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Computation of through-space NMR shielding effects by functional groups common to peptides

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Abstract

The GIAO-HF method in Gaussian 03 was employed to calculate the isotropic shielding values of a covalently bonded hydrogen probe and to predict the through-space proton NMR shielding increment surfaces near models of simple structures containing functional groups common to peptides. The functional groups examined include the carboxylate anion, carboxylic acid, amide, amino, ammonium and guanidinium groups. Our previously developed methodology involving the use of diatomic hydrogen as a probe of through-space shielding effects was employed. Substantial shielding or deshielding effects were observed only in the cases of the charged (ionic) groups, each of which displayed shielding or deshielding effects of greater than 1 ppm at distances comparable to those observed in peptides. Equations for predicting the shielding increments of these groups as a function of the Cartesian coordinate position of the affected proton were determined. The validity of using simple structures as models of shielding by comparable functional groups in peptides was confirmed by computing the shielding effects at selected positions above a model of glycylglycylglycine and its hydrogen-bonded dimer. Knowledge of these through-space shielding effects should aid in the tertiary structure determination of peptides by NMR.

Keywords: NMR; Through-space shielding effects; GIAO; Peptides

1. Introduction

We have previously reported the results of HF-GIAO calculations to develop through-space NMR shielding equations for a number of common organic functional groups, including the aromatic ring [1,2], the carbon–carbon double bond [3–6], the carbon–carbon triple bond, the carbon–nitrogen triple bond, the nitro group [7] and the carbonyl group [8]. The shielding predictions derived from calculations of small molecule models of those functional groups proved to be successful at accurately predicting through-space chemical shift effects in more complex molecules that contained those functional groups. We now report our computational study of the through-space NMR shielding of models of simple structures containing functional groups common to peptides including the carboxylate ion, carboxylic acid, amide, amino, ammonium ion and the guanidinium ion. The results of this research may lead to a better understanding of some unusual proton chemical shifts observed for some peptides, and may allow more accurate determination of the tertiary structure (folding pattern) of peptides using NMR spectroscopy.

Peptides consist of various amino acids linked together by amide bonds. Some amino acids have an additional carboxylic acid group, and some have an additional amino group. At physiological pH, most of these ionizable groups exist in their ionic forms, as a carboxylate ion or an ammonium ion. Ionic species exert substantial through-space NMR shielding or deshielding effects on nearby covalently bonded protons primarily due to the shielding or deshielding effect of the charge (Fig. 1). A positive ion attracts the bonding electrons of a nearby covalently bonded hydrogen toward that hydrogen, causing it to experience greater shielding. A negative ion repels bonding electrons from the hydrogen, resulting in its deshielding.

The reported ranges of chemical shift values of a given hydrogen in a given amino acid residue of a peptide span upwards of 7 ppm for many of the amino acids [9]. As an example, reported chemical shifts for the α protons of glycine range from 0.34 to 6.17 ppm. This large spread may be

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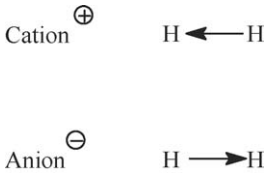

Fig. 1. Induced polarization of the bonding electrons of the diatomic hydrogen probe by a cation and by an anion.

explained in part by through-space interactions. Through-space shielding (or deshielding) effects of some functional groups are transmitted for several Angstroms, comparable to the through-space distances (2.0–4.0 Å) between atoms in amino acid residues that may be separated by several or even many amino acids along the peptide backbone, but are nearby because of folding (tertiary structure) of the peptide chain.

In this paper, we report the results of a computational study of the through-space NMR shielding effects of simple molecules that contain functional groups common to peptides. The functional groups included in this study are the carboxylate ion, carboxylic acid, amide, amino, ammonium and guanidinium groups.

2. Computational methods

Simple molecules and ions containing functional groups commonly found in peptides were used as models. These included the formate ion, formic acid, formamide, ammonia, ammonium ion and the guanidinium ion (Fig. 2). Models of these were built in Titan [10] on a Dell Dimension 4600i 3.31 GHz PC, and then a geometry optimization calculation was performed at the Hartree-Fock level of theory using the 6–31G(d, p) basis set [11]. The first three of these structures and the guanidinium ion have a planar structure which allowed only *X* and *Y* coordinates to be used in the Cartesian coordinate molecule description. A diatomic hydrogen (H_2) probe [12], geometry optimized at HF/6–31G(d, p), was placed along the *Z* axis with the proximal hydrogen at a distance of 2.0 Å from the plane of each planar molecule. A series of single point NMR calculations was performed in Gaussian 03 [13] on these supramolecules using the same method and basis set, moving the H_2 in 1.0 Å increments in both the *X* and *Y* directions in separate calculations. The process was repeated with the H_2 probe at distances of 2.5, 3.0 and 4.0 Å from the plane of the molecule being studied. These calculations covered a 3 Å × 3 Å grid in each quadrant and a 6 Å × 6 Å grid overall. The symmetry of formate ion allowed only half of the grid to be calculated and the data to be replicated by a reflection across the *Y* axis. The orientations of formate ion, formic acid, formamide and guanidinium ion in the *XY* plane are shown in Fig. 3.

