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Calculations of the Contribution of Ring Currents to the Chemical Shielding Anisotropy

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There is interest in understanding how much secondary shielding mechanisms contribute to the chemical shielding anisotropy[1] (CSA, $\Delta\sigma$). Accurate information about the CSA especially for the backbone nuclei of proteins, including its site variability, is necessary for the quantitative analysis of local dynamics and also essential for the increasingly important TROSY spectroscopy.[2] In the following we discuss the effects of ring currents upon the anisotropy of the shielding tensor. The concept of ring currents was introduced to NMR by Pople[3a,b] and developed further by McConnell,[4a] Waugh and Fessenden[4b] (W−F), Johnson and Bovey[4c] (J−B), and Haigh and Mallion.[4d,e] Ring-currents provide a relatively small long-range contribution to the total magnetic induction, and the shielding tensor of a nucleus, σ, can be expressed as[5] $\sigma = \sigma_{\mathrm{local}} + \sigma_{\mathrm{rc}}$ where σ_{rc} is the contribution from ring currents and σ_{local} is the contribution from all other shielding mechanisms, including electric field and solvent effects.[5,6] The (W−F) and (J−B) model considers that an additional magnetic field is induced at a probe nucleus from a pair of circular current loops of radius *a* positioned ±0.64 Å[4c] above and below the plane of an aromatic ring. The influence of this additional magnetic field at the probe nucleus can be expressed using the shielding tensor σ_{rc}. The contribution to σ_{rc} from *each* current loop is calculated in a coordinate frame whose origin is at the ring center with the *z*-axis defined by the ring normal and, due to the axial symmetry of the system, the *x*-axis can be chosen along the azimuthal direction toward the probe nucleus so that the field induced by the ring current has no *y*-axis component. Following the approach outlined in ref 4c and employing the results of an electrodynamics treatment described by Smythe[7] the components σ_{zz} and σ_{xz} of the tensor σ_{rc} can be expressed via eqs 1and 2. Equation 1 was derived by Johnson and Bovey,[4c] while eq 2, to the best of our knowledge, is reported for the first time. In eqs 1 and 2 (ρ, z) are the cylindrical coordinates of the probe nucleus in the ring frame, measured in units of *a*, relative to the center of a current loop, $K(k)$ and $E(k)$ are complete elliptic integrals of the first and second kind for which the modulus[4f] $k = [4\rho/\{(1 + \rho)^2 + z^2\}]^{1/2}$, I is the intensity factor[4g] determined by the type of aromatic ring, and $D = (10^6)(\mu_0/4\pi)(3e^2/2\pi a m_e)$. The shielding tensor σ_{rc}, in the ring reference frame defined above, is expressed using eq 3, and the zero-rank component appearing on the rhs gives values agreeing with those of Bovey.[8] The last term of eq 3 contains the second-rank shielding components of interest here.

$$\sigma_{zz}^{\mathrm{rc}}(/\mathrm{ppm}) = \frac{ID}{[(1+\rho)^2 + z^2]^{1/2}}\left[K(k) + \frac{1-\rho^2-z^2}{(1-\rho)^2+z^2}E(k)\right] \tag{1}$$

$$\sigma_{xz}^{\mathrm{rc}}(/\mathrm{ppm}) = \frac{ID\,z}{\rho[(1+\rho)^2 + z^2]^{1/2}}\left[-K(k) + \frac{1+\rho^2+z^2}{(1-\rho)^2+z^2}E(k)\right] \tag{2}$$

$$\sigma_{\mathrm{rc}} = \begin{bmatrix} 0 & 0 & \sigma_{xz}^{\mathrm{rc}} \\ 0 & 0 & 0 \\ 0 & 0 & \sigma_{zz}^{\mathrm{rc}} \end{bmatrix} = \frac{\sigma_{zz}^{\mathrm{rc}}}{3}\begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} + \frac{\sigma_{xz}^{\mathrm{rc}}}{2}\begin{bmatrix} 0 & 0 & 1 \\ 0 & 0 & 0 \\ -1 & 0 & 0 \end{bmatrix} + \frac{1}{6}\begin{bmatrix} -2\sigma_{zz}^{\mathrm{rc}} & 0 & 3\sigma_{xz}^{\mathrm{rc}} \\ 0 & -2\sigma_{zz}^{\mathrm{rc}} & 0 \\ 3\sigma_{xz}^{\mathrm{rc}} & 0 & 4\sigma_{zz}^{\mathrm{rc}} \end{bmatrix} \tag{3}$$

