Non Empirical Quantum Mechanical Calculations of the ^{1}H, ^{13}C, ^{15}N and ^{17}O Magnetic Shielding Constants and of the Spin–Spin Coupling Constants in Formamide, Hydrated Formamide and N-Methylformamide

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The magnetic shielding constants of the different atoms of formamide, hydrated formamide and N-methylformamide are calculated by an *ab initio* method. For the protons of formamide the measured differences between their chemical shifts are correctly reproduced by theory, provided that the molecular geometry used as input is carefully chosen. The differences between the values of the magnetic shielding constants calculated for formamide and hydrated formamide show that intermolecular hydrogen bonding produces variations of chemical shifts for all the atoms of the molecule except the formyl proton. The calculated chemical shift variations between formamide and N-methylformamide are compared to the experimental values and discussed in relation with different hydrogen bonding possibilities of the two molecules. The calculation of the contact term of the spin–spin coupling constants of formamide and hydrated formamide shows that in most cases the measured trends are satisfactorily reproduced and that the variations of these terms upon hydration are less than 3%.

Key words: Magnetic shielding constants – Spin – spin coupling constants – *ab initio* – Formamide – Hydration effect.

1. Introduction

The experimental Nuclear Magnetic Resonance studies on amides have shown that the measured values of the chemical shifts depend to a large extent upon the conditions of experiment. Such variations are reported not only for the NH proton [1–11] and the oxygen atom [12–13] which are directly engaged in the inter-molecular bonds that amides can form with the solvent, with ions or with themselves through autoassociation, but also for the carbon [14–18], the nitrogen [10, 19–21] nuclei and the CH protons [2, 4, 9, 11] which are not. On the other hand there are some indications that the spin-spin coupling constants, although strongly determined by the chemical structure and the conformation of the molecule studied, are also influenced by intermolecular interactions [1, 3, 17, 22].

For amides there exist no measurements in the gas phase, the experimental conditions which are free from intermolecular interactions, or in solution in inert solvents in which such interactions are limited. Thus, it is not possible to determine which part of the measured variations between the spectra of closely related molecules is due to the differences between their chemical structure proper and which part is due to possible differences in their hydrogen bonding to the surrounding medium. This situation can even be complicated by an averaging over several conformations when there is a low barrier of rotation about one bond of the molecule.

Since NMR experiments are increasingly used for the determination of the conformation of peptides in solution as well as for the study of their inter-molecular interactions, we think that theoretical studies of the influence of the molecular structure and of the hydrogen bonding on the NMR spectra of amides can help the interpretation of the data, by giving indications on the direction as well as on the magnitude of the variations of the chemical shifts and of the spin–spin coupling constants due to hydrogen bonding and to chemical substitu-tion respectively.

The NMR spectra of the different types of nuclei of formamide and N-methyl-formamide [1, 2], [11–13], [17–21], [23–25] have been measured in one or several solvents and the results of several theoretical studies on the structure of their first hydration shell [26–31] and on their mode of association in solution [27, 28] are available. This sum of results makes these two molecules very attractive for a theoretical study of the respective influence of the chemical structure and solvent effect on the chemical shifts and spin–spin coupling constants of amides which are the building units of peptides and proteins. Therefore we have undertaken the calculation of the magnetic shielding constants of all the nuclei of formamide and N-methylformamide as well as of the spin–spin coupling constants of formamide which have been measured. Furthermore, in the case of formamide, the same calculations have been carried out for the molecule surrounded by its first hydration shell. The results of this exploratory study will give informations on the intrinsic substituent effect of the methyl group, on the influence of its con-formation on chemical shifts in N-methylformamide and on the variation of the

shifts which are due to the different possible amide–water hydrogen bonds. These data will be utilized to discuss the available experimental observations concerning the two molecules considered.

2. Computational Methods and Basis Sets

The magnetic shielding constants and the spin–spin coupling constants are calculated by self-consistent perturbation methods. The perturbation treatments as well as the determination of the unperturbed SCF wavefunctions are carried out at the *ab initio* level using gaussian basis functions.