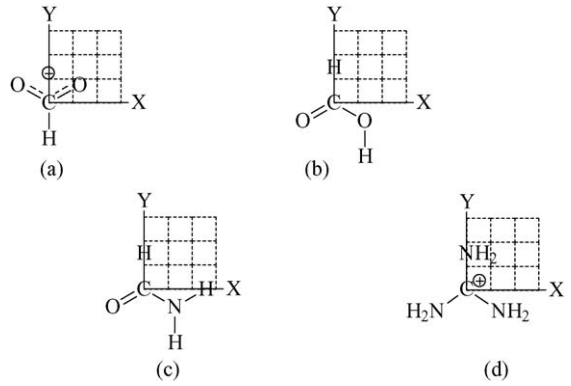

Fig. 3. Cartesian coordinate orientations of (a) formate ion, (b) formic acid, (c) formamide and (d) guanidinium ion.

Shielding values near ammonia and ammonium ion were calculated with the hydrogen probe at two different positions. The nitrogen atom of ammonia or ammonium ion was placed at the origin of Cartesian space and three hydrogens were oriented in the negative *Z* direction, equidistant from the *XY* plane with one N–H bond in the *XZ* plane. For the first probe position (Fig. 4a), a diatomic hydrogen (H_2) was placed along the positive *Z* axis at a *Z* displacement of 2.0 Å from the nitrogen of ammonia (or nearest hydrogen of the ammonium ion). The other probe position was in the *Z* axis on the same side as the three hydrogens of ammonia (Fig. 4b) or ammonium ion. It was initially placed with the proximal hydrogen at a *Z* value 2.0 Å more negative than the *Z* value of the three hydrogens.

The shielding increment ($\Delta\sigma$) at a given point in Cartesian space was determined by taking the difference between the calculated isotropic shielding value of the H_2 probe alone and that of the proximal hydrogen of the H_2 probe at that point relative to the modeled molecules. Isotropic shift values greater than the calculated isolated H_2 isotropic shielding value (26.77 ppm) give positive (shielding) $\Delta\sigma$ values, and those with smaller values give negative (deshielding) $\Delta\sigma$ values. The shielding increments ($\Delta\sigma$) are therefore equal in magnitude but opposite in sign to differences in ^{1}H NMR chemical shifts ($\Delta\delta$). Three-dimensional NMR shielding increment surfaces ($\Delta\sigma$ versus *X* and *Y* at a fixed value of *Z*) were prepared using TableCurve 3D [14] to represent graphically the locations and magnitudes of shielding and deshielding regions of the molecules and ions.

For each structure that exhibited a substantial (>1 ppm) shielding or deshielding effect at 2.5 Å, a mathematic equation was determined to predict the shielding increment as a function

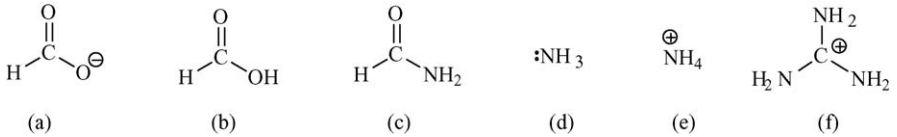

Fig. 2. Simple molecules and ions used as models for the functional groups common to peptides: (a) formate ion, (b) formic acid, (c) formamide, (d) ammonia, (e) ammonium ion and (f) guanidinium ion.

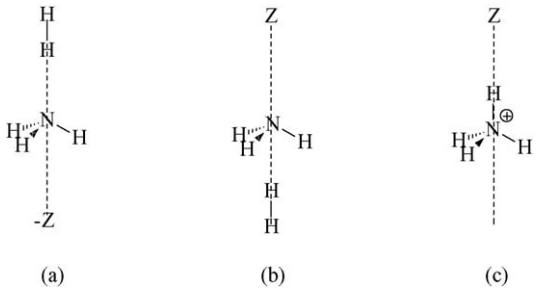

Fig. 4. Cartesian coordinate orientations of (a) ammonia with the H_2 probe in the *Z* axis opposite three hydrogens, (b) ammonia with the H_2 probe located on the side of three hydrogens and (c) ammonium ion with one hydrogen in the *Z* axis.

the Cartesian coordinates of the affected proton. This was accomplished by a method developed previously [1–8], using TableCurve3D to find a single mathematical equation type that fit the shielding increment surface of a given test structure at each of several distances (*Z*). Then MSExcel [15] was used to determine quadratic equations that related each of the variables and constants in those functions to the *Z* distance. Substituting these quadratic equations into the shielding surface equation gives one equation for predicting the shielding increment as a function of *X*, *Y* and *Z*.

