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Anomeric effect plays a major role in the conformational isomerism of fluorinated pnictogen compounds

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According to our theoretical studies, the anomeric effect, an stereoelectronic interaction between lone pair and a vicinal antibonding orbital, has shown to contribute decisively for the conformational isomerism of 1-fluoro-*N,N*-dimethylmethanamine (1) and of its corresponding P, As and Sb analogues (2–4). C—X bonds in 2–4 are larger than in the parent compound 1, thus providing a LP_X/C—F* interaction progressively weaker on going from 1 to 4. However, such hyperconjugation contributed by more than 1.3 kcal mol^{-1} for the stabilization of *anti* conformer in 4 ($\theta_{LP—X—C—F} = 180^\circ$), increasing to 24.1 kcal mol^{-1} in 1. An isodesmic reaction model supported these findings. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: conformational analysis; anomeric effect; DFT calculations; fluorinated group 15 compounds

INTRODUCTION

Many molecules may undergo rotational isomerization around one or more of their chemical bonds, and this must affect the spectroscopic behaviour, binding orientation in active sites and synthesis of the rotationally flexible compounds. The stability of conformers is traditionally assigned as from steric and electrostatic nature, but non-classical interactions are often invoked when natural Lewis structure does not provide sufficient basis on conformational energies.

Electron delocalization from occupied to nearly unoccupied orbitals has shown to be at least competitive with classical interactions operating in simple systems, such as the ethane molecule.[1–4] Hyperconjugation is also assumed to be an important/major factor controlling the *gauche* effect in 1,2-disubstituted ethanes,[5–8] though the origin of this effect may also be due to electrostatic interaction.[9,10] One of the most recognized 2 electrons–2 orbitals interaction, which plays an important role in conformational isomerism, is the anomeric effect (formally a negative hyperconjugation), firstly observed in pyranose rings by Edward in 1955.[11] *Antiperiplanar* symmetry is required for such interaction and it is well established when oxygen lone pairs are taken into account, but sulfides and sulfoxides also demonstrated significant ability in donating sulphur lone pairs to vicinal C—Cl antibonding orbitals.[12] Other higher-row elements containing lone pair(s) have also shown to be electron donors, and thus the corresponding compounds experience the anomeric effect, though in weaker extent when compared to compounds based on first-row elements.[13–18] However, such behaviour in nitrogen derivatives has not been so extensively studied as in oxygenated compounds, as well as the influence of bond size on the strength of anomeric effect. Thus, these issues may be properly addressed by using model compounds derived from the nitrogen family elements on the basis of NBO analysis.[19] In our computational studies (DFT calculations), we have explored the conformational preferences of 1-fluoro-*N,N*-dimethylmethanamine (**1**) and its phosphorus (**2**), arsenic (**3**) and antimony (**4**) analogues (Fig. 1).

THEORETICAL CALCULATIONS

The energy minima were identified by building potential energy surfaces, obtained through scanning the dihedral angle F—C—X—CH_3 (X = N, P, As and Sb) in steps of 10°, at the B3LYP/6-31g(d,p) level using the Gaussian 03 programme.[20] For **4**, the LANL2DZ basis set was used. Each minimum was then optimized at the B3LYP/aug-cc-pVTZ level and the orbital interactions were computed by using an NBO analysis[19] at the same level of theory, including deletion of all Rydberg and antibonding interactions. For **4**, the aug-cc-pVTZ-PP basis set[21] was applied. Isodesmic reactions were calculated at the same level of theory applied in the geometry optimizations.