For the magnetic shielding constants the method of computation was developed by Ditchfied [32] using gauge invariant atomic orbitals; this method, utilized in previous studies [33–35], has given results in satisfactory agreement with experimental data for intra-as well as for intermolecular problems. For the spin–spin coupling constants we have utilized within an *ab initio* framework the self-consistent perturbation method developed by Blizzard and Santry [36, 37] and used by these authors within the framework of the semi-empirical INDO molecular orbital method [37]. In the present calculations the unperturbed wavefunction is obtained from an *ab inito* calculation and all the integrals which appear in the self consistent perturbation equations are calculated exactly with the basis functions used for the determination of the unperturbed SCF molecular orbitals. We have calculated only the contact term of the coupling constants since in the kind of compounds studied here the orbital and dipolar contributions to couplings are likely to be an order of magnitude smaller than the contact term [37, 39].

Most of the forthcoming results are obtained with the minimal basis set that has given us satsifactory results in previous work [33–35]. But since Ditchfield [32] has shown that the values of the magnetic shielding constants are very sensitive to the basis set used, even at the qualitative level, we have repeated some of our calculations (*vide infra*) with a split basis for the valence shell. For this purpose, we have utilized the $(7s, 3p)$ sets of gaussian functions determined by Roos and Siegbahn [40] for the C, N and O atoms and the $(4s)$ set of Huzinaga [41] for hydrogen. These primitives have been contracted as before [34] into 3 atomic s orbitals [5, 1, 1], plus 2 atomic p orbitals [2, 1] for the C, N and O and into 2 atomic s orbitals [3, 1] for H. We shall abreviate the name of this basis as "split". Finally two calculations have been carried out with the 4-31G basis set [41] which was recommended by Ditchfield for the calculations of magnetic shielding constants. Both the 4-31G basis set and the smaller split basis set share the feature of a split valence shell, thus increase the number of empty orbitals corresponding to the unperturbed wave function thereby contributing to the improvement of the perturbation computation [32–35]. The split basis has the advantage to shorten the computations compared to 4-31G and is a compromise between accuracy and computational feasibility.

3. Results and Discussion

3.1. Magnetic shielding constants:

3.1.1. Formamide (F): Effects of Geometry and Hydration

The molecular geometry of formamide in the gas phase, the experimental conditions giving informations on the isolated molecule, has been determined by two different methods: microwave spectroscopy [43] (geometry A of Table 1) and gas electron diffraction [44] (geometry B of Table 1). Since the bond lengths obtained by the two methods appear to differ by quantities somewhat larger than the experimental uncertainties (Table 1) we have performed, using the minimal basis set, the calculation of the magnetic shielding constant of the nuclei of formamide with these two geometries as input data. The corresponding results reported in Table 2, show that the calculated values of the magnetic shielding constants, although very similar and showing the same trends for A and B, are not insensitive to the molecular geometry. In order to test more thouroughly the

Table 1. Geometries of formamide used as input; bond lengths in Ångströms and bond angles in degrees[a]

	A [43]	B [44]	C [45]	D [46]	E [48]
CN	1.352	1.368	1.403	1.300	1.320
CO	1.219	1.212	1.218	1.255	1.220
CH	1.098	1.125	1.105	1.100	1.080
NH_c	1.002	1.027	1.014	1.000	1.000
NH_t	1.002	1.027	1.013	1.000	1.000
NCO	124.70	125.00	124.30	121.50	120.00
NCH	112.70	112.70	111.40	119.25	120.00
CNH_c	118.50	118.70	120.10	118.50	120.00
CNH_t	120.00	119.70	121.60	120.75	120.00

[a] The notation used for the different hydrogens is given in Fig. 1 Structures: A: gas microwave; B: gas electron diffraction; C: optimized STO3G; D: crystal; E: standard.