Models of the simple tripeptide glycylglycylglycine (GGG) and its antiparallel hydrogen-bonded dimer (Fig. 5), both in planar *trans*-peptide conformation with zwitterionic end groups, were optimized at the HF-6/31G(d, p) level. Diatomic hydrogen probes were placed sequentially at selected positions (A–E in Fig. 5) 3.0 Å above the molecular plane near the ammonium ion, the amide group, and the carboxylate ion, and the through-space shielding effects were determined as with the simple models for the functional groups.

3. Results and discussion

The charged species (formate ion, ammonium ion and guanidinium ion) showed the greatest shielding (or deshielding)

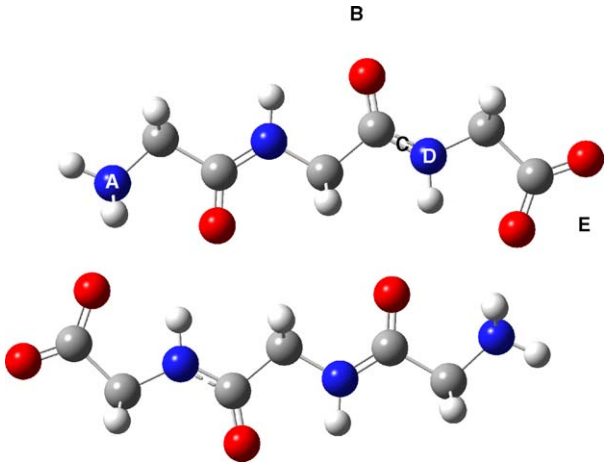

Fig. 5. Glycylglycylglycine (top structure) and its antiparallel hydrogen-bonded dimer (both structures), in planar *trans*-peptide conformation with zwitterionic end groups with probe positions (A–E) indicated.

effect, depending on the sign of the charge. Neutral molecules such as formic acid, formamide and ammonia showed a much smaller effect. The exception to this was on the side of ammonia opposite three hydrogens, where substantial deshielding was observed, presumably because of proximity to the non-bonding (lone) pair of electrons.

The formate ion showed deshielding (negative $\Delta\sigma$ values) over the whole molecule (Fig. 6). The region between the oxygen atoms exhibited the greatest deshielding. The maximum deshielding at 2.5 Å was −1.38 ppm. This implies that a covalently bonded hydrogen located at this distance above the region between the oxygen atoms of a carboxylate anion group of a peptide should appear in the ^{1}H NMR spectrum nearly 1.4 ppm farther downfield than expected based solely on through-bond deshielding effects.

The shielding surface of formic acid (Fig. 7) is quite different from that of formate ion. Formic acid has a zone of deshielding near each of the oxygen atoms. The magnitude of deshielding over the region occupied by the lone pair of electrons on the hydroxyl oxygen is somewhat greater than that near the carbonyl oxygen. However, the maximum value of the shielding or deshielding increment at 2.5 Å is 0.2 ppm, which is only slightly greater than the uncertainty of the method (0.15 ppm), and is thus negligible.

The formamide molecule was the only molecule studied that showed both shielding and deshielding at all distances from the H_2 probe. Unexpectedly, the hydrogen probe above formamide showed the greatest deshielding near the nitrogen atom at 2.5 Å from the molecule (Fig. 8). As the hydrogen probe was moved away from formamide to the 3.0 and 4.0 Å levels, the region near the oxygen atom showed the greatest deshielding. This may be expected because of the high electron density on oxygen from amide resonance. The magnitude of through-space shielding or deshielding was not substantial, however, especially at a distance of 3.0 Å or greater.

Ammonia and ammonium ion showed quite different shielding surfaces. A smooth mound of deshielding was found at all distances over the region generally considered to be occupied by the lone pair of electrons of ammonia (Fig. 9). Only shielding was found on the side of the molecule with three hydrogens at distances greater than 2.5 Å (Fig. 10), but the magnitude of maximum shielding is 0.04 ppm, which is less than the uncertainty in the method.

The ammonium ion produced similar results for both probe orientations: a uniform zone of shielding (Figs. 11 and 12), with slightly greater shielding on the side nearest three hydrogens. The magnitude of shielding by the ammonium cation is greater than that caused by ammonia because of the positive charge of ammonium ion. As expected, the shielding by ammonium ion is diminished as the distance between the probe and the molecule is increased.

