of the NBO analysis for **1H**$^+$, *cis*-**2H**$^+$ and *trans*-**2H**$^+$ are provided in the ESI (Table S3).† The data in Table 4 show that the L.p. (N) → σ*(C1–C2)/σ*(C1–C3) delocalizations with $\Delta E^{(2)}$ of 1.88 kcal mol^{-1} contribute only marginally to the stabilization of **1a** (for labeling of atoms see Scheme 4).



Scheme 4

A strong interaction is discernible for electron density delocalization into the σ*(C1-H$_a$) NBO. The strength of the

Table 4 Strengths of the important hyperconjugative interactions $\Delta E^{(2)}_{\sigma\sigma}$ (kcal mol^{-1}) in the conformers of **1′** *cis*-**2′**, and *trans*-**2′**[a]

Donor	Acceptor	X = Y = H		X = F, Y = H			X = H, Y = F		
NBO	NBO	**1′a**	**1′b/1′c**	*cis*-**2′a**	*cis*-**2′b**	*cis*-**2′c**	*trans*-**2′a**	*trans*-**2′b**	*trans*-**2′c**
σ(C1–N)	σ*(C2–Y)	0.84	0.82	0.74	0.73	0.70	1.27	1.22	1.10
σ(C1–N)	σ*(C3–H_t)	0.84	0.71	0.85	0.83	0.82	0.72	0.56	0.69
σ(C2–X)	σ*(C1–H_a)	1.49	1.58	—	—	—	1.11	1.25	1.14
σ(C2–X)	σ*(C3–H_t)	1.50	1.45	—	—	—	1.18	1.24	1.18
σ(C3–H_c)	σ*(C1–H_a)	1.49	1.47	1.65	1.69	1.50	1.28	1.23	1.35
σ(C3–H_c)	σ*(C2–Y)	1.50	1.48	1.66	1.49	1.55	2.48	2.48	2.38
σ(C2–Y)	σ*(C1–N)	2.05	1.96	1.89	1.85	1.49	0.66	0.65	0.73
σ(C2–Y)	σ(C3–H_c)	1.42	1.41	1.27	1.11	1.13	—	—	—
σ(C3–H_t)	σ*(C1–N)	2.05	2.38	1.75	1.87	2.17	2.12	2.48	2.07
σ(C3–H_t)	σ*(C2–X)	1.42	1.44	2.42	2.36	2.52	1.47	1.46	1.44
σ(C1–H_a)	σ*(C2–X)	1.37	1.62	2.28	2.28	2.46	1.30	1.62	1.45
σ(C1–H_a)	σ*(C3–H_c)	1.37	1.51	1.28	1.56	1.45	1.44	1.65	1.71
L.p. N	σ*(C1–H_a)	12.62	4.14	13.39	2.93	6.12	12.99	4.41	4.04
L.p. N	σ*(C1–C2)	1.88	—	2.66	15.52	—	3.62	—	14.71
L.p. N	σ*(C1–C3)	1.88	14.51	2.57	—	14.52	1.52	15.34	—
σ(N–H)[b]	σ*(C–C)	9.96	4.69	9.94	5.38	5.03	9.30	4.98	4.75
σ(C–C)[b]	σ*(N–H)	5.54	2.53	5.53	2.51	2.91	5.59	2.37	2.73
σ(C2–C3)	σ*(C1–N)	3.89	5.43	3.26	4.52	4.38	4.09	6.08	5.76
	Total	53.11	49.13	53.14	46.63	48.75	52.14	49.02	47.23

[a] Labeling of atoms according to Scheme 4. [b] Sum of interaction energies between the corresponding donor and acceptor NBOs.

L.p (N) → σ*(C1-H_a) delocalization decreases from 12.66 kcal mol^{-1} in **1a** to 4.14 kcal mol^{-1} in **1b/1c**. However, for **1b/1c**, the NBO analysis predicts strong (14.51 kcal mol^{-1}) interaction between the L.p. (N) orbital and the σ*(C1–C3) NBO. These findings suggest that electron density delocalization from L.p. (N) is not responsible for the conformational preferences of **1**. Examination of the data from Table 4 shows that the most striking differences between **1a** and **1b/1c** concerns the σ(N–H) → σ*(C–C) and σ(C–C) → σ*(N–H) delocalizations. Compared to **1a**, all these interactions are weaker in **1b/1c**. Note that the NBOs σ(C1-N) and σ*(C1-N) are also involved in the hyperconjugative interactions. The sum of the stabilizing interactions present in **1a** decreases from 53.11 kcal mol^{-1} to 49.13 kcal mol^{-1} in **1b/1c** (Table 4).