Table 2. Magnetic shielding constants (in ppm) of the atoms of formamide as a function of molecular geometry and basis set

Basis set Input geometry[a]	Minimal					4–31G		Split
	A	B	C	D	E	D	E	B
σN	240.97	235.29	233.26	244.90	246.34	164.10	186.02	200.74
σC	110.22	110.42	107.76	100.52	109.46	33.14	35.05	56.61
σO	−221.80	−216.50	−245.63	−248.38	−235.85	−109.85	−124.31	−83.80
$\sigma H(C)$	23.60	23.27	23.31	22.97	23.46	25.46	24.39	23.88
$\sigma H(N)c$	28.06	27.32	27.79	27.74	28.02	28.59	29.07	28.68
$\sigma H(N)t$	27.89	27.20	27.52	28.07	28.31	29.19	29.62	28.62

[a] Notation as in Table 1 for A, B, C, D, E.

influence of bond lengths and bond angles on the computed values of the magnetic shielding constants we have repeated the calculations with three other geometries commonly used in theoretical studies on formamide (Table 1); geometry C is the optimized STO3G geometry [45], geometry D [46] comes from the crystal study [47] and geometry E is the so-called standard geometry [48]. The corresponding calculated values of the shielding constants reported in Table 2 confirm the appreciable influence of the variations of the bond lengths and angles on the values of the magnetic shielding constants; the largest spread of values is calculated for the oxygen atom, more than 30 ppm, but even for the protons the value of σ varies by 0.6 to 1.1 ppm with the molecular geometry. The problem of the numerical value of the calculated magnetic shielding constants is not crucial in itself since experimental data are only concerned with chemical shifts which are differences between the magnetic shielding constant of nuclei of the same type of atoms, but the results of Table 1 show that for the protons of the molecule the differences between their screening constants (which are identical to the differences between the measured chemical shifts of the hydrogen nuclei) are also sensitive to the molecular geometry. The comparison of the calculated differences between the magnetic shielding constants of the protons with the differences between their measured shifts [1, 2, 11] (Table 3) shows that the five calculations agree with experiment on the fact that the CH proton is less shielded than the NH ones. But as concerns the difference between the NH protons, the computations using the gas phase or STO3G structures give the *trans* NH proton *less* shielded than the *cis* one, in agreement with the measured shifts, while the two other calculations (standard and crystal structure) give the reverse order. In order to check that the above result is not related to the use of a minimal basis set, we have repeated some of the calculations with split valence-shell basis sets. We have utilized the 4-31G basis for the crystal and for the standard geometries, and our smaller split basis set for the gas electron diffraction structure. The corresponding values of the shielding constants are reported in Table 2 and 3. They show that, as expected, the numerical values computed are extremely sensitive to the choice of the basis set but that the relative order of the shielding constants of the *cis* and *trans* NH protons are primarily determined by the molecular geometry. Whatever the basis set, it thus appears that gas phase experimental geometries or the optimized STO3G geometry (which is close to the formers) lead to a reasonable agreement between theory and experiment for $\sigma H(N)_c - \sigma H(N)_t$ (Table 3) whereas the crystal or standard geometry do not. The scrutinization of the values reported in Table 1 indicates that the geometrical parameters which seem determinant for the relative order of $\sigma H(N)_c$ and $\sigma H(N)_t$ are the CN bond length and the NCO and NCH bond angles; geometries A, B and C have in common a longer CN bond, a larger NCO angle and a smaller NCH angle than geometries D and E.

On the other hand, it is observed that the computed difference between the magnetic shielding constants of the formyl proton and those of the amido protons is about 4 ppm for a measured value of less than 1 ppm and that this result is little modified by the use of a split basis set.

Table 3. Differences (in ppm) between the proton chemical shifts (δ) or proton magnetic shielding constants (σ) in formamide[a]

Experimental[b]		Calculated	Minimal					4-31G		Split
			A	B	C	D	E	D	E	B
$\delta H(C) - \delta H(N)c$	0.80	$\sigma H(N)c - \sigma H(C)$	4.46	4.05	4.48	4.77	4.56	3.13	4.65	4.80
$\delta H(C) - \delta H(N)t$	0.43	$\sigma H(N)t - \sigma H(C)$	4.29	3.93	4.21	5.10	4.85	3.73	5.23	4.74
$\delta H(N)t - \delta H(N)c$	0.37	$\sigma H(N)c - \sigma H(N)t$	0.17	0.12	0.27	-0.33	-0.29	-0.60	-0.55	0.06

[a] In order to tabulate quantities of the same sign, the experimental and calculated differences are reported with opposite sign since, for a given nucleus, the value of its chemical shift decreases when its magnetic shielding constant increases.
[b] From data at infinite dilution in water [11].