Ammonia with the H_2 probe on the side of the three hydrogens showed greater deshielding than shielding at the 2.0 Å distance (measured from the plane of three hydrogens), but only shielding was observed at greater distances (Tables 1 and 2). The proximity of the H_2 probe to the high electron density of nitrogen is the likely reason for this deshielding at

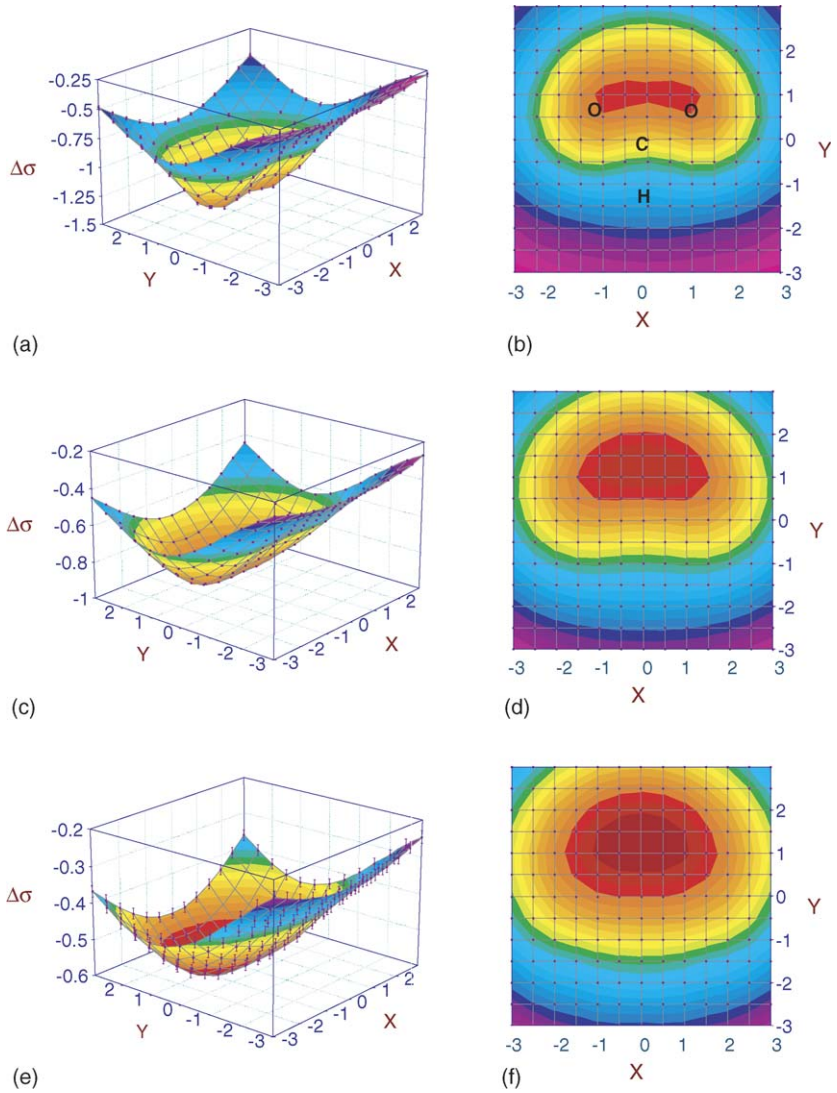

Fig. 6. Calculated NMR shielding increment surfaces (ppm) of the formate ion using diatomic hydrogen as the probe molecule at (a) 2.5 Å side view, (b) 2.5 Å top view, (c) 3.0 Å side view, (d) 3.0 Å top view, (e) 4.0 Å side view and (f) 4.0 Å top view.

close proximity to nitrogen. As the probe is moved to greater distances, the deshielding effect by the nitrogen diminishes and the effect of the partial positive charge on the three hydrogen atoms becomes dominant. At a probe distance of 2.5 Å there is a distinct flattening of the shielding surface with a cavity of diminished shielding in the center; this is a consequence of offsetting effects of deshielding by nitrogen and shielding by the hydrogens.

The shielding surfaces for two distances above the guanidinium ion are shown in Fig. 13. At 2.5 Å, a region of shielding is located above the central carbon, with less shielded regions above each of the more electronegative nitrogen atoms.

