JCTC Journal of Chemical Theory and Computation

Frequency-Dependent Polarizabilities of Amino Acids as Calculated by an Electrostatic Interaction Model

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Received March 4, 2005

Abstract: The frequency-dependent polarizability of the 20 essential amino acids has been calculated by an electrostatic interaction model where an Unsöld-type of model has been adopted for the frequency dependence. The interaction model has previously been parametrized from Hartree−Fock calculations on a set of molecules, and the model is in this work extended by sulfur parameters by including a set of 18 small sulfur compounds. The results for the amino acids by using the interaction model compare well with Hartree−Fock calculations with deviations of around 5% for the isotropic polarizability. Furthermore, the intrinsic (or optical) dielectric constant related to the polarizability has been calculated for three small proteins, ribonuclease inhibitor, lysozyme, and green fluorescent protein, adopting the interaction model. The results are consistent with the intrinsic dielectric constants found for proteins in the literature.

I. Introduction

Molecular models of polarization are of importance in many aspects of computational molecular sciences. For example, when molecules interact with each other, they are polarized by the electric field of the surroundings.[1−3] In many cases, explicit polarization has also been included in force fields,[4−17] and its relevance for protein simulations has also been discussed.[4−21] In addition, the frequency-dependent polarizability also describes the response to an external electric field.[1,22,23] The polarizability is thus the microscopic counterpart to the macroscopic refractive index and dielectric constant, which are of fundamental importance in the design of new electro-optical materials.[24−26]

The modeling of molecular polarizabilities is thus of fundamental importance in molecular sciences. They may be calculated in quantum chemical calculations, but even though the method development has been substantial over the last years including new density functional theory (DFT) methods,[27,28] these methods are restricted to rather small systems. On the other hand, in simulations of molecular liquids, the polarization energy is calculated repeatedly for systems with a large number of molecules.[15,29,30] In a force field, atom-type parameters are used to model the molecular charge distribution, and consequently the molecular polarizability is in most cases described in terms of atomic or bond polarizabilities.[15,19,31−33]

We have developed a molecular mechanics model for molecular polarizabilities,[34−37] which is based on the point-dipole interaction (PDI) model originally suggested by Silberstein,[38−40] and to a large extent exploited by Applequist.[41,42] The model is based on the fact that a molecule is regarded as a set of (isotropic) atomic polarizabilities. In an external electric field, atomic dipole moments are induced which results in an additional electric field on the surrounding atoms. A set of coupled equations is obtained, where the solution gives the molecular polarizability tensor. The model includes a set of atom-type polarizabilities which may be parametrized from known molecular polarizabilities. In our work, the model has been parametrized from quantum chemical calculations, and the frequency-dependence has

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10.1021/ct050053c CCC: $30.25
Published on Web 06/04/2005

been included as an Unsöld model.[34] The model for including the damping of the interatomic interactions at short distances has been improved,[37] and the model has been extended by boron parameters.[36] The model has also been extended to second hyperpolarizabilities.[43−46]

The polarizabilities of the essential amino acids are studied in this work. It may be regarded as a first step toward a polarizable force field for peptides and proteins, but peptide systems are also strong candidates for materials in nonlinear optics.[47,48] To include also the sulfur-containing amino acids, the model has to be extended with sulfur parameters. The work is thus divided into three parts: a parametrization of sulfur, calculations on amino acids, and calculations on three small proteins.

II. Theoretical Background

Considering a set of N interacting atomic polarizabilities, the atomic induced dipole moment, μ_I^{ind}, of atom I due to an external electric field, E^{ext}, is given by

$$\mu_{I,\alpha}^{\text{ind}} = \alpha_{I,\alpha\beta}(E_\beta^{\text{ext}} + \sum_{J\neq I}^{N} T_{IJ,\beta\gamma}^{(2)} \mu_{J,\gamma}^{\text{ind}}) \tag{1}$$

where $T_{IJ,\beta\gamma}^{(2)}$ is the dipole interaction tensor given as

$$T_{IJ,\beta\gamma}^{(2)} = \frac{3R_{IJ,\beta}R_{IJ,\gamma}}{R_{IJ}^5} - \frac{\delta_{\beta\gamma}}{R_{IJ}^3} \tag{2}$$

