NMR Spectroscopy: a Tool for Conformational Analysis

Cláudio F. Tormena, Rodrigo A. Cormanich, Roberto Rittner*

Physical Organic Chemistry Laboratory, Chemistry Institute, State University of Campinas, C.P. 6154, 13083-370 Campinas, SP, Brazil

rittner@iqm.unicamp.br

Matheus P. Freitas

Chemistry Department, Federal University of Lavras, C.P. 3037, 37200-000, Lavras, MG, Brazil

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Abstract: *The present review deals with the application of NMR data to the conformational analysis of simple organic compounds, together with other experimental methods like infrared spectroscopy and with theoretical calculations. Each sub-section describes the results for a group of compounds which belong to a given organic function like ketones, esters, etc. Studies of a single compound, even of special relevance, were excluded since the main goal of this review is to compare the results for a given function, where different substituents were used or small structural changes were introduced in the substrate, in an attempt to disclose their effects in the conformational equilibrium.*
Moreover, the huge amount of data available in the literature, on this research field, imposed some limitations which will be detailed in the Introduction, but it can be reminded in advance that these limitations include mostly the period when these results were published.

1. Introduction

This review will include only the results published from 1994 onwards since this subject was reviewed in depth at that time by Eliel *et. al.*[1] An earlier extensive review on the rotational isomerism about sp^2-sp^3 carbon-carbon single bonds was published by Karabatsos and Fenoglio[2] in 1970. Another review was also written by Olivato and Rittner[3] in 1996.

Most of the selected compounds follows the scope proposed by Karabatsos and Fenoglio,[2] including only the rotational isomerism for Y-C-C=O systems, where Y=heteroatom.

Despite the wide variety of physical methods available for such studies like measurements of dipole moments, microwave spectroscopy, Raman spectroscopy, use of shift reagents, etc.[1] the present work will concentrate on the analysis of data from NMR and IR spectroscopies and from theoretical calculations.

A few concepts are briefly presented to make the whole text useful for a beginner in this field. All these concepts are detailed and spread in a large number of books at different levels.[1,4,5]

Conformation

It is important to distinguish the terms configuration and conformation. Both involve a 3D structure. The first refers to the attachment of an atom or a group of atoms to a given center in a given fixed order. Thus, two enantiomers differ in their configuration since

they have an opposite order of the substituents attachment. This means that to change from one configuration to another configuration it is necessary to break bonds and to form new bonds. However, the situation with conformations is very different. For any given configuration, it is possible to have several conformations, which only differ in the value of a given dihedral angle, with bonds being neither made nor broken.

Ethane is the simplest example of a compound which exhibits two different conformations, usually called *conformers* (Fig. 1). They differ by *ca.* 2.93 kcal mol^{-1}, the staggered conformation being the only one stable, since the eclipsed conformation corresponds to a maximum in energy (Fig. 2).

Staggered conformation Eclipsed conformation

Figure 1. Stable conformers for ethane.

An energy diagram for this rotational equilibrium is shown in Fig. 2. Although it was believed that the higher energy of the eclipsed form was due to steric effects of each pair of hydrogens facing each other, Weinhold[6] and Pophristic and Goodman[7] showed that this energy difference can be attributed to $\sigma_{CH} \rightarrow \sigma^*_{CH}$ hyperconjugative orbital interactions stabilizing the staggered form. However, several papers from the literature severely criticized such interpretation and showed that the major contribution for ethane conformational preferences comes from steric effects (two thirds of the ethane rotational barrier energy).[8-10] Notwithstanding, due to the large amount of different interpretations, the controversies remain and the debate will likely to keep on.[11]

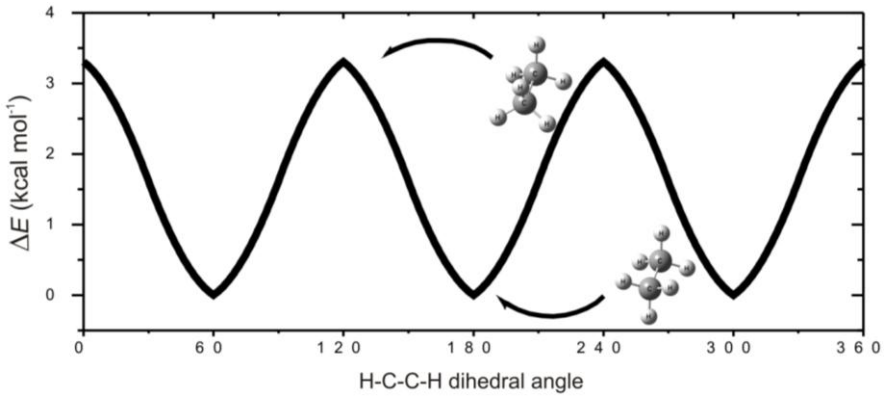
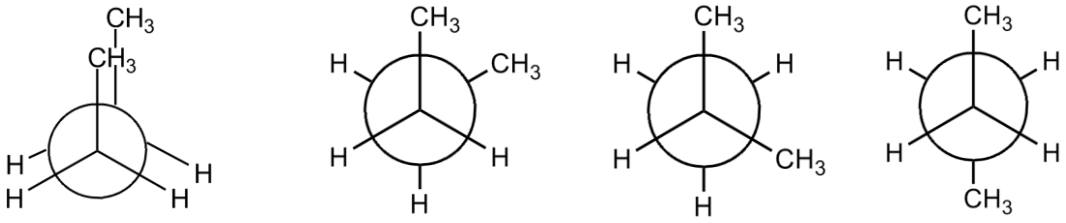


Figure 2. Energy diagram for changes in the ethane conformations.

The first studies on the rotational isomerism in ethane and similar compounds appeared in the last decade of the 19th century and probably the first paper where the "free" rotation about single bonds was the subject of discussion is attributed to Bischoff.[12] This was followed by a large number of papers and a first reliable value for rotational barrier in ethane (3.15 kcal mol^{-1}) was obtained by Kemp and Pitzer in 1936,[13] in close agreement with recent experimental values (2.89-2.93 kcal mol^{-1}).

Here it is important to define the conformation according to the substituent arrangements around the selected bond. The IUPAC specification of the torsion angles as proposed by Klyne and Prelog,[14] is not as widely used as the practical assignments of *cis* (synperiplanar), *gauche* (+synclinal for +30 to +90 and +anticlinal for +90 to +150) and *trans* or *anti* (antiperiplanar) (see the C-C-C-C dihedral angle of butane in Fig. 3 as an example).



cis (*synperiplanar)*

gauche (*synclinal)*

gauche (*anticlinal)*

anti or *trans* (*antiperiplanar*)

Figure 3. Practical assignments of conformer arrangements due to rotation of a single bond, in the C-C-C-C butane dihedral angle.

Conformations of cyclic compounds

Despite early attempts to understand the conformational properties of cyclic compounds, mostly cyclohexane derivatives, it was the remarkable paper of Barton[15] which established the correct stereochemistry of these compounds and granted him the Nobel Prize in 1969. In that paper he showed that it was possible to distinguish two types of CH-bonds: those lying perpendicular to the plane containing the six carbon atoms called *polar* (axial) and those lying approximately in this plane called *equatorial.*

The main difference between the acyclic and cyclic compounds is the large barrier to convert an equatorial to an axial substituted cyclohexane, which is in the range of *ca.* 10 kcal mol^{-1}.[1]

Substituent Effects

In order to interpret and to explain the results of the large number of published papers an extensive review was presented by Zefirov,[16] which describes the substituent effects in classical terms as "steric" and "electrostatic" interactions or in quantum mechanical terms. However, some specific terms were also introduced such as "hockey-sticks", "*gauche*-effect", "rabbit-ears", "anomeric", etc.

The results presented in the present review will be interpreted using mostly classical terms and/or orbital interactions obtained from theoretical calculations.

2. Methodology

The spectroscopic detection of individual conformers depend on the following conditions:[17]

I. The average lifetime of the species must be larger than the inverse frequency ($1/\nu$) of the radiation it is absorbing (Table 1). II. Each conformer must possess different absorption characteristics and must be present within the detection limits of concentration.

The limitation for NMR spectroscopy can be overcome by working at sufficiently low temperatures, whenever it is possible.

Table 1. Minimum lifetimes for detecting stable conformers in conformational equilibrium.