From Table 4 it is evident that the stabilizing interactions of the conformers, *cis*-**2** and *trans*-**2**, have a comparable nature to those of **1a** and **1b/1c**. Similar to the case of **1a** and **1b/1c**, the total hyperconjugative interactions of the **2b** and **2c** structures are weaker than those of the corresponding **2a** forms (Table 4). The reasons for this behavior are the same as in the case of **1a** and **1b/1c**. The total stabilization energy of *cis*-**2a** is slightly stronger than that of *trans*-**2a**. However, as *trans*-**2a** is the most stable form, this finding suggests that stabilizing interactions in *cis*-**2a** do not make up for repulsive interactions between fluorine and nitrogen, as it was the case in *gauche*-**3a**. This is due to the rigid structure of the small carbocycle. The F ⋯ N distance of *cis*-**2a** (2.799 Å) is shorter than that of *gauche*-**3a** (2.839 Å) and consequently repulsive F ⋯ N interactions are stronger in the former structure. As in the case of 2-fluoroethylamine (**3**), upon going from the conformers of *cis*-2-fluorocyclopropylamine (*cis*-**2**) to those of the *trans*-isomer, *trans*-**2**, the poor σ*(C–H) acceptor is replaced by the good σ*(C–F) one and the poor σ(C–F) donor is replaced by the better σ(C–H) donor. Thus, compared to the *trans*-**2** conformers, the σ(C2-Y) → σ*(C1-N) interactions are stronger for the *cis*-**2** conformers and those from the σ(C1-N) → σ*(C2-Y) hyperconjugation are weaker (Table 4). As a result of these interactions, one can expect that the electron density at nitrogen in the *cis*-**2** conformers should be larger than that in the *trans*-**2** ones. However, hyperconjugative interactions of the nitrogen lone-pair orbital and the N–H bonds do also contribute. Consequently, the electronic properties of the amino group, such as the charge of the nitrogen and the hybridization and energy of the lone-pair orbital, will result from complex combination of all particular charge flows. It is obvious that all these properties are inherently connected with the basicity of the conformers and their reactivity in the protonation reactions.

The calculated NPA charge (q) of the nitrogen atom as well as the hybridization (sp^n), energy (ε_i) and electronic population (OCC) of the nitrogen lone-pair orbital of the relevant conformers (see Table 2) for the protonation reaction of **1**, **2**, and **3** are collected in Table 5. These data suggest that the basicity of the conformers is controlled by the charge of the nitrogen atom and/or the hybridization of the nitrogen lone-pair. Thus, the larger proton affinity of *gauche*-**3a** *vs.* that of *anti*-**3b** is due to the charge on the nitrogen atom which in the former conformer is more negative than in the latter one. This property is mainly due to the σ(C1-N) → σ*(C2-Y) hyperconjugation whose strength increases from 1.41 kcal mol^{-1} in *gauche*-**3a** to 2.09 kcal mol^{-1} in *anti*-**3b** as well as to the σ(C2-Y) → σ*(C1-N) hyperconjugation whose strength decreases from 4.13 kcal mol^{-1} in *gauche*-**3a** to 1.26 kcal mol^{-1} in *anti*-**3b**.

Table 5 Electronic properties of the nitrogen lone-pair and the charge (q) of the nitrogen atom from the NBO and NPA population analyses

Conformer	L.p.(N)[a]	ε_i (a.u.)	OCC[b]	q NPA (N)
gauche-**3a**	$sp^{3.67}$	–0.49841	1.96807	–0.82602
anti-**3b**	$sp^{4.04}$	–0.49562	1.96543	–0.81465
s-*trans*-**1a**	$sp^{3.97}$	–0.48690	1.96509	–0.81822
cis-**2c**	$sp^{4.34}$	–0.48148	1.95625	–0.81329
trans-**2a**	$sp^{4.07}$	–0.49836	1.96267	–0.81741

[a] Hybridization of the nitrogen lone-pair. [b] OCC gives the electronic population of the nitrogen lone-pair.