The Greek subscripts, α, β, ..., denote the Cartesian coordinates x, y, or z. In eq 1 the Einstein summation convention for repeated Greek subscripts has been employed, and it is used throughout this work. The molecular polarizability is obtained as[41]

$$\alpha_{\alpha\beta}^{\text{mol}} = \sum_{I,J}^{N} B_{IJ,\alpha\beta} \tag{3}$$

here **B** is the relay matrix defined as

$$\mathbf{B} = (\alpha^{-1} - \mathbf{T}^{(2)})^{-1} \tag{4}$$

An improved model is obtained if the contributions from a smeared-out charge distribution is included in terms of a damping of the interaction in eq 1 by modifying the $T_{IJ,\alpha\beta}$ tensor.[49,50] The damping of the interactions arises from the overlap of the smeared-out charge distributions, and the model used here is obtained by considering the overlap between two Gaussian charge distributions.[37] We obtain the damped interaction by modifying the interaction tensors

$$T_{IJ,\alpha_1\ldots\alpha_n}^{(n)} = \nabla_{\alpha_1}\ldots\nabla_{\alpha_n}\left(\frac{1}{S_{IJ}}\right) \tag{5}$$

which is equivalent to replacing R_{IJ} by S_{IJ} and $R_{IJ,\alpha}$ by $S_{IJ,\alpha}$ in the regular formulas for the interaction tensor. We utilize the following "scaled distance"[37]

$$S_{IJ} = \sqrt{R_{IJ}^2 + \frac{\pi}{4a_{IJ}}} \tag{6}$$

where a_{IJ} is given by $a_{IJ} = \Phi_I\Phi_J/(\Phi_I + \Phi_J)$, and Φ_I is the damping parameter (the width of a Gaussian charge distribution) of atom I.

Well below the first electronic absorption, the frequency-dependence of the molecular polarizability is often approximated with an Unsöld-type of expression.[22] Here we assume that the atomic polarizability has a similar frequency-dependence[34]

$$\alpha_I(-\omega;\omega) = \alpha_I(0;0) \times \left[\frac{\bar{\omega}_I^2}{\bar{\omega}_I^2 - \omega^2}\right] \tag{7}$$

where $\bar{\omega}_I$ is an atom-type parameter and ω is the frequency.

For a given polarizability tensor $\alpha_{\alpha\beta}$, the *isotropic* (or mean) polarizability is defined as

$$\bar{\alpha} = \frac{1}{3}\alpha_{\alpha\alpha} \tag{8}$$

and here the *anisotropic* polarizability is calculated as

$$(\Delta\alpha)^2 = \frac{1}{2}\sum_{\alpha\beta}(3\alpha_{\alpha\beta}\alpha_{\alpha\beta} - \alpha_{\alpha\alpha}\alpha_{\beta\beta}) \tag{9}$$

III. Calculational Details

For the quantum chemical computations of frequency-dependent polarizabilities we use the Dalton program package[51] as described in refs 52−54 using linear response functions at the SCF level. The basis set of Sadlej[55] was employed since it has been shown previously that it gives good results for polarizabilities considering its limited size.[56] The following frequencies have been used: ω(au)/λ(nm) = 0.0/∞, 0.02389/1907, 0.04282/1064, and 0.0774/589 (1 au = 27.21 eV). For the parametrization of sulfur, a series of 18 molecules[57] containing S atoms has been added to the original set of 187 molecules used in our previous study.[37] The geometries of the new molecules containing S atoms have been optimized at the PM3 level with the Gaussian 98 program package.[58] The geometries of the amino acids have been generated in a similar manner, but these molecules were not included in the trial set. The choice of basis set and optimization level is dictated by our previous work.[37] Although optimizing the geometries at a higher level of theory, like DFT, would be preferable, it is not deemed necessary for the present work since the geometry dependence of the molecular polarizability may be assumed to be modeled by the $T^{(2)}$ tensor.

The structures for the three proteins ribonuclease inhibitor (RNI), lysozyme (LYS), and green fluorescent protein (GFP), were taken as the crystal structures from the Protein Data Bank with entry code 1BTA, 135L, and 1GFL, respectively. For LYS hydrogen atoms were added, and the water molecules were removed using PyMol.[59] For GFP only the monomer (chain A) was used, and again hydrogen atoms were added, and water molecules were removed using PyMol. Besides this no other refinements of the stuctures have been done in this work. Cartoon models of RNI, LYS, and GFP are displayed in Figures 1−3, respectively.