Technique	$1/\nu$/s	Minimum lifetime/s
NMR	10^{-8}	10^{-5}
IR	10^{-12}	10^{-8}

2.1. NMR Spectroscopy

The application of NMR spectroscopy in conformational analysis was clearly established by Garbisch,[18] based on the first observations of Eliel.[19] However, Garbisch's method required the use of models with a fixed geometry, which are not available for aliphatic compounds.

The NMR method involves the averaged chemical shift or coupling constant determination for a given hydrogen atom of a compound in conformational equilibrium.

The observed property value P_{exp} (δ or J) is related to the conformer populations by Eqns [1] and [2]:

$$P_{exp} = n_A P_A + n_B P_B \quad [1]$$

$$n_A + n_B = 1 \quad [2]$$

Here, we have two equations and four unknowns. This system can be solved if more data are collected by changing the solvent, since the populations may change with the solvent, while the coupling constant is almost invariant with the solvent. The other parameter, the chemical shift, is not suitable since δ_A and δ_B also change with the solvent.

Moreover, when one or more conformers exists in more than one optical isomer, the statistical weight of this conformer must be considered. *E.g.* for n-butane (Fig. 3) the population of the *gauche vs. anti* is given by:

$$n_g/n_a = 2 \exp(-\Delta E/RT) \quad [3]$$

$$\Delta E = E_g - E_a \quad [4]$$

The factor 2 arises due to the presence of two equivalent *gauche* forms, *i.e.* for n-butane *gauche*/*anti* ratio is of 2:1.

This system can be solved using a method proposed by Abraham based on solvation theory.[20] In this procedure, the geometries are obtained from theoretical calculations with a suitable software like e.g. GAUSSIAN,[21] GAMESS[22] or Dalton[23] and the data are transferred to CHARGE,[24] which gives the Z-matrix used as an input for MODELS,[20] allowing the determination of all necessary parameters to obtain the solvation energies. Then, these energies are introduced in the BESTFIT program,[25] which calculates the *J* values for the individual rotamers and the energies in every solvent. These data lead to the conformer ratios in every solvent. The conformers must have different dipole moments to make the equilibrium sensitive to changes in solvent polarity.

However, the development of an increased precision in the calculation of *J* values simplified this procedure, since it is possible to calculate these values for every conformer and to obtain straightway the population conformer ratios. This alternative procedure was successfully used for the first time in a recent paper on stereoelectronic interactions and their effects in the conformational preferences for 2-substituted methylenecyclohexanes.[26]

Detailed data for chloroacetone is given below (Section 3.1) as an example of the NMR method's application.

2.2. IR Spectroscopy

Most of the early work on conformational analysis published in the first half of the 20th century was performed by microwave spectroscopy. The progress in the electronic industry in the 1940 decade allowed the construction of commercial infrared spectrometers, which became the preferred technique for organic chemists, both for compound identification and for conformational analysis. One of the first papers using the later technique in the conformational analysis of simple aliphatic compounds is due to Jones and Noack on diethyl ketone.[27]

The main advantage of infrared spectroscopy in comparison to NMR spectroscopy is the possibility of observing a single band for every conformer due to a functional group absorption. In general, these bands are partially superimposed (Fig. 4) or in an extreme case coincident. Now, they can be easily separated using specific software[21-23,28,] and can be assigned to each conformer using calculated frequencies obtained from such

softwares.

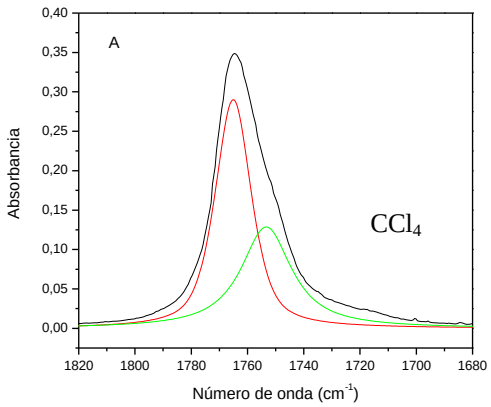


Figure 4. Carbonyl stretching band from the IR spectrum of 2-chlorocyclopentanone in CCl_4, showing the deconvoluted bands for the two conformers.[29]

Although an estimation of the conformer populations ratio can be done from the bands area, this may lead to an erroneous value, as the area depends upon the molar absorptivity for each conformer. This was demonstrated by a study with □-bromocyclohexanone,[30] which has shown that the axial and equatorial conformers have molar absorptivities (α) of 417 and 8181 mol^{-1} cm^{-1} in CCl_4, respectively, while in CH_3CN they were 664 and 2931 mol^{-1} cm^{-1}, respectively.

2.3. Theoretical Calculations

Theoretical calculations are used in conformational analysis for obtaining the geometries and energies for the most stable conformers of a given compound. In the first step the Potential Energy Surface (PES) is constructed by changing a given dihedral angle in steps of 10 degrees, from 0 to 180 degrees for symmetrical dihedral angles and from 0 to 360 degrees for nonsymmetrical dihedral angles. The minima in this PES correspond to the existing conformers. In the following step, the geometries corresponding to these minima are optimized using a higher level of theory, giving now the best values for bond lengths, bond angles, dihedral angles, dipole moments and energies for every conformer. All these calculations can be performed using a DFT or *ab initio* method, with different basis set, available in softwares for theoretical calculation.[21-23] The energy difference gives the conformer population ratio in the gas phase.

3. Compounds

The results from the conformational equilibrium for some series of compounds will be described according to their organic functional groups. The results presented in early reviews will not be discussed here.[1-3]

3.1. Ketones

The first series of compounds is the □-haloacetones, where halo=Cl, Br and I. The fluoro-derivative is not included here, and also for the other series of carbonyl compounds, since it presents a unique behavior and it will be discussed separately. A detailed discussion is given here, since it exemplifies the approach used for almost all series of carbonyl compounds studied in our laboratory.

Theoretical calculations at B3LYP/6-311++G(d,p) for chloroacetone (CA) and bromoacetone (BA) and at B3LYP/6-311++G(d,p)/LANL2DZ for iodoacetone (IA) showed that the isolated form energy difference ($E_{cis} - E_{gauche}$) for CA, BA and IA is 1.4, 1.4 and 1.6 kcal mol^{-1}, respectively (Fig. 5).[31] It must be noted that there are two equivalent *gauche* conformers and, thus, eqn [3] and [4] must be applied.

cis *gauche*

Figure 5. Stable conformers for chloroacetone.

Experimental $^3J_{CH}$ couplings, obtained in solvents of different relative permittivities, were used in conjunction with data from *ab initio* calculations and with the solvation theory, giving energy differences ($E_{cis} - E_{gauche}$) of 1.7 kcal mol^{-1} (CA), 1.8 kcal mol^{-1} (BA) and 1.1 kcal mol^{-1} (IA), in the vapor, which are in reasonable agreement with the theoretical values. The solvent effects in the conformational equilibrium of chloroacetone is shown by data in Table 2. Similar results were obtained for BA and IA.

The increased stability of the *cis* conformer in solution, for the three α-haloacetones may be explained by a solvation effect, where the solvent molecules gather around the compound, a dipole-dipole stabilisation.

The larger stability of the *gauche* conformer, in the isolated form, may be attributed not only to the strong C-X and C=O dipole repulsion in the *cis* form, but also to the stabilising effect of the $n_x \rightarrow \pi^*_{C=O}$ interaction occurring in the *gauche* form.[32] Some other examples of haloacetones have also been studied: the 1,1- and 1,3-dihaloacetones. In the case of the 1,1-dichloro- and 1,1-dibromo-acetone, the conformer presenting the hydrogen atom eclipsing the carbonyl group and the two halogen atoms symmetrically arranged in a *gauche* orientation is the most stable in the gas phase and in non-polar solvents. However, the equilibrium is partially shifted to the other isomer (halogen eclipsing the carbonyl group) in polar solvents.[32]

Table 2. Energy differences (kcal mol^{-1}), *cis* and *gauche* molar fractions, and calculated and observed coupling constants ($^3J_{C,H}$/Hz) for chloroacetone.[31]

Solvent	E_{cis}-E_{gauche}	$^3J_{CH}$ (calc.)	$^3J_{CH}$ (obs.)	% *cis*	% *gauche*
CCl_4	0.76	1.5	1.5	10.3	89.7
$CDCl_3$	0.00	1.7	1.8	39.9	60.1
CD_2Cl_2	-0.47	1.9	1.9	49.8	50.2
Pure liq.	-0.95	2.1	2.1	69.6	30.4
Acetone	-0.93	2.1	2.1	69.6	30.4
CD_3CN	-1.27	2.2	2.2	79.4	20.6
DMSO	-1.40	2.3	2.3	89.3	10.7