Table 4. Magnetic shielding constants of hydrated formamide calculated with the minimal basis set (see Fig. 1 for the position label of the water molecules)

	F	F—(H$_2$O)$_4$[a]	F—(H$_2$O)$_2$		F—(H$_2$O)			
			I+II	III+IV	I	II	III	IV
σN	235.99	225.03 (10.96)	230.84	232.43	234.51	232.45	233.20	235.24
σC	110.42	103.05 (7.37)	106.09	107.54	107.03	109.25	109.08	108.87
σO	-216.50	-88.47 (-128.03)	-126.93	-181.01	-169.88	-169.27	-195.70	-201.71
σH(C)	23.27	23.22 (0.05)	23.18	23.33	23.16	23.31	23.40	23.21
σH(N)c	27.32	24.99 (2.33)	26.93	25.49	27.24	27.02	25.24	27.61
σH(N)t	27.20	24.60 (2.60)	26.79	25.08	27.01	26.99	27.29	25.01

[a] In parenthesis are the calculated values of the hydration shifts (in ppm).
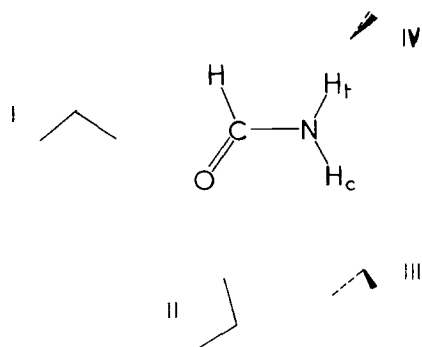
Fig. 1. Geometrical arrangement of the molecules of water of the hydration shell of formamide

Let us consider now the effects of hydrogen bonding. They have been evaluated for a formamide surrounded by its first hydration shell (Fig. 1), (we use the term "first hydration shell" as defined in Ref. [28], that is comprising only the four molecules of water directly bound to the solute). Geometry B and the minimal basis set have been used throughout in all the hydration computations. We have limited the computations to geometry B because the results obtained for the effect of hydration on the shifts of the NH protons are too small (*vide infra*) to invert the order obtained for these two protons with the extreme geometries D or E (it can reasonably be expected that in solution the formamide geometry is intermediate between the gas phase and the crystal ones).

The results tabulated in the first two columns of Table 4, show that the formation of the water-formamide hydrogen bonds produces a large variation of the magnetic shielding constants of all the nuclei, with the only exception of the formyl proton, which does not participate to the intermolecular hydrogen bonds [28].

As expected the amido protons are shifted downfield by several ppm, so that the differences between their shielding constants and that of the formyl proton are of 1.4 and 1.8 ppm, differences now much closer to the experimental ones measured at very low concentration in water [1, 2, 11, 17]. The calculated values of $\sigma H(N)_c - \sigma H(N)_t$ is now of 0.39 ppm for a measured one of 0.37 ppm at infinite dilution in water, while for the isolated formamide the computed value was 0.12 ppm. This shows that it is possible to reproduce with a fair accuracy the differences, measured in water, between the shifts of the different protons of the molecule if the four molecules of water directly hydrogen-bonded to formamide are taken into account.