Similar arguments explain also the larger proton affinity of s-*trans*-**1a** *vs.* that of the *cis*- and *trans*-conformers of **2**. However, the larger proton affinity of *cis*-**2c** as compared to that of *trans*-**2a** cannot be related to charge distributions. The NPA charge q of the nitrogen atom calculated for *cis*-**2c** is slightly less negative than that of *trans*-**2a**. For *cis*-**2c** and *trans*-**2a**, differences are discernible for the hybridization of the nitrogen lone-pair (L.p.). Upon going from *cis*-**2c** to *trans*-**2a**, the hybridization of the L.p. (N) changes from $sp^{4.34}$ to $sp^{4.07}$. Due to the higher s-character, the energy of the L.p.(N) in *trans*-**2a** (–0.49836 a.u.) is lower than in the case of *cis*-**2c** (–0.48148 a.u.). These finding suggest that the basicity of *cis*-**2c** and *trans*-**2a** is overlap controlled as a result of the different hybridization of the nitrogen lone-pair.

Conclusions

The conformational preferences and basicity of cyclopropylamine (**1**), and *cis*- and *trans*-2-fluorocyclopropylamines (**2**) were studied in comparison to 2-fluoroethylamine (**3**) using the MP2 and SCS-MP2 methods with extended basis sets. The potential energy profile for the rotation of the amino group in *cis*-**2** differs from that of *trans*-**2** and **1**, whose rotational curves are very similar. Stereoelectronic effects were analyzed with the help of the NBO procedures. The global minimum conformer *trans*-**2a** is 2.57 kcal mol^{-1} more stable than the lowest energy *cis*-conformer **2c**. In accord with the experimental pK_a values of compounds *cis*-**2′** and *trans*-**2′** in solution,[2] the calculated proton affinity of *cis*-**2c** is larger than that of the *trans*-form **2a**. Similar results are also observed for the *gauche*- and *anti*-forms of **3**. The changes of basicity with respect to the particular molecular conformation are due to stereoelectronic effects from hyperconjugative interactions which lead to different local charge distributions and different hybridization of the nitrogen lone-pair. The basicity of *gauche*-**3a** and *anti*-**3b** is controlled by the charge of the nitrogen atom, which in the former structure is more negative. The charge of the nitrogen atom of *cis*-**2c** is slightly less negative than that of *trans*-**2a** and the basicity of these forms is overlap controlled due to the different p-character of the nitrogen lone-pair [$sp^{4.34}$ (*cis*-**2a**), $sp^{4.07}$ (*trans*-**2a**)]. Similar to the case of *gauche*-$\mathbf{3H^+}$, intramolecular C–F $\cdots$ H–N interactions contribute also to the stability of *cis*-$\mathbf{2H^+}$. The MP2 and SCS-MP2 relative enthalpies agree well with the available experimental data, but the accuracy of the later calculated values is better than that of the former ones.

Acknowledgements

Support of this work from the Deutsche Forschungsgemeinschaft in the framework of the SFB 424 ("Molekulare Orientierung als Funktionskriterium in chemischen Systemen") is gratefully acknowledged.

References

1 (*a*) P. Love, R. B. Cohen and R. W. Taft, *J. Am. Chem. Soc.*, 1968, **90**, 2455–2462; (*b*) M. Schlosser, *Angew. Chem., Int. Ed.*, 1998, **110**, 1496–1513; (*c*) J. T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, 1991; (*d*) B. E. Smart, *J. Fluorine Chem.*, 2001, **109**, 3–11; (*e*) G. Haufe, T. C. Rosen, O. G. J. Meyer, R. Fröhlich and K. Rissanen, *J. Fluorine Chem.*, 2002, **114**, 189–198; (*f*) I. Hyla-Kryspin, G. Haufe and S. Grimme, *Chem.–Eur. J.*, 2004, **10**, 3411–3422; (*g*) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander and M. Stahl, *ChemBioChem*, 2004, **5**, 637–643 and references cited therein; (*h*) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Application*, Wiley-VCH, Weinheim, 2004; (*i*) R. Fröhlich, T. C. Rosen, O. G. J. Meyer, K. Rissanen and G. Haufe, *J. Mol. Struct.*, 2006, **787**, 50–62; (*j*) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, 2006; (*k*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319; (*l*) *Fluorine and Health. Molecular Imaging, Biomedical Materials and Pharmaceuticals*, ed. A. Tressaud and G. Haufe, Elsevier, Amsterdam, 2008.