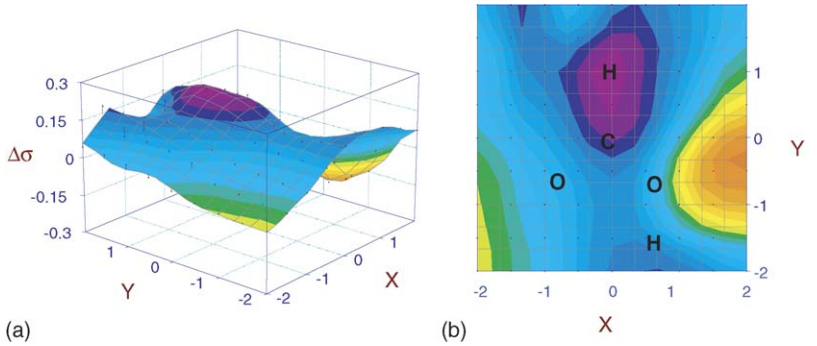

Fig. 7. Calculated NMR shielding increment surfaces (ppm) of formic acid using diatomic hydrogen as the probe molecule at (a) 2.5 Å side view, (b) 2.5 Å top view.

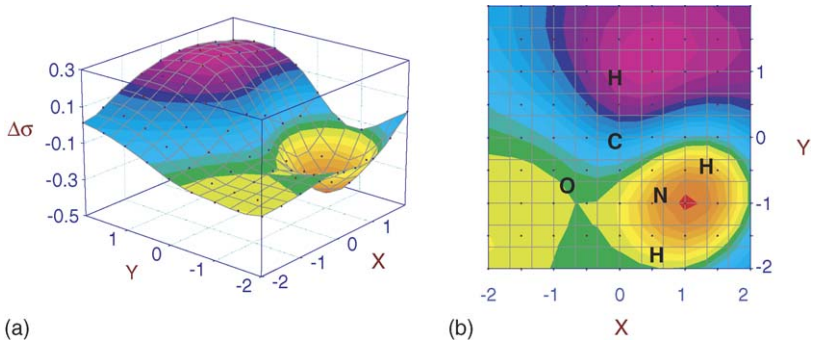

Fig. 8. Calculated NMR shielding increment surfaces (ppm) of formamide using diatomic hydrogen as the probe molecule at (a) 2.5 Å side view, (b) 2.5 Å top view.

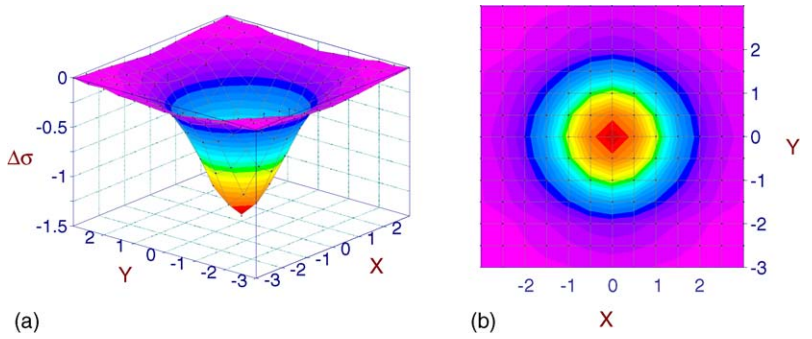

Fig. 9. Calculated NMR shielding increment surfaces (ppm) of ammonia with diatomic hydrogen as the probe molecule on the side opposite three hydrogens 2.5 Å from nitrogen: (a) side view, (b) top view.

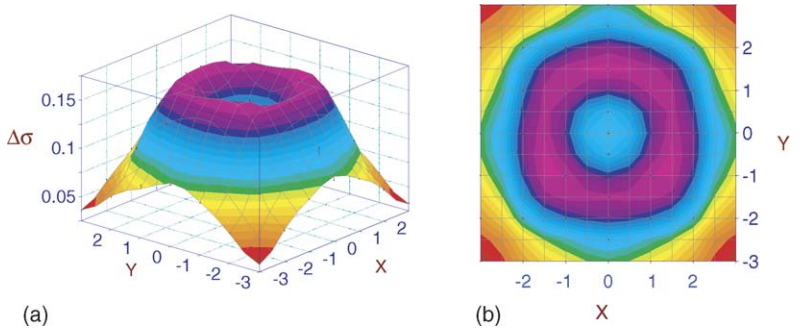

Fig. 10. Calculated NMR shielding increment surface (ppm) of ammonia with diatomic hydrogen as the probe molecule on the same side as three hydrogens 2.5 Å from the plane of three hydrogens: (a) side view, (b) top view.