RESULTS AND DISCUSSION

Anti conformation (LP—X—C—F dihedral angle = 180°) is supposed to experience the anomeric effect, as a result of favourable $LP_X \rightarrow \sigma^*_{C—F}$ interaction. The corresponding $LP_X \rightarrow \sigma^*_{C—H}$ interaction in the *gauche* conformer is a weaker stabilizing, stereoelectronic interaction. Potential energy surfaces obtained at the B3LYP/6-31g(d,p) level (LANL2DZ basis set for **4**) confirm that the *anti* conformer in **1** is significantly more stable

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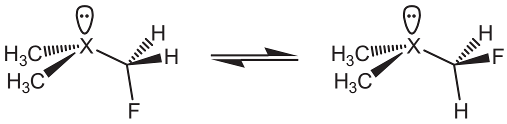


Figure 1. *Anti* and *gauche* conformations of **1**–**4**, X = N, P, As and Sb

than the *gauche* conformer, but only slightly preferred in **2**–**4**. In addition, the first transition state (LP—X—C—F dihedral angle = 0°) is lower in energy when compared to the other eclipsed conformation (Fig. 2). These suggest that the anomeric effect is stronger in **1** than in the remaining compounds, as preliminary observed in a comparison between —NH_2 and —PH_2 systems,[22] and that a *synperiplanar* $LP_X \rightarrow \sigma^*_{C—F}$ interaction determines the lower rotational barrier.

Each minimum and transition states were then optimized by using the improved aug-cc-pVTZ basis set (aug-cc-pVTZ-PP[21] for **4**) and NBO analyses were then performed to account for the

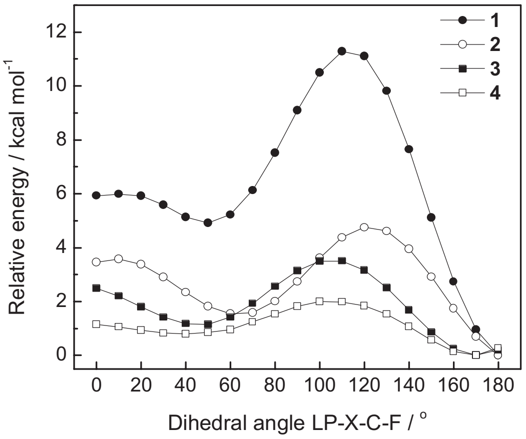
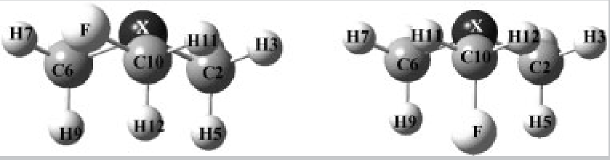


Figure 2. Potential energy surfaces obtained at the B3LYP/6-31g(d,p) level for **1**–**4** (X = N, P, As and Sb)

Table 1. Geometrical and energetic (kcal mol^{-1}) parameters obtained from the DFT calculations