To test that eqs 1−3 can provide a reasonable estimate for the contribution of σ_{rc} to the shielding tensor $\sigma = \sigma_{\mathrm{local}} + \sigma_{\mathrm{rc}}$ a series of density functional theory (DFT) computations were conducted with two simple atomic models using Gaussian98.[9a] The models were composed of an *N*-methyl acetamide (NMA) probe molecule with either a benzene or a 1,3 cyclohexadiene (CYH) ring,[4b,e] Figure 1, A and B. The shielding tensor σ for the $^1H^N$ atom of NMA was calculated in two different ways: (i) directly from DFT calculations using the atomic model with the benzene ring and (ii) as $\sigma = \sigma_{\mathrm{local}} + \sigma_{\mathrm{rc}}$ where σ_{local} is obtained via DFT computations using a model with CYH replacing the benzene ring and with σ_{rc} calculated via eqs 1 and 2 (both σ_{local} and σ_{rc} were obtained in the *same* reference frame). For computations of σ_{local} we assume that a CYH molecule provides an olefinic analogue for benzene.[4b] A series of models were

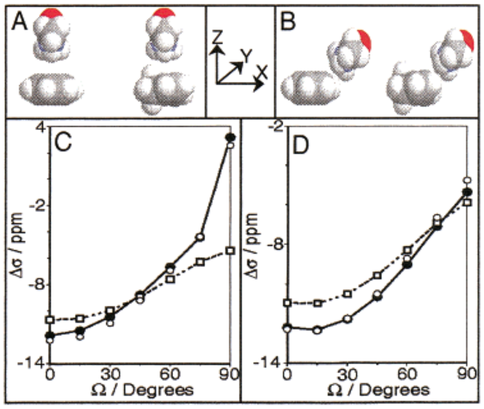

Figure 1. The initial geometry of the models used for calculating the shielding tensor, σ. The rings are in the *xy* plane with the center of mass of the carbons on the *z*-axis. For the models in (A) the NMA is positioned so that the $^1H^N$ and N atoms are aligned on the *z*-axis with a distance of 3.65 Å between the $^1H^N$ atom and the center of the ring. For the models in (B) the $^1H^N$ and N atoms and the origin are aligned along an axis inclined at 54.7° to the *z*-axis with a distance of 4 Å between the $^1H^N$ atom and the center of the ring. The geometry of the models was modified by applying the rotation Ω as described in the text and no significant van der Waals violations occur with the molecular separations described above. The DFT based shielding calculations used the hybrid B3LYP exchange-correlation functional,[9a,b] the 6-311++G(2d,p) basis set[9a] and gauge-including atomic orbitals.[9a,b] Equations 1 and 2 used $I = 1$ and $a = 1.39$. The eigenvalues of the traceless symmetric portion of the H^N shielding tensor were ordered with $\sigma_{11} < \sigma_{22} < \sigma_{33}$. $\Delta\sigma$ was calculated using the convention described by Grant[10] so that $\Delta\sigma$ changes sign as σ_{22} crosses the midpoint between σ_{11} and σ_{33}. Panels (C) and (D) display the variation of $\Delta\sigma$ with change in model geometry starting from the fragments in (A) and (B), respectively. The plots show $\Delta\sigma$ from the DFT computations using the NMA−CYH model (open squares, dashed line), the NMA−benzene model (filled circles, solid line) and $\Delta\sigma$ from the summation of the NMA−CYH DFT results (σ_{local}) with the ring current contribution (σ_{rc}) from eqs 1 and 2 (open circles).

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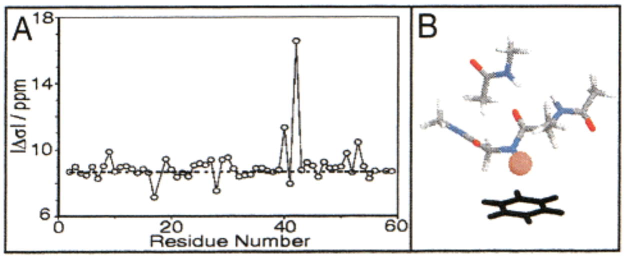

Figure 2. The variation in the absolute value of the anisotropy $|\Delta\sigma|$ of the $^1H^N$ shielding tensor ($\sigma_{local} + \sigma_{rc}$) as a function of residue number for the second type-2 module of the protein fibronectin.[11] To form ($\sigma_{local} + \sigma_{rc}$) both σ_{local} and σ_{rc} have been transformed into the molecular frame. The principal components of the uniform centrosymmetric shielding tensor σ_{local} were assumed to be $\{-5.8, 0, 5.8\}$,[12] with σ_{33} collinear with the N−H bond and σ_{11} orthogonal to the peptide plane. The dashed line corresponds to $|\Delta\sigma_{local}| = 8.7$ ppm. σ_{rc} computations used values for *I* and *a* from ref 4g. The standard deviation of $|\Delta\sigma|$ is 1.2 ppm. (B) The fragment modeling the environment of residue G42 used in DFT computations of its $^1H^N$ shielding tensor employing parameters identical to those used for Figure 1. The molecular geometry was generated from the coordinate file[11] by terminating the chain at the Cα positions of W40 and T43 and the Cβ position of C41 with methyl groups. The donor in the CO···HN (C41 to G54) hydrogen bond was modeled using a NMA molecule. The side chain of F19 is modeled using a benzene ring shown in black. The distance from the ring center to the $^1H^N$ atom, shown as a sphere, is 2.48 Å.