IV. Parametrization of Sulfur

We adopt the same scheme as used in our previous work to optimize the parameters describing the frequency-dependent

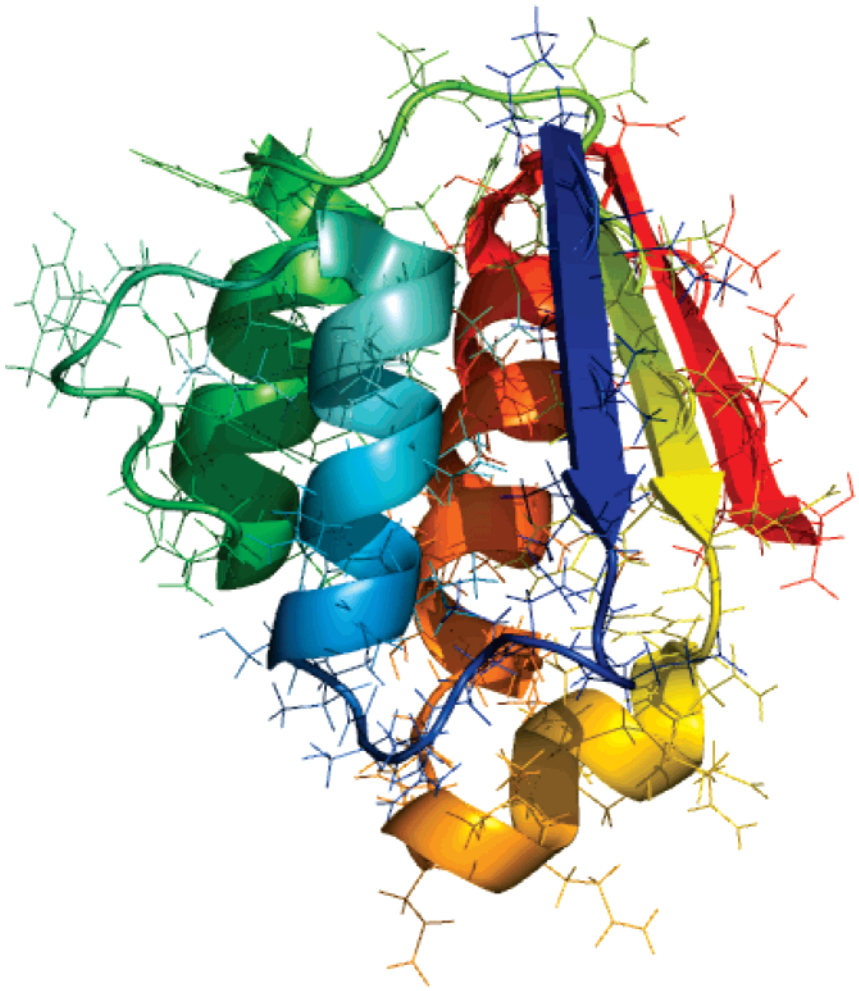

Figure 1. Cartoon of the ribonuclease inhibitor protein made using PyMol.[59]

polarizabilities.[37] For the static polarizability, the root-mean-square (rms) of the differences between the quantum chemical molecular polarizability tensors, $\alpha_{\alpha\beta,i}^{QC}$, and the model molecular polarizability tensors, $\alpha_{\alpha\beta,i}^{model}$, have been minimized as

$$\mathrm{rms} = \sqrt{\frac{\sum_{i=1}^{N}\sum_{\alpha,\beta=1}^{3}(\alpha_{\alpha\beta,i}^{model} - \alpha_{\alpha\beta,i}^{QC})^2}{N-1}} \tag{10}$$

where N is the number of molecules.

In a similar manner, the parameters describing the frequency-dependence of the molecular polarizability have been optimized by minimizing

$$\mathrm{rms} = \sqrt{\frac{\sum_{i=1}^{N}\sum_{\alpha,\beta=1}^{3}[(\alpha_{\alpha\beta,i}^{model}(\omega) - \alpha_{\alpha\beta,i}^{model}(0)) - (\alpha_{\alpha\beta,i}^{QC}(\omega) - \alpha_{\alpha\beta,i}^{QC}(0))]^2}{N-1}} \tag{11}$$

i.e. we parametrize the frequency-dependence only and do not attempt to correct for errors introduced in the parametrization of the static polarizability.