In Table 4 are also reported the magnetic shielding constants calculated for formamide hydrogen-bonded to one or two of the 4 molecules of water of the F—(H$_2$O)$_4$ complex. The values obtained in these cases for the amido protons show that if the formation of the NH···O hydrogen bonds produces a downfield shift of about 2 ppm, the formation of the OH···O= C hydrogen bonds shifts also these protons by 0.4 ppm in the same direction. The magnitude of this last effect which appears large when compared to the shift produced by the *in situ* NH · · · O hydrogen bonds can unfortunately not be confirmed by experimental data. For the

trans NH proton the two molecules of water I and II produce similar shifts (0.2 ppm) while for the *cis* NH proton, water II which is closer to it, produces a larger effect than water I.

Let us turn now to the carbon, nitrogen and oxygen atoms. For the carbon atoms we obtain a downfield shift of 7.4 ppm upon tetrahydration. This is in qualitative agreement with experimental data on the variation of the shift of the carbon atoms of carbonyl groups with the formation of hydrogen bonds between the carbonyl oxygen and some proton donor. Such results have been reported not only for the carbonyl of the amide group [50–55] but also for the carbon atom of carbonyl groups of all types of molecules [56–62]. For formamide no measured values of $\Delta\delta C$ with the formation of hydrogen bonds is available from the literature since the variations observed for this nucleus with dilution were measured in water [7] in which the number of hydrogen bonds per molecule of formamide is the same as in the pure liquid; but in most cases the measured chemical shift variations are of several ppm, showing that our results are of correct order of magnitude. It is to be noted that the values reported in Table 2 for the $F-(H_2O)_2$ systems show that the largest shift is produced by the formation of the $H\cdots O = C$ bonds but that the formation of the $NH\cdots O$ ones also contribute to the shifts of the carbon of the carbonyl (more than 25%). In addition the results for the different $F-(H_2O)$ systems show that the water molecules I and IV are those responsible for the larger shifts for the carbon nucleus.

For the nitrogen nucleus we calculate a downfield shift of 10.2 ppm with hydration. This is in agreement with experimental data which have shown that in amides [19, 63, 10] and peptides [64] the nitrogen resonance is very sensitive to solute-solvent hydrogen bonding. The downfield shift of 7.4 ppm which is calculated between formamide being only a proton donor $(F-(H_2O)_2)$ III + IV and formamide being a proton donor and a proton acceptor $(F-(H_2O)_4)$ is in good agreement with the experimental value of 6 ppm measured between solution of formamide in acetone and in methanol [19] or upon dilution of formamide in dioxane [11]. We can also mention that it has been observed [65] that the NH nitrogen of pyrrole undergoes a downfield shift if the NH group acts as a proton donor, in qualitative agreement with our results for $F-(H_2O)_2$ when the two molecules of water are bound to the NH's. Interestingly the results on $F-(H_2O)$ indicate that water IV has a smaller effect on the nitrogen magnetic shielding constant than the two waters bound to the oxygen of the carbonyl.

Finally the values of Table 4 show that the largest chemical shift variation due to hydration is calculated for the oxygen atom (128 ppm) but, in the present case, the shift is upfield. The values reported for the complexes $F-(H_2O)_2$ show that the shift occuring when the oxygen atom is directly involved in the hydrogen bond is much larger than the one occurring when the water molecules are bound to the NH bonds, but the variation is calculated upfield in both cases. Some very recent ^{17}O NMR experiments on formamide in different solvents [13] have shown that the oxygen atom of the molecule is shifted upfield when going from acetone to water but the measured shift (53 ppm) is smaller than the one calculated between

$F-(H_2O_2)$ III + IV and $F-(H_5O)_4$ (93 ppm). Therefore, if we suppose that the shielding constant of the formamide's oxygen in the formamide-acetone complex can be approximated by that of this atom in the formamide$-(H_2O)_2$ III + IV complex, it appears that our results, obtained with the minimal basis set, are in qualitative agreement with experiment but seem to overestimate the effect of water-carbonyl hydrogen bonds on the ^{17}O chemical shift [13, 67]. As a whole the results obtained on the different $F-(H_2O)_n$ systems studied show that the agreement between theoretical and experimental proton shifts measured in water is improved if the first hydration shell is taken into account in the computations, and that the chemical shift variations produced by each of the four molecules of water are in a first approximation, additive. As a working hypothesis for the following part of the discussion, we will make the assumption that the calculated hydration shifts are at least representative qualitatively of the shifts produced by amide-solvent hydrogen bonds at the corresponding positions. Concerning NMF, it does not form the same number of H bonds than F, but since it was found that the hydrogen bonds formed by the two molecules are of very similar energies and geometrical arrangement [31, 67] it seems that we can reasonably assume that the chemical shift variations due to one particular hydrogen bond will be similar for the two compounds.