generated from those in Figure 1 by applying a rotation to the NMA molecule while holding the benzene or CYH ring fixed. The rotation is defined as: the rotation axis is parallel to the *y*-axis, and the pivot coincides with the H^N atom. The amplitude of the rotation, Ω, is varied from 0° to 90° with a step size of 15°. For example a rotation of $\Omega = 90°$ applied to the model in Figure 1A results in the NMA peptide plane being oriented parallel to the plane of the ring, with the position of the H^N atom and the ring unaltered.

The starting geometries of the models in Figure 1, A and B, were chosen so as to ensure that σ_{rc}, calculated via eqs 1 and 2 in the ring reference frame, consists solely of either σ_{zz} or σ_{xz}, respectively. Clearly, the magnitude of either σ_{zz} or σ_{xz}, in the ring reference frame, do not change as a function of the specific rotation described above. However, the relative contributions of σ_{local} and σ_{rc} vary with the rotation Ω, testing the approximation $\sigma = \sigma_{local} + \sigma_{rc}$ under a variety of conditions. The results are illustrated in Figure 1, C and D, for $\Delta\sigma$ of the $^1H^N$ shielding tensor (see Figure caption for the definition of $\Delta\sigma$). The closed circles connected by the solid line show data for $\Delta\sigma$ from DFT computations of the NMA−benzene models. The open squares joined by the dashed line show $\Delta\sigma_{local}$ from the NMA−CYH models without including σ_{rc}. The open circles show the values for $\Delta\sigma$ from $\sigma = \sigma_{local} + \sigma_{rc}$ where σ_{local} was obtained from the NMA−CYH models with σ_{rc} calculated via eqs 1 and 2. These results indicate that, for the particular model system used here, including the additive term σ_{rc} improves agreement to the benchmark $\Delta\sigma$ values obtained from DFT computations of the NMA−benzene models. The isotropic shielding from the DFT computations of the NMA−benzene and NMA−CYH series of models differ by 0.99 ± 0.05 and -0.05 ± 0.14 ppm, which compare favorably to the values calculated from σ_{rc} of 1.04 and 0 ppm respectively.

Calculations were performed to assess the contribution of ring currents to the CSA of backbone $^1H^N$ nuclei in proteins using a structure of the second type-2 module from fibronectin[11] (where it is assumed that eqs 1−3 can be applied to each aromatic amino acid). For every $^1H^N$ a total σ_{rc} was formed from the summation of a contribution from each aromatic amino acid after transforming the individual σ_{rc} generated in each local ring frame into the molecular frame. The data for $|\Delta\sigma|$ in Figure 2A were extracted from the shielding tensor ($\sigma_{local} + \sigma_{rc}$). These data exhibit a maximum CSA of 16.6 ppm for the $^1H^N$ of G42. The large perturbation to σ by the ring current term σ_{rc} for this residue is caused, almost exclusively, by the side chain of F19. The structure[11] of this protein strongly suggests there is a N−H···π hydrogen bond[13] involving the $^1H^N$ of G42 as the donor with F19 acting as the π-acceptor. The presence of an aromatic hydrogen bond[13a,14] is supported by the experimental chemical shift for this $^1H^N$ resonance at $\delta_{expt} = 3.59$ ppm.[11] The large CSA extracted from the tensor ($\sigma_{local} + \sigma_{rc}$) is supported by a DFT shielding calculation using the molecular fragment in Figure 2B. The DFT derived eigenvalues were $\{-9.8, -2.3, 12.1\}$ppm giving $\Delta\sigma = 18.2$ ppm in reasonable agreement with the CSA from ($\sigma_{local} + \sigma_{rc}$). The isotropic shielding from this DFT calculation of $\sigma_{calc} = 29.81$ ppm, when converted to the shift scale, gives $\delta_{calc} = 3.63$ ppm[15] in good agreement with δ_{expt}.

Using the approach described here the effect of ring currents upon the CSA can be assessed. A series of similar calculations suggests the method is also applicable to a fused ring system such as indole. For protons there is predicted to be a significant contribution from the ring currents of aromatic amino acids to the proposed CSA site variation.[12] The contribution into the CSA of $^{13}C'$ and ^{15}N nuclei of the peptide backbone typically causes a rmsd variation of <1 ppm. For a N−H···π hydrogen bond the contribution of ring currents to the $^1H^N$ CSA is predicted to be pronounced.

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(14) Using definitions in ref 13a the parameters *A*, *B*, ω, α, and θ have the values 0.71 Å, 2.37 Å, 17°, 49°, and 146° respectively. This set of values is consistent with a NH···π aromatic hydrogen bond interaction.[13a,b]
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