2 T. C. Rosen, S. Yoshida, K. L. Kirk and G. Haufe, *ChemBioChem*, 2004, **5**, 1033–1043.

3 (*a*) S. Yoshida, T. C. Rosen, O. G. J. Meyer, M. J. Sloan, S. Ye, G. Haufe and K. L. Kirk, *Bioorg. Med. Chem.*, 2004, **12**, 2645–2652; (*b*) S. Ye, S. Yoshida, R. Fröhlich, G. Haufe and K. L. Kirk, *Bioorg. Med. Chem.*, 2005, **13**, 2489–2499; (*c*) S. Yoshida, O. G. J. Meyer, T. C. Rosen, G. Haufe, S. Ye, M. J. Sloan and K. L. Kirk, *J. Med. Chem.*, 2004, **47**, 1796–1806; (*d*) T. C. Rosen, S. Yoshida, R. Fröhlich, K. L. Kirk and G. Haufe, *J. Med. Chem.*, 2004, **47**, 5860–5871.

4 (*a*) S. Hruschka, T. C. Rosen, S. Yoshida, K. L. Kirk, R. Fröhlich, B. Wibbeling and G. Haufe, *Bioorg. Med. Chem.*, 2008, **16**, 7148–7166; (*b*) S. Hruschka, S. Yoshida, K. L. Kirk and G. Haufe, *J. Fluorine Chem.*, 2008, **129**, 875–880.

5 (*a*) C. D. Cox, M. J. Breslin, D. B. Whitman, P. J. Coleman, R. M. Garbaccio, M. E. Fraley, M. M. Zrada, C. A. Buser, E. S. Walsh, K. Hamilton, R. B. Lobell, W. Tao, M. T. Abrams, V. J. South, H. E. Huber, N. E. Kohl and G. D. Hartman, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2697–2702; (*b*) R. Zheng and J. S. Blanchard, *Biochemistry*, 2000, **39**, 16244–16251; (*c*) R. W. Fuller, B. B. Molly, The Effect of Aliphatic Fluorine on Amine Drugs, in *Biochemistry Involving Carbon–Fluorine Bonds*, ACS Symposium Series, vol. 28, ed. R. Filler, American Chemical Society, Washington D.C., 1976, pp. 77–98.

6 (*a*) S. Wolfe, *Acc. Chem. Res.*, 1972, **5**, 102–111; (*b*) K. B. Wiberg, *Acc. Chem. Res.*, 1996, **29**, 229–234.

7 (*a*) R. J. Abraham and R. H. Kemp, *J. Chem. Soc. B*, 1971, 1240–1245; (*b*) D. Friesen and K. Hedberg, *J. Am. Chem. Soc.*, 1980, **102**, 3987–3994; (*c*) P. Huber-Wälchli and H. H. Günthard, *Spectrochim. Acta, Part A*, 1981, **37**, 285–304; (*d*) T. Hirano, S. Nonoyama, T. Miyajima, Y. Kurita, T. Kawamura and H. Sato, *J. Chem. Soc., Chem. Commun.*, 1986, 606–607; (*e*) J. R. Durig, J. Liu, T. S. Little and V. F. Kalasinsky, *J. Phys. Chem.*, 1992, **96**, 8224–8233.

8 (*a*) K. B. Wiberg and M. A. Murcko, *J. Phys. Chem.*, 1987, **91**, 3616–3620; (*b*) D. A. Dixon and B. E. Smart, *J. Phys. Chem.*, 1988, **92**, 2729–2733; (*c*) K. B. Wiberg, M. A. Murcko, K. E. Laidig and P. J. MacDougall, *J. Phys. Chem.*, 1990, **94**, 6956–6959; (*d*) H. Senderowitz, L. Goldener and B. Fuchs, *Tetrahedron*, 1994, **50**, 9707–9728; (*e*) P. R. Rablen, R. W. Hoffmann, D. A. Hrovat and W. T. Borden, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1719–1726; (*f*) L. Goodman, H. Gu and V. Pophristic, *J. Chem. Phys. A*, 2005, **109**, 1223–1229.

9 For some recent examples of the fluorine-*gauche* effect see: (*a*) R. D. Amos, N. C. Handy, P. G. Jones, A. J. Kirby, J. K. Parker, J. M. Percy and M. D. Su, *J. Chem. Soc., Perkin Trans. 2*, 1992, 549–558; (*b*) D. O'Hagan, C. Bilton, J. A. K. Howard, L. Knight and D. J. Tozer, *J. Chem. Soc., Perkin Trans. 2*, 2000, 605–607; (*c*) C. R. S. Briggs, D. O'Hagan, J. A. K. Howard and D. S. Yufit, *J. Fluorine Chem.*, 2003, **119**, 9–13; (*d*) C. R. S. Briggs, D. O'Hagan, H. P. Rzepa and A. M. Z. Slawin, *J. Fluorine Chem.*, 2004, **125**, 19–25.