Since we already have obtained parameters for the elements H, B, C, N, O, F, and Cl in our previous work on a trial set of 187 molecules,[37] only the S parameters have been optimized, and the parameters for the other elements have been kept fixed. The optimized parameters are collected in Table 1 together with the obtained rms. The rms for the static polarizability is only 2.47 au considerably lower than the rms of 5.29 au found previously.[37] Therefore, we conclude that it is not needed to perform a refit of all parameters. This illustrates that the inclusion of new elements in the optimization can be performed by only optimizing the parameters for the new elements, at least as long as the new molecules included in the trial set are similar to the existing molecules. One would expect on the basis of atomic numbers that the "atomic" polarizability of S would be lower than that of Cl; however, we find the opposite to be the case. However, a better measure is the radius of the atoms since the classical polarizability of a conducting sphere (CS) is given by $\bar{\alpha}^{CS} = R^3$ where R is the radius of the sphere. Using this criteria we would expect an ordering of the atomic polarizability as H < F < O < N < C < B < Cl < S, if we use the covalent atomic radius adopted from WebElements.[60] If we compare with the polarizability in Table 1, this ordering is in agreement with our results. A similar trend has also been found in the work by Swart et al.[33] using the PDI model by Thole. The rms of 0.77 au found for the frequency-

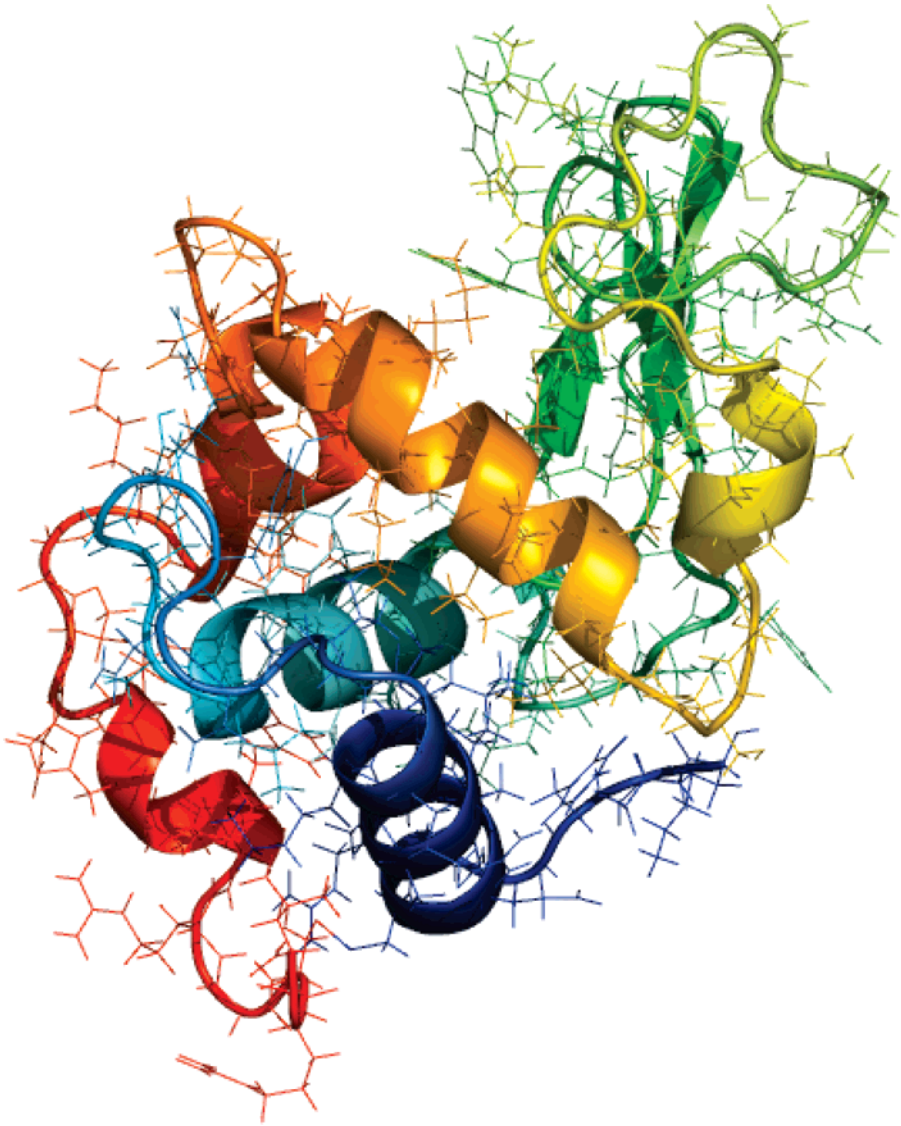

Figure 2. Cartoon of the lysozyme protein made using PyMol.[59]