3.1.2. N-methylformamide (NMF)

In Table 5 we report the calculated values of the magnetic shielding constants of the different atoms of N-methylformamide for the two conformations of the molecule shown on Fig. 2. The molecular geometry utilized is the gas microwave structure [49] as is structure B of formamide. Since the NMR spectra show that the methyl group is rapidly rotating, it is possible that in solution the two conformations are present simultaneously. The tabulated values show that the conformation of the methyl group has an influence on the numerical value of the magnetic shielding constant of all the nuclei of the molecule.

For the nitrogen atom the calculations using the minimal basis set predict a large upfield shift going from F to NMF, in contradiction with the experiment. This discrepancy seems difficult to explain by the introduction of solvation: in effect, in the proton-acceptor solvents used by the experimentalists [19] N-methyl-formamide can form only one hydrogen bond when formamide forms two, both shifting the nitrogen resonance downfield. Therefore if the qualitative variation of the effects is conserved, the nitrogen magnetic shielding constants should undergo a smaller downfield shift in the case of N-methylformamide than in the case of formamide, thus should remain upfield with respect to it. On the other hand the results of the computations using the split basis do reproduce the small measured shift between the two molecules. It seems that we have here encountered an effect which requires a split basis to be correctly accounted for.

For the carbon atom our results with both basis sets indicate a downfield shift for NMF with respect to F while an upfield one has been measured. But both the calculated and measured variations are small. In addition the experiments have

Table 5. Magnetic shielding constants of formamide and N-methylformamide

		Experimental[a]		Theoret. Min. Basis			Theoret. Split Basis		
		F	NMF	F	NMF A	B	F	NMF A	B
τN[b]	σN	265.5–274.0	266.4–272.0	235.29	259.29	258.17	200.74	201.74	198.25
δC[c]	σC	165.5	163.4	110.42	107.47	108.11	56.61	54.64	54.73
δO[d]	σO	283–300	306	−216.50	−226.50	−204.50	−83.80	−89.19	−65.54
δH(C)[e]	σH(C)	7.96	7.90	23.27	23.34	23.40	23.88	24.01	24.06
δH(N)c[e]	σH(N)c	7.16		27.32			28.68		
δH(N)t[e]	σH(N)t	7.53	7.52	27.20	27.97	28.19	28.62	29.47	29.50
δC(CH$_3$)[c]	σC(CH$_3$)		23		211.32	213.40		190.07	193.09
δH(CH$_3$)[e]	σH(CH$_3$)$_3$		2.76		29.84	29.76		29.86	29.76

[a] Note that for N the experimental data are expressed on the τ scale which runs parallel to σ while for the other atoms the chemical shifts are reported on the δ scale.
[b] [19].
[c] [23].
[d] [12, 13].
[e] [11].

been carried out on pure liquids or concentrated solutions, conditions which imply that the molecules are autoassociated through hydrogen bonds. N-methylformamide can form only two hydrogen bonds with other *NMF* molecules while formamide can be hydrogen-bonded to four other *F* molecules.

Since our calculations on hydrated formamide have shown that the magnetic shielding constant of the carbon nucleus is shifted downfield by the formation of hydrogen bonds the discrepancy between the experimental and theoretical variations of the shielding of the carbon nucleus can perhaps be interpreted as follows: σC is larger for *F* than for *NMF* when the molecules are isolated and this quantity is more decreased by the intermolecular hydrogen bonds so as to appear in these conditions at lower field in the case of *F* than in the case of *NMF*. This would indicate that the intermolecular interactions can reverse the sign of a substituent effect on the chemical shift of a given atom.