	1		**2**		**3**		**4**	
Parameter	*Gauche*	*Anti*	*Gauche*	*Anti*	*Gauche*	*Anti*	*Gauche*	*Anti*
E (a.u.)	−273.82398	−273.83104	−560.45075	−560.45361	−2455.02181	−2455.02361	−459.38979	−459.39086
E_{rel}	4.43	0	1.79	0	1.13	0	0.67	0
E_{hyp}	271.84	280.77	193.73	196.76	175.89	178.52	155.91	161.14
$r_{C10–X}$ (Å)	1.42	1.40	1.87	1.86	2.00	1.99	2.21	2.20
$r_{C10–F}$	1.40	1.44	1.40	1.40	1.39	1.40	1.40	1.40
$r_{C10–H11}$	1.10	1.09	1.09	1.09	1.09	1.09	1.09	1.09
$r_{C10–H12}$	1.09	1.09	1.09	1.09	1.09	1.09	1.09	1.09
$<_{C2–X–C6}$ (°)	113.65	115.97	99.09	99.80	96.59	97.12	94.25	94.02
$<_{C2–X–C10}$	113.54	113.76	96.86	99.80	94.78	97.12	92.52	95.26
$<_{C6–X–C10}$	114.28	115.97	100.24	100.60	97.78	98.11	95.24	94.19
$<_{X–C10–F}$	110.11	113.69	109.99	114.46	109.90	113.57	110.29	112.19
$\theta_{F–C10–X–C6}$ (°)	−75.25	68.69	−76.79	51.33	−78.32	49.59	−82.32	47.07
$\theta_{H12–C10–X–C6}$	−173.47	42.45	42.76	−69.12	41.05	−70.64	36.88	166.99
$\theta_{H11–C10–X–C6}$	166.55	−49.14	164.65	171.79	162.94	169.83	158.42	−72.74
$\sigma_{C10–H11} \rightarrow \sigma^*_{X–C6}$	4.32	5.42	1.13	1.42	0.69	0.86	—	—
$\sigma_{X–C6} \rightarrow \sigma^*_{C10–H12}$	—	1.50	—	1.20	—	—	—	0.53
$\sigma_{X–C6} \rightarrow \sigma^*_{C10–H11}$	1.24	—	1.10	—	0.89	—	0.50	—
$\sigma_{X–C6} \rightarrow \sigma^*_{C2–H3}$	1.32	1.31	1.41	1.37	1.19	1.15	0.80	0.78
$\sigma_{X–C10} \rightarrow \sigma^*_{C6–H8}$	1.17	0.93	1.48	1.43	1.24	1.18	0.82	0.76
$\sigma_{X–C10} \rightarrow \sigma^*_{C2–H4}$	1.07	0.93	1.53	—	1.24	1.18	0.79	0.76
$\sigma_{X–C2} \rightarrow \sigma^*_{C6–H7}$	1.22	1.31	1.30	1.20	1.08	1.15	0.50	0.78
$\sigma_{X–C2} \rightarrow \sigma^*_{C10–H11}$	0.62	1.50	—	—		—	—	0.53
$\sigma_{C10–F} \rightarrow \sigma^*_{X–C6}$	1.59	—	—	—	—	—	—	—
$LP_X \rightarrow \sigma^*_{C6–H9}$	8.37	7.71	2.88	2.79	1.65	1.56	0.83	0.73
$LP_X \rightarrow \sigma^*_{C10–H11}$	—	1.50	—	—	1.28	—	—	—
$LP_X \rightarrow \sigma^*_{C10–H12}$	8.21	1.50	2.33	—	—	—	0.58	—
$LP_X \rightarrow \sigma^*_{C10–F}$	9.91	24.07	0.66	5.43	—	2.98	—	1.37

hyperconjugative interactions operating in the conformers of **1**–**4** (Table 1). The calculated energy difference between *anti* and *gauche* conformers in **1** is 4.4 kcal mol^{-1}, which is in agreement with previous findings,[23] decreasing to 1.8, 1.1 and 0.7 kcal mol^{-1} to **2**, **3** and **4**, respectively. This behaviour clearly shows that the replacement of N in **1** by P, As and Sb reduces the anomeric effect, due to the larger $\mathrm{LP_N}/\sigma^*_{\mathrm{C—F}}$ overlap as a result of better compatibility of orbitals. NBO data confirm the more effective anomeric effect in **1**, in which the *antiperiplanar* $\mathrm{LP_X} \rightarrow \sigma^*_{\mathrm{C—F}}$ interaction corresponds to 24.1 kcal mol^{-1}, whilst the respective values for **2**, **3** and **4** are 5.4, 3.0 and 1.4 kcal mol^{-1}. The corresponding $\mathrm{LP_X} \rightarrow \sigma^*_{\mathrm{C—H}}$ interaction in the *gauche* conformer of **1**, **2**, **3** and **4** are 8.2, 2.3, <0.5 and 0.6 kcal mol^{-1}, respectively. This trend is congruent with that found for the O, S, Se and Te series of model compounds,[17] as well as for $\mathrm{CH_2(XH_2)_2}$ (X = N, P and As) compounds.[18] Despite the lower energy of $\mathrm{LP_X} \rightarrow \sigma^*_{\mathrm{C—F}}$ interaction in *anti* conformers of **2**, **3** and **4** when compared to **1**, it may not be ignored. Not all geometrical parameters of Table 1 support the energetic findings because in general there are small changes in *gauche* and *anti* bond lengths and angles; however, some trends suggest the occurrence of anomeric effect in **1**–**4** and its major force in **1**. For example, the $\mathrm{(CH_3)_2X^+{=}CH_2\cdots F^-}$ resonance structure is expected from the anomeric effect in the *anti* conformer; this shortens X—C and lengthens C—F bond distances in comparison to the *gauche* conformer, and the methylenic carbon assumes a sp^2 character. The calculated X—C bond length in the *anti* conformer is 0.01–0.02 Å shorter than in the *gauche* conformer, and the referred angle is significantly larger; the effect on the C—F bond length is particularly large in **1**.