dependence is larger than the value of 0.37 au that was obtained previously. Due to the very different frequency-dependence of the molecules containing B atoms, we found in our previous work a significant improvement by adopting a separate set of ω_p parameters for the boron molecules.[37] This may also be the case for the molecules containing S atoms. However, the frequency-dependence is in general very modest, and, therefore, we will keep the more general set of parameters.

V. Calculations on Amino Acids

The essential amino acids have not been included in the trial set and will therefore allow us to test the accuracy of the PDI model with the parameters adopted from Table 1. The frequency-dependent mean polarizabilities of the amino acids calculated with the PDI model, $\bar{\alpha}^{\mathrm{PDI}}$, have been plotted versus the polarizabilities obtained using the SCF method, $\bar{\alpha}^{\mathrm{SCF}}$, in Figure 4. In Figure 5, the corresponding plot is presented for the anisotropic polarizabilities. Furthermore, the static mean and anisotropic polarizabilities for the amino acids have been collected in Table 2.

In Table 2 and Figure 4, a good agreement is found for the mean polarizability between the PDI model and SCF results. The deviation in the static mean polarizability is on average 4.9% with the largest deviations of 8.5% for aspartic acid and 8.3% for glutamic acid. Among the 20 amino acids, it is only cysteine and methionine which contain an S atom, and the mean polarizability of these molecules is well described with the PDI model again illustrating the accuracy of the new S parameters. For all amino acids, the mean polarizability calculated with PDI is larger than the SCF polarizability.

In general, it is expected that the inclusion of electron correlation in the quantum chemical calculations will increase the values of the polarizabilities since the SCF method is known to underestimate the polarizability. If we compare our SCF values for the polarizability with the DFT results of Swart et al.[61] we find that this is indeed the case. Swart et al.[61] also presented a parametrization of the original Thole PDI model for the 20 amino acids against polarizabilities calculated using DFT. If we compare our results with both their reported DFT results and the Thole PDI model results we find a good agreement.