The magnetic shielding constant of the oxygen atom of *NMF* exhibits the largest variation with the conformation of the methyl group; conformation B in which one of the methyl CH bond is *cis* coplanar with the CO bond corresponding to an upfield shift and conformation A to a downfield shift. Experimentally the oxygen atom of *NMF* is downfield with respect to the shift of this nucleus in *F*. Our calculations are in agreement with the experiments if we suppose that conformation A of *NMF* is the most populated but in contradiction if it is conformation B or if the two conformers are equally populated. We have seen previously that the magnetic shielding of the oxygen is very sensitive to the solute-solvent hydrogen bonds. For the measurements made on pure liquids the experimental shifts concern molecules which do not participate in the same number of hydrogen bonds. If the results reported in Table 4 are representative and assuming again that they can be extrapolated to *NMF*, the oxygen resonance would be shifted upfield by the intermolecular hydrogen bonding with respect to its position for the isolated molecules with an effect larger for *F*, which can form four hydrogen bonds with another *F*, than for *NMF*, which can form only two hydrogen bonds with another molecule. In this case the upfield shift computed for *NMF* compared to *F* may be correct for the isolated molecules.

For the formyl proton which we have found to be very little influenced by intermolecular interactions, calculations with both basis sets agree with the experiments on the sign and on the magnitude ($\simeq +0.05$ ppm) of the variation of its magnetic shielding constant between formamide and N-methylformamide.
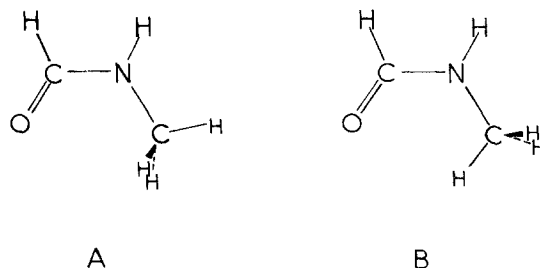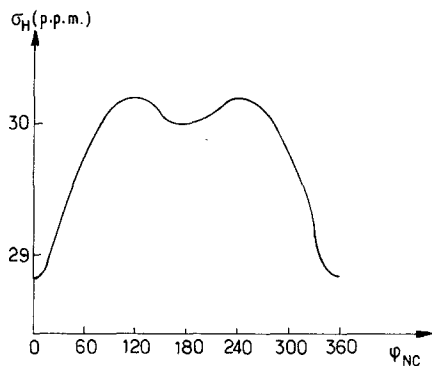

Fig. 2. Conformation *A* and *B* of
N-methylformamide   A   B

σ_H(p.p.m.)

Fig. 3. Variation of the magnetic shielding constant of the proton of the methyl group of N-methylformamide as a function of the rotation angle about the CN bond ($\varphi_{CN} = 0$ when the CH bond is *cis* coplanar with the C=O bond)

The trans amido proton is the only one which is common to both molecules and the computations in both basis sets overestimate somewhat its upfield shift from F to *NMF*. Concerning the methyl group it is seen that calculations carried out with the split basis set reproduce very well the differences (Table 5) measured between the formyl carbon and the methyl carbon as well as between the formyl proton and the methyl protons. With the minimal basis set the calculated differences give only the correct trends.

Although measurements on *NMF* give only one value for the three protons of the methyl group, the calculations give the magnetic shielding constants of the individual protons. In Fig. 3. we report the dependence of σH of a proton of the methyl as a function of the rotation angle about the CN bond. The large calculated variation indicates that the chemical shift of the $C_\alpha H$ proton of peptides may contain some information on the value of the rotation angle Φ about the NC_α bonds of these molecules.

3.2. Spin–spin coupling constants:

In Table 6 the measured and calculated values of spin–spin coupling constant of formamide are reported. In the case of coupling constants the measured values are absolute ones like the results of calculations so that the two sets of numbers are directly comparable. The examination of the values reported show that with both basis sets the calculated coupling constants are of a reasonable order of magnitude with the exception of the one bond CN coupling constants, in all the cases in which the sign of the coupling constant is known, theory and experiment are in agreement. Lazzeretti [38], who has used for the calculation of the coupling constants of methanol a non-empirical method very similar to ours, has obtained the same level of agreement in spite of the fact that his basis set is very different from ours.