For the 1,3-dihaloacetones, there is a predominance of the *gauche-gauche'* isomer (**5**) in the gas phase for the dichloro- and dibromo-derivative, which turns into a mixture of three conformers (**4** – **6**) in solution (Fig. 6) whose populations depend on the solvent polarity, as observed from their infrared spectra.[33]

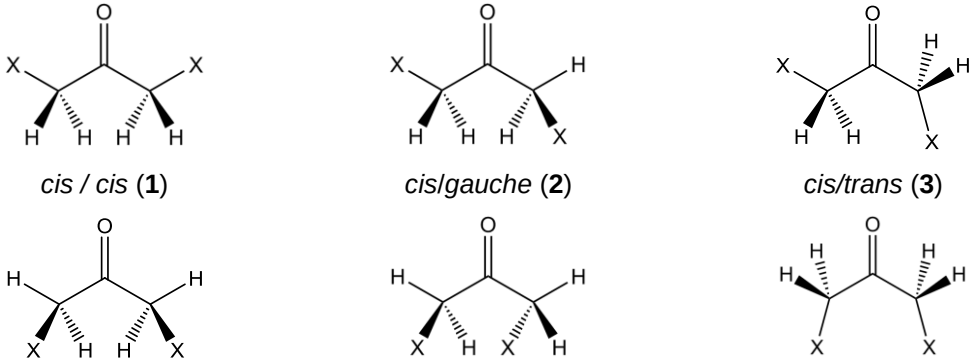


Figure 6. Possible rotamers for 1,3-dihaloacetones.[33]

Aminoacetone[34] presents an interesting case since its *cis* isomer is far more stable than the *gauche* isomer (E_{gauche} -E_{cis} = 3.00 kcal mol^{-1}). In the *cis* isomer there is a stabilizing electrostatic attraction between the amino hydrogens and the non-bonding electron pairs of oxygen, but there is also a destabilizing repulsion between the nitrogen lone pair and the carbonyl-oxygen high electronic-density region. However, the main effects which stabilize the *cis* arrangement are the hyperconjugative effects obtained from NBO calculations.[35]

The geometries for the corresponding *N*,*N*-dimethylaminoacetone can only be obtained from 3D potential energy surfaces, varying the ϕ (N-CH_2-C=O) and θ (LP-N-CH_2-C=O) dihedral angles (Fig. 7).

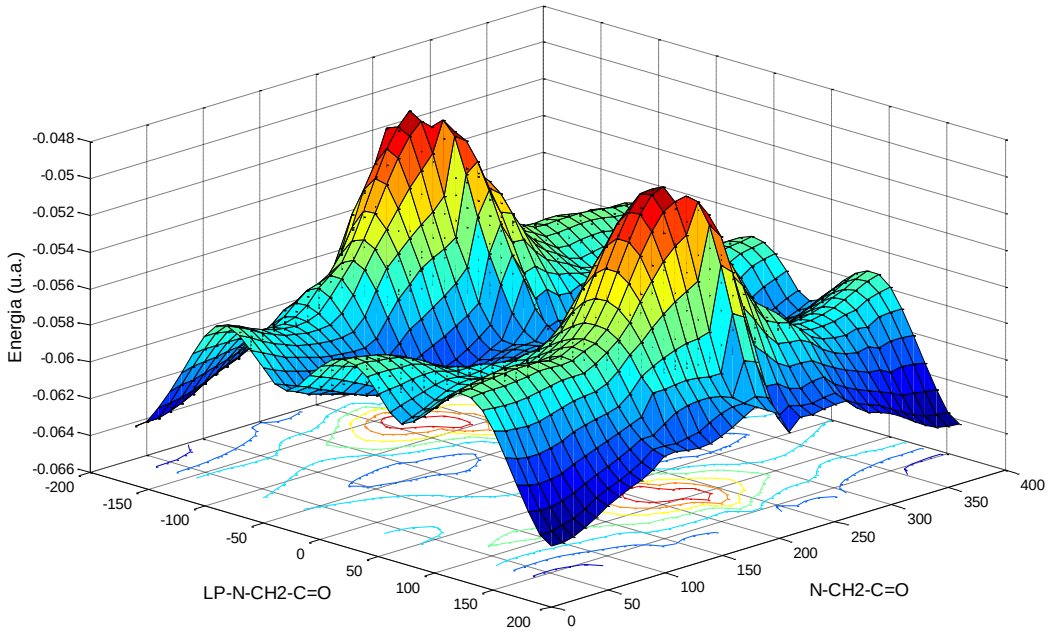


Figure 7. 3D Potential energy surface obtained by rotating ϕ (N-CH_2-C=O) and θ [LP-N-CH_2-C(=O)] dihedral angles. The energy levels (AM-1 method) contour plot is showed in the x-y plane.

The removal of equivalent geometries (specular relationship) leads to two main isomers: synperiplanar-antiperiplanar (ϕ=0°, θ=-180°) (*Sp-Ap*) and synclinal-synclinal (ϕ=135°, θ=-52°) (*Sc-Sc*), which are rather similar to the *cis* and *gauche* isomers. Here, the energy difference is 0.81 kcal mol^{-1} ($E_{Sp\text{-}Ap}$-$E_{Sc\text{-}Sc}$). It is noteworthy that despite the large stabilization energies, due to orbital interactions, for the *Sp-Ap* in relation to the *Sc-Sc* conformer, there is still a predominance of stereo-electronic repulsive effects making the later the most stable conformer (Fig. 8).[34]

Sp-Ap *Sc-Sc*

Figure 8. Sp-Ap and Sc-Sc conformers for *N*,*N*-dimethylaminoacetone.

3.2. Esters

A series of methyl α-haloacetates, similar to acetones, was also studied.[36] Here, there are two possible dihedral angles to be analysed [O=C-O-R and X-C-C=O). The first would lead to the *s-cis* and *s-trans* isomers (Fig. 9), whose energy difference for the unsubstituted methyl acetate is *ca.* 7.8 kcal mol^{-1}, which is too high and means that only the *s-cis* must be considered. Considering only the most stable *s-cis* geometry, now the other dihedral angle gives two main isomers (Fig. 10).

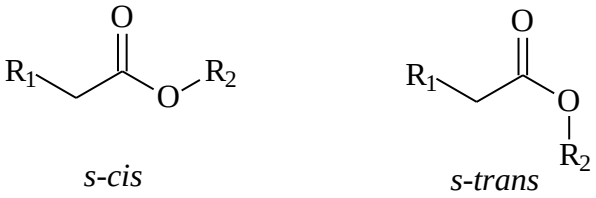


Figure 9. *s-cis* and *s-trans* isomers for aliphatic esters.

Figure 10. *cis* and *gauche* conformers for α-substituted aliphatic esters.

Here, the conformational preferences for methyl chloroacetate (MCA), methyl bromoacetate (MBA) and methyl iodoacetate (MIA) were analyzed using experimental infrared data, theoretical calculations and NBO analyses. The conformational equilibria of these three compounds can be represented by their *cis* and *gauche* rotamers. The *gauche* form of MCA is stable in the isolated form by only 0.1 kcal mol^{-1} ($E_{cis} - E_{gauche}$), and also in a non-polar solvent, but the *cis* is predominant in a polar solvent [($E_{cis} - E_{gauche}$) = 0.53 to 0.66 kcal mol^{-1}, from CD_2Cl_2 to DMSO]. For MBA the *gauche* form is more stable than the *cis*, in both the vapor and in solution, but for compound MIA only the *gauche* form was observed both in isolated form as in solution. These conformational preferences were attributed to an *unexpected* orbital interaction, not yet reported in the literature, between two antibonding orbitals, $\pi^*_{C=O} \rightarrow \sigma^*_{C-X}$, which occurs only in the *gauche* rotamer. The iodo-

derivative (MIA) presents the highest energy for this $\pi^*_{C=O} \rightarrow \sigma^*_{C-X}$ interaction (19.2 kcal mol^{-1}), followed by bromo-derivative (MBA) (11.9 kcal mol^{-1}), then by chloro-derivative (MCA) (5.0 kcal mol^{-1}). The occupancy and energy for the antibonding orbitals $\pi^*_{C=O}$ and σ^*_{C-X} are presented in Table 3. The occupancy values around 0.2, for the three compounds, obtained for $\pi^*_{C=O}$ orbital are too high for an antibonding orbital, but they can be justified by the high energy (48 kcal mol^{-1}) of the $LP_{O_2} \rightarrow \pi^*_{C=O}$ interaction, which increases the electron density at the $\pi^*_{C=O}$ orbital.