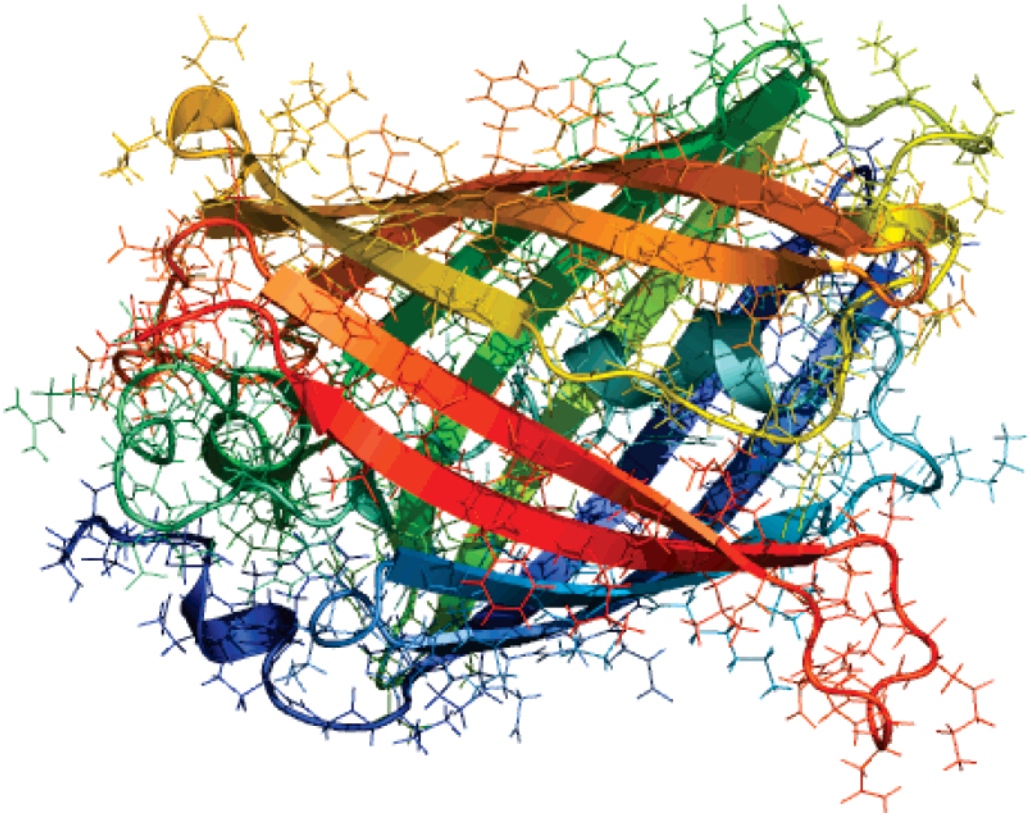

Figure 3. Cartoon of the green fluorescent protein made using PyMol.[59]

Table 1: Atomic Parameters Fitted To Model the Frequency-Dependent Polarizability Using the PDI-SQRT Unsöld Model[a]

atom	α_p	Φ_p	ω_p
H	1.280	0.358	0.413
B	8.649	0.074	-
C	8.465	0.124	0.784
N	6.169	0.268	0.658
O	3.754	4.103	0.493
F	1.907	1.468	0.896
Cl	13.081	0.453	0.375
S	19.617	0.120	0.534
rms[b]	2.47		0.77

[a] In au, 1 au = 0.1482 Å^3. The parameters for the elements H, B, C, N, O, F, and Cl have been taken from ref 37, and only the S parameters have been optimized in this work. [b] Optimized error, see eqs 10 and 11.

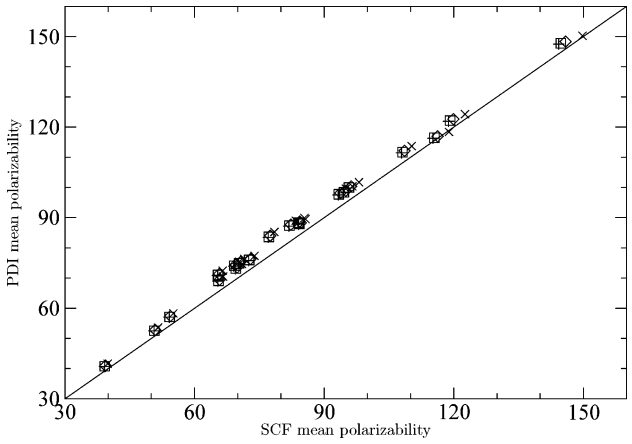

Figure 4. The isotropic polarizability in au calculated using PDI vs SCF for the frequencies ω(au) = 0.0 (+), 0.02389 (□), 0.04282 (◇), and 0.0774 (×).

For the anisotropies in Figure 5 and Table 2, a larger deviation is found between the PDI model and the SCF results. The average deviation is 25.9% with the largest deviation of 64.1% for isoleucine. In general, anisotropies are much more difficult to model than the mean polarizability, and it is therefore not surprising that the deviation is larger in this case. Furthermore, according to eq 10 the absolute error of the tensor components is minimized, which may result in large relative errors in cases where the absolute values are small. For the aromatic amino acids, phenylalanine, tyrosine, and trypthophan, we see that not only the anisotropy is modeled accurately but also the anisotropy of arginine is modeled successfully by the PDI model. These molecules have a large polarizability as compared with the other amino acids, and also the mean polarizability of these molecules are modeled very well with the PDI model. We note that in all cases the PDI model predicts anisotropic polarizabilities which are larger than the corresponding SCF value.

In Figures 4 and 5, a similar accuracy is obtained for the frequency-dependent polarizabilities of the amino acids. This is expected due to the small dispersion in the frequency range investigated here. Again the amino acids containing S atoms give similar results to the other amino acids.