With the minimal basis set we have calculated the same coupling constants for the hydrated formamide and the values reported in Table 6 show that the variations due to hydration are smaller than 5 Hz. This result is in agreement with the experiments which reports only small variations for the couplings constants with solvents [1, 17, 22] a feature which appears to be general for all types of molecules

Table 6. Spin–spin coupling constants in formamide (in Hz)

	Experimental	Theoret. F	Min. F—(H$_2$O)$_4$	Theoret. Split F
^{1}J NC[a]	±14.8	−36.2	−33.8	−41.9
^{2}J NH(C)[bc]	−14.5−−23.3	−10.0	−7.7	−16.7
^{1}J NH(N)c[bc]	−86.5−−95.4	−114.5	−113.6	−96.1
^{1}J NH(N)t[bc]	−91.3−−91.9	−117.7	−118.4	−96.6
^{1}J CH(C)		230.4	225.6	201.2
^{2}J OH(C)	∓11.0	−3.0	−3.1	−10.0
^{3}J H(C)H(N)c[b]	13.6	9.5	8.7	8.5
^{3}J H(C)H(N)t[b]	0.8	1.0	2.1	0.8
^{2}J H(N)cH(N)t[b]	∓2.3	0.3	−0.9	4.8

[a] [17]; by analogy with acetamide [68] the sign of this coupling constant is certainly negative.
[b] [1].
[c] [21].
[d] [24].

[69]. So the present results confirm that spin–spin coupling constants are relatively little sensitive to intermolecular interactions.

4. Conclusion

The present study has shown that the magnetic shielding constants and spin–spin coupling constants calculated with basis sets of moderate size reproduce correctly the characteristics of the NMR spectra of molecules like formamide and N-methylformamide provided that the molecular geometry used as input is carefully chosen, and proper consideration is given to intermolecular interactions. The results reported have shown the extreme sensitivity of magnetic shielding constants to hydrogen bonding. The large variations of chemical shift which are calculated for *all* the atoms of formamide except the formyl proton when the molecule is hydrated are in agreement with the available informations from carbon 13 and nitrogen 14 and 15 and oxygen 17 studies [13, 53, 54, 57–59, 64]. The study of the individual effect of each hydrogen bond on each atom appears as a valuable source of information. An important outcome of the present studies is that the variation of the values of chemical shifts with intermolecular hydrogen bonding may be important even when the studied nucleus does not belong to the chemical group engaged in the hydrogen bond. Thus, we confirm the experimental results [19] on the variation of the shielding constant of the nitrogen of formamide with the formation of a hydrogen bond between the carbonyl oxygen and a proton donor, and we predict the existence of such a variation also for the carbon nucleus not only when the carbonyl groups is hydrogen-bonded but also when a hydrogen bond is formed between the amido protons and a proton acceptor. Similarly a shift of the carbonyl oxygen occurs upon hydrogen bonding to the NH protons. Finally, the amido protons are affected by formation of hydrogen bonds on the carbonyl oxygen. It seems furthermore, from the discussions of the experimental results on

liquid formamide and N-methylformamide that the intrinsic shifts computed for hydrogen bonding of formamide to water at different sites can be taken as representative (at least qualitatively) of the effect of the corresponding hydrogen bonds in the self association of these molecules.

The calculations carried out using the two different basis sets confirm that a split valence shell gives better numerical results for magnetic shieldings, in agreement with Ditchfield's results [32], but that in nearly all the cases the correct trends are obtained with our minimal basis set [33, 34].

Finally the sensitivity of the computed shielding constants to the molecular bond lengths and angles, already found in the case of ^{31}P in the phosphate group [34] appears as a general feature, and invites to some caution in the choice of input geometries for this kind of computations.

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