Table 3. NBO occupancy and energies (eV) for the antibonding orbitals calculated at the B3LYP/aug-cc-pVTZ level for the *gauche* conformer of the methyl haloacetates (halo= Cl, Br and I).[36]

	Occupancy			Orbital Energy		
Orbital	Cl	Br	I	Cl	Br	I
$\pi^*_{C=O}$	0.220	0.225	0.232	-0.00728	-0.00457	-0.00296
σ^*_{C-X}	0.014	0.016	0.017	0.08484	0.03331	0.01904
ΔE	-	-	-	0.09212	0.03788	0.02200

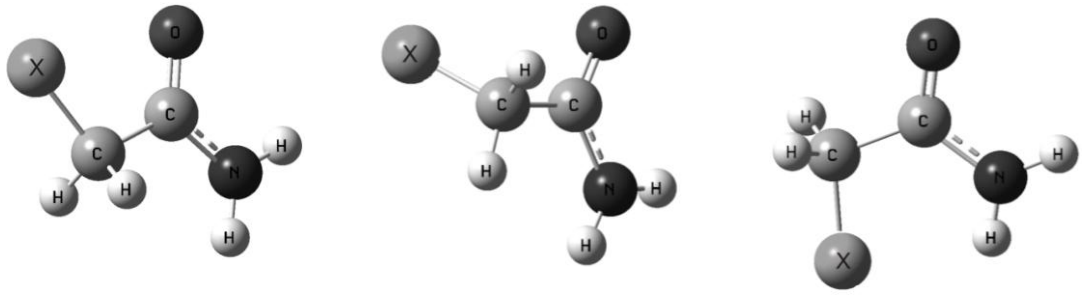
3.3. Amides

Here, we will discuss separately the results obtained for the α-haloacetamides and *N,N*-dimethyl α-haloacetamides.

3.3.1. α-Haloacetamides

NMR data for $^2J_{C-H}$ and for $^3J_{C-H}$ for the two studied amides – the α-chloroacetamide (CA) and α-bromoacetamide (BA),[37] did not show any changes on varying the solvent polarity, precluding the use of the NMR method. The next step was to check for the occurrence of possible conformers from the potential energy surfaces (PES), using theoretical calculations. These calculations were done using the DFT/B3LYP method with different basis set [cc-pVDZ, 6-31g(d,p) and *aug*-cc-pVDZ] in the isolated form to identify the energy minima corresponding to each rotamer and including the Polarizable Continuum Model (PCM) to take into account the solvents effects on the rotational isomerism. Subsequent optimizations of the most stable rotamers were performed at the B3LYP/*aug*-cc-pVTZ in the isolated form and in different solvents (CH_3CN, DMSO and H_2O).

It was observed only the *trans* conformer for BA, while for CA a *cis* and a *trans* conformer were present, despite the very large energy difference between them [$\Delta E(cis\text{-}trans)$ = 4.2 kcal mol^{-1}] (Fig. 11).



cis *gauche* *trans*

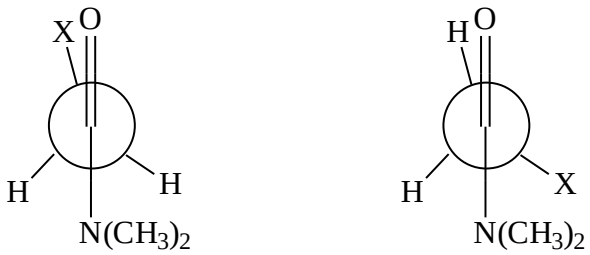
Figure 11. *cis and trans* stable conformers for chloro- (X=Cl) and *trans and gauche* conformers for bromo-acetamide (X=Br).

This energy difference changes with solvent and a value of 2.0 kcal mol^{-1} was obtained in DMSO. Thus, a comparison of the averaged experimental couplings with theoretically calculated values, and taking into account the calculated energy difference between the two conformers, allowed the conclusion that both for CA as for BA the *trans* form was the most stable conformer in all solvents. Despite the occurrence of several orbital interactions, the $LP_N/\pi^*_{C=O}$ interaction, presents in both compounds, was 6.0 kcal mol^{-1} more energetic for the *trans* conformer, which explains its larger stabilization. For BA the *gauche* form only occurs in polar solvents as 20% [from theoretical data in DMSO; $\Delta E(gauche\text{-}trans)$ = 0.9 kcal mol^{-1}] or as 40% (from the calculated coupling constants values). These relative larger populations for BA *gauche* conformer in polar solvents, can be attributed to an unexpected interaction, between two antibonding orbitals ($\pi^*_{C=O}$ and σ^*_{C-X}), as described for *N,N*-dimethylbromoacetamide (see Section 3.3.2).[38]

3.3.2. N,N-Dimethyl-α-haloacetamides

All structures for *N,N*-dimethylchloroacetamide (DMCA) and *N,N*-dimethylbromoacetamide (DMBA) were fully optimized at DFT/B3LYP/*aug*-cc-pVTZ level, to give the correct description of Cl and Br atoms, since it includes additional diffuse functions (prefix aug-), which take into account the relatively diffuse nature of the lone pairs. For the iodo-derivative (DMIA) the geometry optimization was performed at DFT/B3LYP and *aug*-cc-pVTZ basis set for C, H, O and N atoms, while for the iodine atom a correlation consistent basis set *aug*-cc-pVTZ-PP,[39] with small-core relativistic pseudo-potential was applied.

The calculated energy values showed that the *gauche* was the only conformer in the isolated form [$\Delta E(cis\text{-}gauche)$ > 3.0 kcal mol^{-1}], for these haloacetamides. Infrared data in different solvents are in agreement with these results. Even in very polar solvents the *gauche* conformer largely predominates over the *cis* conformer. The orbital interactions (NBO analysis) can be invoked to explain why the *gauche* conformer is the most stable form in the isolated form and condensed phase (Fig.12).



cis *gauche*

Figure12. The most stable rotamers *cis* and *gauche*, for *N*,*N*-dimethyl-2-haloacetamides (halo=F, Cl, Br and I).

The main orbital interaction in amides is the $n_N/\pi^*_{C=O}$ with energies around 66 kcal mol^{-1}, which is very similar for both conformers. Several other interactions also occur in the three amides, but they are very similar for both conformers. However, the unexpected interaction between two antibonding orbitals ($\pi^*_{C=O}$ and σ^*_{C-X}), due to the larger occupancy of the $\pi^*_{C=O}$ (~0.3), which is only present in the *gauche* conformer, can explain why it is more stable than the *cis* conformer. This interaction decreases in the order Br>I>Cl, which is the same as the *gauche/cis* population ratio (Table 4).[38]

4. α-Fluorcarbonyl compounds

4.1. Ketones

Fluoroacetones have been extensively investigated in the search of the possible effects of the introduction of a second fluorine atom at the α-carbon or α'-carbon, or one or more methyl groups also at both carbon atoms.

It is noteworthy that while most of the halo-substituted carbonyl compounds (halo = Cl, Br and I) present *cis* and *gauche* isomers, the monofluoro-derivatives present *cis* and *trans* isomers, as it will be shown in the following discussion.

This series of compounds has a first study using the methodology proposed in Section 2.1 using experimental coupling constants ($^4J_{HF}$) and solvation theory in the conformational equilibrium of α-fluoroacetone (FA) and α,α'-difluoroacetone (DFA).[40] The solvation theory gave [$\Delta E(cis\text{-}trans)$ = 2.2 kcal mol^{-1}] for FA in a good agreement with theoretical calculations (2.9 kcal mol^{-1}) at MP4/6-31G* level of theory. That value changes from 1.0 in CCl_4 to -1.3 kcal mol^{-1} in DMSO. This corresponds to a change from 97% in the vapor to 85% in CCl_4 to 11% in DMSO for the *trans* conformer.