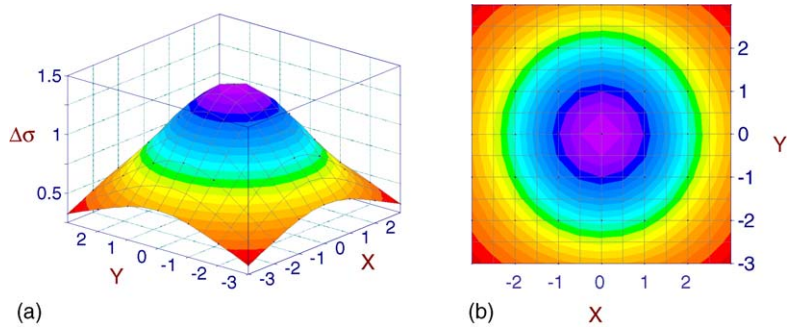

Fig. 11. Calculated NMR shielding increment surface (ppm) of ammonium ion with diatomic hydrogen as the probe molecule on the same side as three hydrogens 2.5 Å from the plane of three hydrogens: (a) side view, (b) top view.

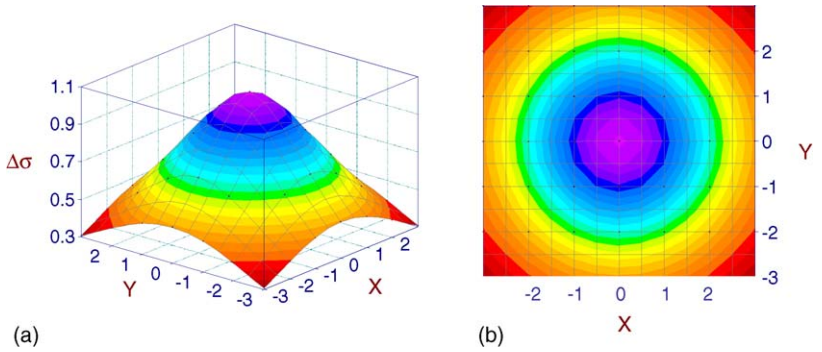

Fig. 12. Calculated NMR shielding increment surface (ppm) of ammonium ion with diatomic hydrogen as the probe molecule on the same side as one hydrogen 2.5 Å from the hydrogen: (a) side view, (b) top view.

At 3.5 Å, the graph shows only a smooth mound of shielding. The delocalized nature of the positive charge in the guanidinium ion results in a more moderate shielding effect than is observed in the ammonium ion.

Among the group of structures representing the functional groups studied, the ammonium ion showed the greatest shielding, regardless of the position of the H_2 probe. The probe orientation (along positive or negative Z axis) had little effect on the shielding observed. Although the ammonium ion was not the only functional group model to bear a positive charge, the charge is much more localized in ammonium ion than in the guanidinium ion, resulting in greater shielding. The maximum shielding values of the simple structures at each of the distances from the H_2 probe calculated are shown in Table 1.

The formate ion was the only structure examined that showed substantial deshielding at all distances from the hydrogen probe. It is also the only anionic structure in the study. The electrostatic repulsion of the bonding electrons of the H_2 probe by the negative charge of the formate ion resulted in greater deshielding than any of the other groups studied. The minimum shielding increments of the simple structures modeled are shown in Table 2 (note that a negative value of $\Delta\sigma$ is deshielding).

Two ionic species were found to exert substantial through-space NMR effects: formate anion and ammonium cation. Equations were determined for the shielding surfaces of formate ion and ammonium ion at distances from 2.5 to 4.0 Å from the plane of formate ion or from the plane of three hydrogens of ammonium ion. These two ions are the most commonly found forms of the carboxyl and amino groups of amino acids at physiological pH. Distances closer than 2.5 Å are unlikely to be encountered in peptides as that distance approaches the sum of the van der Waals radii, so data from calculations at 2.0 Å were not included. The general shielding increment equation found by TableCurve 3D for formate ion was $\Delta\sigma^{-1} = a + bX^2 + cY + dY^2$; the general equation for the ammonium ion was $\Delta\sigma^{-1} = a + bX^2 + cY^2$. The r^2 values for the fit of these equations to the data at each distance of the probe molecule from the ion was >0.99. The values of the constants and variables at each Z distance are found in Table 3 (formate ion) and Table 4 (ammonium ion). Quadratic equations, each having $r^2 = 1$, were found to relate each of the constants and variables to the Z distance. These quadratic equations are shown in Table 5 (formate ion) and Table 6 (ammonium ion). Substituting these quadratic equations into the general shielding increment equation for each structure gave an

Table 1
Maximum shielding increments (ppm) of the proximal hydrogen of the H_2 probe at 2.0, 2.5, 3.0 and 4.0 Å from various simple functional group models

Model structure	Distance from H_2 probe (Å)			
	2.0	2.5	3.0	4.0
Formate ion	−0.28	−0.28	−0.27	−0.25
Formic acid	0.10	0.21	0.20	0.10
Formamide	0.23	0.25	0.20	0.11
Ammonia (H_2 opposite 3 hydrogens)	0.09	−0.01	−0.02	0.12
Ammonia (H_2 on 3 hydrogen side)	0.16	0.17	0.15	0.22
Ammonium ion (H_2 on 1 hydrogen side)	1.36	1.05	0.82	0.54
Ammonium ion (H_2 on 3 hydrogen side)	1.68	1.39	1.09	0.69
Guanidinium ion	0.76	0.87	0.69	0.48