10 (*a*) I. V. Alabugin, *J. Org. Chem.*, 2000, **65**, 3910–3919; (*b*) I. V. Alabugin and T. A. Zeidan, *J. Am. Chem. Soc.*, 2002, **124**, 3175–3185, and references cited therein; (*c*) J. J. Urban, *J. Phys. Org. Chem.*, 2005, **18**, 1061–1071.

11 R. Ahlrichs, M. Bär, H.-P. Baron, S. Bauernschmitt, S. Böcker, P. Deglmann, M. Ehrig, K. Eichkorn, S. Elliot, F. Furche, F. Haase, M. Häser, H. Horn, C. Hättig, C. Huber, U. Huniar, M. Kattannek, A. Köhn, C. Kölmel, M. Kollwitz, K. May, C. Ochsenfeld, H. Öhm, H. Patzelt, O. Rubner, A. Schäfer, U. Schneider, M. Sierka, O. Treutler, B. Unterreiner, M. von Arnim, F. Weigend, P. Weis and H. Weiss, *TURBOMOLE* (Version 5.7), University of Karlsruhe, Karlsruhe, Germany, 2005.

12 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo,

R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Oritz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzales and J. A. Pople, *Gaussian 03 Rev. C01*, Gaussian, Inc., Wallingford CT, 2004.

13 C. Møller and M. S. Plesset, *Phys. Rev.*, 1934, **46**, 618–622.

14 (*a*) S. Grimme, *J. Chem. Phys.*, 2003, **118**, 9095–9102; (*b*) T. P. M. Goumans, A. W. Ehlers, K. Lammertsma, E.-U. Würthwein and S. Grimme, *Chem.–Eur. J.*, 2004, **10**, 6468–6475; (*c*) S. Grimme, *J. Phys. Chem. A*, 2005, **109**, 3067–3077; (*d*) S. Grimme, C. Mück-Lichtenfeld, E.-U. Würthwein, A. W. Ehlers, T. P. M. Goumans and K. Lammertsma, *J. Phys. Chem. A*, 2006, **110**, 2583–2586; (*e*) R. A. DiStasio, Jr. and M. Head-Gordon, *Mol. Phys.*, 2007, **105**, 1073–1083; (*f*) T. Takatani and C. D. Sherrill, *Phys. Chem. Chem. Phys.*, 2007, **9**, 6106–6114; (*g*) see also: A. Szabados, *J. Chem. Phys.*, 2006, **125**, 214105-1–214105-7.

15 (*a*) J. A. Pople, M. Head-Gordon and K. Raghavachari, *J. Chem. Phys.*, 1987, **87**, 5968–5975; (*b*) T. Helgaker, P. Jørgensen and J. Olsen, *Molecular Electronic Structure Theory*, Wiley, Chichester, 2000.

16 F. Jensen, *Introduction to Computational Chemistry*, Wiley, Chichester, 1999.

17 S. Grimme, E. Izgorodina, *RICC (Version 1.7): A coupled cluster program that uses the resolution of the identity method*, University of Münster, Münster, Germany, 2003.

18 (*a*) O. Vahtras, J. Almlöf and M. W. Feyereisen, *Chem. Phys. Lett.*, 1993, **213**, 514–518; (*b*) F. Weigend and M. Häser, *Theor. Chem. Acc.*, 1997, **97**, 331–340.

19 (*a*) The basis sets and the corresponding auxiliary basis sets for the RI approximation are available from the TURBOMOLE homepage http://www.turbomole.com in the subdirectory basen, and cbasen, respectively, where they are labeled as TZVPP; see also; (*b*) A. Schäfer, C. Huber and R. Ahlrichs, *J. Chem. Phys.*, 1994, **100**, 5829–5835; (*c*) F. Weigend, M. Häser, H. Patzelt and R. Ahlrichs, *Chem. Phys. Lett.*, 1998, **294**, 143–152; (*d*) F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, **7**, 3297–3305.

20 E. D. Glendening, J. K. Badenhoop, A. E. Reed, J. E. Carpenter, F. Weinhold, *NBO 4.0.*, Theoretical Chemistry Institute, University of Wisconsin, Madison WI, 1996.