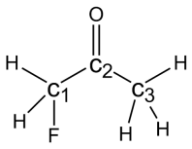
Table 4. NBO occupancy and energies (eV) for the antibonding orbitals calculated at the B3LYP/aug-cc-pVTZ level for the *gauche* conformer of the *N,N*-dimethyl-2-haloacetamides (halo= Cl, Br and I).[38]

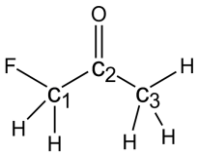
	Occupancy			Orbital Energy		
Orbital	Cl	Br	I	Cl	Br	I
$\pi^*_{C=O}$	0.309	0.313	0.315	0.02428	0.02836	0.02977
σ^*_{C-X}	0.019	0.023	0.023	0.09865	0.04532	0.05799
ΔE	-	-	-	*0.07437*	*0.01696*	*0.02822*
*Gauche popul.(%)**	-	-	-	56	93	80

(*) In CH_3CN solutions. In the gas phase *ΔE(cis-gauche)* > 3 kcal mol^{-1} for the three compounds.

NBO calculations showed that the orbital interactions for the *cis* conformer amount to 6.56 kcal mol^{-1}, while for the *trans* conformer they correspond to only 1.97 kcal mol^{-1} (Table 5). However, steric and electrostatic interactions predominate over those orbital interactions leading to a higher stabilization for the *trans* conformer. These results superseded the data from Durig *et al*.[41] from Raman spectroscopy.

Table 5. Orbital interactions for the *cis* and *trans* conformers of fluoroacetone



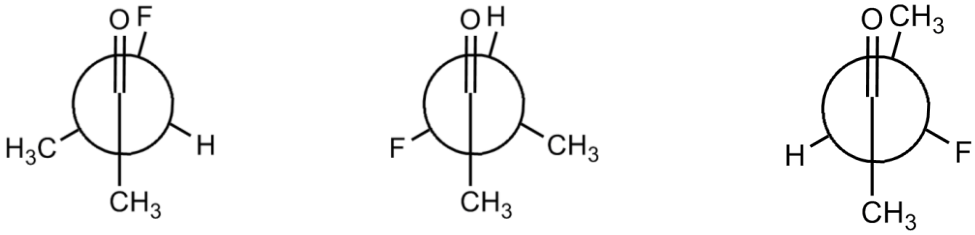


Trans		*cis*	
Interaction	E(kcal)	Interaction	E(kcal)
$\sigma_{C(1)-F} \rightarrow \sigma^*_{C(2)-O}$	1.44	$\sigma_{C(1)-H} \rightarrow \sigma^*_{C(2)-O}$	5.07
$\sigma_{C(2)-O} \rightarrow \sigma^*_{C(1)-F}$	0.53	$\sigma_{C(2)-O} \rightarrow \sigma^*_{C(1)-H}$	1.49
	ΔE= 1.97		ΔE= 6.56

For DFA the equilibrium between the *cis* (H-C-C=O 0°) and a *gauche* conformation (H-C-C=O 104°) involves 0.8 kcal mol^{-1} [*ΔE(gauche-cis)*] in the isolated form, decreasing to 0.1 in CCl_4 to -1.23 kcal mol^{-1} in DMSO. These data are in agreement with the infrared spectra recorded as pure liquid, in CH_2Cl_2, $CHCl_3$, CCl_4 and in isolated form. It is also interesting that its most stable conformer (*cis*) has two fluorine atoms in a *gauche* relationship to the carbonyl group which operates as a resulting dipole opposed to the carbonyl group, giving a system rather equivalent to the *trans* conformer of fluoroacetone.

It is also remarkable that the $^4J_{HF}$ follows an approximate $\cos^2 \theta$ dependence , where θ is the F-C-C-C torsional angle. Thus, for θ equals 0 or 180° the coupling is large (5.0 and 3.4 Hz, respectively) while for θ equals 60° the coupling is much smaller (0.6 Hz).

Further work with two other fluoroketones, 3-fluorobutan-2-one (FB) and 3,3-difluorobutan-2-one (DFB) was performed, to determine the methyl group effect on the conformational behavior of this kind of compound.[42] Despite the possible occurrence of a larger number of conformers in comparison to fluoroacetone, NMR and IR experimental data as well as theoretical calculations showed the presence of only two conformers (*cis* and *trans*) for FB and a single conformer (*cis* C-C-C=O 0°) for DFB (Fig. 13).



Cis *trans* *cis*

Figure13. Stable conformers for FB (*cis* and *trans*) and for DFB (*cis*).

Here, the $^{4}J_{HF}$ value, for FB, also shows significant changes with the solvent (4.92 in CCl_4 to 3.86 Hz in DMSO) and was used for the analysis of its conformational behavior. Its IR spectra correlate well with the NMR data showing either a shoulder or two partially resolved carbonyl bands (Fig. 14).

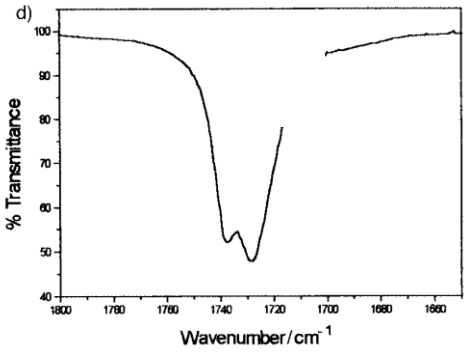


Figure 14. Carbonyl stretching band for FB in CH_3CN solution.[42]

The energy difference ($\Delta E_{cis\text{-}trans}$) for FB was 3.67 kcal mol^{-1} in isolated form (theoretical calculations) in excellent agreement with 3.7 kcal mol^{-1} from NMR data and solvation theory.

Despite the large solvent effect in the equilibrium, even in DMSO the *trans* is still more stable than the *cis* (ΔE = 0.14 kcal mol^{-1}). It is noteworthy that the *trans* conformer was not considered by Shapiro *et al.*,[43] in a paper on solvent effects in the NMR spectra of FB.

A different behavior was observed for DFB. Theoretical calculations just show a single conformer (*cis*) (Fig. 13), which is agreement with NMR data since no changes were observed, on changing the solvent polarity, for all couplings [$^{3}J_{HF}$, $^{4}J_{HF}$, $^{1}J_{CF}$, $^{2}J_{CF(F\text{-}C\text{-}C=O)}$ and $^{2}J_{CF(F\text{-}C\text{-}CH_3)}$) and its IR spectra exhibited a very sharp carbonyl band confirming the occurrence of the single conformer. Its geometry is similar to the *cis* conformer of α,α'-difluoroacetone[41] and its stability was explained by similar reasons.

More crowded fluoroketones, *i.e.* 3-fluoro-3-methyl-2-butanone (FMB) and 1-fluoro-3,3-dimethyl-2-butanone (FDMB), were also analysed.[44] These compounds allowed the study of two methyl groups effect attached at the same carbon atom bearing the fluorine atom and the three methyl groups (a t-butyl group) effect away of the fluorine atom. The corresponding conformers are presented in Fig. 15.

The large predominance of the *trans* form for FMB (ΔE = 3.20 kcal mol^{-1}, in the vapour phase) was attributed to the steric effect between the two methyl groups, one attached to the α carbon and the acetyl methyl group. However, it is noteworthy that for FDMB there is no significant steric effect (ΔE = 1.70 kcal mol^{-1}, in the isolated form), which is even smaller than the energy difference observed for fluoroacetone (ΔE = 2.20 kcal mol^{-1}, in the vapour phase). The solvent effects were similar to the other fluoroketones here described. A comparison of the conformational behavior of 1,3-difluoroacetone with all fluoroketones described above showed a similar behavior.[45] The conformer presenting a fluorine atom *trans* to the carbonyl oxygen predominates in the equilibrium, which is the *cis/trans* form (structure **3**, X=F, Fig. 6), in relation to the second more stable *gauche/gauche'* conformer (structure **5**, X=F, Fig. 6) (ΔE = 1.30 kcal mol^{-1}, in the isolated form). This is true even in different solvents, although in acetonitrile there is a significant amount (34%) of the *cis/cis* conformer.

All these results show that in the isolated form the fluorine atom is *always trans* to the carbonyl oxygen atom indicating a strong electrostatic repulsion between them reinforced by a $n_F \rightarrow \pi^*_{CO}$ orbital interaction and by an electrostatic attractive interaction, such as hydrogen bonding, involving the methyl hydrogen and the fluorine atom. The latter interaction is in agreement with the calculated distance (H…F) of 2.63 Å in comparison with the sum of van der Waals radii which is 2.67 Å. Moreover, in more polar solvents the equilibria are shifted towards a conformer which has the fluorine atom *cis* to the carbonyl oxygen due to the solvent cage. Then, the electrostatic interaction between solute and solvent become the main factor, which leads to the stabilization of the more polar rotamer (*cis*) with increasing the solvent polarity.