In addition to better $\mathrm{LP_N}$ donation toward C—F* orbital in comparison to the other analogues, **1** is supposed to experience an intramolecular hydrogen bonding $\mathrm{CH_3^{\delta+}\cdots{}^{-\delta}F}$, both in *anti* and *gauche* conformers, as a result of the interaction between the positively charged methyl hydrogens (average Mülliken charge of +0.24 for both conformers) and the negatively charged fluorine (average Mülliken charge of −0.51 and −0.47 for *anti* and *gauche* conformers, respectively). The partial positive charge on methyl hydrogens in **2**–**4** is significantly lower (+0.16 to +0.19). However, two methyl groups interact through hydrogen bonding with the fluorine in the *anti* conformer, whilst only one methyl group experiences such interaction in the *gauche* conformer. This electrostatic interaction could not be calculated directly, but it is supposed to stabilize more the conformation in which the maximum number of such interaction is allowed, the *anti* conformer. The LUMO of *anti* conformer in **1** is also distributed around the methyl hydrogens (Fig. 3), demonstrating their acidity and ability in forming hydrogen bonding with electron donors, such as the fluorine substituent. The LUMO in **2**–**4** is essentially on the $\mathrm{X—CH_3^*}$ orbital.

We approach the charge delocalization, inherently stabilizing forces, by examining the internal rotation about the LP—X—C—F dihedral angle when all hyperconjugative interactions are removed (antibonding and Rydberg orbitals deleted, Fig. 4). Our DFT approach shows that curves with hyperconjugation absence exhibit global minima with the LP—X—C—F dihedral angle going from 60° to 110°, even for **1**, where the electrostatic interaction $\mathrm{CH_3^{\delta+}\cdots{}^{\delta-}F}$ contributes to the stabilization of the *anti* conformer. For **2**–**4**, such minima nearly coincide with the structure of the higher transition state of the real system, while the *anti* structure becomes unstable. These results provide evidence for hyperconjugative preferential stabilization of the *anti* conformation for the whole series of the studied compounds, as demonstrated by the hyperconjugation energies (E_{hyp}) shown in Table 1. Data in Table 1 also suggest that charge transfers between bonds and antibonds plays the major role in describing the conformational preferences of **1**–**4**; this may be obtained from dissection of the full conformational energy into hyperconjugative and Lewis-type energies ($E_{\mathrm{full}} = E_{\mathrm{hyp}} + E_{\mathrm{Lewis}}$). The key component of the hyperconjugative interactions involving the *anti* conformer, which rules the anomeric effect, is the C—F* orbital. Thus, deletion of hyperconjugative interactions involving this orbital indicates the importance of the anomeric effect, not of all hyperconjugative interactions, for the conformational isomerism of **1**–**4**. Figure 4 shows that the global minimum in the curves obtained with all hyperconjugations deleted, and those with only C—F* interactions deleted, are nearly congruent, with the *syn* transition state very higher in energy in the curve computed with C—F* interactions removed, especially for **1**. This proves the major contribution of the anomeric effect for the total hyperconjugative interactions operating in **1**–**4**, and denotes the significant *synperiplanar* $\mathrm{LP_N} \rightarrow \sigma^*_{\mathrm{C—F}}$ interaction in the first transition state (LP—N—C—F dihedral angle = 0°, Table 2).