VI. Calculations on Proteins

To illustrate the usefulness of the PDI model to calculate the polarizability of large systems where quantum chemical

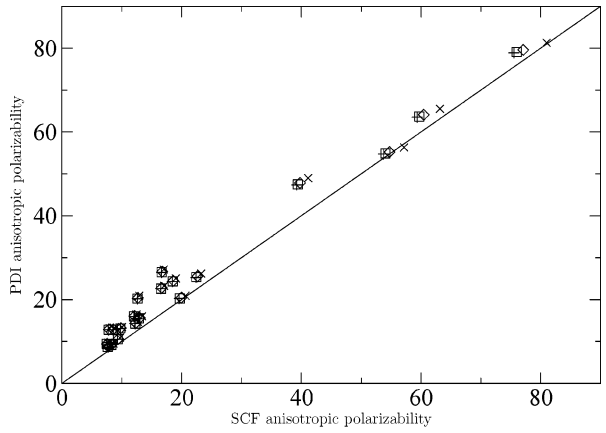

Figure 5. The anisotropic polarizability in au calculated using PDI vs SCF for the frequencies ω(au) = 0.0 (+), 0.02389 (□), 0.04282 (◇), and 0.0774 (×).

Table 2

amino acid	$\bar{\alpha}^{SCF}$	$\bar{\alpha}^{PDI}$	dev[a] (%)	$\Delta\alpha^{SCF}$	$\Delta\alpha^{PDI}$	dev[b] (%)
alanine (A)	50.59	52.46	3.7	9.32	10.52	12.9
arginine (R)	107.90	111.47	3.3	19.62	20.23	3.1
asparagine (N)	70.16	74.79	6.6	12.87	15.47	20.2
aspartic acid (D)	65.34	70.89	8.5	8.54	12.76	49.5
cysteine (C)	69.41	73.07	5.3	7.65	8.66	13.2
glutamine (Q)	81.84	87.18	6.5	16.52	22.58	36.6
glutamic acid (E)	77.09	83.48	8.3	12.62	20.17	59.8
glycine (G)	39.16	40.70	3.9	12.22	14.25	16.7
histidine (H)	95.49	99.80	4.5	39.23	47.37	20.7
isoleucine (I)	83.89	88.16	5.1	7.79	12.79	64.1
leucine (L)	84.12	87.78	4.4	9.76	13.10	34.2
lysine (K)	93.25	97.59	4.7	16.65	26.48	59.1
methionine (M)	94.37	98.26	4.1	22.40	25.27	12.8
phenylalanine (F)	115.16	116.30	1.0	53.76	54.73	1.8
proline (P)	69.05	73.94	7.1	18.45	24.28	31.6
serine (S)	54.13	57.02	5.4	8.25	9.22	11.8
threonine (T)	65.44	68.98	5.4	12.03	15.95	32.6
tryptophan (W)	144.28	147.52	2.2	75.54	78.88	4.4
tyrosine (Y)	118.79	121.95	2.7	59.38	63.51	7.0
valine (V)	72.54	75.82	4.5	7.51	9.39	25.0

[a] Deviation of $\bar{\alpha}^{PDI}$ from $\bar{\alpha}^{SCF}$. [b] Deviation of $\Delta\alpha^{PDI}$ from $\Delta\alpha^{SCF}$.

calculations are unfeasible, PDI calculations have been performed for the static polarizability of three proteins. The three proteins are ribonuclease inhibitor (RNI) which contains 89 residues (1434 atoms), lysozyme (LYS) which contains 129 residues (1950 atoms), and green fluorescent protein (GFP) which contains 230 residues (3604 atoms). Cartoons of the proteins are presented in Figures 1−3, respectively. For RNI, we obtain a mean polarizability of $\bar{\alpha}$ = 6903.64 au and an anisotropy of $\Delta\alpha$ = 667.62 au. The mean polarizability for LYS is $\bar{\alpha}$ = 9506.30 au with an anisotropy of $\Delta\alpha$ = 1344.43 au. For the largest protein studied here, GFP, we obtain a mean polarizability of $\bar{\alpha}$ = 17443.98 au and an anisotropy of $\Delta\alpha$ = 2300.4 au

The mean polarizability obtained with the PDI model is compared with an additive model for the polarizability, $\bar{\alpha}^{add}$, i.e., the sum of the polarizability of the residues in the protein. This simple additive model does not take into account the differences due to the peptide bond formations in the proteins and will therefore only be able to give a rough estimate of the polarizability. For RNI we get an additive polarizability of $\bar{\alpha}^{add}$ = 7344.77 au, for LYS $\bar{\alpha}^{add}$ = 10220.65 au, and for GFP $\bar{\alpha}^{add}$ = 18844.68 au. For these proteins, the simple additive model overestimates the mean polarizability by 6.3% for RNI, 7.5% for LYS, and 8% for GFP. Although the additive model seems to be reasonable for the mean polarizability, the model is trivially unable to describe the anisotropic polarizability since this is not related to the sum of the residues.