It is noticeable that all compounds bearing a single fluorine atom present only *cis* and/or *trans* conformers, but none has a *gauche* conformer. This reinforces our conclusions about the factors which determine the conformer stabilities.

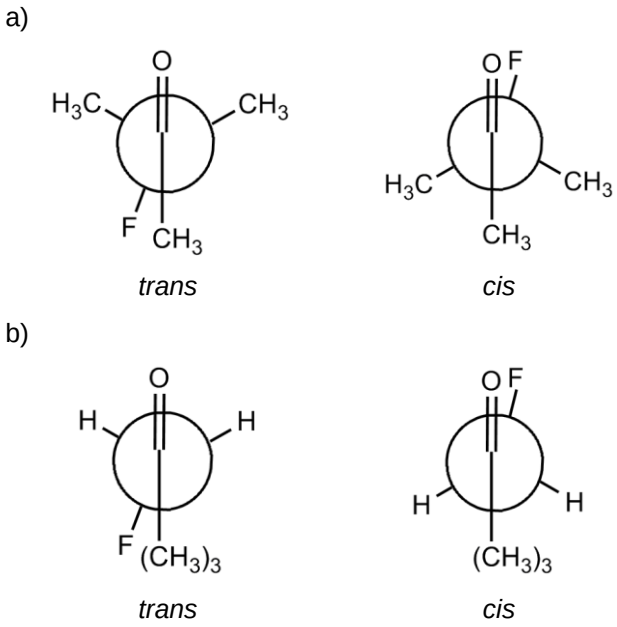


Figure 15. a) *trans* and *cis* conformers for FMB; b) *trans* and *cis* conformers for FDMB.

4.2. Esters

Despite the significant importance of fluoroesters, a single paper reported the study of methyl fluoroacetate (MFA) and methyl difluoroacetate (MDFA), but using Raman and infrared spectroscopy and *ab initio* calculations at 4-21G and 6-31G level of theory.[46] However, it is well known that larger basis sets and correction for electron correlation may lead to enormous difference in the results.

Thus, a later study on these compounds (MFA and MDFA) using NMR data ($^1J_{CF}$) and infrared spectroscopy ($\pi_{C=O}$) in several solvents, and also theoretical calculations at B3LYP/6-311+G(d,p) have given more accurate data for their conformational equilibria.[47] Theoretical calculations for MFA gave only two energy minima corresponding to the *cis* (F-C-C=O 0^o) and *trans* (F-C-C=O 180^o) conformers, while the *gauche* conformer was not a minimum in the energy surface. The observed coupling constants, when analysed by solvation theory lead to an energy difference ($E_{cis} - E_{trans}$) of 0.90 kcal mol^{-1} in the vapour phase, decreasing to 0.41 kcal mol^{-1} in CCl_4 and –0.71 kcal mol^{-1} in DMSO. In MDFA, the DFT calculations gave two minima for the *cis* (H-C-C=O 0^o) and *gauche* (H-C-C=O 141.9^o) conformers, with an energy difference ($E_{cis} - E_{gauche}$) of 0.2 kcal mol^{-1}. The FTIR spectrum of MDFA in a non polar solvent (CCl_4) showed the presence of two resolved bands, but in the other solvents of medium and high polarity the carbonyl absorption appears as a single sharp band (Fig. 16).

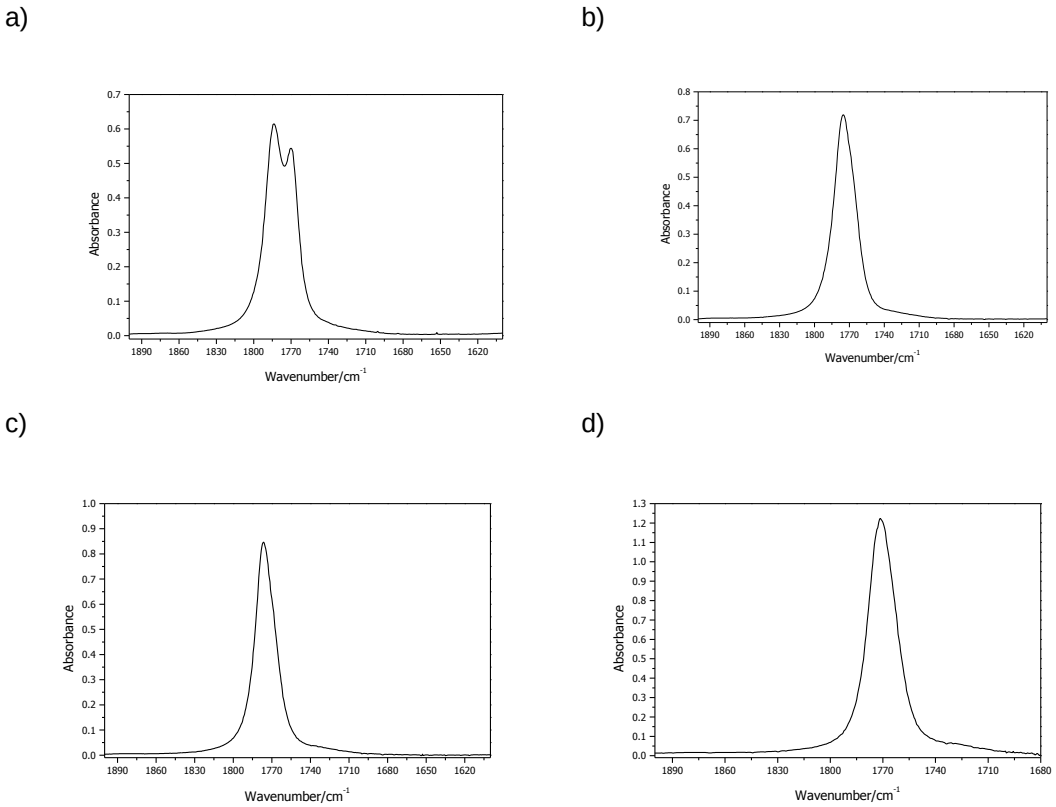


Figure 16. The carbonyl absorption band in the IR spectrum of MDFA in: a) CCl_4; b) CH_2Cl_2; c) CH_3CN and d) DMSO.[47]

The NMR data do not show significant changes with solvent, confirming that there is only one stable conformer in the latter solvents for MDFA. The conformational behavior of some other fluoroesters was also reported.[48] For methyl 2-fluoropropionate (MFP), methyl 2-fluorobutyrate (MFB), methyl 2-fluoro-*tert*-butylacetate (MBA) and methyl 2-fluorophenylacetate (MFPA) (Fig. 17) the potential energy surfaces (PES) were obtained at the B3LYP/6-31g(d,p) level, which showed two stable rotamers: *cis* and *trans*. Their geometries were optimized at B3LYP/6-311++g(d,p) level of theory giving very similar energies for both rotamers of the four studied compounds, in the isolated form.

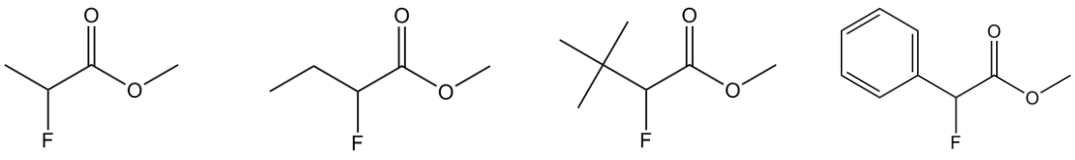


Figure 17. Structures of α-fluoroesters: methyl 2-fluoropropionate (MFP), methyl 2-fluorobutyrate (MFB), methyl 2-fluoro-*tert*-butylacetate (MBA).

Thus, MFP was synthesized for the study of its behavior in solution, and its NMR and IR spectra recorded, and its results extrapolated to the other esters. The significant changes in $^1J_{CF}$ (184.1 to 177.8 Hz), corroborated by the changes in the infrared spectra, showed that the *trans* conformer population varies from 56% in the vapor to 49% in CCl_4, to 19.8% in DMSO. The *trans* form shows distinct effects: a repulsive dipolar $F^{\delta-}/^{\delta-}OCH_3$ effect and an attractive $n_F/\pi^*_{C=O}$ interaction (hyperconjugation). For the *cis* rotamer the $F^{\delta-}/^{\delta-}O{=}C$ repulsive interaction is progressively decreased with the increase in the solvent polarity.