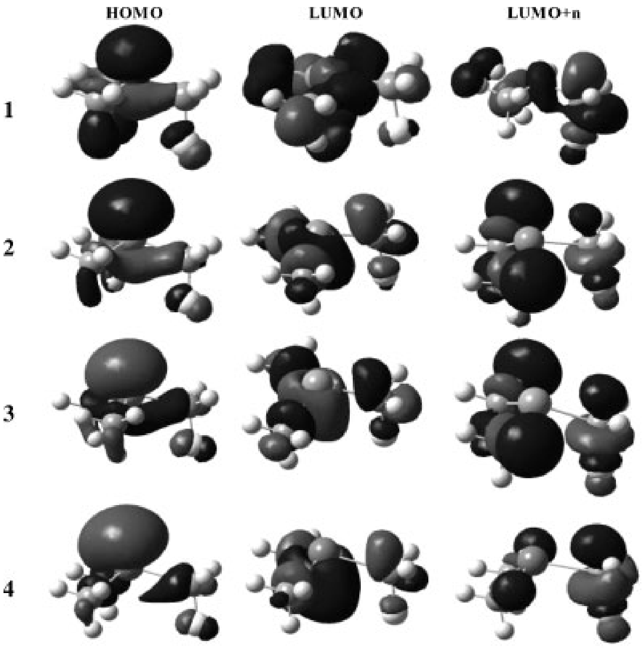


Figure 3. Representation of the main orbitals of **1**–**4** in the *anti* conformation, obtained at the HF/6-31g(d,p) level. HOMO is essentially on the lone pair of the nitrogen family elements; LUMO in **1** is also distributed around the methyl hydrogens, which demonstrated their ability to interact with fluorine through hydrogen bonding; LUMO + *n* includes the C–F* orbital (**1**: *n* = 1; **2**, **3** and **4**: *n* = 4; Isovalue = 0.05)

Isodesmic reaction

Isodesmic bond separation energies were analysed in order to give another insight about the anomeric stabilization in **1**, as well as a comparison with the corresponding effect in **2**–**4**. The following Eqn (1) was considered, in which the ΔE value accounts for the gain or loss in energy after transformation (from left to

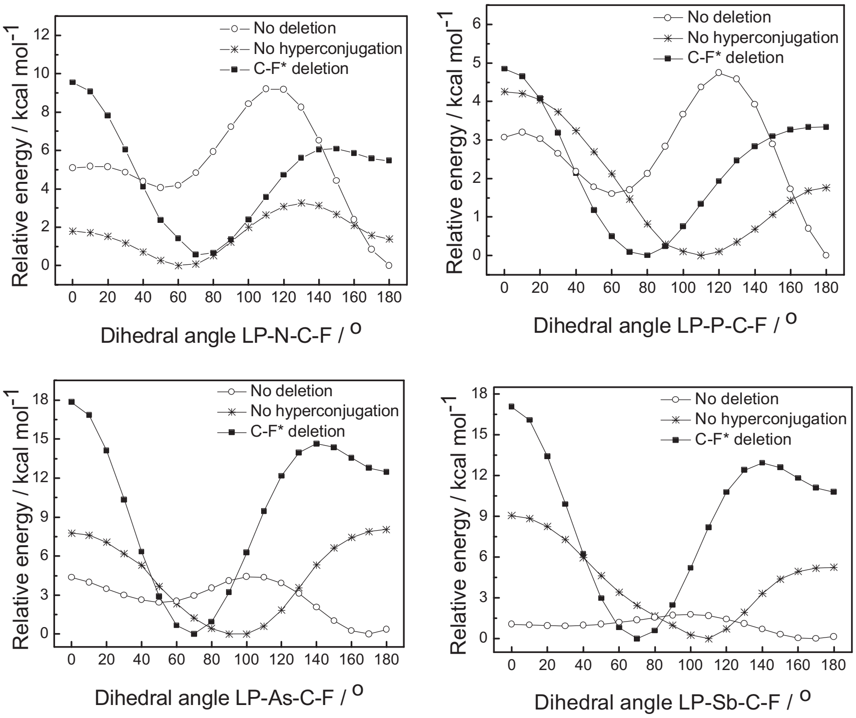


Figure 4. Dihedral angle dependencies of energy of real **1**–**4** (no deletion), hypothetical **1**–**4** with all hyperconjugative interactions absent (no hyperconjugation) and **1**–**4** with interactions involving C–F* orbital removed (C–F* deletion)

right side of the equation).

$$(CH_3)_2XCH_2F + CH_4 \rightarrow (CH_3)_3X + CH_3F \qquad (1)$$

where X = N, P, As and Sb.