Table 2
Minimum shielding increments of the proximal hydrogen of the H_2 probe at 2.0, 2.5, 3.0 and 4.0 Å from various simple functional group models (negative value indicates deshielding)

Model structure	Distance from H_2 probe (Å)			
	2.0	2.5	3.0	4.0
Formate ion	−2.77	−1.38	−0.96	−0.62
Formic acid	−1.11	−0.21	−0.05	0.02
Formamide	−1.86	−0.42	−0.12	−0.05
Ammonia (H_2 opposite 3 hydrogens)	−3.58	−1.45	−0.73	−0.32
Ammonia (H_2 on 3 hydrogen side)	−0.34	0.03	0.04	0.03
Ammonium ion (H_2 on 1 hydrogen side)	0.31	0.31	0.29	0.25
Ammonium ion (H_2 on 3 hydrogen side)	0.32	0.33	0.32	0.28
Guanidinium ion	−0.54	0.39	0.35	0.30

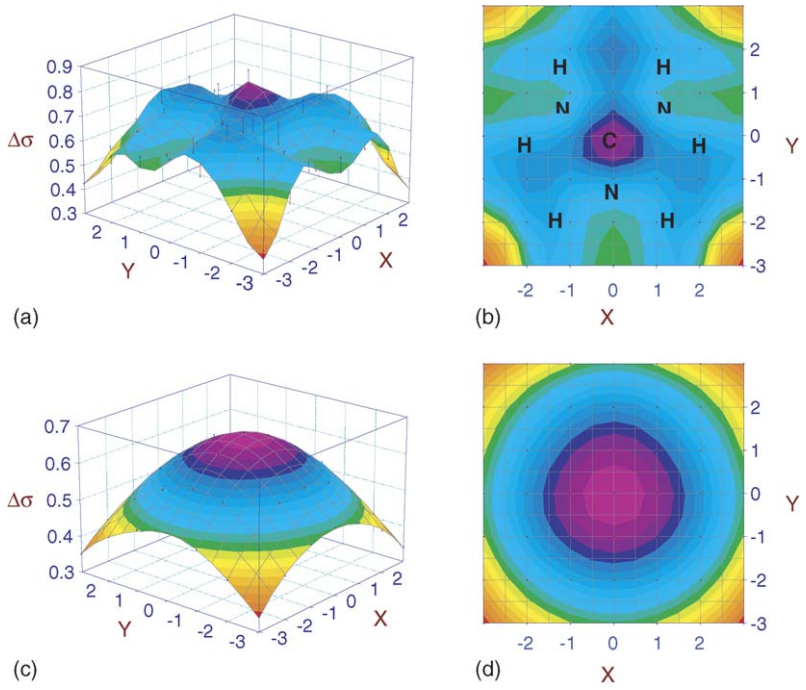

Fig. 13. Calculated NMR shielding increment surfaces (ppm) of guanidinium ion using diatomic hydrogen as the probe molecule at (a) 2.5 Å side view, (b) 2.5 Å top view.

Table 3
Values of the constant a and the variables b and c in the equation ($\Delta\sigma^{-1} = a + bX^2 + cY + dY^2$) for the shielding increment surface as a function of distance (Z) above the formate ion

Parameter	2.5 Å	3.0 Å	4.0 Å
a	−0.7929	−1.1344	−1.6936
b	−0.0562	−0.0553	−0.0641
c	0.2397	0.2402	0.2242
d	−0.1317	−0.1155	−0.1065

overall shielding increment equation for each structure as a function of X, Y and Z.

The overall equation derived for formate ion is:

$$\Delta\sigma^{-1} = 0.0824Z^2 - 1.1362Z + 1.5323 + (-0.0071Z^2 + 0.041Z - 0.1143)X^2 + (-0.0114Z^2 + 0.0634Z + 0.1521)Y + (-0.0155Z^2 + 0.1176Z - 0.3286)Y^2$$

Table 4
Values of the constant a and the variables b and c in the equation ($\Delta\sigma^{-1} = a + bX^2 + cY^2$) for the shielding increment surface as a function of distance (Z) above three hydrogens of the ammonium ion

Parameter	2.5 Å	3.0 Å	4.0 Å
a	0.6852	0.8882	1.4161
b	0.1157	0.1137	0.1106
c	0.1109	0.1109	0.1093

Table 5
Quadratic equations relating the constants and coefficients in the equation for the shielding increment surface to the distance Z above formate ion