A comparison with the corresponding α-fluoroketones shows that again the fluorine atom prefers the *trans* arrangement in relation to the carbonyl group.

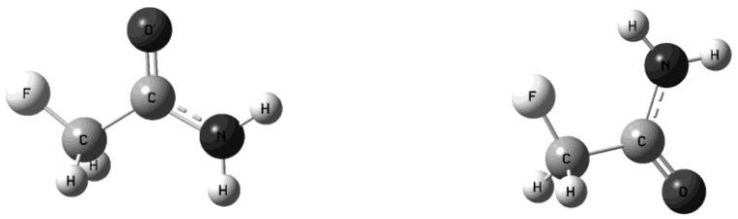
4.3. Amides

Here, it will discussed separately the results obtained for the α-fluoroacetamide, *N*-methyl α-fluoro-*N*-methylacetamides and α- fluoro-*N,N*-dimethylacetamides.

4.3.1. α-Fluoroacetamide

The conformers stability of □-fluoracetamide in the gas phase and in solution was also recently published.[37] All theoretical calculations were performed as described in Section 3.3.1. for other α-haloacetamides.

The *trans* conformer is far more stable than the *cis* ($\Delta E_{cis\text{-}trans}$ = 3.4 kcal mol^{-1}), in the isolated form, but this energy difference decreases to ~2.0 kcal mol^{-1} in solution (Fig. 18). However, no significant changes were observed for $^2J_{C\text{-}H\alpha}$ and for $^3J_{C\alpha\text{-}H}$ which precluded the use of the classical NMR method, as described in the introduction to determine the conformers ratio. However, the energy differences and theoretically calculated coupling constants allowed us to conclude that fluoroacetamide adopts the *trans* conformation in the isolated form (~100%) and it largely predominates in solution (97%). Besides the steric and electronic interactions, there is a very favourable interaction between the C-F and N-H dipoles in the *trans* isomer. Additional stabilization comes from the LP_N/π^*_{CO} interaction which is 6.0 kcal mol^{-1} more energetic for the *trans* conformer, both in the isolated form as in solution, as shown by NBO calculations.



cis *trans*

Figure 18. Stable conformers for *cis and trans* fluoracetamides.

4.3.2. α-Fluoro-N-methylamides

Theoretical calculations plus the solvent dependence of the ^{13}C NMR and IR spectra were used for the analysis of the conformational equilibrium in *N*-methyl-α-fluoroacetamide (MFA) and *N*-methyl-α-fluoropropionamide (MFP).[49] A*b initio* calculations were used to identify the stable rotamers and obtain their geometries and the application of solvation theory on the $^1J_{CF}$ coupling constant gave the rotamer populations in the solvents studied. In MFA *ab initio* calculations at the CBS-Q level yielded only two stable rotamers, the *cis* and *trans*, with $\Delta E(cis\text{-}trans)$ = 4.71 kcal mol^{-1}. The presence of two conformers, in solution, was confirmed by the FTIR spectra. Assuming these forms, the observed couplings when analysed by solvation theory gave ΔE = 5.09 kcal mol^{-1} in the isolated form, decreasing to 2.13 kcal mol^{-1} in $CHCl_3$ and to 0.19 kcal mol^{-1} in DMSO (Fig. 19). The corresponding $^1J_{CF}$ couplings changed from 185.4 (in $CDCl_3$) to 180.2 Hz (in DMSO).

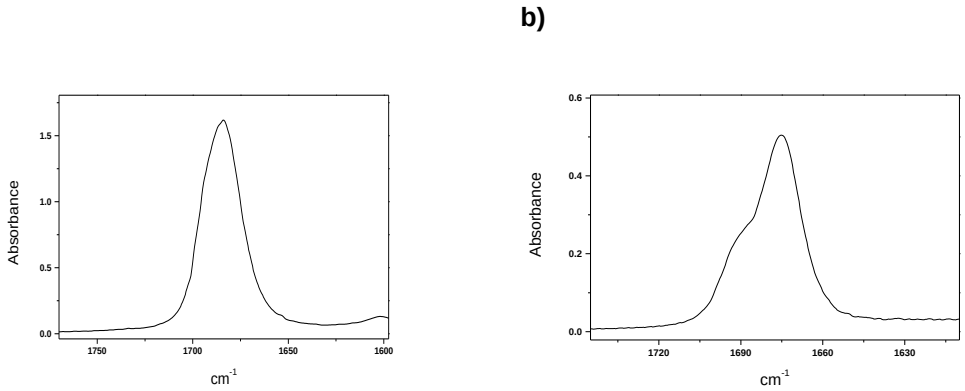


Figure 19. The carbonyl absorption band in the IR spectrum of MFA in: a) $CHCl_3$, b) DMSO.[49]

For MFP, the B3LYP calculations at the 6-311++g(2df,2p) level gave only the *trans* as a stable rotamer, while the *gauche* form was a *plateau* in the potential energy surface. However the FTIR spectra clearly showed the presence of two conformers. Therefore, new theoretical calculations were performed using the SCRF (self consistent reaction field) routine, which allowed the identification of a minimum for the *gauche* rotamer, in DMSO solution (Fig. 20).

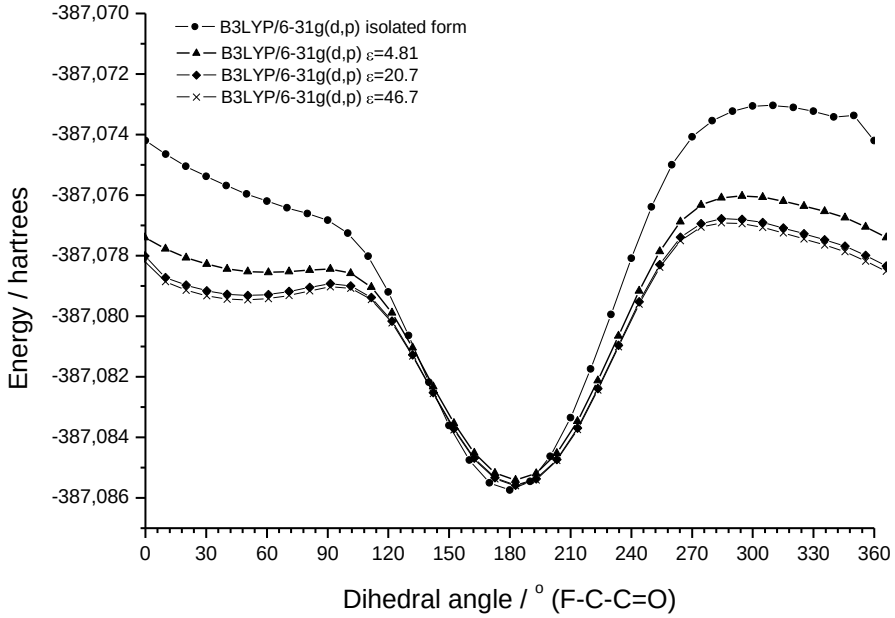


Figure 20. PES for *N*-methylfluoropropionamide at B3LYP/6-31g(d,p) level at different values of medium relative permittivity ($CHCl_3$, ε = 4.81; acetone, ε = 20.7; DMSO, ε = 46.7).[49]

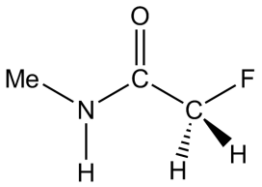
The equilibrium in MFP was therefore analysed by solvation theory in terms of the *trans* and *gauche* rotamers to give $\Delta E(gauche\text{-}trans)$ = 3.80 kcal mol^{-1} in the isolated form, decreasing to 2.58 kcal mol^{-1} in CCl_4 ($^1J_{CF}$ = 182.9 Hz) and to 0.12 kcal mol^{-1} in DMSO (179.2 Hz). The *trans* form of both compounds is stabilized, in the isolated form and in solution, by the natural repulsion between the F atom and the carbonyl group in the *cis* conformer, and also by the possible formation of a hydrogen bond between the NH hydrogen and the F atom, since they are apart by only 2.18 Å in the *trans* conformer (Fig. 21).

It is also important to note that the *cis* conformer does not occur due to the strong steric repulsion between the 2-methyl and the $NH(CH_3)$ group, which are too close when the F is *cis* to the C=O group.