21 A. E. Reed, L. A. Curtiss and F. Weinhold, *Chem. Rev.*, 1988, **88**, 899–926.

22 (*a*) I. Hyla-Kryspin, S. Grimme, H. H. Büker, N. M. M. Nibberg, F. Cottet and M. Schlosser, *Chem.–Eur. J.*, 2005, **11**, 1251–1256; (*b*) M. Swart, E. Rösler and F. M. Bickelhaupt, *J. Comput. Chem.*, 2006, **27**, 1486–1493; (*c*) I. Despotović, Z. B. Maksić and R. Vianello, *Eur. J. Org. Chem.*, 2007, 3402–3413 and references cited.

23 (*a*) J. E. Del Bene, in *Molecular Structure and Energetics: Bonding Models*, ed. J. F. Liebmann and A. Greenberg, VCH, Deerfield Beach, Fl, 1986, vol. 1, pp. 319–349; (*b*) K. S. Pitzer, *Quantum Chemistry*, Prentice-Hall, Englewood Cliffs, NJ, 1961.

24 C. Kind, M. Reiher, J. Neugebauer and B. A. Hess, SNF (Version 2.2.1), *A program for Numerical Frequency Analyses*, University of Erlangen, 2002.

25 G. Schaftenaar and J. H. Nordik, *MOLDEN*: a-pre- and post-processing program for molecular and electronic structures, *J. Comput. Aided Mol. Des.*, 2000, 123.

26 M. Pelissier, C. Leibovici and J.-F. Labarre, *Tetrahedron*, 1972, **28**, 4825–4833.

27 A. R. Mochel, J. E. Boggs and P. N. Skancke, *J. Mol. Struct.*, 1973, **15**, 93–102.

28 D. A. C. Compton, J. J. Rizzolo and J. R. Durig, *J. Phys. Chem.*, 1982, **86**, 3746–3753.

29 V. F. Kalasinsky, D. E. Powers and W. C. Harris, *J. Phys. Chem.*, 1979, **83**, 506–510.

30 A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441–451.

31 (*a*) T. Iijima, T. Kondou and T. Takenaka, *J. Mol. Struct.*, 1998, **445**, 23–28; (*b*) M. Rall, M. D. Harmony, D. A. Cassada and S. W. Staley, *J. Am. Chem. Soc.*, 1986, **108**, 6184–6189.

32 (*a*) A. D. Walsh, *Discuss. Faraday Soc.*, 1947, **2**, 18–25; (*b*) H. A. Bent, *Chem. Rev.*, 1961, **61**, 275–311.

33 K.-M. Marstokk and H. Møllendal, *Acta Chem. Scand., Ser. A*, 1980, **34**, 15–29.

34 (*a*) L. Radom, W. A. Lathan, W. J. Hehre and J. A. Pople, *J. Am. Chem. Soc.*, 1973, **95**, 693–698; (*b*) T. Lotta, J. Murto, M. Räsänen, A. Aspiala and P. Särkkä, *J. Chem. Phys.*, 1985, **82**, 1363–1375.

35 (*a*) C. R. S. Briggs, M. J. Allen, D. O'Hagan, D. J. Tozer, A. M. Z. Slawin, A. E. Goeta and J. A. K. Howard, *Org. Biomol. Chem.*, 2004, **2**, 732–740; (*b*) see also: N. E. J. Gooseman, D. O'Hagan, M. J. G. Peach, A. M. Z. Slawin, D. J. Tozer and R. J. Young, *Angew. Chem.*, 2007, **119**, 6008–6012, (*Angew. Chem., Int. Ed.*, 2007, **46**, 5904–5908).

36 (*a*) S. Scheiner, *Hydrogen Bonding*, Oxford University Press, New York, 1997; (*b*) G. R. Desiraju and T. Steiner, *The Weak Hydrogen Bond*, Oxford University Press, Oxford, 1999.

37 (*a*) A. Skanke and J. E. Boggs, *J. Mol. Struct.*, 1978, **50**, 173–182; (*b*) S. Durmaz and H. Kollmar, *J. Am. Chem. Soc.*, 1980, **102**, 6942–6945; (*c*) T. Clark, G. W. Spitznagel, R. Klose and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1984, **106**, 4412–4419; (*d*) D. Cremer and E. Kraka, *J. Am. Chem. Soc.*, 1985, **107**, 3811–3819; (*e*) I. F. Tupitsyn, A. Yu. Shibaer and Yu. V. Puzanov, *Teor. Eksp. Khim.*, 1985, **21**, 399–407.