Equation
$a = 0.0824Z^2 - 1.1362Z + 1.5323$
$b = -0.0071Z^2 + 0.041Z - 0.1143$
$c = -0.0114Z^2 + 0.0634Z + 0.1521$
$d = -0.0155Z^2 + 0.1176Z - 0.3286$

The overall equation derived for ammonium ion is:

$$\Delta\sigma^{-1} = 0.0813Z^2 - 0.0411Z + 0.2798 + (0.0006Z^2 - 0.007Z + 0.1298)X^2 + (-0.001Z^2 + 0.0054Z + 0.1037)Y^2$$

Table 7 shows the shielding increments calculated at selected positions 3.0 Å above the plane of glycylglycylglycine (GGG). Table 8 shows the shielding increments calculated at the same positions 3.0 Å above one molecule in the antiparallel hydrogen-bonded dimer of GGG.

Table 6
Quadratic equations relating the constants and coefficients in the equation for the shielding increment surface to the distance Z above three hydrogens of the ammonium ion

Equation
$a = 0.0813Z^2 - 0.0411Z + 0.2798$
$b = 0.0006Z^2 - 0.007Z + 0.1298$
$c = -0.001Z^2 + 0.0054Z + 0.1037$

Table 7
Calculated shielding increments ($\Delta\sigma$, in ppm) of selected probe positions 3.0 Å over simple models,[a] glycylglycylglycine (GGG), and the differences in calculated shielding increments between the simple model and the peptide

Probe	$\Delta\sigma$ (ppm), simple model	$\Delta\sigma$ (ppm), GGG monomer	Difference (ppm)
A	1.3	1.2	0.1
B	−0.1	−0.1	0.0
C	0.0	0.1	−0.1
D	−0.1	0.0	−0.1
E	−0.9	−0.7	−0.2

[a] The simple model used for A: ammonium ion; B, C and D: formamide; E: formate ion.

Table 8
Calculated shielding increments ($\Delta\sigma$, in ppm) of selected probe positions 3.0 Å over simple models,[a] the anti-parallel hydrogen-bonded dimer of glycylglycylglycine (GGG), and the differences in calculated shielding increments between the simple models and the peptide dimer

Probe	$\Delta\sigma$ (ppm), simple model	$\Delta\sigma$ (ppm), GGG dimer	Difference (ppm)
A	0.7	0.7	0.0
B	−0.1	−0.1	0.0
C	0.0	0.1	−0.1
D	−0.1	0.0	−0.1
E	−0.4	−0.3	−0.1

[a] The simple models used for A and E: ammonium ion and formate ion; B, C and D: formamide.

The shielding increments for comparable probe positions in models of the simple molecules having the corresponding functional groups are included for comparison, along with differences in shielding increments between the corresponding simple molecule and the peptide. For positions A (3.0 Å over the ammonium nitrogen) and E (3.0 Å above the line bisecting the O–C–O bond of the carboxylate ion, 1.5 Å beyond the carbon) in the dimer, the predicted shielding influence of both the formate ion and the ammonium ion were added together to obtain the predicted shielding increment based on simple models. This was necessary because in those locations in the dimer, the carboxylate ion and the ammonium ion are near each other.

4. Conclusions

Diatomic hydrogen (H_2) was used as a computational probe of the through-space NMR shielding of models of simple molecules and ions having functional groups common to peptides. The functional groups studied include the carboxylic acid, carboxylate ion, amide, amino, ammonium ion and guanidinium ion. Substantial shielding or deshielding effects were found primarily near the ionic species (formate ion, ammonium ion, and to a lesser extent, guanidinium ion) and also on the side of ammonia occupied by the lone pair of electrons. Equations have been developed to predict the through-space shielding increment for the ions that exhibited substantial shielding or deshielding: formate and ammonium. These equations should prove useful in determining or confirming tertiary structure of peptides based on NMR chemical shifts.

The validity of using simple structures as models of the functional groups common to peptides was established by calculating the through-space shielding increments at selected positions near a model of a simple tripeptide, glycylglycylglycine (GGG) and its antiparallel hydrogen-bonded dimer (Fig. 5), both in planar *trans*-peptide conformation with zwitterionic end groups. Diatomic hydrogen probes were placed sequentially at selected positions 3.0 Å above the molecular plane of each peptide model near the ammonium ion, the amide group, and the carboxylate ion, and the through-space shielding effects were determined as with the simple models for the functional groups. These results were compared to shielding increments calculated at similar positions in the simple model structures. In most cases, identical shielding was observed (within the uncertainty of this method, 0.15 ppm). Only one probe position gave greater deviation: the position near the negative oxygens of the carboxylate ion (E) in the monomer. The difference at position E was 0.2 ppm, only slightly greater that the uncertainty of the method.

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