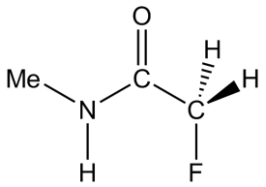
4.3.3. α-Fluoro-N,N-dimethylamides

Two α-fluoro-*N,N*-dimethylamides were studied: the acetamide (DMFA) and propionamide (DMFP) derivatives.[50] Two rotamers: gauche (97%) and cis (3%), in the isolated form, were found for DMFA, with an energy difference ($\Delta E_{cis\text{-}gauche}$ = 4.71 kcal mol^{-1}). This equilibrium is shifted to the *cis* conformer in polar solvents, as confirmed by the large changes in the $^1J_{CF}$ experimental values (180.2 to 170.3 Hz) on increasing the solvent relative permittivity, leading to 90% of the *cis* in DMSO).

a)

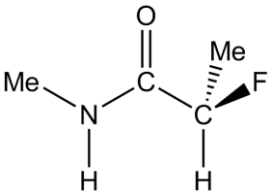


cis

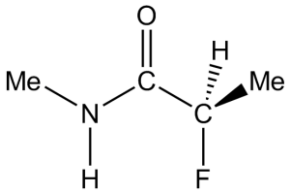


trans

b)



gauche



trans

Figure 21. Possible conformers for: a) NMFA and b) NMFP.

The interpretation is similar to the other amides. The predominance of the *gauche* conformer in the isolated form is due to the strong repulsion between the F and the C=O group, which is stronger than the repulsion between the F and the $N(CH_3)_2$ group. However, in a polar solvent the *cis* form is stabilized by the interaction with the solvent and, then, the repulsion between the $N(CH_3)_2$ group and the F atom predominates.

This was confirmed in a further work on several fluoro-derivatives of *N,N*-dimethylacetamides,[51] through infrared spectroscopy, whose spectra clearly show the population changes with the solvent polarity (Fig. 22).

The equilibrium for the DMFP, in the isolated form, is similar. But, here, there are two *gauche* rotamers (Fig. 23) of very similar energies [($E_{gauche1} - E_{gauche2}$) = 0.3 kcal mol^{-1}], and the energy difference for the two main conformers ($E_{cis} - E_{gauche2}$) was 2.5 kcal mol^{-1}, corresponding to 97 % of the *gauche* conformers, in the isolated form. The solvent effect was also similar to DMFA, with $^1J_{CF}$ experimental values varying from 178.4 to 170.1 Hz, from CCl_4 to DMSO, respectively, giving 86% of the *cis* in DMSO solution, resulting in a similar interpretation. Difluoroamides were also studied,[51] but they are out of the scope of the present review.

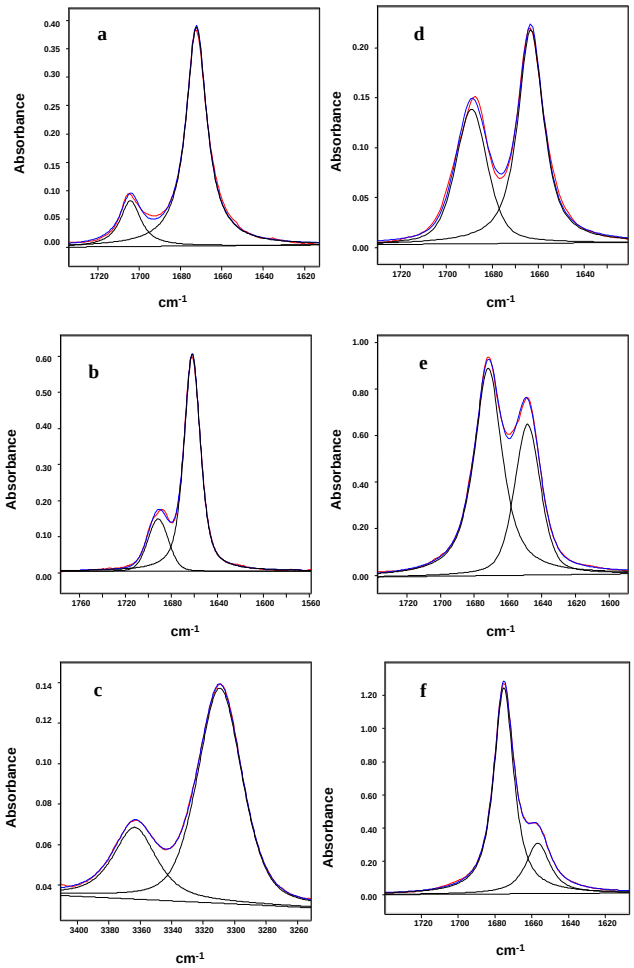
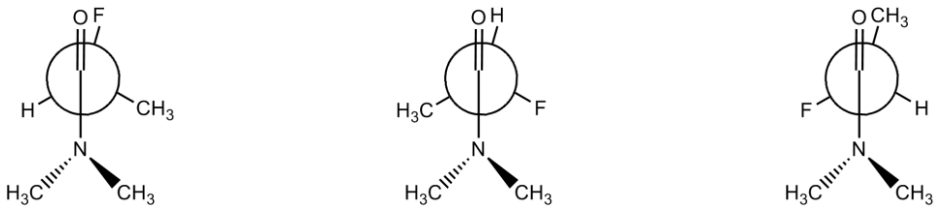


Figure 22. IR spectra of DMFA showing the analytically resolved carbonyl stretching bands, in n-hexane (a), carbon tetrachloride [fundamental (b) and 1st overtone (c)], toluene (d), chloroform (e) and acetonitrile (f).[51]



cis *gauche-1* *gauche-2*

Figure 23. *cis* and *gauche* rotamers for α-fluor-*N,N*-dimethylpropionamide [*gauche*-1 (F-C-C=O, 144.7°); *gauche*-2 (F-C-C=O, -124.1°)]

5. Conclusions

The systems described in this review involved mostly simple carbonyl compounds, *i.e.* aliphatic ketones, esters and amides, presenting a single halogen atom at the α position in relation of the carbonyl group. Very few examples presented two or more halogen atoms.

The conformational equilibrium displayed for the selected compounds was analysed using data from NMR and infrared spectroscopy experiments, complemented by data from theoretical calculations.

The results for the three series of mono-substituted compounds bearing Cl, Br and I presented a very similar behavior in the isolated state and in non-polar solvents. The *gauche* conformer largely predominates over the *cis* conformer for the ketones and esters and the *trans* is more populated for the amides. However, this is reversed in solution of polar solvents like acetonitrile and dimethylsulfoxide, when the *cis* population increases and in most cases supersedes the population of the other conformer, due to a dipole-dipole interaction with the solvent.

The predominance of the *gauche* was attributed to stereoelectronic effects, *i.e.*, there is a steric repulsion between the halogen atom and the carbonyl oxygen atom. Hyperconjugative interactions ($n_x \rightarrow \pi^*_{C=O}$) also contribute to stabilize the *gauche* conformer for the ketones, esters and amides. For these two latter series and additional interaction ($\pi^*_{C=O} \rightarrow \sigma^*_{C-X}$) plays an important stabilizing effect in the *gauche* conformer.

Fluor-derivatives display a specific behavior since the fluorine atom is much more electronegative than the other halogen atoms and a very small volume, as shown by the van der Waals radii (F=1.47; Cl=1.75; Br=1.85 and I=1.98 Å). Thus, the strong field effect of the fluorine atom,[52] results in a strong repulsion in the *cis* isomer driving the fluorine atom as far as possible from the carbonyl group, *i.e.*, to a *trans* arrangement. All fluor-ketones present the *trans* conformer as the most stable form in the isolated state and in non-polar solvents. However, the high polar *cis* conformer (*e.g.* μ=4.18 D, for fluoroacetone) is stabilized in polar solvents becoming the prevalent conformer in DMSO. The same occurs in the fluoro-esters, and also in the amides. In the amides, there is an additional steric effect between the amino group and the fluorine atom, but this interaction is smaller than between the fluorine and the carbonyl group.

Several orbital interactions occur in these systems, but in most cases they are not strong enough to change the conformational preferences.

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Fig. 4. *Spectrochim. Acta A* 72, 1089 (2009); Fig. 7. *J. Mol. Struct. (THEOCHEM)* **2006,** *766*, 177; Fig. 22. *J. Mol. Struct.* **2002,** *607*, 87; Table 2. *Spectrochim Acta, Part A*

2005, *61*, 2221; Table 3. *Spectrochim. Acta Part A* **2006,** *63*, 511; Table 4. *J. Mol. Struct. (THEOCHEM)* **2005,** *728*, 79; were published by this review's authors in Elsevier journals.

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