The group separation reaction above was calculated to be endothermic for the *anti* conformer of **1** ($\Delta E = 12.8$ kcal mol^{-1}). Since the anomeric effect and group separation energies are presumed to have the same origin, the group separation reactions were therefore taken as measures of the anomeric effect,[14,17,24] although other interactions, for example, intramolecular hydrogen bonding and steric effect, may contribute. When X is P, As and Sb (**2**–**4**), the group separation energies for the *anti* conformation are smaller (1.94, 1.12 and −0.25 kcal mol^{-1}, respectively) than for **1**, in agreement with the trends in hyperconjugation along the series. The stabilization energies decrease from X = N to X = P by *ca.* 10.9 kcal mol^{-1}. The values for X = P, As and Sb are roughly similar. This behaviour comes from a weaker anomeric effect involving the higher row elements, which is parallel to those results observed for a series of O, S, Se and Te-based compounds.[17] The negative ΔE value found for **4** suggests that steric interaction involving the fluorine substituent prevails on the anomeric effect. When one considers the Eqn (1) for the *gauche* conformer, the resulting energy difference is lower or even negative (exothermic) (8.37, 0.15, −0.01 and −0.92 kcal mol^{-1}, for **1**–**4**, respectively), since the contribution of $LP_X \rightarrow \sigma^*_{C-F}$ hyperconjugation is absent.

Table 2. Energy results (kcal mol^{-1}) for the transition states of **1–4**^{a} obtained at the B3LYP/aug-cc-pVTZ level (B3LYP/aug-cc-pVTZ-PP for **4**)

Parameter	1		2		3		4	
	TS-1	TS-2	TS-1	TS-2	TS-1	TS-2	TS-1	TS-2
E_{rel}	4.49	10.77	3.35	4.37	2.15	2.87	1.18	1.97
$LP_X \rightarrow \sigma^*_{C10-H11}$	—	5.86	0.62	—	—	—	—	—
$LP_X \rightarrow \sigma^*_{C10-H12}$	5.99	3.81	0.62	0.55	—	—	—	—
$LP_X \rightarrow \sigma^*_{C10-F}$	15.89	2.08	2.08	2.30	1.04	1.44	0.57	—

The full energy is relative to the corresponding global minimum.

[a] TS-1 corresponds to the transition state with fluorine nearly eclipsed to X lone pair, and TSm with fluorine nearly eclipsed to methyl group (X = N, P, As and Sb).

Overall, we found that the *anti* conformer is the most stable form in all four model compounds studied, and that the anomeric effect is an important, if not determining, factor operating in these systems, even for **2**–**4**, in which the X—C bond length is large due to the great X radius (X = P, As and Sb), and then the non-bonding/C—F* interaction was expected to be negligible (the intrinsic interaction matrix element $h_{LP-\sigma^*}$ will be significantly smaller in higher-row elements than in **1**). Additionally, the electronegativity of the heteroatom also influences the relative stabilities of the conformations, due to the lower energy of the LP orbital for the more electronegative elements, resulting in more stabilizing LP–σ* interaction. As far as we are aware, the anomeric effect involving the whole series of heavy nitrogen family elements has not previously been discussed, and the effect on nitrogen compounds is scarcely available when compared to oxygen derivatives, although it seems a significant contributor to synthesis and conformation analysis of interesting nitrogen and phosphorus-containing compounds,[25–28] such as nitrogen bases and ATP analogues.

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