Dielectric properties of proteins are important for their structural and functional characteristics.[18,62−71] The concept of a dielectric constant of a protein depends on the model in which it is used, and the value therefore varies in different applications.[68] However, in general it is agreed on that the intrinsic dielectric constant of proteins are in the range 2−4 which is consistent with measurements on dry proteins.[72,73] The intrinsic (or optical) dielectric constant means here the part which is related to the polarizability or induced polarization. The contribution to the dielectric constant arising from the permanent polarization (the static dielectric constant) is not considered here.

The intrinsic dielectric constant is related to the susceptibility, i.e., polarizability per volume, by[74]

$$\epsilon = 1 + 4\pi\chi^{(1)} = 1 + 4\pi\frac{\bar{\alpha}}{V} \qquad (12)$$

where $\chi^{(1)}$ is the susceptibility or polarizability per volume V. The volume of the proteins may be estimated by using an average van der Waals radius of 1.5 Å for the atoms, which gives the following volumes $V^{RNI} = 1.04 \times 10^4$ Å^3, $V^{LYS} = 1.46 \times 10^4$ Å^3, and $V^{GFP} = 2.69 \times 10^4$ Å^3. Using these estimates and the mean polarizability calculated for the proteins, an intrinsic dielectric constant may be obtained for the proteins. For RNI we get ϵ = 2.24, for LYS ϵ = 2.21, and for GPL we get ϵ = 2.21. This estimate for the intrinsic dielectric constant is in good agreement with both measurements on dry proteins and the values generally adopted. It is noted that the value of the intrinsic dielectric constants for the three proteins investigated are very similar.

VII. Discussion and Conclusions

The focus of this work has been to study the polarizability of the amino acids by means of a PDI model. Therefore, to also study the sulfur containing amino acids we extended our existing PDI model to also include the sulfur atom. It was shown that this was straightforward by adopting the parameters obtained previously for the PDI model and only optimize the S parameters to a small set of molecules. The PDI model with the new parameters was subsequently tested on the amino acids. We compared the results from the PDI model with SCF calculations. This comparison showed that the PDI model is capable of reproducing the SCF polarizabilities to an accuracy of 5% for the mean polarizability. The description of its anisotropy is reproduced within 25%. Although accurate calculations of the polarizability requires the inclusion of electron correlation, especially for the anisotropic polarizability, it is clear that the PDI model reproduces the polarizability accurately enough for many

purposes. We also showed that a similar accuracy can be obtained for the frequency-dependent polarizability well below any electronic transitions. Therefore, we conclude that the PDI model produces an accurate description of the polarizability for the amino acids. Since the PDI model represents an atomistic model for the polarization, it is well suited for adoption in classical force field see e.g. refs 6, 13, 21, and 75−77 or combined quantum mechanics and molecular mechanics (QM/MM) models, see e.g. refs 4 and 78−82.

To test the PDI model on systems for which quantum chemical calculations would be unfeasible, the static polarizability has been calculated for three proteins. The polarizability obtained with the PDI model has been compared to an additive model, i.e., the sum of the polarizability of the amino acids residues. This showed that the simple additive model is good to within 10%. We have also calculated the intrinsic dielectric constant for the three proteins. For all three proteins, we found an intrinsic dielectric constant of 2.2 which is in good agreement with measurement on dry proteins.

Acknowledgment. P.-O.Å. has received support from the Norwegian Research Council (NFR) through a Strategic University Program (Grant no 154011/420), a NANOMAT program (Grant no 158538/431), and a grant of computer time from the Norwegian High Performance Computing Consortium (NOTUR). K.V.M. thanks the Danish Natural Science Research Council, the Danish Technical Research Council, the Carlsberg Foundation, the Danish Center for Scientific Computing, and the EU-network NANOQUANT for support.

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CT050053C